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Re: Draft Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS
Comments (75 Fed. Reg. 28610 (May 21, 2010), Docket ID No. EPA-HQ-ORD-2010- 0395

Dear Dr. Armitage:

The General Electric Company (GE) appreciates the opportunity to provide preliminary comments on EPA's *Draft Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* (Draft Reanalysis). As an initial matter, we share the concerns regarding the timetable established for this review that are detailed in comments filed by the Texas Commission on Environmental Quality, the Dow Chemical Company and US Magnesium. It is particularly troubling that the first in person meeting of the SAB review panel will occur less than seven weeks after the 1,800+ page Draft Reanalysis was provided to the SAB panel members and the public for review, and approximately ten weeks before the end of the public comment period, even though EPA's "New Process for Development of Integrated risk Information System [IRIS] Health Assessments" (May 2009), which EPA says it is following, calls for the peer review meeting to occur no sooner than ten working days after the close of the public comment period. The schedule virtually guarantees that neither the SAB members nor the interested public has had sufficient time to review and evaluate the Draft Reanalysis, and gives rise to the impression that the considered judgments of both the SAB and the public count for little at EPA.

To rectify this situation, the July 13th-15th meeting of the review panel should be limited to clarification of the existing charge questions, identification of additional questions that the panel should consider, and information gathering. In addition, to ensure that the review panel has sufficient time to review the Draft Reanalysis and to consider public comments before attempting to reach consensus on the issues, the second meeting of the review panel should not be held until at least six weeks after the close of the public comment period. Given the complexity of the scientific issues, public commenters should each be given up to 30 minutes for oral presentations on technical issues at the second public meeting.

Turning to the substance of the Draft Reanalysis, we note that EPA derives Cancer Slope Factors and non-cancer Reference Doses for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) only. EPA fully intends, however, to apply those risk values to other "dioxin-like compounds" (DLCs), including the so-called dioxin-like polychlorinated biphenyls (PCBs), through the use of the "toxic equivalency" approach (TEQ approach) and the "toxic equivalency factors" (TEFs) derived by the World Health Organization (WHO) (WHO2005 TEFs). See EPA's September, 2009 draft Guidance on Recommended Toxicity Equivalency Factors (TEFs) for Human Health Risk Assessments of Dioxin and Dioxin-like Compounds, 74 Fed. Reg. 45437 (Sept. 2, 2009)(Draft TEF Guidance); see also EPA's January, 2010 Draft Recommended Interim Preliminary Remediation Goals for Dioxin in Soil at Superfund and RCRA sites, 75 Fed. Reg. 984 (January 7, 2010)(Draft PRGs). It therefore is critical to determine whether the TEQ approach, and the WHO2005 TEFs, are scientifically valid and appropriate for use with mixtures of DLCs.

The NAS committee that reviewed the 2003 draft Dioxin Reassessment was asked to "provide scientific judgment regarding the usefulness of toxicity equivalence factors (TEFs) in the risk assessment of complex mixtures of dioxins and the uncertainties associated with the use of TEFs." (NAS 2006¹, p. 13, Box S-1.) In response to that charge, the NAS committee made multiple recommendations, including the following:

- "A significant degree of uncertainty exists in the current consensus TEFs, and the quantitative weighting considerations that have gone into their establishment are not clear, . . . Accordingly, the committee endorses the recommendation of some of the members of the 2000 EPA SAB Panel 'that, as a follow-up to the Reassessment, the EPA should establish a task force to build 'consensus probability density functions' for the thirty chemicals for which TEFs have been established, or to examine related approaches such as those based on fuzzy logic.' [Citation omitted.]" (NAS 2006, p. 86)
- "It remains to be determined whether the current WHO TEFs, which were developed to assess the relative toxic potency of a mixture to which an organism is directly exposed by dietary intake, are appropriate for body burden toxic equivalent quotient (TEQ) determinations, which are derived from the concentrations of different congeners measured in body fat. *If body burdens are to be used as the dose metric* [the approach employed in the Draft Reanalysis], *a separate set of body burden TEFs should be developed and applied for this evaluation. Without these corrected values, the overall TEQs estimated by use of intake TEFs might be substantially in error.* [NAS 2006, p. 193 (emphasis added); see also *Id.*, p. 86.]
- "[S]ome species-specific differences in AHR ligand binding affinity of TCDD, other dioxins and DLCs have been observed. However, because TEF values are expressed relative to that of TCDD in the individual species, the TEF values for . . . DLCs appear to be similar between species. *If significant differences in the REP of DLCs are found between humans and other species, then adjustments should be made in the TEFs, and these should be acknowledged in the Reassessment.*" (NAS 2006, p. 87)

To date, EPA has not implemented any of the NAS committee's recommendations relating to TEFs, nor indicated any intent to do so. EPA also has elected not to address those recommendations in the Draft Reanalysis. Instead, EPA has proposed draft guidances that adopt the WHO2005 TEFs for

¹ National Academy of Sciences (NAS). 2006. Health risks from dioxin and related compounds: evaluation of the EPA reassessment. Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds, National Research Council of the National Academies. Washington, DC.

conducting risk assessments on mixtures of DLCs, and simply assume that the TEQ approach, and the WHO2005 TEFs, are valid and reliable.

GE filed extensive comments on both the draft TEF Guidance and the Draft PRGs that built upon, and supplemented, the NAS committee's recommendations. In particular, GE's comments demonstrate that –

1. The WHO2005 TEFs fail to recognize compelling evidence of significant species differences in the relative potencies of dioxin-like PCBs;
2. The WHO2005 TEFs fail to recognize substantial evidence that the potencies of dioxin-like PCBs are not additive;
3. The dose-response relationship is not the same for dioxin and PCBs at all doses and for all endpoints; and
4. The development of the WHO2005 TEFs has not followed established practices for ensuring scientific reliability and clarity.

GE also noted that neither the Draft TEF Guidance nor the Draft PRGs acknowledge EPA's existing Integrated Risk Information System (IRIS) values for PCBs, or show how the two sets of risk values are to be reconciled. (A copy of GE's comments on the Draft PRGs – GE's most recent comments on the TEQ approach and the WHO2005 TEFs -- is attached to these comments.)

The peer reviewers of the Draft TEF Guidance found it to be deficient in a number of significant respects:

Most reviewers thought that the document needs to provide more description or direction on using or capturing the underlying uncertainty in the information used to generate the TEFs. One example of this point is that the van den Berg paper lists the underlying assumptions for, and limitations of, the TEF approach, and these need to be listed in this EPA guidance.

....

All the reviewers were disappointed with the extent and scope of the uncertainty analysis section in the document. . . . The reviewers agreed that the guidance document needs a specific section on uncertainty analysis. This section should provide specific direction on conducting qualitative and quantitative uncertainty analysis for use of TEFs.

Several of the reviewers took issue with the recommendation that the TEFs should be used for all cancer and non-cancer effects . . . The reviewers questioned the use of TEFs if cancer potency factors for specific congeners are available.

The reviewers had a range of opinions on the recommendation that the TEFs may be applied to other exposure routes (i.e., dermal or inhalation) as an interim estimate. Some felt that application of the current TEFs to non-dietary exposure routes is not scientifically supportable at the present time.

Peer Review Summary Report, External Peer Review of *Recommended Toxicity Equivalence Factors (TEFs) For Human Health Risk Assessments of Dioxin and Dioxin-Like Compounds*, pp. 4-5 (Nov. 4, 2009) (Peer Review Panel Report). The deficiencies of the Draft TEF Guidance prompted Dr. Nigel Walker of the National Toxicology Program to say:

[The Draft TEF Guidance] was too short and did not provide sufficient specific guidance for a lot of the recommendations and especially on issues regarding uncertainties in the TEF scheme and its use, that risk managers may need. I fear that many folks may be left scratching their heads about exactly what to do beyond simply calculating a TEQ, and that subsequent analyses and risk management decisions may vary considerably in how different issues are approached.

Id., p. 8. (A copy of the Peer Review Panel Report is attached to these comments.)

The NAS committee's recommendations, the comments filed by GE and others on the Draft TEF Guidance and the Draft PRGs, and the report of the expert panel that reviewed the Draft TEF Guidance raise serious questions about the validity and reliability of the toxic equivalency concept when applied to human health risk assessment, especially for PCBs. PCBs interact with the aryl hydrocarbon (Ah) receptor in a different manner than dioxins and furans, displaying different, weaker ligand binding properties. PCBs recruit different co-factors to the DNA-binding complex, and most "dioxin-like" PCBs have been demonstrated to act only as partial agonists. Furthermore, recent genomics studies have definitively determined that many of the actual genes regulated by the Ah receptor in response to dioxin and dioxin-like compounds are not conserved across species, particularly between rodents and humans. The transcription factor binding sites upstream of regulated genes are not well conserved even between rats and mice, and species-specific recruitment of co-factors has been demonstrated upon Ah receptor activation.

On top of these general overriding issues, and as discussed in detail in GE's comments on the Draft TEF Guidance and Draft PRGs, rodent-derived TEFs are not conserved between rodents and humans. These observations are based on the most potent PCB congener, PCB 126, which GE tested in several human cell types, including cell lines, and freshly isolated human hepatocytes and normal human epidermal keratinocytes, across several donors. We have consistently found the estimated human relative potency of PCB 126 to be about 50 times lower than its rodent-derived TEF. These findings are supported by recent genomics analyses in both species showing that many human genes, potentially regulated by aryl hydrocarbon receptor activation, also show the same 50-fold discrepancy, compared to rats. This clearly demonstrates that this phenomenon is not only limited to the CYP1A1 biomarker gene typically evaluated. The aforementioned results using liver cell lines and fresh hepatocytes have been published, as two separate articles, in the journal *Toxicological Sciences*.² Overall, one can only conclude that EPA's proposed use of the WHO2005 TEFs in human health risk assessment is not appropriate for mixtures containing PCBs.

² Carlson, E. A., McCulloch, C., Koganti, A., Goodwin, S. B., Sutter, T. R., and Silkworth, J. B. (2009). Divergent Transcriptomic Responses to Aryl Hydrocarbon Receptor Agonists between Rat and Human Primary Hepatocytes. *Toxicol. Sci.* 112(1), 257-272.

Silkworth, J. B., Carlson, E. A., McCulloch, C., Illouz, K., Goodwin, S., and Sutter, T. R. (2008). Toxicogenomic analysis of gender, chemical, and dose effects in livers of TCDD- or Aroclor 1254- exposed rats using a multifactor linear model. *Toxicol. Sci.* 102(2), 291-309.

GE recognizes that EPA has not asked the current SAB panel to comment upon the use of TEQ approach or the WHO2005 TEFs. Since, however, dioxin is typically found in mixtures that contain DLCs, and EPA appears to be intent upon applying the TEQ approach using the WHO2005 TEFs, all of the effort to determine accurate risk values for dioxin will be of little value if the TEQ approach and inappropriate, uncorrected WHO2005 TEFs are used to evaluate the toxicity of mixtures of dioxins and DLCs. Thus, the SAB review panel should first consider whether it is scientifically appropriate to use the TEQ approach and the WHO2005 TEFs absent, at minimum, implementation of the recommendations of the NAS committee. Second, the SAB panel should probe the basis for EPA's apparent conclusion that it is scientifically appropriate and necessary to treat mixtures of PCBs as if they are mixtures of dioxins when assessing the risks of PCBs.

We appreciate the review panel's consideration of these comments.

Sincerely,

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April 2, 2010

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Re: Draft Recommended Interim Preliminary Remediation Goals for Dioxin in Soil at CERCLA and RCRA Sites (75 Fed. Reg. 984 (Jan. 7, 2010), Docket ID No. EPA-HQ-SFUND-2009-0907)

Dear Dr. Stanislaus:

The General Electric Company (GE) appreciates the opportunity to comment on the *Draft Recommended Interim Preliminary Remediation Goals for Dioxin in Soil at CERCLA and RCRA Sites* ("Draft PRGs"). The Draft PRGs focus on 2,3,7,8-tetrachlorodibenzo-p-dioxin, but also may be applied to other compounds, including certain polychlorinated biphenyl (PCB) congeners, through application of the World Health Organization's "toxic equivalency factors" (TEFs) and the "toxic equivalency" (TEQ) approach. Draft PRGs, pp. 2-3.

In the attached comments, GE has provided and discussed information relevant to the application of the TEQ approach to PCBs that is not addressed in the Draft PRGs. This information includes, among other things, scientific literature; recommendations from the authors of the WHO TEFs; recommendations set forth in the 2006 National Academy of Sciences report, *Health Risks From Dioxin And Related Compounds: Evaluation Of The EPA Reassessment*; and recommendations set forth in the Peer Review Summary Report, External Peer Review of *Recommended Toxicity Equivalence Factors (TEFs) For Human Health Risk Assessments of Dioxin and Dioxin-Like Compounds*.

GE's comments demonstrate that the use of the TEQ approach for PCBs is not justified by current science. EPA's longstanding practice of assessing PCB risks by use of Integrated Risk Information System (IRIS) values should not be replaced by an approach that is fundamentally flawed, even though the IRIS values are outdated and more conservative than justified by current science. Instead, EPA should reassess the toxicity of PCBs, and update the IRIS values, as EPA committed to do in *Central and Southwest Services, Inc. vs. EPA*, 220 F.3rd 683, 2000 U.S. App. Lexis 20006, *34 (5th, Cir. 2000), *reh. and reh. en banc den.*, 2000 U.S. App. LEXIS 29058, (Nov. 2, 2000), *cert. den.*, 2001 U.S. LEXIS 4158 (2001).

Thank you for your consideration of these comments.

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Enc.

COMMENTS OF THE GENERAL ELECTRIC COMPANY
ON THE
PUBLIC REVIEW DRAFT
DRAFT RECOMMENDED INTERIM PRELIMINARY REMEDIATION GOALS
FOR DIOXIN IN SOIL AT CERCLA AND RCRA SITES

75 Fed. Reg. 984 (January 7, 2010)
Docket ID No. EPA-HQ-SFUND-2009-0907

April 2, 2010

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I. INTRODUCTION

President Obama and EPA Administrator Lisa Jackson repeatedly have stated their intent “to ensure that federal policies are based on the best and most unbiased scientific information.”¹ President Obama and Administrator Jackson also have repeatedly stated their commitment to “transparency in the preparation, identification, and use of scientific and technological information in policymaking.”² As Administrator Jackson has stated:

Science must be the backbone for EPA programs. The public health and environmental laws that Congress has enacted depend upon rigorous adherence to the best available science. . . . When scientific judgments are suppressed, misrepresented or distorted by political agendas, Americans can lose faith in their government to provide strong public health and environmental protection.

The laws that Congress has written and directed EPA to implement leave room for policy judgments. However, policy decisions should not be disguised as scientific findings. I pledge that I will not compromise the integrity of EPA’s experts in order to advance a preference for a particular regulatory outcome.³

The *Draft Recommended Interim Preliminary Remediation Goals For Dioxin In Soil At CERCLA and RCRA Sites* (“Draft PRGs”) fall far short of these commitments. As demonstrated in comments filed by the American Chemistry Council and the Dow Chemical Company,⁴ neither the proposed, noncancer-based interim preliminary remediation goals (PRGs) nor the alternative, cancer-based PRGs are supported by the latest, best available science. In these comments, the General Electric Company (GE) demonstrates that application of the interim PRGs to polychlorinated biphenyls (PCBs) through use of “toxic equivalency factors” also is not based upon the latest, best available science.

II. EXECUTIVE SUMMARY

The best available science for dioxin and the so-called dioxin-like compounds (DLCs) lies in the vast body of scientific literature that has been published since EPA first issued PRGs for dioxin in 1998. The great majority of that literature is reviewed in the 2006 NAS report, *Health Risks from*

¹Transcript, Remarks by the President at the National Academy of Sciences Annual Meeting, p. 6 (April 27, 2009), available at http://www.whitehouse.gov/the_press_office/Remarks-by-the-President-at-the-National-Academy-of-Sciences-Annual-Meeting/; see also *Opening Memo to EPA Employees* (Jan. 23, 2009), available at <http://blog.epa.gov/administrator/2009/01/26/opening-memo-to-epa-employees/> (“Public trust in the Agency demands . . . that we consider the views and data presented carefully and objectively”); *Memo to EPA Employees: Scientific Integrity* (May 9, 2009), available at <http://blog.epa.gov/administrator/2009/05/12/memo-to-epa-employees-scientific-integrity/>.

² *Presidential Memorandum For The Heads of Executive Departments And Agencies on Scientific Integrity* (Mar. 9, 2009), available at http://www.whitehouse.gov/the_press_office/Memorandum-for-the-Heads-of-Executive-Departments-and-Agencies-3-9-09/; see also *Memo to EPA Employees: Transparency in EPA’s Operations* (Apr. 23, 2009), available at <http://blog.epa.gov/administrator/2009/04/24/memo-to-epa-employees-transparency-in-epas-operations/>.

³ *Opening Memo to EPA Employees* (Jan. 23, 2009).

⁴ GE hereby endorses and incorporates by reference the comments of the American Chemistry Council and the Dow Chemical Company.

Dioxin and Related Compounds – Evaluation of the EPA Reassessment (“NAS Report”).⁵ Virtually none of that science is mentioned, let alone analyzed in a meaningful way, in the Draft PRGs. Nor is the NAS Report carefully considered. Instead, EPA has (1) used unspecified criteria to select for evaluation a handful of cancer and noncancer toxicity values for dioxin that were developed previously by EPA or other entities, and (2) after cursory analysis, selected a cancer value dating to 1985 and a noncancer value dating to 1998 to develop the proposed and alternative interim PRGs for dioxin.

EPA then states that the Draft PRGs may be used to evaluate the risks of the DLCs, including PCBs, “using toxicity equivalence factors (TEFs) to calculate dioxin toxicity equivalent (TEQ) concentrations.” Draft PRGs, pp. 2-3. In stating this conclusion, the Draft PRGs do not mention or discuss (1) EPA’s 1996 Reassessment of the carcinogenicity of PCBs⁶; (2) the IRIS values for PCBs that resulted from the 1996 Reassessment and are the present basis for EPA’s PCB risk assessments; (3) the NAS Report’s recommendations regarding the TEFs; (4) the public comments on EPA’s External Peer Review Draft of Recommended [TEFs] for Human Health Risk Assessments of Dioxin and Dioxin-Like Compounds (“Draft TEF Guidance”); or (5) the significant criticisms raised by the expert panel that on November 4, 2009 reviewed the Draft TEF Guidance.

