

**DRAFT MINUTES FROM THE EPA SCIENCE ADVISORY BOARD**  
**Perflouroctanoic Acid (PFOA) Draft Risk Assessment Review Panel**  
**Telephone Conference Meeting**  
**July 6, 2005**

**PURPOSE:** The Perflouroctanoic Acid (PFOA) Draft Risk Assessment Review Panel of the EPA Science Advisory Board (SAB) met on July 6, 2005 via telephone. The purpose of the teleconference meeting was for the SAB PFOA Review Panel to review their draft report and to discuss revisions. Attachment A is the Federal Register notice announcing the teleconference (70 FR 8, January 12, 2005). A meeting agenda is included as Attachment B.

**LOCATION:** SAB Conference Center, Woodies Building, 3<sup>rd</sup> floor, 1025 F St., NW, Washington, DC

**DATE AND TIME:** July 6, 2005, 8:30 - 5:00 pm Eastern Time.

**PARTICIPANTS:** The following individuals participated in this meeting: PFOA Review Panel Members - Drs. Deborah Cory-Slechta (Chair), James Kehrer, Norman Drinkwater, James Klaunig, Ron Melnick, Ernest Abel, Thomas Zoeller, Steve Roberts, Mathew Longnecker, Michael Kamrin, Melvin Andersen, William Hayton, Frank Mink, George Corcoran, David Ozonoff, and Anne Sweeney. The PFOA Review Panel roster is included as Attachment C and a set of biographical sketches is included in Attachment D. SAB Staff - Dr. Vanessa Vu, SAB Staff Office Director, and Dr. Sue Shallal, Designated Federal Officers (DFO); EPA Staff Presenter - Dr. Jennifer Seed of the EPA Office of Pollution Prevention and Toxics; Other Participants – Approximately 80 other EPA Staff and members of the public were registered to listen in (Attachment E)

**MEETING SUMMARY:** The meeting followed the agenda (Attachment B). A summary of the meeting follows.

Convene the Meeting and Introductory Remarks – Dr. Suhair Shallal, Designated Federal Officer (DFO), opened the meeting at 2:00 pm. She presented background information on the SAB panel formation process and the previous meetings, and on the January teleconference and the February face-to-face meeting of the PFOA Review Panel. She informed the audience that the SAB operates under the rules and regulations of FACA where all meeting that have deliberations are held in public. She also reminded the members of the panel and the audience that the background materials for this review are located on the SAB website; this includes the draft panel report being discussed during the teleconference (Attachment F).

Dr. Cory-Slechta then reviewed the agenda and explained the purpose of the teleconference. She stated that we will begin with comments from the Agency and the panel members will be able to ask questions. Then members of the public, namely

representatives from Dupont and 3M, will present oral comments and the panel members may ask questions of them. She then outlined the procedure she will use to make sure that all panel members have an opportunity to make comments, namely to call on each members and determine if they wish to make any comments. The desired outcome of this teleconference is that we are able to agree to transmit the report pending changes to the chartered SAB for approval, she said.

Dr. Jennifer Seed reminded the panel that as new data is developed, the draft risk assessment will be revised as appropriate. She then presented the Agency's request for clarification (Attachment G). She sought clarification on the panel's comments regarding the use of human epidemiology data. Dr. Seed also asked that the Executive Summary be revised to reflect the information in the body of the report. Panel members had no questions for Dr. Seed.

Dr. Cory –Slechta asked the public commenters to proceed with their presentations

**Public comments from Dupont and 3M.**

David Boothe of Dupont introduced the 2 presenters that are speaking on behalf of Dupont, Dr. John Vanden Heuvel and Dr. Gerry Kennedy.

Dr. Vanden Heuvel began by introducing himself as an Associate Professor of Molecular Toxicology. He said that he is currently with Penn State and has spent 15 years studying perfluorinated chemicals. He stated that the target of PFOA is hypothesized to function through 5 proteins PPAR  $\alpha$ ,  $\beta$ ,  $\gamma$ , LSR  $\alpha$  and LSR  $\beta$ . The mouse, rat and human forms have been compared with pharmaceuticals in regard to the potency and efficacy. PFOA is found to be less efficacious and less potent. PFOA is a weak activator of PPAR  $\alpha$  and has low carcinogenic potential, he said.

