

Compilation of Board Comments on Draft PFOA Panel Report
[2-15-2006]

A. Lead Reviewers:

1. Dr. James Bus

SAB review of EPA's Draft Risk Assessment of the Potential Human Health Effects Associated With PFOA and Its Salts

Are the original charge questions presented to the SAB adequately addressed?

The report clearly indicates that the SAB panel did not reach agreement to the answers of several of the important charge questions (e.g., MOA; cancer descriptor; toxicity endpoints selected for risk assessment; adequacy of human exposure data for MOE calculations). Although the positions of the panel members apparently supporting the majority position were described in some detail, corresponding commentary describing the positions of the minority were generally not as detailed. Thus it is difficult for the reader and ultimately the EPA to judge the merits and weight of the balancing positions. The Panel should consider expanding the text describing the dissenting opinions in order to more clearly delineate the strengths and weaknesses of the Panel answers to the charge questions.

The Panel comment on the proposed descriptor for carcinogenic potential of PFOA does not appear to have fully considered the breadth of the available data. The Panel concluded that the cancer descriptor proposed by the EPA draft ("suggestive evidence") should be replaced with the stronger descriptor of "likely to be carcinogenic". This conclusion was based on the Panel evaluation that PFOA represents a "multi-site and multi-gender" carcinogen. The public record of external comment provided to the Panel indicates that it was provided with a detailed analysis of the significance of the rat mammary tumors reported in the 1987 Sibinski study. This analysis included a report of an expert Pathology Working Group that concluded that PFOA did not produce any excess of benign or malignant mammary tumors, in agreement with the conclusions of the original study authors. Importantly, the value of a Pathology Working Group evaluation of the mammary tumor question in facilitating the cancer evaluation appears to have emerged from early Panel discussions. However, both the Letter to the Administrator and draft Panel report itself make no specific mention of the strong conclusions of this report. If the report is to retain the statement that PFOA represents a multi-gender and multi-site carcinogen, and since this conclusion appears to be a primary rationale for elevation of the cancer descriptor, the reasons for dismissing the conclusions of both the Sibinski report itself and the subsequent PWG must be transparently delineated. In addition, the draft Panel report does not make it clear that the two primary cancer bioassays for PFOA replicated cancer at only a single site – testicular Leydig cell tumors. Both the hepatocellular and pancreatic acinar cell tumor responses observed in the Biegel

study were not observed in Sibinski, despite similarities in dose, route of administration, and test species. Thus, more discussion is merited as to why these data, taken in their whole, should be taken as evidence of multi-site carcinogenicity of sufficient weight to justify elevation of the cancer descriptor from that proposed in the EPA draft risk assessment (or expansion of dissenting opinion?).

Is the SAB Panel draft report clear and logical?

Given the observations raised above, the Panel position of PFOA as a “likely” human carcinogen is not clearly and logically supported and should either be more fully justified or reconsidered.

The Panel specifically comments that application of internal dose metrics for use in MOE calculations constituted a “significant step toward reducing uncertainty related to cross-species extrapolation”, particularly as it relates to the approximate 3X uncertainty factor accounting for toxicokinetic differences. Despite this important conclusion, and the Panel’s observation that the toxicokinetic factor for PFOA “would fall within the range of one to three”, it was recommended that the full inter-species default factor of three be retained. Thus, it is not clear how Panel believes the internal dose metric approach would indeed contribute to a reduction in uncertainty if it is unwilling to suggest that such dose metrics should be used. Is the Panel endorsing the fundamental approach suggested by the draft assessment, but is recommending either further PFOA-specific or generic research to justify actual use of this approach? The Panel should consider that the US FDA routinely constructs pharmaceutical risk evaluations based on internal dose comparisons between human clinical drug/metabolite concentrations and equivalent animal AUC/Cmax data. The Panel should further consider recommending that the future use of these types of data comparisons would benefit from a multi-agency discussion and agreement on acceptable approaches to this important concept.

The report specifically comments (p.27) on the implications of an association between PFOA worker exposures, altered lipid levels and a potential for increased cerebrovascular disease mortality. However, given that this review was not specifically charged to review human data in detail, and consequently did not examine the full range of epidemiological and medical monitoring studies available for PFOA, this suggestion is clearly not warranted and likely extends a conclusion well beyond existing data. The Panel should also consider the contradicting observation that a study examining the relationship of potential PFOA exposure to death from cerebrovascular disease found no evidence of a causal association (DuPont comments submitted to EPA, Feb. 7, 2006).

Are the conclusions drawn and/or recommendations made supported by information in the body of the draft report?

See comments above.

The Panel review concludes that the weight of evidence is sufficient to support a PPAR α MOA for liver tumor induction in rats. Although the review expresses concerns that potential alternative mechanisms might also contribute to PFOA tumorigenicity, these suggested alternative MOAs would also be expected to operate by nonlinear dose-responses. Thus, the Panel should affirm that regardless of the debate surrounding potential MOA within the Panel members, the proposed EPA MOE risk assessment approach represents the most appropriate methodology for the assessment.