As GE discussed in its October, 2009 comments on the Draft TEF Guidance⁷, fundamental assumptions upon which the TEFs and the TEQ approach are based do not withstand scrutiny.

- The TEFs assume that there are no differences in the response of humans and rodents to dioxin and PCBs, including PCB 126.

Repeated investigations have shown that:

(1) humans are an order of magnitude less sensitive to dioxin than responsive rodents;

(2) humans are 2-3 orders of magnitude less sensitive to the most toxic “dioxin-like” PCB – PCB 126 – than responsive rodents.

- The TEQ approach assumes that there is a reliable estimate of the carcinogenicity of dioxin itself; in fact, there is no scientific consensus on that cancer slope factor.
- The TEQ approach assumes that the interactions of dioxin-like chemicals with the aryl hydrocarbon receptor (Ah receptor or AHR) are additive (i.e., the toxicity of a PCB mixture can be determined by multiplying the concentration of each individual congener by the toxic equivalency factor (TEF) for that congener, and summing the products).

The assumption of additivity ignores, among other things, competition among molecules to bind with the Ah receptor. Additivity has not been demonstrated across congeners and endpoints in animal studies.

⁵ National Academy of Sciences (NAS). 2006. Health risks from dioxin and related compounds: evaluation of the EPA reassessment. Committee on EPA’s Exposure and Human Health Reassessment of TCDD and Related Compounds, National Research Council of the National Academies. Washington, DC.

⁶ EPA. 1996. PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/600/P-96/001F.

⁷ Available at <http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480a38f45>.

- The TEQ approach assumes that the dose-response relationship is the same for dioxin and PCBs at all doses and for all endpoints, such that the dose-response curves are parallel.

Studies done by the National Toxicology Program have shown that this assumption is invalid.

The use of the WHO TEFs and the TEQ approach is subject to additional limitations:

- The authors of the WHO TEFs acknowledge that they are based on feeding studies, and therefore should be used only to assess risks from dietary intake. Using the TEFs to assess risks from dermal exposure or body burdens of dioxin-like compounds is not appropriate. At minimum, the TEFs need to be adjusted to take into account the differential bioavailability of each congener present in a mixture for each potential exposure route other than dietary intake.
- The WHO TEFs were not developed in accordance with established principles for ensuring scientific reliability, including the principle that a review of relevant studies should include an explanation 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.
- The Draft PRGs do not address the IRIS values for PCBs or show how the two sets of risk values are to be reconciled.
- There is no validated method for performing the PCB congener analysis required to implement the TEQ approach for PCBs. EPA's interlaboratory study demonstrates that Method 1668A, which purports to analyze all 209 PCB congeners, does not produce reliable data, and does not produce results that can be replicated consistently across laboratories.
- Human epidemiological studies do not support the conclusion 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.
- The Draft PRGs do not acknowledge that the peer reviewers of EPA's Draft TEF Guidance found the document deficient in a number of key respects, and recommended significant changes to the document.

The Draft PRGs do not reflect a transparent, objective use of the latest, best available science for dioxin or PCBs. Consequently, the Draft PRGs do not comport with applicable Information Quality Guidelines that were designed to maximize and ensure the quality, utility, objectivity and integrity of information that EPA disseminates to the public. The Draft PRGs therefore should be withdrawn and reconsidered in the context of a thorough review of the relevant scientific literature after the dioxin reassessment has been completed.

If OSWER nevertheless chooses to finalize the Draft PRGs, all references to PCBs and the WHO TEF values for PCBs should be deleted, and the Regions and states should be advised to continue using the IRIS values and PCB-specific evidence to evaluate the risks of PCBs. If OSWER finalizes the Draft PRG Guidance with PCBs included, OSWER should state that the TEF value for PCB 126 should be reduced by two to three orders of magnitude, and re-evaluate the TEFs for other PCB congeners, to reflect PCB-specific evidence and the scientific consensus — based on multiple studies — that

humans are at least an order of magnitude less sensitive than rodents to dioxin. In either case, OSWER should instruct the Program Offices and Regions that, consistent with the OMB Bulletin on Good Guidance Practices⁸, use of the TEFs or TEQ approach cannot be imposed upon any entity for any purpose, and regulated entities are free to use either the IRIS values for PCBs or TEFs that have been revised downward to reflect the evidence discussed in these comments.

III. COMMENTS

A. The Draft PRGs Do Not Reflect A Transparent Evaluation Of The Latest, Best Available Science

When Administrator Jackson announced the Dioxin Science Plan⁹ in May 2009, she said that EPA would recommend interim PRGs “informed by the latest science” by the end of 2009. In November 2009, EPA issued for comment a “Plan For Developing Interim [PRGs] For Dioxin In Soil” (PRG Plan).¹⁰ The PRG Plan reaffirmed that the interim PRGs would be “informed by the latest science.” PRG Plan, pp. 1, 3. The Draft PRGs, however, explicitly “do not take into account peer review comments on the new science that was reviewed by the NAS, and new science that was released since the NAS review” in 2006. Draft PRGs, p. 3. In fact, the Draft PRGs do not even mention the NAS Report. By the Agency’s own admission, the Draft PRGs are not “informed by the latest science.”

The latest science on the alleged cancer and noncancer effects of dioxin¹¹ does not justify lowering the PRGs. For example, EPA has been trying to establish that dioxin is carcinogenic to humans for at least a decade, but neither the SAB nor the NAS panels that reviewed the Draft Dioxin Reassessment found the evidence strong enough to endorse that classification. EPA 2001, p. 4, fn. 6)(“Just over one-third of the Panel supported classifying TCDD as a human carcinogen”); NAS, 2006, p. 14)(“[T]he NRC committee was split on whether the evidence met *all* the criteria necessary for classification of TCDD as ‘carcinogenic to humans’ . . . The committee concludes that the weight of epidemiological evidence supporting classification of TCDD as a human carcinogen is not ‘strong.’”). As for noncancer effects, the NAS panel — which produced the most recent peer review of EPA’s assessment of the toxicity of dioxin and the DLCs — concluded that the evidence of an association between exposure to dioxin and non-cancer effects (with the exception of chloracne) in humans, is, at best, suggestive. See NAS 2006, p. 173.

Given the NAS’s conclusions and the fact that levels of dioxin and PCBs in human diet and blood are low and continue to decline,¹² EPA would have been more than justified in maintaining the current PRGs, including the PRG of 1 ppb for residential uses. Instead, EPA is proposing interim PRGs

⁸ OMB, Final Bulletin for Agency Good Guidance Practices, 72 Fed. Reg. 3432, 3433 (Jan. 25, 2007)(“The purpose of Good Guidance Practices is to ensure that guidance documents of Executive Branch departments and agencies are: . . . not improperly treated as legally binding requirements.”).

⁹ Available at <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=209690>.

¹⁰ Available at <http://www.epa.gov/superfund/policy/remedy/pdfs/dioxinoutreach.pdf>.

¹¹ 2,3,7,8-terachlorodibenzo-p-dioxin (TCDD).

¹² E.g., CDC. Fourth National Report on Human Exposure to Environmental Chemicals, Fact Sheet – Dioxins, Furans and Dioxin-Like Polychlorinated Biphenyls (Feb. 11, 2010), available at http://www.cdc.gov/exposurereport/DioxinLikeChemicals_FactSheet.html (“levels of most of these chemicals have decreased by more than 80% since the 1980s”).

approximately 10 times more stringent than the current PRGs that could be in effect for as few as six months.¹³

EPA expended resources to develop the interim PRGs. Multiple stakeholders have expended resources to prepare comments on the interim PRGs. Public and private entities that are responsible for cleanups at CERCLA and RCRA sites will expend resources to meet the interim PRGs, and then expend more resources if EPA alters the PRGs after it finalizes the dioxin reassessment.¹⁴ Initiating all of these activities might have made sense if EPA had provided evidence that refuted the NAS's conclusions, or otherwise demonstrated that the current PRGs are not protective. EPA has not done so. Instead, EPA simply states that the current PRGs did not consider (1) the potential non-cancer effects of dioxin, and (2) dermal exposure, particularly for outdoor workers. Draft PRGs, p. 6.

The NAS Report concluded that the evidence of noncancer effects is, at best, "suggestive". See NAS, 2001, p. 173. In addition, there is no indication in the draft 2003 Dioxin Reassessment that EPA considered dermal exposure to be a significant exposure route. EPA has not shown in the Draft PRGs that the NAS Report is wrong about noncancer effects or that dermal exposure is a significant exposure route. Thus, the fact that the current PRGs did not consider noncancer effects or dermal exposures does not warrant the conclusion that the current PRGs are not protective.

In the absence of evidence that the current PRGs are not protective, EPA's issuance of interim PRGs that could be in effect for as few as six months makes sense only if EPA anticipates that the final PRGs will be the same as the interim PRGs, without regard to the recommendations and conclusions of the NAS Report or public comments such as these. If that is indeed the result, it will confirm that the interim PRGs are being driven by something other than the latest, best available science.

B. Use Of The WHO TEFs And The TEQ Approach For PCBs Does Not Reflect A Transparent Evaluation Of The Best Available Science

For more than fifteen years, EPA, the states and others have established cleanup levels for PCBs at numerous sites using cancer slope factors (CSFs) and oral Reference Doses (RfDs) set forth in IRIS. E.g., Interim Record of Decision, Palos Verde Shelf, Operable Unit 5 of Montrose Chemical Corporation Superfund Site (Sept. 2009), p. 36¹⁵; See also *Development Of An Analytic Approach To Determine How [EPA's] Integrated Risk Information System Is Used By Non-EPA Decision Makers*, p. 3 (Jan. 10, 2008) ("for domestic regulatory purposes there is no satisfactory alternative to IRIS. Other

¹³ The Dioxin Science Plan and the Draft PRGs both indicate that the interim PRGs will be issued in June 2010, and then used to select remedies for sites until EPA finalizes the Dioxin Reassessment. At that time, the interim PRGs, and any remedies based thereon, will be re-evaluated. Since EPA has stated that it intends to finalize the Dioxin Reassessment by the end of the year, the interim PRGs could be in effect for as little as six months.

¹⁴ The Draft PRGs do not discuss at all how many sites – including sites at which construction of the remedy has been completed – will be affected by the change in the PRGs. The Draft PRGs also do not discuss at all the financial consequences of this change in the PRGs for EPA, the states or public and private entities that have conducted or are conducting cleanups of affected sites.

¹⁵ Available at

<http://yosemite.epa.gov/r9/sfund/r9sfdocw.nsf/3dc283e6c5d6056f88257426007417a2/50f1119f38a795bc8825765100645c5b!OpenDocument> . See also EPA/ROD/R01-98/126, EPA Superfund Record of Decision: New Bedford, EPA ID: MAD980731335, OU 1, New Bedford, MA (Sept. 25, 1998), App. B, available at <http://www.epa.gov/superfund/sites/rods/fulltext/r0198126.pdf> .

databases exist that can provide some assistance, but there is no substitute for an IRIS file for regulatory support.”).¹⁶ In the Draft PRGs, EPA is recommending that the risks of dioxin-like PCBs alternatively be evaluated by comparison to dioxin using “toxic equivalency factors” (TEFs). This proposal is being made without any consideration of (1) EPA’s own 1996 Reassessment of the carcinogenicity of PCBs; (2) the vast body of literature on the toxicity of PCBs that has developed since 1996; (3) relevant recommendations of the National Academy of Sciences’ panel that reviewed EPA’s 2003 draft Dioxin Reassessment; (4) the public comments on EPA’s Draft TEF Guidance; and (5) the recommendations of the experts who participated in the October 22, 2009 peer review of the Draft TEF Guidance.

The Draft PRGs devote one paragraph to DLCs. It states that the interim PRGs can be used to evaluate the risks of DLCs “after adjustment to account for relative toxicity using toxicity equivalency factors (TEFs) to calculate dioxin toxicity equivalent (TEQ) concentrations.” Draft PRGs, p. 3. The Draft PRGs recommend the use of TEFs published in van den Berg et al. (1998, 2006) (“WHO TEFs”), and gives a simple example of how to calculate the total TEQ concentrations of dioxin and a DLC in soil. Id. The Draft PRGs then “acknowledge[] that there is uncertainty associated with risk estimates based on TEQs”, and advise risk assessors to “identify the fraction of the TEQ attributable to dioxin and to each chemical class of [DLCs].” Id. The Draft PRGs do not, however, offer any guidance on what risk assessors should do with that information.

As explained below, the use of the WHO TEFs and the TEQ Approach for PCBs does not reflect a transparent, objective evaluation of the best available science.

1. The WHO TEFs Are Based Upon Assumptions That Are Not Supported By Evidence Or Have Questionable Evidentiary Support

The TEQ approach assumes that:

- There is no difference between species in sensitivity to dioxin and the DLCs;
- There is a reliable estimate of the carcinogenic potential of dioxin itself;
- The toxic effects of all the congeners in a mixture are additive; and
- The dose-response relationship for dioxin and the DLCs is the same for all doses and endpoints, such that the dose-response curves are parallel.¹⁷

None of these assumptions has merit. We discuss the assumptions and the state of the relevant evidence below.

a. The WHO TEFs Fail To Recognize Compelling Evidence That Humans Are Less Sensitive To Dioxin And PCBs Than Rodents

¹⁶ Available at <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=190284>; see also, EPA/635/R-02/004, Needs Assessment for U.S. EPA’s Integrated Risk Information System, (Sept. 2003), p. 2 (“IRIS is relied upon by EPA programs and states to support risk-based decisionmaking, and is widely utilized nationally and internationally in the risk assessment community.”), available at http://www.epa.gov/ncea/iris/iris_needs.pdf.

¹⁷ See EPA, 2003, p. 9-10; see also van den Berg et al. 2006, pp. 224-25.

The WHO TEFs are based primarily on studies performed on rodents, and assume that the toxicities of dioxin and DLCs do not vary among species. For example, the WHO TEFs for dioxin and PCB 126 are 1.0 and 0.1, respectively, whether the TEFs are applied to rodents or to humans. The assumption that underlies the WHO TEFs is that dioxin and each of the listed DLCs have the same potencies for humans as for rodents, at least within an order of magnitude. However, it has long been recognized that humans are approximately 10 times less sensitive than rodents to dioxin, and recent evidence, discussed below, indicates that humans are about 100 times less sensitive than rodents to PCBs. The WHO TEF for dioxin does not account for the observed difference in species sensitivity to this reference chemical, and the WHO TEFs for PCBs do not account for the even greater differences in species sensitivities to PCBs.

The issue of whether the evidence supports the assumption that humans and rodents exhibit essentially the same sensitivity to dioxin and DLCs has been addressed in *The 2005 World Health Organization Re-evaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-like Compounds*. van den Berg et al. 2006. The views expressed by the authors of that report – the scientists who derived the current WHO TEFs – carry particular weight in interpreting the TEFs and identifying the critical evidentiary issues they contain. On species differences, the authors state:

Literature data also indicate that the PCB 126 REP [relative effect potency] for enzyme induction in human cell systems, including primary hepatocytes, breast cancer cell lines and primary lymphocytes, may be one or two orders of magnitude lower [citations omitted]. In addition, the apparent binding affinity of 2,3,7,8-TCDD to the human AhR is generally 1/10th that of the AhR of the more sensitive species, but significant variation among individual humans occurs [citations omitted]. It has been suggested that on average, humans are among the more dioxin-resistant species, but the human data set is too limited to be conclusive [citations omitted]. . . . *Taken together, this information warrants more research into REP values in human systems to establish if the present TEFs based on rodent studies are indeed also valid for humans.*

van den Berg et al. 2006, pp. 225-226 (emphasis added).

Very similar views on this issue, which is central to the use of TEFs in human risk assessment, were expressed in 2006 by the NAS in its review of EPA's Dioxin Reassessment:

Numerous investigators have reported species-specific differences in AHR ligand binding affinity of TCDD, other dioxins, and DLCs. Depending on the system examined, the estimated affinity of binding of TCDD (and related compounds) to the human AHR is about 10-fold lower than that observed to the AHR from "responsive" rodent species and is comparable to that observed to the AHR from "nonresponsive" mouse strains (Roberts et al. 1990; Ema et al. 1994; Poland et al. 1994; Ramadoss and Perdew 2004).

NAS 2006, p. 81.

As the following review of recent literature will show, enough is known about rodent and human sensitivity to dioxin and DLCs that recognition of species differences, particularly those between the rodents on which the studies are typically performed and humans for whom risk assessments are undertaken, needs to be taken into account in calculating TEFs.

In this review, we focus on the differences in the potency of dioxin and PCB 126 for rodents and humans. Dioxin is addressed because it is the reference point for the WHO TEFs. PCB 126 receives special emphasis for two related reasons:

(1) PCB 126 is regarded as the most potent of the PCBs assigned TEFs. Its assigned TEF — 0.1 — is half an order of magnitude greater than PCB 169, and at least two and a half orders of magnitude greater than any other PCB with an assigned TEF.

(2) As a result of its assigned TEF, PCB 126 frequently contributes much of the total dioxin-like toxicity of an environmental mixture of PCBs. PCB 126 therefore is considered to be the PCB congener by which people are exposed to the greatest toxic potency. It dominates the calculation of risk from PCBs in most human health risk assessments that employ the WHO TEFs. (This dominant position is not supported, however, by recent data from studies conducted using human-derived tissue and cell lines.)

A rudimentary understanding of the biological effects of dioxin and DLCs is necessary to understand the relevant advances in scientific knowledge that have been achieved in the last decade. There is agreement that the DLCs — seven dioxins, ten furans, and twelve coplanar PCBs — bind a receptor protein, the aryl hydrocarbon receptor (AHR); this is followed by the induction, or turning on, of various genes. Many of these genes produce enzymes, particularly those in the cytochrome P450 (CYP) family, which includes CYP1A1, CYP1A2, and CYP1B1. The enzyme activity is frequently measured as EROD (ethoxyresorufin-o-deethylase) activity. The AHR binding, gene induction, enzyme production in the CYP family, and increased EROD activity are considered to be among the early key events in the biological sequence or pathway that leads to tumor development in Sprague-Dawley female rats. The hepatic tumorigenicity of dioxin and DLCs in some strains of rodents has, of course, been established through feeding studies, but such tests cannot be conducted with humans. Consequently, in order to compare the biological action of dioxin and DLCs in humans to that in rodents, exposure is conducted in cell cultures *in vitro*, studying in particular the initial key events that lead to toxicological response *in vivo*. In these tests, immortal human cell lines, typically from the liver, as well as fresh human donor tissue have been treated with the compound under study, and the amount of CYP gene expression or EROD activity has been measured and compared to that in similarly treated rat cells. Often, the EC50 of the compound — the concentration that is halfway between baseline and maximum response after a given exposure time — is used as a metric for the toxicity or potency of the compound. The lower the EC50, the more sensitive the test species is to the compound.

