

**Comments Submitted by Dr. Jay Silkworth, General Electric Company,
to the SAB Dioxin Review Panel on
*EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS
Comments***

June 24, 2010

Good afternoon. First, I would like to thank the Science Advisory Board for this opportunity. My name is Jay Silkworth and I am a toxicologist at the General Electric Company, and I have conducted research on the toxicity of PCBs and dioxins for more than 30 years. In 2004, I addressed the Science Advisory Board for the Dioxin Reassessment and asked them to carefully consider the available evidence regarding differences in human sensitivity to dioxins and dioxin-like compounds, and they did. I am here now to request that this current advisory board also carefully consider some important new research information that was not thoroughly evaluated in the EPA's current Dioxin Reanalysis.

The 2010 Dioxin Reanalysis draft determines Cancer Slope Factors and non-cancer Reference Doses derived from human cohorts primarily exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). It can be assumed that these TCDD-specific risk values will be used in conjunction with the 2005 WHO Toxic Equivalency Factors, or TEFs, to estimate the risk of more complex mixtures containing dioxins and dioxin-like compounds, as outlined in EPA's 2009 TEF Guidance draft.

Although the TCDD-specific risk values were derived from human epidemiological assessments, the TEFs were derived primarily from rodent studies. The National Research Council panel's evaluation of the 2003 Dioxin Reassessment draft emphasized that, "if significant differences in the relative potencies of dioxin-like compounds are found between humans and other species, then adjustments should be made in the TEFs" (page 87). The EPA ignored the possible influence of species differences in potency in both the 2010 Dioxin Reanalysis and the 2009 TEF Guidance draft. Thus, it is currently assumed that there are no species differences when applying the current TEF values.

In some instances, the current TEFs have been demonstrated to predict the toxicities of dioxins and dioxin-like compounds in rodents, both *in vivo* and for cells cultured *in vitro*. However, in actual experimental testing procedures we, and others, have demonstrated that not all rodent-derived TEFs are conserved between rodents and humans. This is true for the most potent PCB congener, PCB 126, which we tested in several human cell types. We have consistently found the estimated human relative potencies to be about 50 times lower than the TEFs derived from rodents. These findings are also supported by recent genomics analyses in both species. In addition, many of the relatively less potent mono-ortho PCBs in rodents have been found to have little or no activity at all in human cells.

The fact is that, based upon actual human cell responses observed using numerous *in vitro* assays, the TEFs are not universally transferrable between rodents and humans. Additionally, a multitude of other problems concerning use of the TEF scheme in human health risk assessment for PCBs continue to remain unanswered. These issues include, but are not limited to, the invalid assumptions of additivity and equal efficacy for all dioxin-like compounds and the lack of a validated method for determining concentrations of dioxin-like PCB congeners in soil, water, and other media.

Thus, in order for this newly-anticipated dioxin risk assessment scheme to quantify the risk of real-world mixtures of dioxins and dioxin-like compounds, the EPA should, at the very least, attempt to reduce some of the inherent uncertainty by dealing with the clear species differences in TEFs. Without such adjustments significant misallocation of limited societal resources will occur in order to address unfounded human health concerns regarding, for example, the safety of the US food supply.

We ask that the Science Advisory Board carefully consider whether the best available modern science has truly been incorporated into the draft Dioxin Reanalysis, particularly regarding species differences.

Thank you.