



February 23, 2011

Dr. Thomas Armitage
Designated Federal Officer
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 Dr. Armitage:

The American Forest & Paper Association (AF&PA) and the American Wood Council (AWC) wish to provide the following comments on the draft report of the Science Advisory Board's (SAB) Dioxin Panel.

AF&PA 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 6 percent of the total U.S. manufacturing GDP, putting it on par with the automotive and chemical industries. Industry companies produce about \$175 billion in products annually and employ nearly 900,000 people earning \$50 billion in annual payroll. The industry is among the top 10 manufacturing sector employers in 47 states.

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 360,000 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.

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.

1. The SAB should strengthen its recommendation regarding Non-Linear Mode of Action.

In its draft cover letter to the Environmental Protection Agency (EPA) Administrator, the Panel gives the following comment/recommendation concerning mode of action.

The SAB finds that the Report did not respond adequately to the NAS recommendation to adopt both linear and nonlinear methods of risk characterization in order to account for the uncertainty of the dose-response curve for TCDD. The Report states that only a linear approach could be justified. We recommend that EPA revise the Report to provide a balanced discussion of evidence of possible modes of action, including linear and nonlinear approaches for cancer endpoint. We note that the EPA might still conclude that, in the absence of a definitive nonlinear mode of action, policy dictates that the linear option is preferred to assure protection of public health.¹

We believe the underlined sentence in the statement should not be included for two reasons. First, EPA clearly recognizes it has discretion to invoke policy in its decision-making. Secondly, the sentence is likely to convey to the reader equivocation by the Panel concerning the need for EPA to give much stronger consideration to a nonlinear mode of action than it has been willing to do thus far, contrary to the NAS recommendations.

Additionally, wording in the first sentence of its recommendation concerning Cancer Assessment – Mode of Action that – “[the] Panel agrees that the exact mechanism of action has not been fully delineated for any distinct TCDD toxicity endpoint”--- may lead the reader to confuse the distinction between “mechanism of action” and “mode of action”. As the Panel is aware, EPA uses mode of action in deciding on a nonlinear vs. linear dose-response. In EPA’s cancer risk assessment guidelines, mechanism of action is defined as “the detailed molecular description of key events in the induction of cancer or other health endpoints”. Mode of action, on the other hand refers to “the description of key events and processes, starting with interaction of an agent with the cell through functional and anatomical changes, resulting in cancer or other health endpoints.” The Panel’s statement should be amended to avoid any possible misunderstanding or confusion. We also note this same concern in the statement at pages 33 and 34 of the draft report which reads:

“Panel members pointed out that much is known about TCDD toxicity and mode of action. Some Panel members felt that the characterization should be ‘reasonably well known’ rather than ‘largely unknown.’ Nevertheless, the Panel agrees that the exact mechanism of action has not been fully delivered for any distinct TCDD-toxicity endpoint.” (Emphasis added).

Here again, knowledge of mechanism of action is not relevant, as opposed to mode of action.

¹ SAB Draft Report at pg ii. (emphasis added).

At page 34 of the draft, the Panel notes that while EPA's draft assessment presents a large amount of data related to the mode of action for the carcinogenicity of TCDD, the draft'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." We wholly agree with the Panel's concern.

The draft report cites a number of literature references on the nonlinear nature of receptor-mediated cellular responses. We recommend at least one important reference be added. Simon et al. (2009)² derived an RfD for TCDD using the recent National Toxicology Program rat cancer bioassay. A non-linear RfD was developed based on an AHR activated tumor-promotion mode of action. Key sentinel events chosen for the mode of action were: (1) toxic hepatopathy, (2) the occurrence of altered hepatic foci positive for gamma-glutamyl transpeptidase (yGT + - AHFs), (3) labeling index at 31 weeks, and (4) adaptive induction of AHR activation-dependent CYP1A1 measured by the dose-related increase in EROD at 53 weeks of the NTP bioassay. RfDs derived for these four key events were highly consistent with the non-linear RfD based on the combined liver tumor response. That is, the non-linear RfDs resulting from these sentinel key events were indistinguishable from that based on the combined liver tumor endpoint, thereby lending significant support to the non-linear mode of action. The Panel should reference this important study in its report.

2. The SAB should provide further analysis and specificity on weaknesses of studies relied upon by EPA for Non-Cancer RfD determination.

The Panel rightfully recommends that "EPA should provide a more balanced discussion of the selection of the Mocarelli et al. (2008) and Baccarelli et al. (2008) studies by providing a better description of the potential weaknesses in these studies and discussing whether they affect the RfD conclusion." In comment and testimony before the Panel, health experts have pointed to a number of serious weaknesses with the two studies relied upon by EPA for the RfD determination. Among the noted weaknesses are:

- Unrepresentativeness of acute exposures from an industrial accident as a data set for deriving an RfD for chronic exposures.
- Possible underestimations of both exposure and the resulting RfD due to exposures to other PCDDs and PCDFs.
- Data limitations relative to judgments of decreased sperm quality based on a single measurement for each patient, and the absence of clinical evidence of impaired fertility.

² 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.

- Questions regarding the clinical relevance of “elevated” neonatal TSH levels that fall within the reported reference range and the normal range for adaptive responses.

While the Panel does mention these concerns, we believe its own critical analyses of these should be further elaborated in its report so as to better guide EPA’s assessment.

3. Hill Coefficient Used in the Emond Model.

We strongly support the Panel’s recommendation for “additional efforts to fully characterize the uncertainty in the models with special consideration of the Hill coefficient value.” EPA’s flawed choice of a Hill coefficient of 0.6 was highlighted in testimony before the Panel by Dr. Thomas Starr and in written comments submitted by Dr. Melvin Anderson. Both aptly described the biological implausibility of such a value, and have recommended a value of 1.0 based on published scientific data.

We very much appreciate this opportunity to comment on the Panel’s Draft 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