In 1996, Wiebel et al. compared the effect of dioxin on AH hydroxylase induction (an indicator of CYP1A1 activity) in rat hepatoma cells, H4IIEC3/T, and human liver-derived HepG2 cells. The human HepG2 cells were found to be twenty times less sensitive than the rat cells to dioxin.

In 2000, Xu et al. compared the effects of dioxin on CYP1A activity measured by EROD activity, protein, and gene expression in primary cultures of rat and human hepatocytes. The authors reported that rat hepatocytes generally responded to dioxin at concentrations ten times lower than required for human cells.

In 2001, Zeiger et al. treated human HepG2 cells and rat cells, H4IIE and rat primary hepatocytes, with dioxin as well as an array of DLCs. The EC50 values for induction of EROD activity were compared. The human cells were an order of magnitude less sensitive to dioxin than were the rat cells.

These studies and others are discussed in a 2006 review article — Connor and Aylward 2006 — that addresses the relative sensitivity of rodent cells and human cells to TCDD. The authors concluded that “human cells have been consistently less sensitive to TCDD for induction of EROD or AHH [aryl hydrocarbon hydroxylase] activity, generally requiring approximately 10-fold higher TCDD concentrations to obtain a half-maximal [EC50] result.” Connor and Aylward 2006, p. 159. These studies and this conclusion are consistent with that reached by the NAS panel, relying on other studies, and set out above :

[T]he estimated affinity of binding of TCDD (and related compounds) to the human AHR is about 10-fold lower than that observed to the AHR from "responsive" rodent species and is comparable to that observed to the AHR from "nonresponsive" mouse strains.

NAS 2006, p. 81. Thus, the evidence supports the view that accurate TEFs should reflect the differential potency of dioxin to rats and humans of an order of magnitude. Given the assumptions that underlie the WHO TEFs, the implication of this correction is that one would anticipate that humans would be at least an order of magnitude less sensitive than rats to the DLCs as well.

Turning to the effects of PCB126, Vamvakas et al. 1996 compared the level of AHH and EROD activity in H4IIE rat hepatoma cells, HepG2 human hepatoma cells and MCF-7 human breast cancer cells that had been treated with TCDD and PCBs 77, 126, and 169 – all coplanar, dioxin-like PCBs. Rat cells were found to be generally more sensitive to all treatments. In particular, the rat cell line demonstrated dose-dependent increases for both AHH and EROD activity for all three PCB congeners, while the human cell lines were unresponsive to PCB 77 and PCB 169. For the TCDD treatment, the AHH EC50 for the rats was 6 times lower than that for humans, and the EROD EC50 for the rats was 42 times lower than that for humans. For PCB 126 treatment, Vamvakas et al. (1996) estimated that human cells were 310 and 110 times less sensitive than rat cells for AHH and EROD induction, respectively.

In the 2001 study already cited, Zeiger et al, treated rat cells and human HepG2 cells with all twelve dioxin-like PCBs: 77, 81, 105, 114, 118, 123, 126, 156, 157, 167, 169, and 189. The EROD activity in the cells was compared. The human cells showed lower sensitivity to EROD induction. In fact, for eight of the PCB congeners (PCBs 169, 105, 118, 123, 156, 157, 167, and 189), EROD activity could not be induced. For PCBs 77, 81, and 114, the EC50 values for H4IIE rat cells ranged from 3.8 to 47.4 times lower than in the human HepG2 cells. For PCB 126, the rat EC50 value was more than 1200 times less than that of the human.

In 2005, Silkworth et al. compared CYP1A gene expression in fresh hepatocytes from human donors, rats, and rhesus monkeys, and HepG2 human hepatoma cells exposed to TCDD and PCB 126 in culture. EROD activity and CYP1A1 and CYP1A2 mRNA were measured. In the case of PCB 126, the EC50s for both EROD activity and CYP1A1 mRNA in the rat were found to be two to three orders of magnitude lower than in the human cells; indicating that human cells were clearly much less sensitive to this PCB congener than rat cells. More recent studies, using more precise gene array technology, have demonstrated that EC50s in rats for CYP1A1, CYP1A2, and many additional genes are also two to three orders of magnitude lower than in humans. Carlson et al. 2009, and see below.

In 2008, Westerink et al. compared CYP1A activity in rat H4IIE cells and human HepG2 cells for an extensive array of chemicals, including TCDD and most dioxin-like PCBs. The PCB 126 EC50 for induction was three orders of magnitude lower in rats than in humans. PCBs 77, 114, 123, and 167 similarly elicited much weaker responses in human cells compared to rat cells. In addition, PCBs 105,

118, 156, 157, 169, and 189 did not induce CYP1A activity in the human cells, in some cases at concentrations three magnitudes greater than those found effective in rat cells.

In 2009, Carlson et al. investigated whether the difference in relative potency of PCB 126 between rats and humans, as measured by induction of CYP1A1, was also true for other AHR regulated genes that could be important to toxic effects subsequent to AHR binding. Two species-specific gene microarrays that could test more than 4,000 genes shared by both rats and humans were used to generate dose response models for genes responding to both TCDD and PCB 126. The median PCB 126 EC50 for 47 human genes responding in a dose response manner consistent with the TEF concept was more than 100 times greater than the median for 79 similarly responding rat genes. Further, the species-specific relative potency of PCB 126 for these genes was estimated. The median relative potency estimate for the human genes was similar to the human hepatocyte-derived potency estimate of 0.003 based on EROD activity developed by Silkworth et al. (2005), while rat genes were consistent with the 0.1 value. This demonstrates that the lower sensitivity of human cells previously observed for both TCDD and PCB126 and the much lower potency of PCB126 relative to TCDD can be extended to many more genes in addition to the CYP genes.

In sum, the research conducted by Wiebel et al. 1996), Xu et al. 2000, and Zeiger et al. 2001, as well as earlier studies reported in Connor and Aylward 2006, show that human cells are at least ten times less sensitive to dioxin (TCDD) than are rat cells. Next, the work of Zeiger et al. 2001, Silkworth et al. 2005, and Westerink et al. 2008 demonstrates that humans are two to three orders of magnitude less sensitive to PCB 126 than are rats, as measured by CYP1A induction and associated EROD activity. Finally, Carlson et al. 2009 have presented evidence that the human insensitivity to PCB 126, shown through induction of CYP1A1 and EROD activity, applies to other potential AHR-regulated genes that respond to both TCDD and PCB 126; however, many of these potential AHR-regulated genes are not shared between the species. This last point is important because it indicates that TCDD and the DLCs act on different genes in humans and rodents, and that there are significant differences in the biological systems of the two species. This evidence contradicts the fundamental assumption that the TEFs may properly be applied to these and other mammalian species because the mode or mechanism of biological action is the same regardless of the species under consideration.

Dr. Silkworth summarized these studies in his brief comments to the peer review panel for the Draft TEF Guidance. Although EPA did not ask the peer reviewers to consider the issue of species differences in sensitivity to dioxin and PCBs, one reviewer — Dr. Thomas Starr — went out of his way to emphasize the importance of this analysis to EPA:

I was very impressed with the very recent work that was presented by Dr. Jay Silkworth in the public comment period, which showed how markedly different human cells are from rodent cells in their in vitro gene array responses to some DLCs. This information should be included in the section on uncertainty because it suggests strongly that humans are not only much less, but also differently (in a qualitative way) responsive, than are rodents to DLCs. In fact, I would go so far as to say that such data, when available, should be employed in place of the TEFs, because they shed light on the very important and still unanswered question of why humans appear to be so refractory to DLC exposure in comparison to the hypersensitive rodent species.

(Peer Review Panel Report).¹⁸ Dr. Starr's comments are equally to the point in the context of the Draft PRGs.

The difference in rodent and human sensitivity to dioxin calls into question the use of all of the WHO TEFs for human health risk assessment. To meet EPA's commitment to use the best available science, EPA should, at minimum, reduce the TEFs for the dioxin-like PCBs by at least an order of magnitude to reflect the differences in sensitivity between rodents and humans. In practical terms, addressing the TEF for PCB 126 is of most importance. For use in human risk assessment, the TEF for PCB 126 should be lowered to 0.003 to be consistent with recently collected data. This value takes into account the species difference in sensitivity to dioxin and the human relative potency difference between dioxin and PCB 126. Silkworth, 2005, p. 514, Table 2. In addition, the WHO TEFs for the other dioxin-like PCBs should be subject to careful scrutiny, as recommended by the NAS Report.¹⁹

b. There Is No Consensus On The Cancer Slope Factor For Dioxin

The TEQ approach was developed so that TEQ concentrations of dioxins and DLCs could be summed and used to estimate the hazard and dose responses of mixtures of these compounds. The approach, which relates the combined amounts of all mixture components to that of dioxin, obviously depends on using hazard values for dioxin itself. However, the cornerstone for using the TEQ approach for cancer risk– the CSF for dioxin – is missing: there is no agreement within the scientific community as to the appropriate CSF for dioxin.

A wide range of CSFs has been proposed for dioxin. These CSFs are based on animal studies and use of a linear, non-threshold cancer model to extrapolate risks to humans at environmentally relevant doses. The proposed CSFs have ranged from 9,000 to 156,000 (mg/kg-day)⁻¹, with differences in values resulting largely from the tumor classification scheme and interspecies scaling factor applied. See EPA, 1994, 2000; FDA, 1993, 1994; Cal. EPA, 2007; Keenan et al. 1991. Recently, in two revisions of the draft Dioxin Reassessment, EPA proposed a CSF for TCDD of 1,000,000 (mg/kg-day)⁻¹ based on EPA's evaluation of human epidemiological data (EPA 2000, 2003) and use of a linear, non-threshold model. However, EPA did not identify and discuss the full range of plausible CSFs for dioxin that could be based on peer-reviewed scientific studies.

The 2000 draft Dioxin Reassessment was reviewed by EPA's Science Advisory Board (SAB) which could not "reach consensus on a single value for a dioxin potency factor". EPA 2001, p. 6. Then, in 2006, the NAS determined that the data support a threshold, nonlinear model rather than the default, non-threshold, linear model that EPA has used historically. NAS concluded:

[A]lthough it is not possible to scientifically prove the absence of linearity at low doses, the scientific evidence, based largely on mode of action, is adequate to favor

¹⁸ Available at http://www.epa.gov/osa/raf/files/hhtef_peer_rvw_summary_report_110409.pdf.

¹⁹It is important not to confuse adjustments that need to be made to the WHO TEFs on the basis of species differences and adjustments that might be suggested on the basis of individual variability. These two sources of possible adjustment are conceptually distinct. In this case, the changes needed to account for species differences are much greater than those that might be suggested to address individual variability. Silkworth (2005, p. 514)("[F]indings that sensitivity differences, measured by either threshold or EC50s, span over three orders of magnitude between human and rat cells, but only vary by a factor of about ten among the human samples, suggest that species differences are a more significant source than individual differences for the uncertainty in risk estimation.")

the use of a nonlinear model that would include a threshold response over the use of the default linear assumption. The committee concludes that four major considerations of the scientific evidence support the use of a nonlinear model for low-dose extrapolation.

* * * *

The committee unanimously agrees that the current weight of evidence for TCDD, other dioxins, and DLCs carcinogenicity favors the use of nonlinear methods for extrapolation below the point of departure (POD) of mathematically modeled human or animal data.

NAS 2006, pp. 122, 190.²⁰

Notwithstanding this unanimous conclusion, the Draft PRGs recommend a CSF for dioxin that was derived using a linear model. Draft PRGs at 8-9, A2-1. The Draft PRGs do not rely on any evidence that postdates the NAS review to justify EPA's continued reliance on a linear model. Instead, using unspecified criteria, EPA "identified" five candidate values. EPA then selected its "preferred" CSF of $1.5E-04$ (pg/kg-day)⁻¹ (i.e., 150,000 (mg/kg-day)⁻¹) because it is "publicly available, transparent as to [its] derivation, . . . adequately peer reviewed . . . [and] based on the incidence of all significant tumors combined, rather than the incidence of liver tumors alone." Draft PRGs, pp. 8-9. While the first three characteristics, if true, permit consideration of classifying this CSF as a Tier 3 value for purposes of OSWER's hierarchy of human health toxicity values, the CSF is not consistent with that hierarchy's guiding policy: "EPA should use the best science available on which to base risk assessments." OSWER Directive 9285.7-53, Human Health Toxicity Values In Superfund Risk Assessments (Dec. 5, 2003), p. 2. For Tier 3 values, "[p]riority should be given to those sources of information that are the most current, the basis for which is transparent and publicly available, and which has been peer reviewed." *Id.*, p. 3. A 20-year old value that relies upon a model dismissed by the NAS in 2006 is not "the best science available" or "the most current" source.

In light of the NAS's finding that the weight of the evidence supports the use of a nonlinear, threshold model for derivation of a CSF for dioxin, the NAS recommended that EPA consider the full range of animal cancer bioassay data, "including the new NTP animal bioassay studies on TCDD, for quantitative dose-response assessment." NAS 2006, p. 191. Until EPA acts on that recommendation, and develops an appropriate CSF that takes recent data into account, the TEQ approach cannot be used to reliably estimate the cancer risk posed by any of the DLCs.²¹ Without a reliable CSF, it is also

²⁰ The "four major considerations" listed by NAS as supporting a nonlinear relationship rather than the default linear model were that:

- TCDD, other dioxins, and DLCs are not genotoxic;
- Receptor-mediated agents have sublinear dose-response relationships;
- Dioxin-induced liver tumors are secondary to hepatotoxicity; and
- Bioassays provide evidence of nonlinearity.

NAS (2006, p. 141).

²¹ Evidence indicates that when CSFs for the TEQ in PCB mixtures are calculated, the CSFs are not equal to the CSF for TCDD in either rodents or humans. In fact, the CSFs for the TEQ component within each type of commercial PCB Aroclor mixture varied over a 24-fold range. Keenan, 2000; Keenan, 2001; Keenan et al. 2003;

impossible to reach a judgment as to whether the use of the TEFs will result in a realistic or entirely fanciful estimate of the cancer risks that might be posed by TCDD and the DLCs.

c. The WHO TEFs Fail To Recognize Substantial Evidence That The Potencies Of DLCs Are Not Additive

The TEQ approach assumes that the potencies of individual DLCs in a mixture are additive. The authors of the WHO TEFs have twice recognized the tenuousness of this assumption. In the initial publication of the WHO TEFs, the authors stated: "The most important limitation is that the combined toxic effects of the components of a given mixture would be additive, neglecting possible synergism or antagonism." Ahlborg et al. 1994, p. 1050. Similarly, the authors of the current WHO TEFs acknowledged that deviations from additivity are not uncommon. van den Berg et al. 2006, p. 224.

Knowledge of the mechanisms by which AHR-active chemicals cause effects suggests that the 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 the bond, 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 the AHR, so that the binding is competitive rather than additive. Gray et al. 2006; Safe, 1990; Walker et al. 2005.

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 such as inducing enzymes that metabolize waste compounds for excretion), an adverse effect (e.g., over production of toxic metabolites and associated products), 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 to the receptor, without activating it, but inhibiting further binding, 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 antagonist occupies the site, an agonist cannot occupy it and cause an effect. Moreover, 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, 2005). Such agonists are sometimes called "partial" or "weak" agonists.

This understanding of the AHR mechanism substantially weakens the assumption of the TEQ approach that the potencies of individual DLCs in a mixture are additive (i.e., combining DLCs proportionately increases toxicity). When antagonists are present in concentrations higher than the concentration of agonists, it is difficult for agonists to bind to receptors. Moreover, partial agonists compete with complete agonists for receptor binding sites. Thus, whenever the human body contains a mixture of full agonists, partial agonists, and antagonists, the total impact on the body cannot be predicted by the sum of the various agonist concentrations.

This issue of additivity is further complicated when PCBs are considered. At sites where PCBs and PCDD/F are both present, potentially antagonistic PCBs are often present at substantially higher

Silkworth and Keenan, 2005. This violates a basic premise of the TEQ approach: that a given dose of TEQ has equal biological potency irrespective of the chemical mixture that makes up the dose (van den Berg et al. 1998).

concentrations than are PCDD/F. In his consideration of the potential additivity of mixtures of these compounds, Safe 1993 concluded that "the TEF approach may significantly overestimate the TEQs for environmental extracts containing PCB, PCDD and PCDF mixtures in which the concentrations of the PCBs were >100-fold higher than the PCDDs and PCDFs." Other studies have indicated that additivity in PCDD/F and PCB mixtures has not been demonstrated across congeners and endpoints in animal studies (Harper et al. 1995; Safe, 1990; Starr et al. 1997). Finally, the initial results of two-year bioassays recently performed by the National Toxicology Program ("NTP") also provide evidence of non-additive interactions among DLCs. NTP 2006a-d.

Thus, additivity does not appear to be demonstrated generally across congeners and endpoints in animal studies, and the applicability of this assumption to humans is even less certain. In these circumstances, it is unwarranted to assume that the toxicity of dioxin and dioxin-like mixtures can be predicted by multiplying the TEFs for the individual congeners by their respective concentrations in the mixture, and summing the results.

**d. The Dose-Response Relationship Is Not the Same
For Dioxin And PCBs At All Doses And For All Endpoints**

It is central to the TEQ approach that one ratio expresses the toxicity of a particular DLC relative to dioxin and, indirectly, to other DLCs, regardless of the dose that a subject receives or the endpoint. Thus, for example, PCB 126, with an assigned TEF of 0.1, should exhibit a potency that is one-tenth that of dioxin at a dose of X, 5X, or 10X, and, consequently, the dose-response curves of dioxin and PCB 126 should be parallel at every dose for every endpoint. That is not true for all endpoints, however. For instance, as part of a National Toxicology Project 2-year rodent carcinogenicity study, Toyoshiba et al. 2004 looked at the effects of dioxin, 4-PeCDF, PCB126, and a mixture of the three on the activity of two liver enzymes induced by dioxin and DLCs. The authors concluded that the dose-response curves for each of the three compounds and for the mixture were significantly different from one another. This study is not discussed in the Draft PRGs.