Dr Zoeller had a question regarding the type of experiments that were done to ascertain this. Are they binding or reporter assays?

Dr. Vanden Heuvel responded that they were reporter assays. He stated that chimeric receptor systems were used, one for each species.

Dr. Zoeller commented that this meant if there are fewer receptors then the assay would be less sensitive.

There are expression differences in different species- the events after binding are unknown, Dr Vanden Heuvel said. PPAR  $\alpha$  is found in 2 pools, in the cytosol and in the nucleus bound to DNA.

There were no further questions for Dr. Vanden Heuvel and Dr Gerry Kennedy was the next presenter.

Dr. Kennedy presented information regarding the epidemiology studies from 2 investigations at the Washington Works Plant. He stated that the study looked at

approximately 1000 workers. They were given a physical exam that looked at health and work history. They underwent testing, including a pulmonary index of exposure and measurement of blood levels of PFOA. Fifty two clinical chemistry and hematology parameters were tested.

They were stated to be healthy individuals. For most of the measurements, no association with PFOA levels was found. Cholesterol levels of 215 U LDL compared to 200-208 U were seen. Their PFOA levels in blood were 0.5-2.5 ppm with some at 10 ppm.

A retrospective study on retired workers was also conducted.

Dr. Longnecker asked about the level of triglycerides. Dr. Kennedy responded that the level of triglycerides was 10 mg/dl.

Dr. Melnick commented that some pharmaceuticals lower cholesterol and triglycerides through a PPAR alpha activation pathway yet there is an increase shown in these studies, why?

Dr. Kennedy stated that there is no direct cause and effect relationship that can be ascertained from the current study.

There were no further questions for Dr. Kennedy. Michael Santoro, a representative of 3M, introduced the 3 representatives speaking on behalf of 3M, Dr. Jerry Hadisty, Dr. Geary Olsen, and Dr. John Buttenoff.

Dr. Hardisty introduced himself as a Veterinary Pathologist and provided a summary of the findings of a Pathology Working Group (PWG) of three pathologists (Drs. Wilson, Ray Brown and Eugene McConnell) sponsored by 3M to reexamine the mammary tumor data of the Sibenski et al study. Dr Hardisty was the chair of the PWG. He stated that the PWG arrived at a consensus diagnosis after applying current toxicological criteria to the review of the tumor histopathology. There were only minor differences compared to the original determinations; the PWG reclassified globular hyperplasia as fibroadenoma. The PWG concluded that the chronic dietary administration of PFOA did not affect the incidence of tumors in female Sprague-Dawley Rats, Dr. Hardisty said.

Dr. Drinkwater asked if only animals that survived were considered in the calculation of tumor incidence. Dr. Hardisty responded that it was a survival adjusted dose-response calculation.

Dr. Melnick asked if the diagnosis criteria were different. Dr. Hardisty responded that the criteria were similar, but the difference was that globular hyperplasia was classified as fibroadenoma. He added that they were under-diagnosed.

Dr. Melnick also asked that the National Toxicology Program's PWGs usually use 9-10 pathologists and only 3 pathologists were used here. Is this a problem? Dr. Hardisty responded that due to the vast experience of these pathologists, it was not a problem.

No other panelists had questions and Dr. Geary Olsen began his presentation.

Dr. Olsen commented that the draft PFOA report states on page 21, line 12, "In the PFOA Draft Risk Assessment document, review of the epidemiological studies, limitations of epidemiological studies are emphasized, while reports of certain adverse effects (cancer, heart disease, blood chemistries) are discounted, based on small numbers .....", which implies that cancer was one of the findings of the epidemiology data. This was not the case and there was however no reference offered to support this statement.

Dr. Ozonoff stated that it was difficult to hear the presentation. Dr. Olsen summarized his presentation for the panel again.<sup>1</sup>

No panel members had questions for Dr. Olsen and Dr. John Butenhoff presented next.

Dr. Butenhoff referred to p. 3 of the Draft report which deals with the cancer descriptor for PFOA. He stated that the classification of PFOA as a "likely" carcinogen overstates the actual case. Since the panel's recommendation is partly predicated on the possibility that PFOA may be causing mammary tumors and this has been discounted by the findings of the PWG that Dr Hardisty had summarized earlier, there is no longer a support for this classification.