Other comments

Letter to the Administrator:

p.1, l. 30-31: It is clear the Panel considered data beyond the “peer-reviewed published” literature. Although this practice is acceptable, the report should specifically note when such data were considered, and more importantly, describe under what conditions the data were generated (e.g., GLP), if the actual study data have been made available to the EPA, the Panel and the public for peer review by these mechanisms.

p.2, l. 39-41: The Panel refers here and in the report to the existence of a “highly exposed” population apart from the occupational environment, and this population provides the rationale for conducting MOE assessments to apparently equivalently exposed occupational cohorts. However, the Panel should note the specific evidence it reviewed to justify the existence of such a “highly exposed” subset of the general population.

Report:

p.8, l.3-5: The statement “no information currently exists with respect to critical periods” is not fully correct. A 2-generation reproduction study contained several perinatal endpoints and observations that were judged by the Panel as useful for evaluating some aspects of developmental susceptibility.

p.9, l. 23-24: It is not clear why the assumption of steady state may not be valid for blood samples collected from children 2-12 years of age. Does the Panel have any data to suggest that serum levels in these children would be expected to higher than those contained in adults? Given the relatively long half-life projected for PFOA in humans (approximately 4 years), environmental exposures to such an agent would not be expected to produce peak serum concentrations rapidly during the early life years, but rather would slowly reach steady state in early adulthood.

p.20, l. 28-30: It is not clear from the statement “Issues on which the Panel members opinions diverged...liver tumor induction might occur in humans” if such “divergence” represented a majority opinion.

p.20, l. 35-36: The lack of data on hepatocyte proliferation and suppression of apoptosis is cited as a “critical deficiency” in the perspectives of “many” Panel members. However, since PFOA also did not produce any PPAR α associated response in receptor knockout animals, did the Panel discuss if such a research tool, that was not available when original cell proliferation and apoptosis criteria were established as PPAR α MOA criteria, is now adequate to supplant the specific absence of these specific data?

p.23, l. 43-45: The statement that “organ and body weights are among the least sensitive endpoints...” should be referenced. This statement is likely not correct.

p.27, l. 33-36: The statement about “zero distance” and “cause” of health effects represents an oversimplification of often very complex evaluations and should be deleted. Thus, just because a serum concentration might be associated within a human health effect does not infer causation.

2. Dr. Genevieve Matanoski

Comments on Panel Report on PFOA

The panel report is very well written and the issues are clearly explained and answered. The document has addressed each of the points on which the EPA has requested advice. The review has shown only two areas that might require some attention by the panel.

1. Page 17 lines 38-41. The sentence has two negative statements, which makes it somewhat difficult to read. Could it be re-worded?
2. Page 29 final paragraph. The discussion refers to findings from studies of siloxanes. Is this discussion included because siloxane should act like PFOA or is this just a general characteristic of chemicals to which the panel wishes to call attention? It might be helpful to clarify this point so the reader can evaluate the strength and relevance of the observation in regard to PFOA.

The only other point that may be worth a comment is in regard to fetal exposures to PFOA. The panel may have had extensive discussion about this and it is not worth a change. I am not asking for any change directly. However, although there is discussion about the problems with extrapolation to children little is said about fetuses except in the early part of the document under tissue differences. However, perhaps there are major differences in the specific tissue dose to fetuses. Proportions of tissue are not the same in the earliest period of development. The toxicokinetic mechanisms may not even be developed at certain embryonic stages. I have no direct data on how these apply but I wondered

if the panel had discussed these potential differences and whether there should be some mention of the fetus, not just the neonate and the child. Since the exposure is ubiquitous, the fetus should have exposure from the maternal blood in early development. This was just a thought as I read the document.

3. Dr. Lauren Zeise

Review of Draft SAB Review of EPA's Draft PFOA Risk Assessment

The SAB draft report is well written and adequately addresses the charge questions. It is clear and logical. The conclusions drawn and recommendations are sufficiently supported by information in the body of the SAB draft.

The cover letter to the Administrator captures the key conclusions of the SAB review. However, it is written more for the technical expert and could be improved by simplifying the language - to the extent possible - so that it would be more understandable to the non-expert educated reader.

Minor editorial comments

P 4, lines 19-20. It is unclear what is intended by the recommendation that "biomonitoring data be included for identifying potential human health effects."

P 16, line 30. Missing word "is" after "thus"

P 19, line 9. Language a little awkward: "the current evidence fails to exceed the descriptor "suggestive" of carcinogenicity."

P 19, paragraph on mammary tumors. Naming the labs for the Sibinski study and the historical Chandra data base would add context to the discussion of the historical control comparisons.

