

COMMENTS ON THE DRAFT REPORT PREPARED BY THE DIOXIN PANEL
OF THE EPA'S SCIENTIFIC ADVISORY BOARD

*Submitted by ENVIRON International Corporation
on behalf of the American Chemistry Council*

May 27, 2011

Introduction

The US Environmental Protection Agency's (EPA's) review of the dioxin literature and determination of carcinogenicity has been underway for nearly 20 years. Most recently, the EPA's Scientific Advisory Board (SAB), Dioxin Review Panel (Panel) released their comments May 4, 2011 on the EPA's 2010 *Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments* (Report). The 2010 EPA Report addressed recommendations from the National Academies (NAS), *Health risks from Dioxin and Related Compounds: Evaluation of the EPA Reassessment* (2006). The NAS committee reviewed the 2003 EPA reported findings on exposure and human health assessment of dioxin risk, and provided recommendations for the EPA to consider in revising their report.

The comments below are offered to the EPA SAB by ENVIRON International Corporation (ENVIRON), on behalf of the American Chemistry Council, in response to the invitation to submit public comments in support of a quality review of the draft report, *SAB Review of EPA's Reanalysis of Key Issues Related to Dioxin Toxicity and Response to NAS Comments*, prepared by the Dioxin Review Panel, an *ad hoc* SAB Panel. Although our comments address the SAB Panel's draft report, they do so in reference to parts of the NAS 2006 recommendations, and the EPA's 2010 report addressing those recommendations, as these are the subjects of the Panel's review.

The scientific basis for many of the comments below comes from a recent critical review and synthesis of the epidemiological literature published since the full-scale scientific review of 2,3,7,8 tetrachlorodibenzo-p-dioxin (TCDD, or dioxin) in 1997 (IARC). The recent review (attached) – authored by Drs. Paolo Boffetta, Kenneth Mundt, Hans-Olov Adami, Philip Cole and Jack Mandel – was provided to EPA and the Panel for their consideration on March 3, 2011 and added to the Public Comments section of the SAB website. The impetus for this critical review was the finding by a 2009 International Agency for Research on Cancer (IARC) review of TCDD (dioxin) as part of a systematic reassessment of all agents classified by IARC as Group 1 (carcinogenic to humans), in which IARC classified the epidemiological

evidence of carcinogenicity in humans as “sufficient,” based on increased risk of all cancers combined (Baan, Grosse, et al. 2009). This latter evaluation, which has not yet been published, was based on a more cursory review of the available data than is generally undertaken for IARC Monographs (given that thirty substances/carcinogens were reviewed in 2009 in the time typically allocated for three carcinogen candidates). Therefore, the detailed review of the epidemiological evidence on which the 2009 reclassification as “sufficient” was made, is not available. Nevertheless, based on our independent systematic review and synthesis of all the epidemiological evidence published since IARC’s 1997 review, we found little scientific support for this conclusion, and therefore no justification for the change in classification of the epidemiological evidence from “limited” to “sufficient.”

At this time we appreciate the opportunity to provide the SAB our comments on the Panel’s review. For clarity, we present comments on three key epidemiological topics relevant to the evaluation of the epidemiological evidence pertaining to cancer risks of dioxin exposure and the carcinogenic classification of dioxin based on the epidemiological evidence:

1. The Panel’s evaluation of EPA’s approach to determining the body of epidemiological evidence relevant to its critical review. In particular, the Panel’s comments regarding the EPA’s justification (or lack thereof) for preferentially excluding studies that did not report increased risks of any cancer among dioxin exposed groups;
2. The Panel’s assessment of EPA’s revised approach to critically assessing and synthesizing the body of epidemiological evidence (assuming that it had been complete) for purposes of determining whether that body of evidence supports a determination that dioxin is carcinogenic to humans; and
3. The Panel’s endorsement of EPA’s decision to base its determination of carcinogenicity on epidemiological findings on “all cancers” as a group (i.e., a results-derived decision), and not on the specific cancer or cancers hypothesized to be related to dioxin exposure.

Each of these key areas of concern is discussed in more detail below. Additional general comments are provided at the end.