There were no questions for Dr. Butenhoff.

Dr Cory-Slechta reminded panel members that, generally, only peer reviewed material would be accepted. She also stated that the draft PFOA risk assessment would be revised and the panel would encourage EPA to look at this information and review it. After each charge question, each Panel member was queried for comment, consensus and agreement as to whether revision of the text by the Chair could address any issues raised.

She then read the first charge question and asked Dr. Drinkwater, the group leader for Issue 1, to begin the discussion of Charge Question 1.

### **Issue 1-**

Dr. Drinkwater began by responding to the comments presented by Dr. Seed earlier. He stated that the available data suggests that the PPAR alpha mode of action (MOA) is responsible for liver tumors in rats. However, inconsistencies were discussed such as lack of increased liver weights in PPAR-null mice compared to the WYETH compound.

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<sup>1</sup> Dr. Olsen provided a hard copy of his comments to the panel after the teleconference concluded (Attachment H )

Apoptosis data was not available and the uncertainty in some data lead the panel to not be completely convinced that PPAR alpha was the only MOA. He also suggested an edit on p1, lines 45-46 (“.....an increase in the number of preneoplastic foci .....”) should be replaced with “induction of clonal expansion”.

After Dr. Drinkwater’s presentation, Dr. Cory-Slechta called on other issue 1 group members to make comments and then on each remaining panel member to add their comments.

Dr. Klaunig agreed with Dr. Drinkwater stating that PPAR alpha MOA was occurring in the rat liver, but data gaps are present. He added that the paper by Yang et al. was not conducted to look at liver effects but rather for immuno-modulation. He was concerned that too much emphasis was being placed on this paper. Dr. Klaunig noted that hyperplastic nodules should not be combined with carcinomas. He indicated that the lack of information on Kupffer cells does not necessarily relate to the carcinogenicity issues since these are only associative.

In response to EPA’s request for clarification, hyperplastic nodules and carcinomas should not be added. Also he stated that the lack of Kupffer Cells is not needed for PPAR alpha agonism. In a 2001 study of CD rats, PFOA was demonstrated to cause increase liver weights.

Dr. Kamrin stated that the range of opinions needs to be made clearer. The emphasis, he noted, should not be on the uncertainties but more on the idea that PPAR-alpha agonism is the MOA.

Dr. Melnick noted that there is inadequate information on apoptosis and cell proliferation and this needs to be added to the executive summary of the report. He continued that we do not know enough about the post activation processes as had been indicated by Dr. Vanden Heuvel and that there are additional uncertainties about PPAR alpha agonism as a sole MOA and that this needs to be included in the report. Unlike Dr. Klaunig, he believes that the liver weight differences between the Wyeth compound and PFOA in the Yang et al. study are straightforward, despite the focus of the study on immunomodulation and that Kupffer cells are important in the PPAR alpha MOA. In addition, PPAR alpha-null mice suggest that other MOA’s may be active.

Dr. Zoeller also indicated that he believed the PPAR alpha-null mouse study is pivotal. It is a good way to determine if this PPAR-alpha signaling pathway is active. While this study was not designed to look at liver effects, it cannot be ignored and must be considered in the MOA.

Dr. Corcoran agreed with Dr. Zoeller.

Dr. Drinkwater noted that the Panel had not reached a unanimous decision in its meeting but had achieved consensus on the issues as reflected in the document. He further agreed that the Yang et al study outcome should not be removed from the document.

Dr. Cory Slechta asked if there were any additional comments. She then asked panel members if they agreed that editorial changes were sufficient to address the concerns raised by panel members. She then read each panel member's name and asked them to respond.

Dr. Corcoran stated that the executive summary discussion of question 1 needed to be made clearer.

Dr. Drinkwater said the report does not overstate the importance of the Yang et al study.

Dr. Kehrer added that the changes seen in the liver may be unrelated to cancer.

Dr. Klaunig indicated that he agreed with the use of editorial changes to clarify and include the views of all panel members (minority views).

Drs. Ozonoff, Roberts and Sweeney agreed and added that a few iterations might be needed.

All other panel members had no additional comments and agreed to editorial changes to be made by Dr. Cory-Slechta.