Walker et al. 2005 analyzed cancer incidence data from the same 2-year rodent carcinogenicity study. The dose-response curves were modeled using four different model conditions. When each data set was modeled with parameters that allowed the individual curves to provide an independent optimal fit, the resultant dose-response curves were not parallel.

Walker et al. 2005 also modeled the data sets using parameters that forced the curves to assume the same shape. Walker et al. 2005 then conducted a statistical analysis of the error associated with the fit of each model, and concluded that the hypothesis that the dose-response curves were all the same shape could not be rejected. The researchers admitted, however, that the statistical power of the tests used to determine whether the null hypothesis could be rejected was rather low, ranging from 0.1 to 0.5. Again, this study is not discussed in the Draft PRGs.²²

2. The WHO TEFs Cannot Be Used To Assess All Noncancer Risks

²² The lack of parallelism is not surprising, because the effect of any particular amount of a DLC relative to dioxin depends upon several dynamic pharmacological characteristics of each ligand, including, but not limited to, receptor affinity, competition, the duration of receptor occupancy, individual ligand efficacy, and even ligand bioavailability.

In order for a chemical to be included in the WHO's TEQ approach, the chemical must be able to (1) bind to the AHR, and (2) elicit AHR-mediated biochemical and toxic responses. Van den Berg et al. 1998. In recognition of those requirements, the Draft TEF Guidance (p. ii) "recommends these TEFs be used for all effects mediated through aryl hydrocarbon receptor binding by the DLCs including cancer and non-cancer effects."

The Draft PRGs do not acknowledge this limitation. Nor do they demonstrate that any of the alleged noncancer effects of any of the DLCs are AHR-mediated. Assuming, for purposes of argument, that the WHO TEFs are otherwise valid, they can only be used to assess the specific noncancer risks of specific DLCs for which there is evidence sufficient to establish that the noncancer effect is AHR-mediated.

3. The WHO TEFs Cannot Be Used To Assess Risks Of DLCs In Soil Or Dermal Risks

It has long been recognized that the TEFs are based on intake or dose and therefore are limited in their application. As the original WHO expert panel observed:

It was recognized that the recommended TEFs have been developed for exposure scenarios, i.e., they are intake TEFs. These values may – or may not – be appropriate for body burden assessments. They may also be reexamined for eco-toxicity purposes. Thus, there may be different classes of TEF values depending upon whether the considerations relate to intake, body burden, or ecological concerns.

Ahlborg et al. 1994, p. 1059.

In the same vein, the authors of the current WHO TEFs stated:

Concern is expressed about the application of the TEF/TEQ approach to abiotic environmental matrices such as soil, sediment, etc. The present TEF scheme . . . and TEQ methodology are primarily meant for estimating exposure via dietary intake situations because present TEFs are based largely on oral uptake studies often through diet. Application of these "intake or ingestion" TEFs for calculating the TEQ in abiotic environmental matrices has limited toxicological relevance and use for risk assessment, unless the aspect of reduced bioavailability and environmental fate and transport of the various dioxin-like compounds are taken into account. *If human risk assessment is done for abiotic matrices, it is recommended that congener-specific equations be used throughout the whole model, instead of using a total TEQ-basis, because fate and transport properties differ widely between congeners.*

van den Berg et al. 2006, p. 237 (emphasis added).

Recent evidence bears out these concerns. Gray et al. 2006 conducted dose-response modeling of the results of the recent NTP bioassays. The authors concluded that the WHO98 TEFs, which were derived from data evaluated on an administered dose basis, substantially overpredict the cancer potency of 4-PeCDF and PCB 126 on a body burden basis.

The NAS reached a similar conclusion concerning the use of the WHO98 TEFs for evaluating risks based on a body burden metric:

It remains to be determined whether the current WHO TEFs, which were developed to assess the relative toxic potency of a mixture to which an organism is directly exposed by dietary intake, are appropriate for body burden toxic equivalent quotient (TEQ) determinations, which are derived from the concentrations of different congeners measured in body fat. If body burdens are to be used as the dose metric, a separate set of body burden TEFs should be developed and applied for this evaluation. *Without these corrected values, the overall TEQs estimated by use of intake TEFs might be substantially in error.* [NAS 2006, p. 193 (emphasis added).]

Most recently, Dr. Martin van den Berg, the lead author of the WHO2005 TEFs and a member of the peer review panel for the Draft TEF Guidance, stated:

I think that the critical remarks made in the last TEF evaluation in 2005 regarding the use of TEF values for abiotic matrices like sediment and soil [sic] are not sufficiently covered in the [Draft TEF Guidance]. *This especially has consequences for contaminated soils and sediments in which no direct ingestion takes place. In reality, there is no scientific rationale for using the TEF system for these situations, except for scaling different environmental matrices without a toxicological significance but for prioritization for remedial actions.* Direct oral ingestion of particles can be included in the TEF system, although bioavailability will play a significant downplaying role in the overall mixture toxicity (TEQs). . . . *Dermal uptake from particles under dry conditions is to my opinion a marginal exposure pathway. It should not be considered using e.g. 100% bioavailability for the human skin and can represent a gross overestimation of systemic exposure and associated risk.*

Peer Review Panel Report, pp. 11-12 (emphasis added). Another reviewer – Dr. Thomas B. Starr – had a similarly strong opinion:

Van den Berg et al. (2006) cite concerns regarding differential bioavailability and the very limited ("almost nonexistent") data that is available from studies using environmental matrices contaminated with DLCs. They cautioned against the extrapolation of risk estimates, obtained using the current TEFs which are largely based on results from dietary intake studies, to non-dietary exposure routes. I agree wholeheartedly with their concerns. In my opinion, application of the current TEFs to non-dietary exposure routes is not scientifically supportable at the present time.

Id. at 22. Two other reviewers – Dr. Peter L. DeFur and Dr. Moiz Mumtaz – agreed that if TEFs are used for the dermal route of exposure, they need to be adjusted to take into account differences in bioavailability and absorption. *Id.* at 21-22. Only one reviewer – Dr. Nigel J. Walker – thought that use of TEFs for the dermal route is justified. *Id.* at 22.

The Draft PRGs ignore the opinions and recommendations of the authors of the WHO TEFs, the NAS and the peer reviewers of the Draft TEF Guidance. Instead, the Draft PRGs propose application of the uncorrected WHO TEFs and TEQ approach to non-dietary exposure as if this extrapolation of the WHO values was unquestionably justified.²³ Draft

²³ The Draft PRGs do state that "risk assessors should identify the fraction of TEQ attributable to dioxin and to each chemical class of [DLCs]", but do not explain what the risk assessors or risk managers should do with that information. Draft PRGs at 3.

PRGs, pp. 2-3. That is not rigorous adherence to the best available science.

4. The Development Of The WHO TEFs Has Not Followed Established Practices For Ensuring Scientific Reliability And Clarity

Among the core principles of science is the precept that observations and experiments must be replicable to be reliable and trustworthy. For other scientists to attempt replication, the authors of the original study must describe their method, materials and reasoning in detail. Further, in critical review work, the authors must explain clearly the reasoning that led them to include some studies and exclude others, and to place weight on one experimental result but not another, so that other scientists can make a fair judgment as to whether the evidence has been properly assessed. One of the functions of peer review is to assure that these principles and standards are met.

Development of the WHO TEFs has not conformed to these fundamental principles. The scientists who developed and updated the WHO TEFs have provided little rationale for considering some studies and not others. They have not provided sufficient detail on how they evaluated and weighed the studies from which the TEFs were derived. They have provided opinion, with virtually none of the reasoning that would make it replicable.²⁴

The lack of adherence to these fundamental principles has pervaded the WHO TEF process. The initial set of WHO TEFs was developed during a nonpublic "expert consultation" consisting of 12 experts, two observers, and WHO staff. Ahlborg et al. 1994, p. 1050. Of 1200 articles on PCBs, 146 were considered useful for developing a database for determining TEFs.²⁵ These articles were analyzed, and the data included in the final database were selected from 57 articles, manuscripts and personal communications using the following criteria:

- At least one PCB congener was studied
- TCDD or a PCB-reference (PCB 77, 126, or 169) also was studied in the same experiment or
- TCDD or a PCB-reference (PCB 77, 126 or 169) was studied with the same experimental design and by the same authors in another experiment
- Endpoints were affected by TCDD or the PCB-reference (PCB 77, 126, 169).

Ahlborg et al. 1994, p. 1051.

The requirements that PCBs be studied on a congener basis, and that such studies include or be tied to a study of TCDD, is understandable when the aim is to look at relative potencies. Those requirements, however, exclude from consideration a great deal of the established literature on PCBs. Two broad areas of PCB analysis are entirely excluded: (1) studies that examined PCBs on an

²⁴ For example, van den Berg et al. 2006 recognized that the REP estimates for the mono-ortho PCB congeners (spanning 4-5 orders of magnitude) may be based upon poor studies utilizing PCB preparations contaminated with other, more potent DLCs. Nonetheless, the WHO panel apparently agreed that these congeners have some AHR agonist activity, and arbitrarily set the TEFs for all mono-ortho PCBs to 0.00003. *Id.* The use of these subjectively determined mono-ortho PCB TEF values in estimating overall TEQ is not reliable.

²⁵ Ahlborg et al. 1994 do not explain why they chose to disregard almost 1000 articles.

Aroclor basis rather than a congener basis, and (2) studies that focused on PCBs without reference to TCDD. An excellent example of the effect of these exclusions is to consider the basis on which EPA established the IRIS values for PCBs. All of the animal studies that EPA relied on involved doses of Aroclors – the commercial mixtures of PCBs actually manufactured, marketed and used in the United States – rather than individual congeners. EPA, IRIS, Polychlorinated biphenyls (PCBs) (CASRN 1336-36-3). The authors of the WHO TEFs did not consider this evidence, thereby ignoring the entire basis on which EPA traditionally has assessed the health risk of PCBs. Similarly, the epidemiological studies obviously do not reflect exposure to a single congener, and they have been ignored by the authors of the WHO TEFs. The authors' consideration of only a subjectively selected subset of the available, relevant evidence on PCBs logically cannot result in the best available science on the toxicity of PCBs.

These and other deficiencies have persisted through the latest iteration of the WHO TEFs. For the 2005 update, the WHO expert panel used a “combination of . . . unweighted REP distributions, expert judgment and point estimates to re-evaluate TEFs.” van den Berg et al. 2006, p. 227. Certain TEFs were “extensively re-evaluated.” *Id.* For each TEF, however, only a one-paragraph explanation of the expert panel's analysis and conclusion is provided.

The expert panels that developed and updated the TEFs have consistently failed to provide sufficient information to replicate their analyses. Consequently, the expert panels' work cannot be peer reviewed in the usual manner. Only the results of the work can be tested against the broader evidentiary material available. As we have shown, such testing demonstrates critical flaws in the assumptions on which the TEFs are premised. Use of the TEQ approach for assessing PCB toxicity should be abandoned.

5. The Draft PRGs Do Not Acknowledge The IRIS Values For PCBs Or Show How The Two Sets Of Risk Values Are To Be Reconciled

Prior to 1996, EPA assessed the cancer risks of PCBs by applying a single dose-response slope ($7.7(\text{mg}/\text{kg}\text{-day})^{-1}$ average lifetime exposure) for any mixture containing PCBs. EPA 1996, p. 6. In 1996, EPA issued a new reassessment of PCB carcinogenicity that evaluated all available cancer studies, and took into account the effects of environmental processes, to provide guidance on choosing an appropriate slope for representative classes of environmental mixtures and different exposure pathways. *Id.*, pp. 6-7. The 1996 Reassessment provided “[a] range of upper-bound potency estimates for PCB mixtures, plus a range of central estimates, with guidance for choosing estimates from these ranges to reflect the effect of environmental processes on a mixture's toxicity.” *Id.* at 7. Those potency estimates, or CSFs, range from a low of $0.04 (\text{mg}/\text{kg}\text{-day})^{-1}$ to a high of $2.0 (\text{mg}/\text{kg}\text{-day})^{-1}$. *Id.*, p. 43, Table 4-1.

The CSFs derived in the 1996 Reassessment are posted in EPA's Integrated Risk Information System (IRIS).²⁶ IRIS also includes oral Reference Doses (RfDs), which are used to assess noncancer risks, for Aroclors 1016 ($7\text{E-}5 (\text{mg}/\text{kg}\text{-day})^{-1}$) and 1254 ($2\text{E-}5(\text{mg}/\text{kg}\text{-day})^{-1}$). These CSFs and RfDs are Tier 1 values within the meaning of OSWER's hierarchy of human health toxicity values. Under that hierarchy, IRIS is the preferred source of toxicity information:

²⁶ Polychlorinated biphenyls (PCBs) (CASRN 1336-36-3), available at **Error! Hyperlink reference not valid.**; Aroclor 1016 (CASRN 12674-11-2), available at <http://www.epa.gov/ncea/iris/subst/0462.htm>; Aroclor 1254 (CASRN 11097-69-1), available at <http://www.epa.gov/ncea/iris/subst/0389.htm>.

EPA should use the best science available on which to base risk assessments. In general, if health assessment information is available in [IRIS] . . . for the contaminant under evaluation, risk assessors normally need not search further for additional sources of information.

OSWER Directive 9285.7-53, p. 2.

The Draft PRGs do not acknowledge the 1996 Reassessment or the existence of the IRIS values for PCBs. The Draft PRGs also do not provide a scientific justification for the apparent belief that the WHO TEFs will enable a more accurate assessment of the risks of PCBs than the IRIS values. Consequently, if the Draft Guidance is finalized, EPA will have two inconsistent sources of toxicity information, based on two distinct bodies of evidence, for assessing the risks of PCBs. That makes no sense whatsoever. The logical approach would be for EPA to update the IRIS values to reflect the PCB literature since 1996, including the literature that demonstrates differences in sensitivity to PCBs between rodents and humans and the epidemiological studies.

6. There Is No Validated Method For Performing The PCB Congener Analysis Required To Use The TEQ Approach For PCBs

The TEQ approach, by definition, requires analysis of individual DLCs, including PCB congeners that are DLCs. The only method of which we are aware that purports to analyze the dioxin-like PCB congeners is EPA's Method 1668B --Chlorinated Biphenyl Congeners in Water, Soil, Sediment, Biosolids, and Tissue by HRGC/HRMS (Nov. 2008)²⁷. That method was developed for "wastewater, surface water, soil, sediment, biosolids and tissue matrices", but states that "[o]ther applications and matrices may be possible, which may or may not require modifications of sample preparation, chromatography, etc." Method 1668B, p. 1. As discussed below, Method 1668B has not been validated as called for by EPA's Agency Policy Directive No. FEM-2005-001, *Ensuring the Validity of Agency Methods – Methods Validation and Peer Review Guidelines* (2005) ("Validation Policy")²⁸ or FEM Document No. 2005-01, *Validation and Peer Review of U.S. [EPA] Chemical Methods of Analysis* ("Validation Guidance").²⁹

An interlaboratory variability study of Method 1668A – the immediate predecessor of Method 1668B – conducted for EPA by qualified labs in 2003-2004 ("EPA study") indicates that the Method is highly problematic. Almost half of the labs that submitted data to EPA were not able to produce data that EPA regarded as usable. *Method 1668A Interlaboratory Validation Study Report* (Nov. 2008) ("EPA Report"), pp. 9-10.³⁰ That fact should have prompted EPA to consider whether this Method can be implemented correctly and consistently by different labs. Instead, EPA simply disregarded the results from the labs whose data EPA regarded as unusable, and proceeded to analyze the data from the remaining six labs that EPA deemed to be usable. Regulated entities, of course, do not know which labs produced usable data, and therefore have at least a 50% chance of hiring a laboratory that will not produce usable data, let alone correct, data.

To the extent that EPA regarded data obtained in the EPA Study as usable, that data does not demonstrate that Method 1668A attained the goals set forth in EPA's Validation Policy (the method

²⁷ <http://www.epa.gov/waterscience/methods/method/files/1668.pdf>.

²⁸ http://epa.gov/osa/fem/pdfs/Method_Vailidity_Policy_092705.pdf.

²⁹ http://epa.gov/fem/pdfs/chemmethod_validity_guide.pdf.

³⁰ <http://www.epa.gov/waterscience/methods/method/files/1668Ato1668B-valdiation.pdf>.

"is suitable for its intended purpose (i.e., yields acceptable accuracy for the analyte, matrix and concentration range of concern))"³¹ or has the "method reproducibility" required by EPA's Validation Guidance.³² Instead, the EPA Report identifies many problems with the "usable" data, including:

- Extreme differences in the recoveries obtained by the labs. Figure 4-1 on p. 14 of the EPA Report shows recoveries ranging from almost 0% to more than 100% for concentrations of PCB congeners in wastewater in the 0 to 2000 pg/L range, and from 60% to more than 100% for concentrations in the 2000 to 3000 pg/L range – the ranges that are targeted by Method 1668A. If EPA had included data from all 11 labs that submitted data, the differences in recoveries might have been even greater.
- Unexplained, higher than expected variability at both high and low concentrations of PCBs in wastewater. EPA Report, Fig. 4-3. The higher variability is consistent with the large differences in the minimum and maximum recoveries in Table 4-3. In fact, the EPA Report states, "The variability is somewhat higher than expected at the higher concentrations, with RSDs of approximately 40%. The reason for these higher than expected RSDs is not known." EPA Report, p. 15. Again, if EPA had included data from all 11 labs that submitted data, the differences in recoveries might have been even greater.
- Inability to calculate recoveries of congeners from tissue and biosolids samples, because the true congener concentrations in those samples were unknown. *Id.* at 14. Consequently, EPA cannot determine the accuracy of Method 1668A for those matrices.
- Insufficient calibration data "to permit revision of the QC acceptance criterion for calibration linearity" (*Id.* at 19,) and to calibrate verification data (*Id.*), which limits EPA's ability to evaluate fully the performance of Method 1668A.
- Precision that is "proportional to concentration" (*Id.*, Sec. 6), meaning that Method 1668A is less precise for lower concentrations of PCB congeners – the concentration ranges actually targeted by Method 1668A – than for higher concentrations.