P 24, line 20. Unclear what is meant by "data will need to be derived in rats"

B. Other Board Members:

1. Dr. A. Myrick Freeman

I have read the Jan. 20, 2006 Draft SAB Review of the EPA Draft PFOA risk assessment. In my judgment, the answers to the 3 reviewers' charge questions are "yes," "yes," and "yes."

2. Dr. Rogene Henderson

I reviewed the letter and the executive summary. I found the report was responsive to the charge. The letter was clear and logical. There was a great deal of "some thought this" and "some thought the other" in the advice. I know of no way to get around that and I suppose it does let the agency know that the issues are controversial. I saw in the news that industry was voluntarily withdrawing this product for many uses. I note one typo. On the third line of the letter, "Perfluorooctonoic" should be Perfluorooctanoic."

3. Dr. Meryl Karol

I think that the draft report is excellent. The charge questions were adequately addressed and the conclusions are supported by information in the draft report. For added clarification, I suggest the following:

> in describing viewpoints of the expert panel members, where there was dissent among the panel, instead of saying “many” or “a few” or “some”, it would be helpful to indicate if the viewpoints represented the majority, a minority, or were isolated viewpoints.

>The section PPAR-alpha-independent liver effects (p. 21, lines 19-34) should be rewritten for clarification. I had to read it several times before I fully understood it.

4. Dr. Jill Lipoti

I read the report and have no comments.

5. Dr. Michael McFarland

In general, the SAB PFOA Panel provided an excellent review of the Agency’s Draft Risk Assessment of Potential Human Health Effects Associated with Perfluorooctanoic Acid (PFOA) and Its Salts. Although the topic under discussion is outside my immediate area of technical expertise, the Panel’s responses to Agency charge questions appear to be comprehensive and sufficiently detailed.

The overarching concern that I had from reading the document was the extensive degree of non-consensus that characterized PFOA panel member positions. The document is replete with examples of where the majority of panel members are of one view with respect to a particular technical issue while a minority of panel members supports an opposing view. In attempting to understand the SAB’s responses to the Agency, it seemed that, on the whole, the Panel believes that much of the data (human biomonitoring as well as animal laboratory studies) being adduced to support the Agency’s position relative to PFOA’s potential human carcinogenicity is inconclusive or, at any rate, open to various interpretations. Moreover, it seems that there is Panel consensus supporting the need for more comprehensive, longer-term studies.

In any event, while it is important to describe where there is significant divergence in scientific opinion, the report, in my view, would be more compelling and strengthened if positions of unanimity were more fully developed (if possible), particularly in the letter to the administrator and in the Executive Summary. To its credit, the Panel’s report provides an excellent description of the uncertainty associated with the interpretation of laboratory and field study results as well as output from toxicokinetic and pharmacokinetic models. On the other hand, it is not entirely clear what specific advice or recommendations are being strongly supported by the SAB.

In reading the report, I surmised that, in many instances, Panel members were at variance with one another on many key scientific issues. Arguably, the inability

to achieve panel consensus on these issues is reflective of the broad range of uncertainty associated with this particular topic. Although I have no doubt that the divergent panelist opinions have scientific merit, providing the Agency with clear and unambiguous guidance as to how they should proceed to resolve uncertainties would enhance the strength of the report.

Minor Edit:

Page 9 Line 17 – I think the word “uncertainly” should be changed to “uncertainty”.

6. Dr. Jana Milford

I have a few minor comments/questions regarding the draft review of the PFOA Risk Assessment. I thought the SAB panel did a good job of addressing the charge questions and found the report well written and well organized. My minor comments are as follows:

1) I don't know if there is a style convention that argues against this, but I felt the executive summary would have benefited from a few citations in places where the panel was referring to one or a few studies that were critical to their points. For example, on p. 5, lines 2-14, the clarity of the presentation would have been helped by citing the Yang et al. (2002) study.

2) On p. 14, lines 28-35, it's not clear whether the statement that compartmental modeling "provides a sound approach" is an assertion by EPA or a conclusion of the panel. I believe this section is meant to be laying out the issues the panel is reviewing, so it should be the former, but that could be clarified.

3) On p. 31, lines 36-40, the panel says that EPA used LOAEL-driven MOE calculations instead of "more appropriate Bench Mark Dose methodologies." This statement seems like it warrants some explanation -- if Bench Mark Dose methods are more appropriate, why didn't EPA use them, and why isn't the panel suggesting they use them? Maybe I missed that explanation somewhere?

7. Dr. Granger Morgan

I've read the PFOA document. Looks to me to be in good shape (except that as usual it is full of duplication).

8. Dr. Rebecca Parkin

I am fine with this report. I found it to be well-written, clear, logical and the conclusions appropriately supported. I have no edits or comments for improvements

9. Dr. Kristin Shrader-Frechette

Sorry not to be able to join you for the PFOA discussion. The report is very good, and I agree with it. I have minor points that would help clarify its message, but substantively, it is superb.

10. Dr. Valerie Thomas

She concurs with the report.