Comments Submitted and Presented by phone by Dr. Jay Silkworth,
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during the EPA LISTENING SESSION, Arlington, VA, for
EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments

July 9, 2010

Good Morning. My name is Jay Silkworth, and I am a toxicologist at the General Electric Company, Global Research Center, Schenectady, NY. I have conducted research on the toxicity of polychlorinated biphenyls (PCBs) and dioxins for more than 30 years. In fact, in 1981, while at the NY State Health Department, my laboratory developed and was the first to apply the concept of dioxin toxic equivalency to estimate the potential health risks associated with the dioxin-like compounds in soot resulting from a large PCB transformer fire in Binghamton NY. Since that time, both analytical capabilities and toxicological characterization of these numerous dioxin-like congeners has greatly advanced, yet the predicted uncertainties in using this approach for human health risk assessment needs have not been fully addressed, especially when extrapolating rodent derived data for use in human health risk assessment.

In the draft Reanalysis, EPA derives Cancer Slope Factors and non-cancer Reference Doses for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) only. It is clear, however, that EPA intends to use those values with the 2005 WHO Toxic Equivalency Factors, or TEFs, to estimate the risk of mixtures containing dioxins and the so-called dioxin-like compounds, including PCBs. This intent is evidenced by EPA's September, 2009 draft Guidance on Recommended Toxicity Equivalency Factors (TEFs) for Human Health Risk Assessments of Dioxin and Dioxin-like Compounds, 74 Fed.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), and by EPA's January, 2010 Draft Recommended Interim Preliminary Remediaton Goals (PRGs) for Dioxin in Soil at Superfund and RCRA sites, 75 Fed. Reg. 984 (January 7, 2010).

In essence, although the newly proposed dioxin RfD and cancer slope factors are based on human epidemiological studies, rodent derived TEFs will be necessarily also used when estimating human health risk of mixtures of dioxin like compounds. Both of these documents assume that the TEF approach, and the WHO2005 TEFs, are valid for PCBs. However, experimental data continues to accumulate that shows that rodent derived TEFs are not valid for human health risk assessment.

GE and others filed extensive comments on both the draft TEF Guidance and the draft Recommended Interim PRGs. Among other things, GE's comments demonstrated that --

1. The WHO TEFs Fail To Recognize Compelling Evidence Of Significant Species Differences in the Relative Potencies of Dioxin-Like PCBs;

2. The WHO 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;

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

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

GE also noted that neither the draft TEF Guidance nor the draft Recommended Interim PRGs acknowledge the existing IRIS values for PCBs, or show how the two sets of risk values are to be reconciled.

GE's comments built upon and supplemented recommendations regarding TEFs made by the NAS panel that reviewed the 2003 draft dioxin reassessment, two of which I will highlight today.

First, the NAS panel stated that "[i]t 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).] EPA has not implemented this recommendation, nor indicated any intent to do so.

Second, the NAS panel recognized that "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 Report, p. 87.) Most importantly, it should be questioned whether any PCBs fit into the toxic equivalency concept when applied to human health risk assessment. PCBs interact with the aryl hydrocarbon 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 aryl hydrocarbon 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 aryl hydrocarbon receptor activation. On top of these general overriding issues, research conducted by GE and others has demonstrated that rodent-derived TEFs are not conserved between rodents and humans, as previously discussed in detail in GE's comments, recently submitted to EPA, on the Draft TEF Guidance and Draft Recommended Interim PRGs.

These observations are based on the most potent PCB congener, PCB 126, which can comprise about 50% of the TEQ of environmental mixtures, and which we tested in several human cell types, including cell lines and freshly isolated human hepatocytes and normal human epidermal keratinocytes, and 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 now further 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 limited to the CYP1A1 gene typically evaluated. Therefore, one can only conclude that the proposed use of the current WHO toxic equivalency factors in human health risk assessment is not appropriate for mixtures containing dioxin-like PCBs.

To date, EPA has not acted upon the NAS's recommendations related to TEFs. Does EPA intend to do so?

Similarly, EPA has not responded to the substance of criticisms of the TEF approach that have been raised by GE, other commenters, and the expert panel that reviewed the draft TEF Guidance in November, 2009. Does EPA intend to provide a substantive response to those criticisms?

Until the NAS's recommendations are implemented, and the criticisms resolved, EPA lacks a sound scientific justification for applying the risk values for dioxin that have been derived in the draft Reanalysis to PCBs through the use of the toxic equivalency approach.

Thank you for the opportunity to comment on the draft dioxin reanalysis.