1. Consideration of the “body of evidence”

The Panel is inconsistent in their comments, both in terms of language and criticisms, on the same topic. For example, in the Executive Summary, the Panel applauds EPA for its methodology, including the selection of studies for review:

“The SAB commends EPA for the comprehensive and rigorous process that was used to identify, review, and evaluate the TCDD literature. ***The criteria for study selection have been clearly articulated, well justified, and applied in a scientifically sound manner***” (emphasis added). p.ii

However, the Panel immediately points out a deficiency in EPA’s methods, specifically their decision to exclude some generally negative studies. While scientifically this is an important potential problem, the language of the Panel’s criticism is mild: “To further improve clarity and transparency of the Report, we recommend that EPA include a better means of tracking and describing which studies did not satisfy inclusion criteria.” In fact, there is no clear method described in the 2010 EPA Report that would allow an independent investigator to replicate the EPA methods – and therefore the methods are not “applied in a scientifically sound manner.” Without clear and replicable methods for selecting and retaining studies for critical review, the “body of evidence” is incomplete and potentially biased through the selection of generally positive studies. The Panel therefore failed to underscore the scientific importance of not only describing methods in a transparent way, but justifying the use of non-standard methods that could have introduced a bias. By first complimenting EPA on their (incomplete and opaque) methods, and then pointing out a way to improve clarity, the Panel misses a critical opportunity to provide necessary constructive criticism to EPA so that the methodology may be improved.

We agree with the Panel’s criticism of EPA’s failure to consider the epidemiological studies that do not find associations between dioxin exposure and either all cancers, or cancer at specific organ sites. “The Panel recommends that EPA provide an assessment of both the null studies and positive studies ***with more discussion and clarity concerning the exclusion of null epidemiologic studies***” (emphasis added). However, lack of consideration of the full “body of evidence” – including studies that do not find associations—may result in a potential bias in the partial body of evidence that EPA did evaluate, subsequently leading the EPA to incorrectly conclude that there is strength and consistency in the epidemiological evidence for carcinogenicity.

Therefore, although the Panel was somewhat critical of the EPA’s methodology, they were not critical of the fact that EPA’s conclusions regarding the “body of evidence” supporting causation was based on an incomplete synthesis of epidemiological evidence. A recent review of the dioxin literature (Boffetta, Mundt, et al. 2011) that clearly delineated selection criteria –and included positive and negative studies – failed to support the same conclusion as the EPA report and as endorsed by the Panel:

“In conclusion, the carcinogenicity of TCDD may be plausible on the basis of animal experiments conducted at high doses, but the epidemiological evidence falls far short from conclusively demonstrating such a relationship in humans. In the case of complex data such as the

epidemiologic studies on TCDD exposure and cancer risk, it is important to consider all the evidence, and not just selected components that might support one particular hypothesis. . . Furthermore, TCDD is a likely example of how epidemiologic studies in a controversial area might be particularly susceptible to multiple types of bias. These considerations support our conclusion that the epidemiological evidence of carcinogenicity of TCDD in humans is not “sufficient” and remains “limited.” (Boffetta, Mundt, et al. 2011)

In contrast, without explaining their own methods for reviewing and synthesizing the literature, the Panel makes the assertive statement that “During the course of its discussion, the Panel did not identify any additional studies that would impact the hazard characterization or the dose-response assessment. However, the Panel found that EPA’s *Report* should provide more clarity on the exclusion of null epidemiologic studies” (pg. 13).

Since the underlying methods used by EPA to identify and evaluate all relevant studies are flawed, we would recommend that the SAB Panel specifically address this point, and request that EPA re-consider their evaluation of the weight of evidence by including all studies – negative and positive – in their synthesis of the evidence and determination of carcinogenicity.

2. Classification of carcinogenicity

As part of their review, the Panel agreed with EPA’s evaluation of carcinogenicity of TCDD based on the epidemiological evidence:

“The Panel agrees on the classification that “TCDD is carcinogenic to humans” under EPA’s 2005 *Guidelines for Carcinogen Risk Assessment*. Available occupational epidemiologic studies provide convincing evidence of an association between TCDD and human cancer that cannot be reasonably attributed to chance or confounding and other types of bias, and with a demonstration of temporality, strength of association, consistency, biological plausibility, and a biological gradient” (p. 33).

Given the lack of consideration of the entire body of evidence as discussed above, we disagree with the Panel’s support of the EPA’s conclusion.