Presumably in recognition of these and other problems, the EPA Report does not state or claim that Method 1668A yields acceptable accuracy for PCB congeners in the matrices and concentration ranges of concern, with adequate precision and reproducibility across labs. Indeed, the EPA Report says only that "[t]his study demonstrated that PCB congeners *can be measured* in water, biosolids, and tissue in multiple laboratories using EPA Method 1668A." EPA Report, Sec. 6 (emphasis added). Even if that is true, the fact that PCBs "can be measured" does not mean that Method 1668A measures PCBs with the requisite precision, accuracy and reproducibility. In addition, EPA has not demonstrated that the changes that it made to Method 1668A to produce Method 1668B are sufficient to correct the problems encountered in the EPA study. Consequently, unless and until a validated method for analyzing soil, sediments and other matrices for individual co-planar PCB congeners is developed, the TEQ approach can not be implemented reliably for PCBs.

7. Epidemiological Studies Do Not Support The Carcinogenicity Of PCBs At Environmental Or Occupational Exposures

A vast body of human epidemiological studies indicates that PCBs are carcinogenic to humans only at very high doses, if at all. More than 50 peer-reviewed, epidemiological cancer

³¹ Validation Policy, p.1.

³² Validation Guidance, p. 11.

studies specific to PCBs have been published over the past 30 years. Many of those studies involved thousands of workers with occupational exposures far greater than those that would result from environmental exposures. None of those studies supports a finding that PCBs are human carcinogens. Two review articles, Golden et al. (2003) and Golden and Kimbrough (2009), are particularly noteworthy.

Golden et al. (2003) discusses the findings in Kimbrough et al. (1999) and Kimbrough (2003), which reported on a cohort of over 7,000 occupationally exposed workers in two GE capacitor manufacturing plants. Kimbrough found no statistically significant increase in deaths due to cancer regardless of degree of exposure to PCBs or length of employment in the plants. Golden also reviewed all of the other human evidence relating to the potential carcinogenicity of PCBs. This paper concluded that “[a]pplying a weight-of-evidence evaluation to the PCB epidemiological studies can only lead to the conclusion that there is no causal relationship between PCB exposure and any form of cancer.” A more detailed review of all the relevant human cancer studies involving exposure to PCBs (Golden and Shields (2000)) concluded that the weight of the human evidence does not support an association, much less a causal relation, between PCB exposure and any type of cancer.

In the 2009 review article, Golden and Kimbrough reviewed an additional 15 articles that had been published since 2003. The review was done using EPA's 2005 Guidelines for Carcinogen Risk Assessments and a method endorsed by ATSDR. None of the studies changes the conclusion drawn in 2003: “the weight of evidence does not support a causal association for PCBs and human cancer.” The authors found no evidence that PCBs would result in human cancer at the level of environmental or occupational exposures.

All of this information indicates that application of the TEQ approach to PCBs would lead to human health risk assessments that significantly and improperly exaggerate risk.

8. The WHO TEFs Should Not Be Used For Risk Assessments Unless And Until EPA Provides Appropriate Guidance That Addresses All Of The Uncertainties And Limitations Of The WHO TEFs And TEQ Approach

As noted above, the Draft PRGs provide virtually no guidance to risk assessors on how to use TEFs. Perhaps that is due to the fact that EPA has not yet finalized the Draft TEQ Guidance, which is not even mentioned in the Draft PRGs. The omission also may be due to the fact that the peer reviewers of the Draft TEQ Guidance found it to be deficient in a number of significant respects:

Most reviewers recommended some augmentation of sections of the document to provide additional context or more complete description, with limited additional text. . . .

Most reviewers thought that the document needs to provide more description or direction on using or capturing the underlying uncertainty in the information used to generate the TEFs. One example of this point is that the van den Berg paper lists the underlying assumptions for, and limitations of, the TEF approach, and these need to be listed in this EPA guidance.

[S]everal reviewers requested some additional explanatory text for using the TEFs . . . to provide users . . . with more “how to” direction. Several reviewers were quite clear that more history and background would improve the usability of the document.

....

All the reviewers were disappointed with the extent and scope of the uncertainty analysis section in the document. . . . The reviewers agreed that the guidance document needs a specific section on uncertainty analysis. This section should provide specific direction on conducting qualitative and quantitative uncertainty analysis for use of TEFs.

Several of the reviewers took issue with the recommendation that the TEFs should be used for all cancer and non-cancer effects . . . The reviewers questioned the use of TEFs if cancer potency factors for specific congeners are available.

The reviewers had a range of opinions on the recommendation that the TEFs may be applied to other exposure routes (i.e., dermal or inhalation) as an interim estimate. Some felt that application of the current TEFs to non-dietary exposure routes is not scientifically supportable at the present time.

Peer Review Panel Report, pp. 4-5. The deficiencies of the Draft TEF Guidance prompted Dr. Peter L. DeFur, the chairman of the panel, to say:

I am not sure that all of the intended users of this document will be sufficiently familiar with all the technicalities of TEFs to be able to pick this document up and use it. I think otherwise, based on my experience with state and local efforts and programs.”

Peer Review Panel Report, p. 6. Similarly, Dr. Nigel Walker of the National Toxicology Program stated:

[The Draft TEF Guidance] was too short and did not provide sufficient specific guidance for a lot of the recommendations and especially on issues regarding uncertainties in the TEF scheme and its use, that risk managers may need. I fear that many folks may be left scratching their heads about exactly what to do beyond simply calculating a TEQ, and that subsequent analyses and risk management decisions may vary considerably in how different issues are approached.

Id., p. 8.

C. The Draft PRGs Do Not Comport With OMB's And EPA's Information Quality Guidelines

If the Draft PRGs are finalized, the interim PRGs and the WHO TEFs will be used to determine cleanup levels at Superfund and RCRA sites, with enormous financial consequences for both the public and private sectors. The Draft PRGs therefore constitute influential scientific information that is subject to the Office of Management and Budget's and EPA's Information Quality Guidelines.³³

³³ "Influential' . . . means that the Agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public polices or important private sector decisions." *Guidelines For Ensuring And Maximizing The Quality, Objectivity, Utility and Integrity of Information Disseminated By The Environmental Protection Agency*, EPA/260R-02-008 (Oct. 2002)("EPA Guidelines"), p. 19; see

OMB's Guidelines direct federal agencies, including EPA, to ensure and maximize the quality, objectivity, utility, and integrity of information disseminated to the public. 67 Fed. Reg. 8452. "Quality" is "an encompassing term comprising utility, objectivity, and integrity." *Id.* at 8459. "Utility" and "objectivity" are both relevant here, and neither of these indicia of "quality" is discussed or fulfilled in the Draft Guidance.

1. The Draft PRGs Are Not Useful

As defined in the OMB Guidelines --

2. "Utility" refers to the usefulness of the information to its intended users, including the public. . . . [W]hen transparency of information is relevant for assessing the information's usefulness from the public's perspective, the agency must take care to ensure that transparency has been addressed in its review of the information.

67 Fed. Reg. at 8459; see also EPA Guidelines at 15.

As explained above, the Draft PRGs lack transparency in a number of key respects. These include, but are not limited to, a complete failure to (1) discuss the pertinent conclusions and recommendations of the NAS Report and the Peer Review Panel Report; (2) discuss the science that contravenes the assumptions that underlie the TEQ approach; (3) identify the criteria that EPA used to select the handful of cancer and noncancer values from which EPA selected the CSF and Reference Concentrations used to calculate the interim PRGs; and (4) qualitatively or quantitatively describe the effect of the change in the PRGs on pending or completed remedies at CERCLA and RCRA sites and the costs of those remedies. Because the Draft PRGs lack information necessary to evaluate the interim PRGs and the use of the TEQ approach, the Draft PRGs lack utility within the meaning of EPA's and OMB's Information Quality Guidelines.

2. The Draft PRGs Are Not Objective

As defined in the OMB Guidelines, "objectivity" comprises both presentation and substance. As to presentation --

a. "Objectivity" includes whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner. This involves whether the information is presented in a proper context. . . . Sometimes, in disseminating certain types of information to the public, other information must also be disseminated in order to ensure an accurate, clear, complete, and unbiased presentation.. Also, the agency needs to identify the sources of the disseminated information . . . and . . . in a scientific . . . context, the supporting data and models, so that the public can assess for itself whether there may be some reason to question the objectivity of the sources. Where appropriate, data should have full, accurate, transparent documentation, and error sources affecting data quality should be identified and disclosed to users

67 Fed. Reg. at 8459; see also EPA Guidelines at 15.

also *Guidelines For Ensuring And Maximizing The Quality, Objectivity, Utility and Integrity of Information Disseminated By Federal Agencies*, Office of Management and Budget, 67 Fed. Reg. 8452, 8460 (Feb. 22, 2002)("OMB Guidelines"). "'Information' means any communication or representation of knowledge, such as facts or data, in any medium or form." OMB Guidelines, p. 8460.

To fulfill the presentation prong of the objectivity component of the Guidelines, EPA should have explained in the Draft Guidance, among other things, that –

- (1) The NAS concluded that the weight of the evidence supports use of a nonlinear, threshold model for evaluating the carcinogenicity of dioxin.
- (2) The NAS concluded that the evidence on noncancer effects is, at best, suggestive.
- (3) It is generally recognized – including by NAS – that humans are substantially less sensitive to dioxin and DLCs than the rodents upon whom the WHO TEFs are based.
- (4) The authors of the WHO TEFs have stated that the use of "intake or ingestion" TEFs for calculating the TEQ in abiotic environmental matrices (such as soil and sediment) and for assessing dermal exposures "has limited toxicological relevance", and that TEFs should not be used to calculate a TEQ in such circumstances.
- (5) The NAS has stated that unless EPA develops a separate set of body burden TEFs, "the overall TEQs estimated by use of intake TEFs might be substantially in error."
- (6) There is no validated method for performing the PCB congener analysis required to implement the TEQ approach for PCBs.

All of this information is necessary to an "accurate, clear, complete, and unbiased presentation," and all of it is missing from the Draft PRGs. The Draft PRGs therefore do not satisfy the presentation prong of the objectivity requirement of the OMB and EPA Guidelines.

In addition to presentation, objectivity –

- b. . . . involves a focus on ensuring accurate, reliable and unbiased information. . . .
 - ii. If an agency is responsible for disseminating influential scientific . . . information, agency guidelines shall include a high degree of transparency about data and methods to facilitate the reproducibility³⁴ of such information by qualified third parties.

OMB Guidelines, 67 Fed. Reg. at 8459; see also EPA Guidelines, p. 22.

In addition to these requirements, influential scientific information that is used to analyze risks to human health or the environment must meet the standard for risk assessments adopted by Congress in the Safe Drinking Water Act of 1996.³⁵ Under that standard, EPA must ensure that the information that it disseminates is based on "(i) the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices and (ii) data collected by accepted methods or best available methods." 42 U.S.C. § 300g-1(b)(3)(A). In carrying out that mandate, EPA must ensure that "the presentation of information on public health

³⁴ "Reproducibility" means that the information is capable of being substantially reproduced, subject to an acceptable degree of imprecision. For information judged to have more . . . important impacts, the degree of imprecision that is tolerated is reduced . . . With respect to analytic results, "capable of being substantially reproduced" means that independent analysis of the original or supporting methods would generate similar analytic results, subject to an acceptable degree of imprecision or error. 67 Fed. Reg. at 8460.

³⁵OMB Guidelines, 67 Fed. Reg. at 8460; see also EPA Guidelines, pp. 22-23.

effects is comprehensive, informative and understandable. The Administrator shall . . . specify . . . to the extent practicable . . . (v) peer-reviewed studies known to the Administrator that support, are directly relevant to, or *fail to support* any estimate of public health effects and the methodology used to reconcile inconsistencies in the scientific data." 42 U.S.C. § 300g-1(b)(3)(B)(emphasis added).

As discussed above, the Draft PRGs and the WHO TEFs are lacking virtually all of these attributes of substantive objectivity, including reproducibility. In particular, there is absolutely no discussion of the evidence — including the NAS Report — that weighs against reducing the PRGs and using the WHO TEFs for PCBs. EPA has failed to "maximize and ensure" the quality of the information contained in the Draft PRGs.

IV. CONCLUSION

The Draft PRGs, including the recommendation regarding the use of the WHO TEFs, are not supported by a transparent evaluation of either the latest science or the best available science. They are "policy decisions . . . disguised as scientific findings." *Opening Memo to EPA Employees* (Jan. 23, 2009). EPA therefore should withdraw the Draft PRGs. If EPA elects not to withdraw the Draft PRGs, EPA should, at minimum, remove all references to PCBs and the WHO TEFs for PCBs from the Draft PRGs. If EPA nevertheless proceeds to finalize the Draft Guidance with PCBs included, EPA should reduce the TEF for PCB 126 by two to three orders of magnitude, and re-evaluate the TEFs for other PCB congeners, to reflect PCB-specific evidence and the generally accepted consensus that humans are less sensitive than rodents to dioxin. EPA also should instruct the Program Offices and Regions that, consistent with the OMB Bulletin on Good Guidance Practices, use of the WHO TEFs or TEQ approach for any purpose cannot be imposed upon any entity, and regulated entities are free to use for PCBs either the IRIS values or TEFs that have been revised downward to reflect the evidence discussed in these comments.

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PEER REVIEW SUMMARY REPORT

External Peer Review of *Recommended Toxicity Equivalency Factors (TEFs) for Human Health Risk Assessments of Dioxin and Dioxin-Like Compounds*

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I. INTRODUCTION

EPA's Risk Assessment Forum (RAF) has recently finalized a document recommending the use of specific TEFs for dioxin and dioxin-like compounds in ecological risk assessment. Parallel to that effort, EPA began developing a document regarding recommendations for TEFs for human health risk assessments. Both the ecological TEFs and EPA's proposed human health TEFs are based on a World Health Organization (WHO) consensus document published in 2005. This draft document, "Recommended Toxicity Equivalency Factors (TEFs) for Human Health Risk Assessments of Dioxin and Dioxin-Like Compounds," describes EPA's updated approach for evaluating the human health risks from exposures to environmental media containing dioxin and dioxin-like compounds. It was developed by EPA's Risk Assessment Forum with extensive input from scientists throughout the Agency. The draft document summarizes the TEF methodology, provides background information and assumptions on how the methodology has evolved, and provides health risk assessors with a recommended approach for application.

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II. CHARGE TO REVIEWERS

Please provide written responses to the following questions:

Charge Questions:

Risk assessments of dioxins and dioxin-like compounds (DLCs) have relied on the dioxin toxicity equivalency factor (TEFs) approach. Various stakeholders, inside and outside the Agency, have called for a more comprehensive characterization of risks; therefore, EPA's Risk Assessment Forum (RAF), located in the Office of the Science Advisor, identified a need to examine the recommended approach for application of the TEF methodology in human health risk assessments. An RAF Technical Panel has developed the draft guidance document, "Recommended Toxicity Equivalency Factors for Human Health Risk Assessments of Dioxin and Dioxin-Like Compounds" that recommends use of the consensus mammalian TEFs developed by the World Health Organization (WHO, 2005; published in Van den Berg et al., 2006) for use in human health risk assessment. The following set of charge questions is to be addressed during the external scientific peer review of this document.

Charge Questions:

History and Background

1. Please comment on whether the TEF methodology is accurately explained and referenced in the document.
2. Is the history of the mammalian TEFs and the process used to develop them by the World Health Organization accurately described and in sufficient detail? Are the WHO (2005) mammalian TEF values and their derivation accurately reported?

Risk Characterization

3. Is the development of the Relative Potency (REP) database presented in Haws et al. (2006) accurately described and in sufficient detail? If not, please provide recommendations for enhancing this description.
4. Is the uncertainty analysis approach described by EPA reasonable?
5. Are there alternative ways to approach uncertainty analysis for the TEFs that you could recommend?

EPA Recommendations

6. Please comment on the recommendation that these TEFs should be used for all cancer and non-cancer effects that are mediated through AHR binding by the DLCs.

7. Please comment on the recommendation that the TEFs are most appropriate for exposures to dioxin-like compounds via the oral exposure route.
8. Please comment on the recommendation that the TEFs may be applied to other exposure routes (i.e., dermal or inhalation) as an interim estimate.
9. Please comment on the recommendation that, if considered in an assessment, the fractional contribution of dermal and inhalation route exposures to the predicted toxicity equivalence (TEQ) should be identified as part of the risk characterization.
10. Is there a currently available approach for calculating the cumulative exposures to DLCs that is more appropriate than the WHO TEF methodology being proposed by EPA?

III. SUMMARY OF PEER REVIEW TELECONFERENCE

The External Peer Review of *Recommended Toxicity Equivalency Factors (TEFs) for Human Health Risk Assessments of Dioxin and Dioxin-Like Compounds* was held as a teleconference on October 22, 2009, from 1:00 to 3:45 PM EDT. The purpose of the teleconference was to facilitate discussion among five experts to provide feedback on EPA's draft document. Five reviewers were selected by Versar for this review based on their experience in areas such as: dioxin toxic equivalency factors (TEFs), toxicology, mixtures component methods, and risk assessment. Each reviewer offered general impressions on the document and contributed to the discussion of ten specific charge questions, taken in order and led by the chair.

In addition to the five reviewers, approximately 25 public observers were present on the call to listen to the reviewers' discussion. Four observers spoke during the public comment period of the teleconference, offering comments on the TEF guidance document. These verbal comments were provided in addition to the written comments submitted to the docket, which the reviewers considered as part of their review.

Each reviewer provided their perspectives on the document, all noting that the authors were to be commended for producing a concise and understandable document. Most reviewers recommended some augmentation of sections of the document to provide additional context or more complete description, with limited additional text. The most commonly occurring comment was the need for more specifics and detail in the section on uncertainty analysis. The uncertainty and variability of the relative potency data (REPs), and the underlying toxicity tests, were the most commonly raised issues during the peer review discussion.

Most reviewers thought that the document needs to provide more description or direction on using or capturing the underlying uncertainty in the information/data used to generate the TEFs. One example of this point is that the van den Berg paper lists the underlying assumptions for, and limitations of, the TEF approach and these need to be listed in this EPA guidance.