## **Issue 2-**

Dr. Melnick began the discussion by referring to EPA's comments. He stated that the Panel did not intend for EPA to add the carcinoma and hyperplastic nodules data together; this was simply done to suggest a continuum of proliferative events exists. A microscopic and statistical reevaluation of the Sibinski study should be done.

He also noted that there were similarities between rat and monkey data. There is a lack of cell proliferation and apoptosis data for both rats and monkeys. There was an increase in Acyl-CoA and increase liver weight, neither have cell proliferation data.

Mitochondrial proliferation may not be related to the increase in liver weight; it may be due to growth factors. The discussion of the "likely" descriptor for cancer should be revised to state that there is no available data to estimate the likelihood or it should be made similar to the language found in the executive summary. He also stated that an independent review of mammary gland and liver tumors should be carried out using procedures comparable to those employed by the NTP.

Dr. Klaunig suggested that the adenomas and carcinomas should not be combined but considered separately. Tumor formation may be due to cell proliferation or a lack of apoptosis.

Dr. Drinkwater noted that the current cancer guidelines did not provide an ideal descriptor for the panel to select. Looking at all of the data, PFOA appears to fit best under the "likely" designation. Additionally, even without the mammary tumor data,

PFOA is still a multi-site carcinogen since there is no defined MOA for either the Leydig cell or pancreatic acinar cell tumors. He then pointed out an error on p. 3, line 15, it should read 15% not 5%.

Dr. Andersen said he did not think that the current data was sufficient to conduct a quantitative risk assessment. He also requested that the breadth of opinions should be presented. In his view at this time, the evidence was consistent with the descriptor 'suggestive'.

Dr. Corcoran had nothing more to add.

Dr. Hayton agreed with Dr. Andersen's comments regarding risk assessment.

Dr. Kamrin stated that the cancer descriptors should not be mentioned together with discussions of likelihood. He reiterated the need to include the breadth of opinions.

Dr. Kehrer noted that he felt the descriptor 'suggestive' was more appropriate but noted that PFOA is an unusual compound and that the rat was not a good model.

Dr. Melnick reminded panel members that the "likely" descriptor was arrived at by an examination of all the data and a determination of where it matched best with the Agency's cancer guidelines. The Panel report does refer to it as the "EPA descriptor". He pointed out that at the face-to-face Panel meeting there was consensus on the issue. Additional data can be used for reconsideration in the future.

Dr. Mink agreed with Dr. Melnick, he added that within the guidelines, we are correct.

Dr. Cory-Slechta then read an excerpt from the EPA cancer guidelines, "...*likely* does not relate to a quantifiable probability....".

Dr. Ozonoff recounted that during the face-to-face meeting, the panel had agreed the current evidence, without dealing with the uncertainties, goes beyond "suggestive".

Dr. Roberts had nothing further to add and Dr. Sweeney agreed with Dr. Ozonoff.

Dr. Zoeller also indicated agreement with Dr. Melnick.

Dr. Cory-Slechta said that she would add more text to try to clarify the range of opinions. All panel members agreed and had no further comments. She then asked Dr. Roberts to discuss question 3.

### **Issue 3**

Dr. Roberts began by addressing Dr. Seed's earlier request for clarification.

He said that the panel had suggested that a quantitative assessment of cancer risk and immunotoxicity risk should be done. He stressed the need for more data on neurotoxicologic effects and hormonal effects. Liver histopathology, other than cancer, lipid metabolism and developmental effects should be discussed in the Agency's draft PFOA risk assessment. The report's executive summary should be made clearer.

Dr. Abel emphasized the importance of neurotoxicology data.

Dr. Longnecker stated that he believed the human epidemiology data has not been reviewed and the executive summary should indicate there was not consensus on its utility.

Dr. Zoeller suggested that the report should be revised to address the Agency's comments. Comparing serum doses in different species is difficult since serum and tissue concentrations may be different in different species.

Dr. Kamrin said he thought the human epidemiology data should not be used.

Dr. Ozonoff questioned why the epidemiology data should not be used since they did reinforce the animal studies. He agreed that they did not inform the cancer effects however. He noted that the rationale provided by EPA for not using them was not appropriate.

Dr. Cory-Slechta stated that she would edit the report in order to clarify the research needs and clarify the use of the epidemiology studies. All panel members agreed. She then called on Dr. Melnick to discuss the panel's responses to issue 4a questions.