More problematic, however, is the Panel’s critical omission in evaluating what we have identified as EPA’s poor adherence to their own 2005 *Guidelines for Carcinogen Risk Assessment*, specifically regarding criteria to be considered in determining causality. The Panel failed to appropriately criticize EPA’s loose and abbreviated explanation for why they dismissed the NAS recommendation (below) in evaluating causation. If the literature does not demonstrate that a causal conclusion is justified for any cancer, classification of the epidemiological evidence as “sufficient” to support a conclusion of carcinogenicity is not scientifically supported.

The NAS 2006 report states:

Pg. 120: The committee was in general agreement that the epidemiological evidence, although not “strong,” was generally consistent with a positive association between occupational dioxin exposure and mortality from all cancers, but the magnitude of the effect was modest, and the limited evidence for any specific tumor type being significantly associated was of some concern. This conclusion is in fact quite similar to EPA’s assessment of the relative strength of the epidemiological evidence (Reassessment, Part III, p. 2-21). In its discussion, the committee remained uncertain about the intent of the language in the 2005 *Guidelines for Carcinogen Risk Assessment* stating that condition (a) could be satisfied if there is “strong evidence of an association between human exposure and either cancer or the key precursor events of the agent’s mode of action but not enough for a causal association” (EPA 2005a, p. 2-54). The committee agreed that there is convincing evidence supporting the interaction of dioxin with the human Ah receptor and that the interaction with the receptor was necessary, but not sufficient, to cause cancer in animals. However, the committee was not in complete agreement about whether these conditions met the stated criterion of a “key precursor event of the agent’s mode of action” (EPA 2005a, p. 2-54).

Pg. 140-141: The committee concluded that the classification of dioxin as “carcinogenic to humans” versus “likely to be carcinogenic to humans” depends greatly on the definition and interpretation of the specific criteria used for classification, with the explicit recognition that the true weight of evidence lies on a continuum with no bright line that easily distinguishes between these two categories. The committee agreed that, although the weight of epidemiological evidence that dioxin is a human carcinogen is not strong, the human data available from occupational cohorts are consistent with a modest positive association between relatively high body burdens of dioxin and increased mortality from all cancers. Positive animal studies and mechanistic data provide additional support for classification of dioxin as a human carcinogen. However, the committee was split on whether the weight of evidence met all the necessary criteria described in the cancer guidelines (EPA 2005a, see also Appendix B) for classification of dioxin as “carcinogenic to humans.” EPA should summarize its rationale for concluding that dioxin satisfies the criteria set out in the most recent cancer guidelines (EPA 2005a, see also Appendix B) for designation as either “carcinogenic to humans” or “likely to be carcinogenic to humans.”

Therefore, the Panel failed to note that the EPA report was not appropriately responsive to the NAS recommendations regarding the faithful application of the 2005 EPA guidelines in evaluating and synthesizing the body of epidemiological literature.

Even if one were to accept that dioxin is carcinogenic to humans based on the epidemiological evidence, the EPA has not described the uncertainties at doses relevant to population exposure levels. The Panel, although they agreed with the determination of carcinogenicity of dioxin based on the epidemiological evidence, they recommended that EPA characterize the uncertainties at low dose:

“EPA should attempt to characterize the uncertainty regarding the carcinogenicity of TCDD at low human exposures, since the minimum dose at which carcinogenetic effects would be expected to occur cannot be clearly delineated from the current epidemiological data” (pg. 34)

Again, our criticism goes beyond the lack of clarity in the write-up, and rests firmly on the application of proper scientific methods, both of which we recommend the Panel ask EPA to more adequately address.

3. Use of “all cancers” for determination of causation and dose-response modeling

We also disagree with the Panel’s acceptance of EPA’s reliance on selected epidemiological results pertaining to “all cancers” rather than any single cancer, or if justified – group of cancers – that have been hypothesized to be associated with TCDD. In occupational epidemiology, reporting of results for “all causes” and “all cancers” and other outcome groups is common, and often provides helpful information on broad issues such as general health status (including such selection forces as the “healthy worker effect”), or as a screening approach in identifying categories of diseases in which some large excess might be present. The latter requires further, more detailed, evaluation to identify the specific disease(s), if any, contributing to the overall excess.