Most reviewers agreed that the document is accurate in terms of descriptions of the TEF mechanism and process, although several reviewers requested some additional explanatory text for using the TEFs. The additional text would be intended to provide users at the state or regional level with more "how to" direction. Several reviewers were quite clear that more history and background would improve the guidance and the usability of the document because there is more experimental background on TEFs and this information would be helpful to the reader. Additional references are also needed on specific background topics.

Most of the reviewers felt that additional information needs to be added in describing the Relative Potency (REP) database presented in Haws et al. (2006). Information on REP variability and distribution needs to be added from the Haws publication. One reviewer suggested that an Excel spreadsheet of the data file supplements provided in the publication could be created and made available to all interested parties and placed on EPA's website for downloading.

Reviewers recommended alternative ways to approach uncertainty analysis for the TEFs. Alternatives recommended by one reviewer include the use of weighted distributions, classifying

congeners based on database strength, assigning different congeners a different level of uncertainty, and classifying TEQs as high, medium, or low potency so the toxicity equivalent (TEQ) contributions from weak congeners can be evaluated.

All the reviewers were disappointed with the extent and scope of the uncertainty analysis section in the document. At least one reviewer thought the document had no real uncertainty section. The reviewers agreed that the guidance document needs a specific section on uncertainty analysis. This section should provide specific direction on conducting qualitative and quantitative uncertainty analysis for use of TEFs. At present, the guidance offers some useful and valuable direction on sensitivity analysis that the reviewers agreed needs to be included in a thorough and careful application of TEFs.

Several of the reviewers took issue with the recommendation that the TEFs should be used for all cancer and non-cancer effects that are mediated through aryl hydrocarbon receptor (AHR) binding by the dioxin-like compounds (DLCs). Several reviewers were confused by the phrase “all cancer” and felt clarification in the document was needed. Most reviewers felt that TEFs are also appropriate for non-cancer effects because these effects are also likely mediated through the AH receptor, though one reviewer cautioned that use of TEFs is as questionable and uncertain for non-cancer as it is for cancer effects. Another reviewer did not agree with a linear approach for carcinogenicity. The reviewers questioned the use of TEFs if cancer potency factors for specific congeners are available. One reviewer noted that the National Toxicology Program has completed toxicity tests for carcinogenicity of 4 of the 5 DLCs that are the top contributors to TEQ, nationally. EPA should add in the option for using these DLC congener-specific cancer slope factors in those cases where applicable, and provide some guidance on what situations would be most applicable.

The reviewers had a range of opinions on the recommendation that the TEFs may be applied to other exposure routes (i.e., dermal or inhalation) as an interim estimate. Some felt that application of the current TEFs to non-dietary exposure routes is not scientifically supportable at the present time. Application to the inhalation route may be justified, but again, there is no scientific evidence supporting this application. Others felt that the recommendation was justified based on evidence of systemic responses after dermal exposure and the expected high bioavailability through inhalation.

The reviewers had various perspectives on alternative approaches to TEFs in dealing with mixtures of DLCs. Some reviewers thought that no other approach is ready for use, some reviewers that that some alternatives could be ready soon or were ready now for application. Several reviewers urged EPA to move forward with implementation of this TEF approach to improve consistency and transparency in risk assessment, management, and communication.

IV. GENERAL IMPRESSIONS

Peter L. deFur

The document is a good and accurate description of the TEF methodology, with background, and explanation of the concept. The technical description is correct, and the development of the TEF is explained well. EPA's conclusions that the TEF method should be used for all Ah mediated responses are sound and supported by a substantial body of evidence. The guidance is concise and to the point, as it should be.

As far as I know, the guidance documents are used by EPA and state agency staff in writing permits, implementing regulations, conducting risk assessments and carrying out cleanup plans. I am not sure that all of the intended users of this document will be sufficiently familiar with all the technicalities of TEFs to be able to pick this document up and use it. I think otherwise, based on my experience with state and local efforts and programs. To correct this problem, I think some text should be added to the current document that gives a bit more context of the TEFs. The reader also needs to be directed to specific references for more information on aspects of the TEF concept and application.

The document does discuss uncertainty, but does not really provide much in the way of direction on how to perform an uncertainty analysis for a TEF approach. The issue here is that the writers and reviewers are familiar with both qualitative and quantitative uncertainty analysis. It is not clear to me what the target is for any uncertainty discussion in this guidance.

As far as risk characterization, the guidance could be more clear and direct in expressing the high degree of certainty (low uncertainty) over the TEF approach. In addition, characterizing risk requires expressing not only the probability, nature and magnitude of harm, but also the quality of information at each step. The TEF approach has high quality information at multiple levels of biological organization.

Moiz Mumtaz

I am a toxicologist interested in mixtures risk assessment methods development. Thus, my comments will bring this perspective that is based on my experience as a mixtures risk assessor. The guidelines for risk assessment of chemical mixtures (EPA, 2000; ATSDR, 2004) recommend three alternative methods viz., whole mixture, similar mixture method, and component based approach. Very few whole mixtures have been tested. For risk assessment of mixtures of environmental chemicals, the most often used method is the component based approach because data are often available on individual chemicals as required by various environmental laws passed by the U.S. congress. Component-based approaches, involving an analysis of the toxicity of components of the mixture, are recommended when appropriate toxicity data on a complex mixture of concern, or on a "sufficiently similar" mixture, are unavailable. The approach proposed in this document focuses on this approach.

TEFs have been proposed and used in risk assessment of chemical mixtures for about two decades. This is a brief document that is technically sound and it very concisely but accurately

explains the TEF methodology to derive individual chemical TEF values. The EPA has used similar methodologies for polycyclic aromatic hydrocarbons (PAHs) and other such chemicals that occur in mixtures for a long time. In this document it is formally recommending the adoption of the 2005 consensus TEF values of the World Health Organization (WHO).

There are several areas of the document that are written very well and can be easily followed with people with a good background or experience in this area of toxicology. The EPA had deliberately tried to be concise so that it can be used by field workers however, some additional text might benefit novices.

A quick look at the table of contents shows that all technical aspects of the TEF approach are included in the document even though some are in brief.

Thomas B. Starr

The draft is generally well-written and straightforward. I enjoyed its brevity. In a few places, the narrative is a bit overreaching in terms of its characterization of the extent to which dose additivity has been, or ever will be, confirmed for DLCs. I called this “wishful thinking” on EPA’s part. I think it’s also overreaching for EPA to want to use TEFs developed primarily with data from oral feeding studies to assess risks from dermal and inhalation exposures, especially since Van den Berg et al. (2006) have recommended against doing this for a number of very good reasons. Overall, though, the draft is reasonably well-balanced and it does note a number of important limitations of the TEF approach, even when it is implemented with the updated TEFs.

I was quite disappointed with EPA’s proposed approach to dealing with uncertainty/variability, but, at least in my view, the authoritative bodies that have developed the TEF values have also missed the boat on this. They just don’t seem to understand that the uncertainty/variability of individual RePs needs to be characterized adequately before the uncertainty/variability of any linear combination of RePs, such as a TEF, can be characterized adequately. Sadly, this aspect of the problem has been ignored by just about everyone.

TEFs remind me of an amusing story. I trained academically at the University of Wisconsin-Madison as a theoretical nuclear physicist, and we physicists, especially the theoretical ones, had a tendency to look down our erudite noses at engineers, who saw fit to get their hands dirty in the real macroscopic world. We had a saying about them: engineers work really hard at finding the best way to do things that probably shouldn’t be done at all. That’s pretty much the way I feel about TEFs. The feeling originates in my deep conviction that a concept as clean and simple as dose additivity, that ignores the realities of competitive antagonism, partial agonism, and the profound differences in efficacy of the various AhR ligands for inducing such a wide spectrum of toxic endpoints, cannot possibly, by any stretch of the imagination, be true. So why should we base a process as important and critical as risk assessment on a false foundation? I don’t have a good answer to that question.

Martin van den Berg

See comments below.

Nigel J. Walker

In essence the guidance this document provides is:

1. EPA recommends to use the WHO-2005 TEFs
2. Calculate a single value TEQ for your matrix
3. Apply it to oral, pulmonary and dermal routes and note how much comes from each,
4. For abiotic matrices consider bioavailability fate and transport
5. Note how much TEQ is due to TCDD, PCB126, 23478PeCDF , 12378PCDD and 123678HxCDD
6. Consider a sensitivity analysis.

Given the topic, this is a short document that succinctly describes the derivation of the WHO TEFs and justifies their use for the cumulative risk assessment for dioxin-like compounds. While this reviewer is in support of the EPA's recommendation to use the WHO TEFs and the TEF scheme in general, given that it is meant to be "guidance" and read as a "stand-alone" document, I felt it was too short and did not provide sufficient specific guidance for a lot of the recommendations and especially on issues regarding uncertainties in the TEF scheme and its use, that risk managers may need. I fear that many folks may be left scratching their heads about exactly what to do beyond simply calculating a TEQ, and that subsequent analyses and risk management decisions may vary considerably in how different issues are approached.

In addition, supporting information is not readily available or presented. It repeatedly references the 2003 draft assessment (which EPA note should not be quoted or cited) and publications that may be inaccessible to many readers.

The description of the Haws and Van den Berg papers I found to be somewhat superficial and did not fully capture much of the nuance of either the ReP database, or how it was used in the derivation of the TEFs.

In addition I found it confusing whether this document was trying to provide guidance on which TEFs to use, how to calculate a TEQ using the TEFs, or application of the TEQ in calculating risks and ranges of risks, interpretation/communication of the TEQ based risks and its uncertainty in the context of an overall site-specific risk assessment.

This reviewer had to get clarification that this is meant to be a stand alone document and not either as a replacement or addendum to chapter 9 of EPA's draft dioxin health assessment. As such this could lead to confusion.

Also if this is meant to be read as a stand alone document, it requires significantly more detail to provide the scientific basis for many of the assumptions used in the TEF scheme (that are already in chapter 9 but need updating in several areas).

The issue of uncertainty and how it should be handled is generally confusing as it seems to be only addressed by assessing the sensitivity. I.e. how much of the TEQ is due to lung/dermal vs. oral. This is not an uncertainty analyses to my mind. The WHO panel recognized that there is uncertainty around the TEF value but no guidance on this provided in this document in any way. The NAS review also noted that the uncertainty needs to be addressed.

V. RESPONSE TO CHARGE QUESTIONS

History and Background

Question 1: Please comment on whether the TEF methodology is accurately explained and referenced in the document.

Peter L. deFur

The explanation of the TEF approach in this guidance document is explained perfectly and referenced adequately. I do think the referencing would be improved by directing readers who need more information to specific references for specific purposes. To some extent, the guidance is written for readers who are more expert than novice and I think additional information for non-experts in dioxin will enhance the use of the guidance.

Moiz Mumtaz

Criteria for using TEF approach include a well defined group of chemicals, a good database, and consistency across endpoints, with a well understood common mechanism or mode of action of toxicity. However, all of these criteria cannot be always met. Even if we could collect enough information to derive TEFs for each of these chemicals (or congeners) the final behavior of all congeners in a particular mixture cannot be certainly predicted. Given this general understanding, the approach has been summarized well and previously published studies have been included for further reading.

My understanding is that the recommendations in these documents are used by EPA's technical staff to conduct preliminary risk assessments of mixtures of chemicals and to provide guidance to representatives of risk assessment community who seek EPA's help.

I believe approaches such as TEFs are needed to advance mixtures risk assessment methodologies because whole mixtures data are rarely available. Thus, often the risk assessors have no other option but to use single chemical data and this is done employing potency weighted dose or response addition. The biggest hurdle to this approach is the potential for interaction among chemical components of a mixture. But there is ample documentation in the literature that shows interactions occur at high doses, and do not play a significant role at environmental levels.

Thomas B. Starr

The description of TEF methodology is generally accurate, well-written, and easy to follow. There are some statements that, at least in my view, are not accurate. On p. 1, lines 8-9, a sentence starts: "Because the combined effects of these compounds have been found to be dose additive, ..." I see this as "wishful thinking" on EPA's part. Toyoshiba et al. (2004) found numerous statistically significant departures from additivity for CYP1A1 and CYP1A2 activity in rats exposed to a mixture of three DLCs in a very well-designed, well-conducted study. There are numerous other demonstrations of synergy and antagonism of DLCs in combination in the

literature. A number of these are cited in Van den Berg et al. (2006). It must also be kept in mind that studies that have failed to find significant departures from additivity may have been very weak, i.e., they may have had little statistical power to detect such departures even if they were present. Remember that an absence of evidence is not evidence of absence.

In 2005, EPA more appropriately characterized additivity as an *assumption*, one of many that underlie the TEF methodology. In truth, how could one ever prove additivity? Any scientific test has limited sensitivity (power), so the possibility always exists that non-additivity occurs but goes undetected. This is exactly same problem that threshold proponents face when they attempt to prove the existence of thresholds.

On p. 2, lines 7-9, a sentence states: “Under dose addition, the toxicokinetics and toxicodynamics of all components are assumed to be similar and the dose-response curves of the components of a mixture are assumed to be similarly shaped.” The word *similar* has been overused in this context (TEFs) and is much too vague. The assumption of dose addition implies *identical* toxicokinetics and toxicodynamics and *identical* dose-response curves, after normalization of the doses by constant, compound-specific dose-scaling factors, i.e., the TEFs.

Martin van den Berg

In general, the document provides an adequate reflection of the procedures followed by the World Health Organization to derive consensus TEFs for humans and wild life. I appreciate the effort put in by the EPA to describe this process and suggest to accept the WHO TEF values. Accepting this methodology and associated TEF values is of global importance with respect to the risk assessment of these compounds for humans and wildlife. Most of the remarks made in the document indeed reflect the development and limitations of the TEF/TEQ methodology. However, a number points in the document could be either more clear or provide more background info. In providing this, it will avoid unnecessary criticism from both industry as well as NGOs. A number of points that could be discussed or provided in more detail will be outlined below and in the follow up questions asked to this reviewer. General comments regarding the EPA TEF document:

a) In the introduction/background a short information could be given regarding the milestones achieved during the different WHO TEF evaluations. Chronologically these are:

Ahlborg 1994 – first global consensus TEFs, inclusion of PCBs including di-ortho congeners;

van den Berg 1998 – use of database compiled by the Karolinska Institute, deletion of di-ortho PCBs from the concept, recognition that TEFs for fish and birds need to be differentiated from humans, and importance of in vivo above in vitro results;

van den Berg 2006 –Extensive use of Haws (2006) database, incorporation of NTP results, stakeholders meeting at the beginning of evaluation, identification of significant shortcomings of the present TEF system and potential other compounds for inclusion

b) Page 7 lines 24-2. Note that the 75th percentile was used a general cut off point to decide whether or not a TEF value had to be re-evaluated (See Van den Berg et al 2006). After this, expert judgment was used with priorities as mentioned in the EPA document.

c) Page 9 line 6 -9. I think that the critical remarks made in the last TEF evaluation in 2005 regarding the use of TEF values for abiotic matrices like sediment and soil are not sufficiently

covered in the EPA document. This especially has consequences for contaminated soils and sediments in which no direct ingestion takes place. In reality there is no scientific rationale for using the TEF system for these situations, except for scaling different environment matrices without a toxicological significance but for prioritization for remedial actions. Direct oral ingestion of particles can be included in the TEF system, although bioavailability will play a significant downplaying role in the overall mixture toxicity (TEQs). I agree that for inhalation this system can also be used (e.g. combustion particles) as an interim approach. Dermal uptake from particles under dry conditions is to my opinion a marginal exposure pathway. It should not be considered using e.g. 100% bioavailability for the human skin and can represent a gross overestimation of systemic exposure and associated risk.

d) Page 13 lines 17-19. I think that AT LEAST these five compounds should be known. In addition, such a priority approach might not work from a risk assessment approach, if it concerns an accidental (food) poisoning from a specific source (food process) or for populations living around an environmental hotspot.

e) Page 13 lines 21-21 and next page. I sincerely question the validity of the statement about using TCDD only here. Sufficient information regarding dose response relationships of 23478-PeCDF and PCB 126 is also known from many studies. Especially the recent NTP studies provide excellent reference material for this, including both neoplastic as well as non neoplastic effects.

Nigel J. Walker

The basic TEF methodology is adequately described though wording could be improved.

It should be noted that not all assays for which RePs are developed are “toxic responses.” In addition it should be noted that PCB126 was often used as an index chemical, under the assumption that it has a TEF of 0.1.

Question 2: Is the history of the mammalian TEFs and the process used to develop them by the World Health Organization accurately described and in sufficient detail? Are the WHO (2005) mammalian TEF values and their derivation accurately reported?

Peter L. deFur

The information that is in the guidance is perfectly accurate and clear regarding the mammalian TEFs and the WHO process and experience. This topic is one that I would recommend a bit more text, perhaps ½ - 1 page more. The authors and reviewers are more than familiar with all the details of the TCDD TEF concept, but I think more context is needed for non-toxicologists and those who are not steeped in dioxin and the TEF concept. The scientific community began developing the conceptual and practical basis for the TEF concept for some years before the first WHO list of TEFs was developed and published. This history is important and should be included to demonstrate the strong scientific foundation and long history of the TEF approach. WHO did not just create the TEF approach all of a sudden. There are still detractors from the TEF concept, despite the scientific consensus and international support.

The document should point the reader to specific references for more information. These references can include the EPA Dioxin Reassessment, the two volumes edited by Arnold Schecter (*Dioxins and Health*), and several papers in the peer-reviewed literature that include mode and mechanism of action.

I also recommend referring the reader to the literature on non-mammalian TEFs for two reasons. First, the application of TEFs to birds and fish provides further evidentiary support for the TEF method. Second, many TEF applications involve non-mammalian vertebrates in addition to mammals.

Moiz Mumtaz

Yes. Briefly but concisely the history has been captured in essence for mammalian TEFs derivation. Enough details are given for those who are familiar with such approaches. How much more can or should be added depends on its intended use. If a lot more information is added this will not remain a quick reference for teams of toxicologists, risk assessors and managers but will become another federal agency document.

Hopefully, this will be part of the overall dioxin risk assessment document that EPA has undertaken to complete by this year, December 2009 and this will be in perspective. EPA and the risk assessors need this methodology to meet its mandate otherwise by default, lack of data, so many mixtures cannot be evaluated without such methodologies. From a public health perspective, we need a practical method that can be used in the field to perform mixtures risk assessment and to present the findings in community and public health meetings.

