Rebutting EPA's Claim that the SAB Fully Endorsed the RfD for TCDD

EPA relies exclusively on two studies to support its RfD derivation for TCDD, Baccarelli et al., (2008) and Mocarelli et al., (2008). EPA plans to issue as final the RfD for dioxin of 0.7 pg/kg bw/day, citing the 2011 Science Advisory Board Report on EPA's noncancer and cancer analyses. As indicated below, however, in deriving and supporting the proposed RfD, EPA failed to conduct a weight of evidence noncancer assessment and a quantitative uncertainty analysis, integral to any scientifically credible assessment.

EPA Failed to Conduct a Weight of Evidence Assessment

SAB: "EPA should incorporate information from studies with dioxin-like chemicals (DLCs) into a qualitative discussion of the weight of evidence for noncancer endpoints." (SAB Report, p.13).

SAB: "In the Baccarelli (2008) study there is limited discussion of how the presence of [PCDDs], [PCDFs] and [PCBs] that were also found in the blood might confound the interpretation of TCDD association with elevated TSH levels. In addition, there is no discussion of the potential impact of residential histories (e.g., individuals who may have moved in and out of Zone A after the incident)." (SAB Report, p. 21).

SAB: "EPA should provide a discussion of the strengths and weaknesses of the Mocarelli et al. (2008) and Baccarelli et al. (2008) studies with an indication of whether the weaknesses affect determination of the RfD." (SAB Report, p. 22.)

SAB: "The strength of the RfD should not be based solely on [Mocarelli et al., and Baccarelli et al.], but rather should be supported by integrating with other similar supporting dioxin and DLC studies." (SAB Report, p. 21). "The comprehensive data base of both animal and human epidemiologic studies, including studies with DLCs, should be discussed...." (SAB Report, p. 22).

SAB: "[SAB] agrees with EPA that the major limitation of the Seveso cohort is the uncertainty arising from how well the effects resulting from high-dose acute exposure translate to low-dose daily exposures.... It would be useful to re-review the animal studies to identify whether there are any studies where dioxin or DLCs were administered by acute as well as chronic (or even subchronic) exposure and comparable endpoints were examined. If so, the information can be used to help confirm or refute the accuracy of the 'average daily dose' adjustment." (SAB Report, p. 27).

Comment: The 2006 NAS panel identified deficiencies in how EPA evaluated and interpreted the dioxin literature in the 2003 dioxin reassessment. NAS noted that "EPA does not use a rigorous approach for evaluating evidence from studies and the weight of their evidence in the Reassessment." (NAS Report, 2006, p. 47.) NAS recommended "that EPA establish formal principles and mechanisms for evidence-based classification and systematic statistical review,

including meta-analysis when possible, for available human, clinical and noncancer end-point data." (NAS Report, 2006, p. 23.) The more recent 2011 NAS report on EPA's draft IRIS formaldehyde assessment underscored the critical importance of consistently applying a weight of evidence approach in IRIS assessments.

A weight-of-evidence evaluation requires careful consideration of: a) the other studies that may or may not corroborate the Seveso endpoints and EPA's interpretation of the data; and b) the clinical interpretation of the data as to whether they are LOAELs or NOAELs, (e.g., the WHO 2010 Semen analysis guidance; the Danish military recruit sperm data (Bonde et al., 2011); the 2007 WHO thyroid guidance, and the Corbetta et al., 2009 study on TSH screening values used in the Lombardy area of Italy.)

EPA Failed to Conduct a Quantitative Uncertainty Analysis

SAB: "In its evaluation of EPA's *2003 Reassessment*, the NAS committee recommended that EPA improve the transparency, thoroughness, and clarity in quantitative uncertainty analysis." (SAB Report, p.35). EPA should fully respond to NAS criticisms. (SAB Report, p. 42).

SAB: SAB rejected as "not scientifically justified," EPA's arguments for not conducting a quantitative uncertainty analysis (QUA). (SAB Report, p. 36). "Most members of the [SAB] Panel indicated that QUA is an integral part of any good assessment, and that one is essential to address the many empirically unresolved questions and issues that have arisen in this assessment...." (SAB Report, p. 38).

SAB: "Without such quantitative analysis, risk management decisions for TCDD will not be adequately informed, and principles other than those of rational decision making (e.g., the biases discussed in Sunstein and Zeckhauser, 2010) may dominate risk management decisions for TCDD. EPA's uncertainty analysis should provide the scientific basis for improved decision making. [EPA's] current decision, in effect, to 'punt' on quantitative uncertainty analysis is not adequate for informing responsible risk management decision and policy-making, and is not justified." (SAB Report, p. 41).