The Panel appears to be aware that looking at individual cancers is important, and made the following recommendation: “Expanded discussion of several other studies [besides Cheng] would support the weight-of-evidence for carcinogenicity in less common cancers such as lymphomas and soft tissue sarcoma” (pg. 36). However, the Panel appears not to recognize that among the reasons that results for all-cancers were selected is the lack of epidemiological evidence for the hypothesized cancers. Even if EPA did do this proper evaluation for these cancers, they would find insufficient evidence in the epidemiological literature to support a causal association between dioxin and these individual cancers.

As has been pointed out in a recent review, the use of “all cancers” is also subject to more potential biases that should be evaluated before causality from a single exposure can or should be associated with all cancers:

“Consistency of results is a key criterion for assessing causality. Shifting the emphasis from specific cancers to all cancer allows for the possibility that different types of cancer-specific biases affecting various studies (e.g., residual confounding by different risk factors) would generate an apparently consistent increase in all-cancer risk. Protection from bias should therefore be subject to more stringent scrutiny when evaluating an epidemiological hypothesis that some risk factor causes all cancers” (Boffetta, Mundt, et al. 2011).

The lack of evidence for any specific cancer (especially any hypothesized to be associated with TCDD) does not justify embracing “all cancers” as an outcome. Although the SAB Panel is mildly critical of the

EPA's important failure to consider negative studies in their synthesis of the literature, they fail to be comparably critical of the EPA's dismissal of studies that lack findings or associations for specific cancer sites. While the Panel considers the exclusion of some of these studies to be acceptable because they might have lacked statistical power to demonstrate an underlying association for specific cancers, an alternative explanation that was not considered by either the EPA Report or the Panels's report is that the lack of findings for individual cancer sites may in fact be indicative of no association with TCDD exposure.

It is not a scientifically valid argument to use "all cancers" as outcome, only because there are dose-response data available for that outcome. In other words, discovering an association between exposure and "all cancers" absent meaningful associations between exposure and the hypothesized cancers might raise the hypothesis that such exposure actually increases risk of all cancers, but then this hypothesis must be properly tested. As noted by Boffetta et al. (2011):

"In addition, the hypothesis of an increase in all-cancer risk would not dispense with the requirement that cancer-specific results have to be consistent across studies, especially in the case of more common cancers, such as lung cancer, for which random fluctuation can hardly be invoked as cause for the lack of consistency. For none of the specific neoplasms is there a consistent pattern showing an increased risk in populations exposed to TCDD" (Boffetta, Mundt, et al. 2011)

The EPA's justification for using "all cancers" for the quantitative dose-response modeling is based on "the general consistency of an increased risk for all-cancer mortality across the occupational cohorts when latency intervals have been incorporated, [which] provides adequate justification for dose-response quantification of all cancer sites combined" (pg. 2-87 EPA 2010 Report). Even if there were any etiological justification for the use of "all cancers" in determining a dose-response risk, as noted above, the weight of the evidence – when all studies are considered – is inadequate to draw a causal conclusion, and therefore, a risk assessment based on the most "positive" study is not justified.

The appearance of a dose-response relationship does not necessarily indicate a positive association. For example, in Steenland 1999, the primary study on which Cheng (2006) was based, an exposure-response with lung cancer is reported in the absence of an overall in lung cancer risk. For all cancers, there was no indication of a statistically significant increased risk for the five lowest septiles of exposure, suggesting at best (i.e., assuming that the data reflect an underlying association with dioxin exposure), a threshold for risk. Furthermore, of the eight plants included in the exposure level analysis, only one (plant number 10) demonstrated a statistically significant increase in all cancer mortality. Plant number

10 also was the only plant with a statistically significant excess of lung cancer, smoking-related cancers combined, laryngeal cancer, or non-malignant respiratory disease mortality (Cheng 2006).

The Panel notes on page 36 that Cheng (2006) “. . . incorporated information on gradation of exposure.” Given that this gradation is based on Steenland (1999), we suggest the Panel recommend that EPA provide a better rationale for their decision, given that the source data are not as uniformly supportive of this “gradation of exposure.” Having embraced the use of the Cheng study on the previous page, “The Panel agrees that it is appropriate to use all-cancer mortality in this case because of the extensive dose-response information,” the Panel goes on to indicate that “The ability of the Cheng study to be informative regarding risks below current background levels is not completely clear” (pg. 37,38). In fact, the data from the Steenland study (1999) show, for the 5 lowest septiles of exposure no increase in risk for all cancers.