Thomas B. Starr

The description of the history and process by which the group of WHO-sponsored experts developed the mammalian TEFs is accurate and about as detailed as it is possible to be. After all, the TEF final values were determined behind closed doors by a select panel of experts, including representatives from EPA. It would be useful and perhaps less self-serving to note in this document that there is not unanimous agreement among all scientists that the TEFs approach (and the process by which TEF values have been established) is an appropriate and scientifically validated way to assess potential health risks from exposures to mixtures. There is a “loyal opposition” who has called for more openness and transparency, objectivity, and sensitivity and attention to limitations, and it is noteworthy that they are not all dependent upon financial support from the various interested parties.

Martin van den Berg

Answers to this question are given already under 1.

Nigel J. Walker

As a stand alone document this document does not fully describe the history of how we came to this point in the development of TEFs. Chapter 9 of the dioxin health assessment document is much more comprehensive and some of the background from that document ought to be included. Moreover it has a fuller description of the database used for the 1998 TEFs and as such provides better context of why there was a need for Haws et al to generate a new database. The current document focuses mainly on the recent 2005 reevaluation by WHO.

Risk Characterization

Question 3: Is the development of the Relative Potency (REP) database presented in Haws et al. (2006) accurately described and in sufficient detail? If not, please provide recommendations for enhancing this description.

Peter L. deFur

The REP database development is well described and covered in the guidance, but somehow the publication by Haws et al. (2006) needs to be more closely associated. I retrieved Haws et al. (2006) when the latest WHO TEFs were published, and find the Haws et al. (2006) publication to be invaluable in effectively dealing with all the issues that arise over TEFs. There is really no way to incorporate Haws et al. (2006) into the Guidance.

Moiz Mumtaz

Yes, the relative potency factor (RPF) approach has been well described in this document by technical staff. Also, please see the comments to question 2.

TEF and RPF values have been proposed for a few of the thousands of chemicals in commerce that have been studied fairly well. For a vast majority of chemicals there are very limited data and no time or financial resources available for traditional testing. Hence, recently both alternative in vitro testing methods and computational toxicology methods are being employed. The NAS has recommended more drastic changes to toxicity testing in the 21st century. As risk assessors and toxicologists, we have to move forward with the development of guidance of using these methods (TEF, RPF) that have been proposed and used for specific scenarios for about two decades.

Several uncertainty factors are employed in the risk assessment and risk characterization process that the estimates are kept with a window referred to as “order of magnitude.” Within this document it could be clarified that RPFs can be used for initial screening of mixtures for the purpose of prioritization. Eventually a more thoughtful consensus approach that engages the interested parties (the polluter, the concerned public, the regulators and the public health officials) right from the initial scoping process can help resolve such problems.

Thomas B. Starr

I have a recommendation relating to gaining access to the underlying data. The Haws et al. (2006) publication has two data file supplements that are available in pdf format, which is an awkward format for most people to work with beyond simple viewing and printing. I think it would be extremely useful to create Excel spreadsheets of the data in these files and make them available to all interested parties via download from the EPA website.

Martin van den Berg

Yes. However, I miss a more thoughtful point of view by the EPA about e.g. using the distribution range for setting TEF values. From a risk management and political point of view different arguments could be given for using e.g. a specific percentile. The major drawback of this approach is that different countries maybe going to use different cut off points and the consensus aspect of the present WHO TEF approach is lost. In addition, such an approach might also cause economical problems as the estimated toxicity in TEQs like with food products could then vary between countries with associated import and export problems.

Nigel J. Walker

This document provides a relatively short summary of the Haws et al paper but omits lots of detail and nuance and does not bring forward from that paper many of the distribution information that is critical to understanding the ReP variability that underlies the uncertainty in the TEF derivation. Given that some readers may not have ready access to the journal article.

This document consistently refers to “exclusion criteria” which is not quite correct. Criteria on what type of info was needed were established, and then each ReP evaluated vs. those criteria. Also it is important to note that this was for the ReP distributions only. During the WHO deliberations, all ReP data was available (even that that did not meet the criteria) for use by the WHO expert panel.

Description of the process used by WHO panel for the TEFs is also not well described. There is much more detail in the Van den Berg paper that is not fully captured in the document, especially use of the 75%ile as key point on the distributions. This is important since REPs were evaluated relative to the ReP distributions and chosen to be on the conservative side vs. a central tendency. This is noted in the Van den Berg paper. In addition it would not be apparent that prior to the WHO meeting was an open public meeting that had presentations on issues for the expert panel, including new data on human specific in vitro RePs.

The issue that the TEF is an “order of magnitude” estimate is not fully discussed either. This is a key point that has been lost in the whole TEF discussion and should be part any uncertainty analysis. Essentially it means that if this order of magnitude of uncertainty were applied to each DLC, in a mixture that has no TCDD, the TEQ could vary +/- half log. The uncertainty associated with the output from TCDD dose response functions is well appreciated, it is probably less well appreciated, and not articulated in this document that this means that the input dose (based on the TEQ) should be considered as range and not a single value

Also it should be noted that while not weighted, in vivo and in vitro RePs were handled differently and distributions were separately presented in the Haws et al paper

A major omission is any guidance about TEFs for mono-ortho PCBs and use of TEQs derived from them. These were a major discussion point in the Van den Berg paper especially concerning possible contaminants, the high uncertainty of the TEFs, the wide range of the ReP distributions. Moreover since these have “mixed” activity there are possible effects that may not be AhR dependent.

In addition there is no guidance issue of interactions of non-dioxin like PCBs and dioxin-like PCBs. Chapter 9 from the dioxin reassessment discusses this in detail. While this has no impact on the TEF for a DLC (since a TEF is derived based on studies of individual congeners) some guidance on the interpretation of what the TEQ is for a mixture that contains both DLCs and interacting compounds for which there is known co-exposure, needs to be included.

As an alternative EPA simply needs to state that it is making certain assumptions in the application of the TEF method to mixtures that cannot be fully addressed due to incomplete scientific knowledge. Eg A policy decision that while interactions have been observed, application of the TEF method and interpretation of the TEQ based risk calculation assumes that there are no interactions with non-DLCs, either positive or negative.

Question 4: Is the uncertainty analysis approach described by EPA reasonable?

Peter L. deFur

This question asks about the “uncertainty analysis approach” which would seem to be the paragraphs on page 14. The guidance presents a reasonable perspective on uncertainty analysis, but not ideal. The text does not present a roadmap of how to consider or evaluate uncertainty for the reader who is faced with data from an effluent or a contaminate site. The document would be improved if a subsection were labeled “Uncertainty Analysis” and expand some (1 page) on the present text. The guidance also needs to make a clear written distinction between uncertainty and sensitivity analysis. The uncertainty approach that seems to be presented is to list the individual congeners/compounds (DLCs), identify the major contributors to total toxicity, and repeat much of the same material that is contained in Haws et al. (2006). I do not read a step by step sequence that should/might be conducted in an uncertainty analysis, and the guidance would be greatly improved with such text.

Uncertainty analysis also needs to address the underestimate of toxicity if the possible DLCs listed in the Guidance are not included and these compounds do, in fact, add to the total toxicity.

Moiz Mumtaz

As a toxicologist I see the need for a practical method for use in the field. The values derived have to be conceptually understood and derived based on good data to be used by risk assessors and practitioners.

The uncertainty analysis and the recommended approach lack clarity for the casual reader. This section should include a good discussion regarding uncertainties related to selection of chemicals in this approach, dose response of individual chemicals, derivation of recommended values, use of animal data to predict human cancer, assumption of common mode of action, and dose additivity for mixtures risk assessment.

Thomas B. Starr

No, it is not. When measurements are compared or contrasted in science, the uncertainty/variability of those measurements is an essential component of the evaluation. A proper uncertainty analysis requires that the uncertainty/variability inherent in the individual RePs which underlie each TEF be identified explicitly. At a minimum, every ReP should have a standard error of estimate or an associated 95% confidence interval. Without such information, it is impossible to test rigorously whether two or more RePs are significantly different from one another.

It is astonishing to me that none of the authoritative bodies who have developed the various sets of TEFs has explicitly considered this uncertainty/variability in their development processes. I can't find a single ReP standard error (or 95% confidence interval) in Haws et al. (2006), van den Berg et al. (1998), or Ahlborg et al. (1993), and I don't understand why this is so. Apparently, these authoritative bodies just don't get it (not that I and others haven't told them!). The individual RePs have instead been treated as if they have no inherent uncertainty/variability at all.

How then can one judge whether a difference between RePs, whether it's $\pm 10\%$ or 100-fold, is too large to be consistent with the underlying null hypothesis that they come from a common distribution whose mean is the true relative potency that a TEF is supposed to reflect? One cannot, so the experts have simply assumed that they do. Are we to just blindly trust that they have somehow got it right in spite of this complete neglect of a critical component of the scientific method? I think not.

There are many reasons to suspect a priori that RePs would be qualitatively different from one another: different endpoints, different species, different strains, different doses, different investigators, different experimental protocols, and different data analysis methods. These are just some of the sources of potential heterogeneity among RePs that need to be assessed objectively, quantitatively, and reproducibly, before RePs can be combined legitimately somehow into a TEF. The numerous pitfalls of meta-analytic evaluations of multiple data sets are very well-known outside of toxicology. Scientists tread very, very carefully even when conducting meta-analyses of well-controlled, randomized clinical trials. Careful attention must be paid to these pitfalls, and so far, this has not been done. If it isn't done before TEFs are incorporated into regulatory decisions that end up costing interested parties lots of money, I foresee a very profitable open-season on those regulatory decisions for defense litigators.

Martin van den Berg

Yes, but see comments under 3.

Nigel J. Walker

There is a need for better clarity and guidance in the document since it is not clear what uncertainty analysis approach is being recommended. A sensitivity analysis is recommended to see how much of the TEQ is driven by route and by the “Big Five” congeners.

Uncertainty could be inferred to refer in some cases to the “variability” in the original ReP calculation, the variance in the distribution of the RePs, uncertainty in the assigned TEF value, the uncertainty in resulting TEQ, uncertainty about relative contribution of route to the TEQ, uncertainty about proportion of some congeners to the TEQ, or uncertainty in the ultimate risk estimates.

As noted above better guidance on the application of the uncertainty is also needed- e.g. if the TEFs have uncertainty of +/- half log then is EPA giving guidance that risk assessors should use the TEF +/- half log in calculating the TEQ?

E.g. upper bound of [TEQ] = [TCDD] + Sum([DLC_i]*TEF_i* 3.162)

Lower bound of [TEQ]= [TCDD] + Sum([DLC_i]*TEF_i/3.162)

This is implied but not stated.

Also the uncertainty associated with different classes of DLCs is not addressed at all yet was of clear concern in the Van den Berg paper. EPA gives guidance to note how much TEQ is from the “top Five” but not how much TEQ is driven by mono-ortho-PCBs which have a very wide ReP range.

Question 5: Are there alternative ways to approach uncertainty analysis for the TEFs that you could recommend?

Peter L. deFur

One could calculate a range of values, using TEFs from Haws et al. (2006), in a bounding exercise. That said, uncertainty should not use a range of TEF values in a probabilistic analysis that applies a distribution to the TEFs. Haws et al. (2006) give ranges for the TEFs developed by WHO, but these ranges are not distributions. These ranges should be the basis for any range of TEF values used in a quantitative uncertainty analysis.

Haws et al. (2006), EPA (Dioxin Reassessment) and Schecter (Dioxins and Health) present some of the factors that affect the cascade of events in the Ah receptor mediated mode of action. A comprehensive uncertainty analysis could discuss/present all that is known of these modifying factors for the specific site or application. This step is merely a more detailed version of what is presented in the guidance document.

Moiz Mumtaz

Hopefully, other reviewers on the panel will add their insights on this issue.

Thomas B. Starr

To do this right, the absence of significant heterogeneity must first be evaluated and confirmed by objective statistical testing. I suspect that a lot of RePs will fall by the wayside from just this one testing step. Furthermore, the power of the test(s) chosen for this purpose must also be characterized explicitly. Only then is it appropriate to consider combining those RePs that are determined not to be inhomogeneous to generate a TEF estimate. Only then is it possible to quantitatively assess the uncertainty/variability inherent in the resulting TEF estimate. A TEF is just a weighted average of the associated RePs. Right now, however, the weights that the experts used in constructing the TEFs are unknown, subjective, and irreproducible. More complex probabilistic risk assessment approaches with great promise, such as those alluded to in Haws et al. (2006), are nevertheless hamstrung at the outset by these serious limitations. This will not change until a bottom-up approach is taken to constructing TEFs in which the uncertainty/variability of individual RePs is characterized explicitly and then propagated through whatever explicit and objective weighting schemes (one simple example is inverse variance weighting) are used in constructing TEFs.

Martin van den Berg

With the present state of the art, No.

Nigel J. Walker

There are several alternatives that have been proposed but these were not discussed. Use of weighted distributions were discussed in the Haws et al and Van den Berg papers but were rejected for the TEF derivation, but nonetheless could be explored. Alternatively classifying based on database strength could be considered. The Haws et al. paper lays out a lot of detail about the distributions, number of endpoints, ranges classified by endpoint etc. These could be used in a non quantitative way as a sensitivity analysis to see how much of the TEQ contributions are from congeners that have a weak dataset. EPA could also choose to give some classes of congeners a different level of uncertainty-e.g. the mono-orthos PCBs could be given a 2 orders of magnitude range of uncertainty- which would be supported by the note in the Van den Berg paper that the ReP range spans 4 orders of magnitude. Alternatively EPA could choose to classify TEQ by high (0.1 and above), med (0.001-<0.01 and low potency (<0.001) TEFs, such that TEQ contributions from weak congeners can be evaluated.

EPA Recommendations

Question 6. Please comment on the recommendation that these TEFs should be used for all cancer and non-cancer effects that are mediated through AHR binding by the DLCs.

Peter L. deFur

The EPA is correct that the WHO TEFs should be used in assessing or estimating the effects of DLCs for cancer and non-cancer endpoints. The TEF approach is also valid for non-mammalian vertebrate systems, as described in the WHO recommendations (Van den Berg, 2006). The

scientific literature supports the use of TEFs, based on experimental and ecological results at multiple levels of organization.

Moiz Mumtaz

EPA is correct in making these recommendations for those health effects that are mediated through AhR binding. However, some noncancer effects such as developmental effects are a major public health concern. For developmental toxicity, the window of exposure is small, well defined and there is no latency period associated as is with cancer. EPA should add caveats and provide insights in the guidance for specific conditions.

Thomas B. Starr

I'm not sure I understand this recommendation. The phrase "all cancer" is confusing. Does it mean any specific cancer, e.g., hepatocellular carcinoma or squamous cell carcinoma of the lung? Or does it mean any and all forms of cancer, as would be included in an estimate of "all cancer" mortality, i.e., death from any of all specific cancers?

In either case, I have difficulty with the recommendation. For example, mammary cancer was significantly reduced by TCDD exposure in the original Kociba et al. (1978) study. Would the TEFs methodology be used to predict corresponding reductions in human or other mammalian mammary cancer from exposure to the other DLCs? Or would the liver cancer excess seen in the recent NTP study be used to predict an increase in human all cancer mortality, including mortality from breast cancer? This makes little sense to me. It is worth noting that, at least to my knowledge, no specific form of cancer has yet been linked causally to human DLC exposures, and IARC raised this fact as a cautionary point in its 1997 monograph. IARC also characterized the polychlorinated dibenzo-*para*-dioxins other than TCDD as "not classifiable as to their carcinogenicity to humans (Group 3)". In any event, I would want the separate risk contributions of TCDD, other dioxins and furans, and the PCBs to estimated overall cancer risks split out and identified explicitly in any risk assessment that made use of TEFs.

Martin van den Berg

I agree with this approach (but not with linear risk assessment approach by itself for carcinogenicity of these compounds)

Nigel J. Walker

EPA needs to more explicitly state the assumptions it accepts when using the TEF scheme, which ones are science based and which ones are "best interim judgment and policy" based. A lot of these are in the original chapter 9 but missing here.

Question 7. Please comment on the recommendation that the TEFs are most appropriate for exposures to dioxin-like compounds via the oral exposure route.

Peter L. deFur

I agree that the oral (water and food) exposure is most appropriate because that exposure route is where the most data are. The dermal and inhalation will most likely affect absorption and not the steps subsequent to internalization of a DLC.

Moiz Mumtaz

Agree with EPA since most often the exposure is by oral routes, at least at hazardous waste sites. The database for this route of exposure is quite extensive. At the present time this is the best available method that can be employed for such a group of chemicals.

Thomas B. Starr

I agree with this statement. Van den Berg et al. (2006) provide a number of good reasons for this limitation on the risk extrapolations that should be made with the current TEFs.

Martin van den Berg

This issue has been addressed under 1.

Nigel J. Walker

Justified given that most of the studies used for deriving RePs are based on in vivo studies oral routes

Question 8: Please comment on the recommendation that the TEFs may be applied to other exposure routes (i.e., dermal or inhalation) as an interim estimate.

Peter L. deFur

This recommendation is warranted, based on the available data for experimental and ecological results for mammals. The dermal and inhalation routes of exposure do pose somewhat different conditions and some of these differences can be taken into account in a site specific assessment. The principle issue would be differences in absorption between oral, dermal and inhalation. But the basic toxicity level of a specific DLC should be unaffected by route of exposure once the DLC is in the body.

Moiz Mumtaz

Bioavailability and absorption are key issues that should be mentioned in the guidance if TEFs are being recommended for other routes of exposure. Aging in the environment changes the bioavailability of some of these chemicals and could be a source of uncertainty in their absorption.

Thomas B. Starr

Van den Berg et al. (2006) cite concerns regarding differential bioavailability and the very limited (“almost nonexistent”) data that is available from studies using environmental matrices contaminated with DLCs. They cautioned against the extrapolation of risk estimates, obtained using the current TEFs which are largely based on results from dietary intake studies, to non-dietary exposure routes. I agree wholeheartedly with their concerns. In my opinion, application of the current TEFs to non-dietary exposure routes is not scientifically supportable at the present time.

Martin van den Berg

This issue has been addressed under 1.

Nigel J. Walker

Justified based on clear evidence of systemic responses after dermal exposure. Justified for pulmonary given expected high bioavailability from this route. Need to note very limited (if any?) data on clear pulmonary routes studies.