#### **Issue 4a**

Drs. Andersen, Hayton and Kamrin agreed that the report captures the discussion very well. Dr. Kamrin added that there are a few grammatical edits that are needed in the executive summary.

When Dr. Cory-Slechta asked if panel members had any further comments, no one did.

Dr. Hayton also suggested that a comment be added that states other approaches can be used, however, at this time the use of the AUC was a better approach.

Dr. Melnick questioned whether a comment about the validity or appropriateness of the steady-state assumption is needed.

Dr. Andersen responded that this comment could be included in Issue 4b. He also suggested that comments regarding the complexity of the kinetics of PFOA and the surrounding uncertainty should be added. The half-life as described in a one-

compartment model is not correct. There appears to be multiple stages in the elimination of PFOA.

Dr. Andersen responded to Dr. Seed's comments regarding the appendix discussing the use of tissue-based risk assessments and analyte. He stated the "analyte" does not refer to metabolites but the pool of PFOA and different bound forms. He also suggested that EPA undertake a general and PFOA-specific tissue-based risk assessment assumptions discussing dose metrics used, which ones, why, how they impact default values, etc.

No other panel members had comments. Dr. Cory-Slechta said she would add a few clarifications and otherwise this section is fine. All panel members agreed. She asked Dr. Mink to lead the discussion on issue 4b.

#### **Issue 4b**

Dr. Mink stated that the report accurately reflects the discussion of the panel.

Drs. Corcoran and Roberts concurred with Dr. Mink

Dr. Melnick again asked about the steady-state assumptions for children ages 2-12 years.

Dr. Anderson responded that due to the complexity of the metabolism of PFOA and its long half-life, a 2 year old may not have reached steady-state. There is not enough data.

All panel agreed with Dr. Cory-Slechta suggestion of making minor editorial changes. She then asked Dr Sweeney to present Issue 4c comments.

#### **Issue 4c**

Dr. Sweeney stated that she believed the epidemiology data from West Virginia residents should be used in the assessment. Dr. Sweeney added that the presentation of the data should be done in a more informative way.

Dr. Ozonoff had nothing further to add.

Dr. Longnecker questioned if the intent was to protect the general population or a highly exposed segment.

Dr. Kamrin added that this data on p.27 was not peer-reviewed. He further added that he did not agree with bullet 2 on page 21 of the report and the range of opinions should be clarified.

Dr. Melnick disagreed and said the human epidemiology data from the high exposure group should be included in the MOE analysis.

Dr. Ozonoff said the disqualification of the epidemiology study as discussed in the Agency's document and their rationale for not using this data is not valid.

Dr. Longnecker said he would provide some revised language to try to address the panel's concerns about bullet 2 on p. 21.

Dr. Cory-Slechta added that she will make edits to this section and all panel members agreed to this approach. She then asked if there are any further comments.

Dr. Melnick brought to the attention of the panel a statement on page 20 lines 16-19 and suggested that it be deleted or revised. Several thoughts appear to have been melded together and needed to be better defined. All panel members agreed.

Dr. Cory-Slechta then asked if any panel members had comments regarding the executive summary.

Dr. Kamrin stated that a better characterization of the breadth of opinions needed to be added. Dr. Klaunig agreed.

Dr. Longnecker suggested that the sentence on page 4 lines 13-15 should be revised to indicate that the epidemiology data were equivocal and endpoints should not be based on them.

Dr. Melnick asked to whom comments should be sent. He was asked to send them to Dr. Shallal, as were all panel members.

Dr. Ozonoff reminded panel members that there was a considerable amount of consensus in this panel and cautioned that there should not be an overemphasis of minority views.

Dr. Sweeney said she would work with Dr. Longnecker on the revised language he suggested.

Dr. Hayton said he had no further comments.

Dr. Mink agreed with Dr. Ozonoff as to the level of consensus at the face-to-face meeting.

Dr. Andersen wanted to respond to Dr. Ozonoff's comments. There was considerable discussion about the "likely" descriptor, he said and he agreed that there was consensus but was concerned about the addition of caveats. Terminology of "likely" carcinogen makes it appear more solid than it actually was.

Dr. Ozonoff suggested that adjustments be made to restore where the panel was before.

