



May 27, 2011

Stephanie Sanzone,
Designated Federal Officer (DFO)
EPA Science Advisory Board Staff Office
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW.
Washington, DC 20460

Re: SAB's Draft Report on Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments

Dear Ms. Sanzone:

The American Forest & Paper Association (AF&PA) and the American Wood Council (AWC) wish to provide comments to the Environmental Protection Agency's (EPA) Science Advisory Board (SAB) Charter Committee on the Draft Report of the SAB Dioxin Panel (Draft Report).

The American Forest & Paper Association is the national trade association of the forest products industry, representing pulp, paper, packaging and wood products manufacturers, and forest landowners. Our companies make products essential for everyday life from renewable and recyclable resources that sustain the environment. The forest products industry accounts for approximately 5 percent of the total U.S. manufacturing GDP. Industry companies produce about \$175 billion in products annually and employ nearly 900,000 men and women, exceeding employment levels in the automotive, chemicals and plastics industries. The industry meets a payroll of approximately \$50 billion annually and is among the top 10 manufacturing sector employers in 47 states.

The AWC is the voice of North American traditional and engineered wood products, representing over 60% of the industry. From a renewable resource that absorbs and sequesters carbon, the wood products industry makes products that are essential to everyday life and employs over a third of a million men and women in well-paying jobs.

AWC's engineers, technologists, scientists, and building code experts develop state-of-the-art engineering data, technology, and standards on structural wood products for use by design professionals, building officials, and wood products manufacturers to assure the safe and efficient design and use of wood structural components. AWC also provides technical, legal, and economic information on wood design, green building, and manufacturing environmental regulations advocating for balanced government policies that sustain the wood products industry.

The forest products industry has been engaged in EPA's reassessment of dioxin since the mid 1980s. AF&PA and AWC have a substantial interest in ensuring that the best scientific data and analyses are brought to bear in establishing health benchmarks for dioxin. EPA's current assessment falls significantly short of a scientifically sound and balanced approach. We commend the SAB Panel for its evaluation, and for pointing out many of the critical deficiencies in the draft assessment. During the current reassessment process, we provided expert testimony before the Panel, and have submitted written comments. Our intent here is to focus on one of the very key issues of the reassessment, that which deals with dioxin's mode of action, and its bearing on linear versus non-linear low dose extrapolation. We propose how the Panel's recommendations on this critical topic can be strengthened.

(A) The SAB panel has rightfully concluded that EPA's draft assessment "did not respond adequately to the NAS recommendation to adopt both linear and non-linear methods of extrapolation" (Draft Report page 7). The Panel has recommended that "EPA revise the Report to provide a discussion of evidence of possible modes of action that include both linear and non-linear alternatives for cancer endpoint" (Draft Report at ii).

In its 2006 report¹, the NAS Committee stated the following:

Because EPA's assumption of linearity at doses below the 1% excess risk level for carcinogenic effects of TCDD, other dioxins, and DLCs is central to the ultimate determination of regulatory values, it is important to critically address the available scientific evidence on the most plausible shape of the dose-response relationship at doses below the POD (LED01). On the basis of a review of the literature, including the detailed review prepared by EPA and presented in Part II of EPA's Dioxin Risk Assessment and new literature available since the last EPA review, the committee concludes that, although 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 the use of a nonlinear model that would include a threshold response over the use of the default linear assumption.

The NAS Committee concluded "that four major considerations of the scientific evidence support the use of a non-linear model for low-dose extrapolation."

- (1) TCDD, other dioxins and dioxin-like compounds are not directly genotoxic.
- (2) Receptor-mediated agents have sub-linear dose-response relationships.
- (3) Bioassay evidence of non-linearity
- (4) Evidence that liver tumors are secondary to hepatotoxicity.

The NAS report elaborates on each of these pieces of evidence (NAS report at pages 121-128).

The SAB Panel in its draft report observes that despite a large amount of data presented by EPA on mode of action, the agency's "focus appears to be on presenting evidence that supports the use of a default linear approach rather than providing a

balanced evaluation of alternative mode of action hypotheses” (Draft Report at page 35). In addition to the evidence cited by the NAS Committee, support for a non-linear mode of action comes from recent research published by Simon et al. (2009)². The investigators derived a reference dose (RfD) using the recent National Toxicology Program rat cancer bioassay. A non-linear RfD was developed based on AHR activated tumor-promotion mode of action. Four key sentinel events chosen for the mode of action were highly consistent with the non-linear RfD based on the combined liver tumor response. That is, the non-linear RfDs resulting from the sentinel key events were indistinguishable from that based on the combined liver tumor endpoint, thereby lending very credible support to the non-linear mode of action. The Simon et al. study is referenced in the SAB Panel’s draft report.

(B) The Panel’s statement of belief that “the mode of action should be “reasonably well known” rather than “largely unknown” (Draft Report at page 7) should be strengthened.

The Panel’s draft report cites a number of references to support its belief. However, we recommend it be strengthened by summarizing the available evidence as was done, for example, in the NAS Committee report. This is important given the criticality of this issue. In addition, considering the Panel’s belief that the mode of action is “reasonably well known”, we are puzzled by the Draft Report’s brief and seemingly equivocal statement regarding application of mode of action in connection with low-dose extrapolation of the Cheng et al. epidemiologic data.³ To wit, the Panel’s recommendation that:

EPA should expand the discussion in the Report to **consider** the **possibility** that mode of action **considerations could** help to inform **whether** linear extrapolation of the Cheng data to obtain risk estimates in this range of exposures is appropriate.” (i.e. risk below background exposures experienced by the NIOSH cohort) (Draft Report at page 38. Emphasis added).

Low dose extrapolation of the Cheng et al. data is the basis for EPA’s derivation of the cancer slope factors (CSFs). Derivation of the CSFs is a significant element as the CSFs will be used for regulatory purposes. The Panel should state much more emphatically that EPA apply a non-linear model to the data for comparison with its default linear model.

We very much appreciate this opportunity to comment on the Panel’s Report. If you have any questions, please contact Laurie Holmes at (202) 463-5174 or by e-mail at Laurie_Holmes@afandpa.org.

Sincerely,

Paul Noe
Vice President, Public Policy
American Forest & Paper Association

Robert Glowinski
President
American Wood Council

References

1. NRC (National Research Council). 2006. *Health risks from Dioxin and Related 8 Compounds: Evaluation of the EPA Reassessment*. National Academies Press, 9 Washington, D.C. 2.
2. Cheng, H, L. Aylward, C. Beall, T.B. Starr, R.C. Brunet, G. Carrier, and E. Delzell. TCDD exposure-response analysis and risk assessment. *Risk Analysis 2006*. 26: 1059-1071.
3. Simon T, Aylward LL, Kirman CR, Rowlands JC, Budinsky RA. Estimates of cancer potency of 2,3,7,8-tetrachlorodibenzo(p)dioxin using linear and nonlinear dose-response modeling and toxicokinetics. *Toxicol Sci*. 2009 Dec;112(2):490-506.