Question 9: Please comment on the recommendation that, if considered in an assessment, the fractional contribution of dermal and inhalation route exposures to the predicted toxicity equivalence (TEQ) should be identified as part of the risk characterization.

Peter L. deFur

The risk characterization should specifically address the oral and inhalation route of exposure contributions, as well as a range of other factors. EPA and NRC have an abundance of guidance on risk characterization, and there is no doubt that a complete risk characterization would include specific discussion of the dermal and inhalation route contributions.

Moiz Mumtaz

The more explicit the risk characterization the more confidence in the overall risk assessment, so it is a good idea where possible to apportion route specific contributions.

Thomas B. Starr

If this is to be done, and I recommend strongly against doing it, I would want to see the separate contributions from the different exposure routes split out explicitly. Also, as I mentioned in my response to question 6, the separate contributions to risk from TCDD, other dioxins and furans, and the dioxin-like PCBs should be split out and provided for each exposure route. Furthermore, the limitations and cautions noted by Van den Berg et al. (2006) against using what is essentially dietary exposure TEFs to do this should be stated explicitly.

Martin van den Berg

This approach I can agree with, although the quantitative relevance is most likely very limited. From what we know from exposure analyses (where most of the dioxin money went to during the last decades) oral exposure via food is by far the most important source. In specific situations exposure other than via food might play some role. This could for example occur in children playing on contaminated soil (oral and dermal) and inhalation (malfunctioning municipal/chemical incinerator) by the neighboring population.

Nigel J. Walker

Good idea -but also need to better to characterize contributions by classes of materials. This does not substitute for uncertainty analyses.

Question 10: Is there a currently available approach for calculating the cumulative exposures to DLCs that is more appropriate than the WHO TEF methodology being proposed by EPA?

Peter L. deFur

No, not that has been scientifically supported and documented.

Moiz Mumtaz

The use of the TEF approach using additivity as default is the most practical approach available for risk assessment of mixtures of these chemicals. Physiologically based pharmacokinetic (PBPK) modeling is a possibility but development of such models is data dependent and technically challenging to apply consistently in the field.

Thomas B. Starr

I suspect that estimated cancer risks will be the primary drivers in many site-specific risk assessments that involve DLCs. Usually, exposures at such sites are dominated by just a few DLCs, and these may turn out to be DLCs for which valid cancer bioassays have been conducted. 2,3,4,7,8-PeCDF is one specific example. In such cases, it makes little sense to me to “degrade” a DLC-specific cancer potency estimate that is derived from directly relevant carcinogenicity data by substituting the corresponding TEF for that cancer potency. I

recommend instead that EPA consider allowing (in fact, encouraging) the use of RePs obtained from more recent, high quality endpoint-specific data in place of TEFs in risk computations on a case by case basis.

Martin van den Berg

No. Theoretically, a methodology that includes a combination of congener specific exposure information, toxicokinetic tissue specific modeling and tissue specific biological/toxicological response analysis could do the job more accurately. In this case the additivity prerequisite has to be applied, but I think there is enough scientific evidence available for this as a default approach. However, in view of the relative large number of congeners involved, I question if there is sufficient scientific information regarding these aspects available.

Nigel J. Walker

Other possible approaches are almost totally ignored: They are in chapter 9 but not here. Simply in terms of clarity those that are “inappropriate” should still be stated, e.g. inappropriate methods: TCDD only, sum all without addressing different potencies.

Other methods that may have equivalent levels of uncertainty and have not been discussed or explored:

Use of DLC specific dose-response functions where available and use of TEF for those where a specific function is unavailable. E.g. for cancer risk, in vivo rodent cancer bioassay data now exist for 4 of the top 5 TEQ contributors (TCDD, PeCDF, PCB126, HxCDD and also PCB118) and slope factors could be developed for each of these and cumulative risk for these calculated. For the remaining congeners, the TEF/TEQ scheme and TCDD dose response could be used. This would reduce uncertainty for those congeners in a matrix. The TEQ based risk could also be calculated and applied to the dose response functions for TCDD and this would provide a measure of uncertainty.

One could group chemicals in classes and in some cases apply class specific TEF/TEQ- e.g. all mono ortho PCBs with a TEF of 0.00003 could be simply summed and then applied to use a PCB118 slope factor.

Group DLCs by their TEF potency and use dose response functions by “potency class” where available or use TCDD - express risk estimates by this type of class and uncertainty in the TEQ estimate relative to the classes.

Classify DLCs by database uncertainty relative to the number of endpoints- TEQ uncertainty

Use dose response functions where possible? Noted in chapter 9, but not addressed

VI. SPECIFIC OBSERVATIONS

Peter L. deFur

None.

Moiz Mumtaz

Comments will be submitted post meeting.

Thomas B. Starr

p 1, lines 8-9: The phrase starting with “Because” is too strong. See my comments on Charge Question 1.

p 2, lines 7-9: The word “similar” is much too vague. Dose addition implies identical kinetics, dynamics, and dose-response curves up to dose-scaling constants, namely, the TEFs. See my comments on Charge Question 1.

p 3, lines 8-10: I think I know what this sentence is getting at, but it is a clumsy construction. How does one compare “this sum” to “the dose-response function for TCDD”?

p 4, lines 7-8: “similarities between interspecies metabolism”? What is interspecies metabolism? Actually, the assumptions included essentially identical metabolism across species, because any material differences would throw off (contradict) the dose addition assumption across species.

p 4, lines 14-19: It would be useful to distinguish more clearly between “scientific consensus” and “consensus judgment of expert panels”. I see the former as far more inclusive, important, and difficult to achieve than the latter.

p 5, lines 20-21: I realize this is a quote from the NAS report, but why call it to the reader’s attention. I for one, am embarrassed by it. What the heck does “valid, at least in the context of risk assessment” mean? Is it like “good enough for government work”? You can’t prove additivity no matter how hard you try. See my comments on Charge Question 1.

p 6, lines 15-17: I find it ironic that on the few occasions where data were available that shed light on the uncertainty/variability of specific RePs, that information was purposefully excluded from the Haws et al. (2006) analysis. This is exactly the wrong thing to do! See my comments on Charge Questions 4 and 5.

p 7, lines 1-2, 9-10, 11-12, and 13: Same problem as immediately above. This information is precious, as it informs us about ReP-specific uncertainty/variability. Yet it was purposefully excluded. How tragic!

p 7, lines 20-21: There is nothing statistical about the distributions of the RePs for each DLC. They are simply cumulative frequency distributions. Replace “statistical” with “cumulative frequency”.

p 7, line 27 - p 8, lines 1-2: I think it would be clearer to say that the expert panel looked at all the included RePs and then decided on a TEF value by “expert judgment”. They just didn’t choose a consistent percentile, say the 50th percentile, of the cumulative frequency distributions of the included RePs. Too bad that the process they did use is not transparent, objective, or reproducible.

p 9, lines 14-15: First, the phrase “all cancer” needs clarification. Second, I disagree with this recommendation. See my comments on Charge Questions 6 and 10.

p 9, lines 15-18: I think EPA should already be working on endpoint-specific TEFs and/or separate TEFs for systemic toxicity and carcinogenicity endpoints. This is easy to get started. A good first step would involve stratifying the existing RePs data base by endpoint and seeing what’s there and what’s not. Then a research plan to get the needed data could be formulated.

p 13, lines 16-17: The phrase “ReP variability that appears to be small” is unclear. Is this meant to reflect differences in the ReP values for a single endpoint-single DLC, ReP differences across endpoints for a single DLC, ReP differences for a single endpoint across DLCs, or what? Perhaps the inclusion of a relevant figure from Haws et al. (2006) would be helpful in making this point more readily apparent to the reader.

p 14, lines 3-5: It would be useful to be more specific about what EPA has in mind when it uses the phrase “sensitivity analysis” here.

p 14, lines 9-11: The ReP ranges developed by Haws are deficient as a starting point for a sensitivity analysis. Without information on the uncertainty/variability of individual RePs, we have no natural scale on which to measure interReP differences. Determining standard errors and or 95% confidence intervals for individual RePs is the most appropriate starting point. See my comments on Charge Questions 4 and 5.

p 14, line 17: I would strike the word “more” from the phrase “more consistent”.

p 15, lines 1-2: Replace “Despite these challenges” with “Nevertheless”. Replace “recognizes” with “believes”.

p 16, lines 6-7: “new consensus processes” are mentioned. Are there specific plans? If so, how will they differ from previous consensus processes?

Additional Thoughts in Response to Public Comments

The TEFs that EPA has proposed to utilize for risk assessment purposes are all based on in vivo data collected in mammalian species. I originally thought this was a good idea, because previous versions of the TEFs relied heavily on in vitro data, particularly for enzyme induction, and these data are best viewed only as biomarkers for DLC exposure, and not as biomarkers for toxic responses. They are about as far removed from toxicity and carcinogenicity as it is possible to be.

However, I was very impressed with the very recent work that was presented by Dr. Jay Silkworth in the public comment period, which showed how markedly different human cells are from rodent cells in their in vitro gene array responses to some DLCs. This information should be included in the section on uncertainty because it suggests strongly that humans are not only much less, but also differently (in a qualitative way) responsive, than are rodents to DLCs. In fact, I would go so far as to say that such data, when available, should be employed in place of the TEFs, because they shed light on the very important and still unanswered question of why humans appear to be so refractory to DLC exposure in comparison to the hypersensitive rodent species.

Martin van den Berg

See comments above (especially under question 1)

Nigel J. Walker

A general comment is that the document notes TEF scheme should evolve as time goes on to incorporate new data. My question is does EPA envision a point of diminishing return? I.e. is there a point where the impact of new data will be negligible relative to the already known uncertainty, and what new data would be required to reduce uncertainty. It would be good if specific research needs that would address specific deficiencies were articulated. E.g. there is a lot of effort developing human in vitro RePs for some of the DLCs using primary human cells. Under the current scheme these in vitro RePs would be given less weight than rodent in vivo data.

Another concern is how the next “reevaluation” will happen, if at all. My concern is how and when and the process to do this. The desire to “reevaluate periodically” seems to be more of a pragmatic decision that is often driven by specific researchers in the field than it is an agency policy driven to ensure that schemes used are as up to date as can be. There has been much new data since 2005 with no clear idea of how that could impact the EPA TEFs unless WHO decided to do another reevaluation, which based on the 4-yr time cycle is already overdue. While it is unrealistic that at this time the TEF scheme can be “real-time” an outline for the future refinement of the scheme such that it can be responsive to new data would be a valuable addition.

Editorial:

Note- throughout you cannot cite the EPA draft assessment (that says do not quote or cite!) - cite primary literature.

Page v-

ED50 definition is incorrect- It is the 50% of the maximal response above background.

TEQ is Toxic equivalents not equivalence.

Page vii

Define “dioxin”

“Index chemical” needs better clarity- it is the one whose dose response function is used for the estimation of risk. Note PCB 126 was used as an index chemical for derivation of specific RePs

ReP-better definition needed: It’s an estimate of relative potency for a specific endpoint, not study. Multiple RePs can be obtained from a single study. Also what is a general toxic equivalency value? Are you referring to TEFs? TEFs are not an average- In some cases RePs are derived from an average of ratios of dose at different effect levels- see papers by Van Birgelen et al... Note ReP has a different definition in the Van den Berg paper.

TEFs are consensus estimates of potency relative to an index chemical- that are applied to different responses, some of which are “toxicity” endpoints

TEQ- Toxic equivalents is the sum of the products ...

Page 1 line 9-This is written as a factual statement – it is not – it is a scientific conclusion based on various levels of evidence- provide supporting references

Page 2 line 15- note PCB126 is also used as an index chemical for lots of PCB studies.

Page 2 line 21- not all endpoints are “toxicity” endpoints

Page 3- line 1- delete “toxicological”-

Page 3- by definition PCB126 is 0.1 really, since it is used to derive a TCDD ReP under the assumption that its REP is 0.1.

Page 3 line 8 and line 16; poorly written. The TEQ is used as the dose metric in the dose response function for TCDD. It is not “compared” to it.

Page 4 line 3- TEFs goes back to 1984- need better history here.

Page 4 line 12- replace considered vs. provided

Page 9- line7- not sure what this means?

Page 9 line 14- does this mean that it has to have been shown that the effect is mediated via the AhR?

APPENDICES

Appendix A. List of Observers

United States
Environmental Protection Agency

**External Peer Review of
*Recommended Toxicity Equivalency Factors (TEFs) for Human Health Risk
Assessments of Dioxin and Dioxin-Like Compounds***

**October 22, 2009
1:00 p.m.**

Observers

Todd Abel
American Chemistry Council

Steven S. Brown
The Dow Chemical Company

Robert Budinsky
The Dow Chemical Company

Patricia K. Casano
GE/Counsel, Government Affairs

Sandrine E. Deglin
Exponent

David Fairfield
National Grain and Feed Association

Kathryn Gallagher
U.S. EPA/RAF

Annette Guiseppi-Elie
DuPont Engineering

Mark Harris
ToxStrategies, Inc.

Timothy D. Hassett
Ashland Hercules Research Center

Belinda Hawkins
U.S. EPA/NCEA

Laurie Haws
ToxStrategies, Inc.

Robert Kaley
Consultant

Russell E. Keenan
AMEC Earth & Environmental, Inc.

Angus Macbeth
Sidley Austin LLP

Resha M. Putzrath
Navy and Marine Corps Public Health Center

Glenn Rice
U.S. EPA/NCEA

Seema Schappelle
U.S. EPA/RAF

Rosalind A. Schoof
Integral Consulting, Inc.

Jay B. Silkworth
GE Global Research Center

Dan Stralka
U.S. EPA/Region 9

Vickie Tatum
NCASI

Linda Teuschler
U.S. EPA/NCEA

Philip K. Turner
U.S. EPA Region 6

Randall Wentsel
U.S. EPA/ORD

Dwain Winters
U.S. EPA/OPPT

Appendix B. Agenda

United States
Environmental Protection Agency

External Peer Review of *Recommended Toxicity Equivalency Factors (TEFs) for Human Health Risk Assessments of Dioxin and Dioxin-Like Compounds*

Meeting Day and Time: The peer review teleconference will run from 1:00pm to about 3:30p.m. (EDT) on Thursday, October 22, 2009.

Call-In Instructions: To connect to the teleconference line, please dial: 1-877-558-5229.
The pass code is: 7037503000 #

Draft Agenda

THURSDAY, October 22, 2009

- | | |
|--------|---|
| 1:00pm | Welcome, Goals of Conference Call, and Reviewer Introductions
David Bottimore, Versar, Inc. |
| 1:10pm | Chair's Introduction and Review of Charge |
| 1:20pm | Welcome and Background on TEF Document
Kathryn Gallagher, Acting Executive Director, U.S. EPA Risk Assessment Forum |
| 1:30pm | Reviewer Roundtable (Overview Comments) |
| 1:40pm | Observer Comment Period |
| 2:00pm | Reviewer Discussion and Responses to Charge Questions |
| 3:25pm | Summary |
| 3:30pm | Adjourn |

Appendix C. Summary of Observer Comments

Four observers registered to speak during the observer comment period.

The first observer to speak was Dr. Jay Silkworth, a Senior Toxicologist at the GE Global Research Center. Dr. Silkworth stated that given the current state of science, TEFs should not be used to assess human health risks of dioxins and PCBs. There are multiple deficiencies with the TEF/TEQ approach, as outlined by Dr. Silkworth, including the lack of scientific consensus on a potency factor for TCDD. He also stated that EPA has also not acted on a recommendation from the NAS to do a quantitative dose assessment using non-linear methods. Further, he added that there are no validated analytical methods for determining the concentrations of mixtures of dioxin-like PCB congeners in soil, water, and other media that are required to implement the TEQ approach. He also noted that the TEF approach assumes that all species are equally sensitive, which is not true and can vary by as much as 100 fold. Finally, Dr. Silkworth commented that PCB risks have been assessed for more than 20 years at hazardous waste sites using EPA IRIS values for mixtures. If TEFs are finalized, EPA must explain when to use TEFs instead of the IRIS values in assessing the risk of PCB mixtures. Dr. Silkworth concluded that these issues have not been addressed in the draft guidance document or in the charge and must be addressed if TEFs are to have practical value.

The next speaker was Dr. Robert Budinsky, a toxicologist at Dow Chemical Company. Dr. Budinsky brought up several issues. First, clear guidance on utilizing probabilistic methods in the TEF document is needed. The 2005 WHO panel recommended more than just adopting the TEF values and a number of publications have addressed this issue. Second, problems exist in applying TEFs to sediment and soil, an important issue in clean-ups, especially for select furans. A range of TEFs should be used because of uncertainty, as well as site-specific data. Lastly, the possibility or option of eliminating TEF values should be considered especially when congener-specific cancer potency values have been derived. Dr. Budinsky concluded that EPA should include all of the 2005 WHO information in their guidance document. In addition, EPA needs to address the 2006 NAS recommendation to form a task force to address the use of TEFs in risk assessment.

The third observer to speak was Todd Abel of the Chlorine Chemical Division of the American Chemistry Council. Mr. Abel first questioned why some of the significant recommendations of the 2006 NAS panel were ignored by EPA, including the formation of a Task Force. The American Chemistry Council is concerned that EPA will merely adopt the 2005 WHO TEF values while deferring more important and critical scientific issues with respect to TEFs. He asked that the peer review panel consider the effort EPA put into their ecological TEF guidance finalized a year ago. With respect to the charge, a number of comments were made: (1) a detailed uncertainty approach was not presented in the proposed guidance; (2) probabilistic methods should be developed for TEFs; and (3) inhalation/dermal exposure pathways are insignificant and should be ignored. In closing, Mr. Abel encouraged EPA to address stakeholders comments in writing and make it part of the public record.

The final speaker was Patricia Casano, an attorney with GE Corporate Environmental Programs. She agreed with earlier comments of the peer reviewers and previous speakers that the TEF guidance document does not address all of the limitations and uncertainties of the TEFs themselves or use of the TEQ approach. In particular, she commented on various

recommendations made over the years by the SAB and NAS panels and concerns expressed by the authors of the WHO TEFs themselves. She stated that all of the recommendations from the reviewers and previous speakers are necessary if the draft guidance is to accurately explain the TEF methodology and fulfill the administration's commitment to transparency in science. She requested that the peer reviewers recommend to EPA to follow-up on all of the recommendations.