Furthermore, the Cheng (2006) paper’s justification for using “all cancers” – i.e., the long time period of cell proliferation required – contradicts what is known about other late-stage carcinogens, and therefore undermines the EPA’s hypothesis that TCDD can indeed cause all cancers. The recent review noted that the central role of the Ah receptor in causing all cancers has not been convincingly determined:

“A more fundamental challenge in the evaluation of TCDD as a human carcinogen is the emphasis on risk of all cancer rather than specific neoplasms or a specific subset of neoplasms. As already explained in a previous review (Cole, Trichopoulos, et al. 2003), we have not found convincing evidence for a central role of the Ah receptor in dioxin-related carcinogenesis. Hence, the ubiquitous presence of the Ah receptor should not guide the interpretation of the epidemiologic evidence we have summarized above. Indeed, a non-organ-specific carcinogenicity of TCDD would represent a unique feature in cancer epidemiology” (Boffetta, Mundt, et al. 2011).

On April 8, 2011, the National Research Council (NRC) released its report, *Report of the Environmental Protection Agency’s Draft IRIS Assessment of Formaldehyde*, in which the NRC panel was highly critical of EPA for combining “all lymphohematopoietic cancers” – the largest grouping they used (EPA did not consider “all cancers” in that review). The report states:

“Lymphohematopoietic (LHP) cancers are a heterogeneous group of cancers that encompass a wide variety of leukemias and lymphomas. Although they all arise from the hematopoietic system, these cancers are often derived from cells of different origin, can demonstrate unique genetic abnormalities, and may arise in different tissues (Figure 5-1). **Those differences indicate that their etiologic bases may be distinct.**

Although the draft IRIS assessment explores specific diagnoses—such as acute myeloid leukemia (AML), chronic myeloid leukemia (CML), and Hodgkin lymphoma and multiple myeloma (see, for

example, EPA 2010, Table 4-92)—the determinations of causality are made for the heterogeneous groupings “all LHP cancers,” “all leukemias,” and “myeloid leukemias.” The grouping “all LHP cancers” includes at least 14 biologically distinct diagnoses in humans (Figure 5-1) and ***should not be used in determinations of causality*** (p. 80-81) (emphasis added)

Despite the common use of groupings such as “all LHP cancers” or “all leukemias” – and their relative similarities as blood cancers – the NRC warned against the combining of distinct diseases for determining causation. In fact, the NRC provides guidance: “The committee recommends that EPA focus on the most specific diagnoses available in the epidemiologic data such as acute myeloblastic leukemia, chronic lymphocytic leukemia and specific lymphomas” (p. 8). The much broader and diverse categorization of “all cancers” therefore represents an even more egregious violation. The Panel failed to at least raise this as a possible criticism, and accepted EPA’s decision at face value without full scientific justification.

4. General comments pertaining to Panel’s report

In addition to the lack of evaluation of the full body of epidemiological evidence, the Panel correctly notes that the EPA evaluation of the epidemiological literature “was worded awkwardly and that epidemiological terms are misspecified” (pg. 17). We agree with the Panel that epidemiological concepts and terms are not consistently used, and some examples are provided by the Panel:

- Define ‘susceptible to important biases.’ This is a non-specific term and the biases should be explained.
- Clarify what is meant by “control for potential confounding exposures.” Does this refer to only exposure to dioxin-like compound exposures or was it meant to more broadly refer to other exposures as well (NIOSH cohort studies)? Does the text “bias arising from study design” refer to selection bias or is this phrase used more broadly to describe how exposure and outcome are measured and covariate data collected?
- Define what is meant by the phrase “bias arising from statistical analyses.” It is unclear if bias is the correct term, rather this may refer to model misspecification.

The errors in using these terms and concepts underscore the broader epidemiological weakness in the EPA’s Report.

Finally, the Panel notes on page 33 that – “A dissenting opinion (see Appendix A of this report) was expressed by one Panel member who indicated that at best, there is equivocal evidence for the carcinogenicity of TCDD in the occupational setting where body burdens were much higher than current or previous background levels” – which largely agrees with our detailed assessment of the epidemiological literature, and that of Boffetta et al. (2011).

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1 **TCDD and cancer: A critical review of epidemiologic studies**

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23 Key words: dioxin, TCDD, epidemiology, cancer

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