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February 7, 2006

Dr. Granger Morgan, Chair
EPA Science Advisory Board
Science Advisory Board Staff Office (1400F)
c/o U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Dear Dr. Morgan:

Re: PFOA Risk Assessment Science Advisory Board

On behalf of E.I. DuPont de Nemours and Company (DuPont), I want to thank you for this opportunity to provide comments to the PFOA Review Panel of the EPA Science Advisory Board. The following comments pertain to the draft cover letter and draft report entitled *SAB Review of EPA's Draft Risk Assessment of Potential Human Health Effects Associated with PFOA and Its Salts*.

DuPont supports the SAB's strong recommendation to continue to strengthen its risk assessment by incorporating additional data as it becomes available. We also wish to compliment the EPA for its use of an internal dose approach in drafting a scientific-based, balanced risk assessment of PFOA.

DuPont requests that the Oversight SAB consider the following comments and recommendations to address process deficiencies which we believe have impacted the scientific conclusions of the SAB panel. These comments are provided in an effort to clarify and strengthen the EPA risk assessment through the SAB review process:

1. **Criteria for data inclusion/exclusion in the SAB review**

The SAB draft report states their exclusive use of peer-reviewed, published data which ignores potentially relevant scientific information and is inconsistent with the criteria used in the draft EPA risk assessment. The SAB draft report cites three unpublished studies, most notably the extensive use of the unpublished cancer study of Sibinski. While this study does, along with the study reported by Biegel, evaluate the tumorigenic potential of PFOA, other important reports such

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as that of the Pathology Working Group re-examination of the mammary gland tumors in the Sibinski study and the pathology review of the pancreatic tissue (in both long-term studies) are excluded from this analysis. To have a SAB review process not use all relevant scientific information, or worse, to selectively use the information, will clearly result in an incomplete and outdated review.

Criteria for data inclusion/exclusion needs to be clearly stated since new data, which could significantly alter the risk assessment, are always being generated and reported. The EPA draft risk assessment includes data that were available through June 2004. Significant additional data have been generated and provided to the SAB and the EPA since that time. Several of these studies directly addressed data gaps identified by the SAB.

We recommend that the SAB clarify what criteria were used for data inclusion/exclusion. If there is a cut-off date for data inclusion, this should be clearly stated in both the report and the cover letter. The criteria as currently stated in the draft report and the cover letter would require all references to non-published studies be removed from the draft report and all related conclusions and recommendations be reevaluated.

2. Evaluation of the incidence of mammary gland tumors in the 2-year rat study

The SAB draft report continues to state that female rats fed PFOA show an increased incidence of mammary gland tumors. This is not supported by either the original data or the data from an independent histopathology reevaluation as recommended by the SAB Review Panel. This Pathology Working Group, which is also used by the National Toxicology Program (NTP), reviewed the mammary gland slides from the Sibinski study and found no association between PFOA and incidence of tumors. The reevaluation found no statistically significant differences between the PFOA groups and the controls with regard to benign tumors, malignant tumors, or combined benign and malignant tumors.

The SAB based their conclusions solely by comparing the test group results with the concurrent control group. While it is agreed that the concurrent control group is most appropriate, to ignore historical control information, particularly for endpoints such as mammary gland tumors in the rat which are known to be highly variable, is inappropriate. The laboratory conducting the Sibinski study did not have an adequate historical control database as it was the only chronic study conducted at this laboratory at that time. Further, the NTP maintains a historical control database which includes animals of the same species and strain that are taken from studies at different test facilities. Indeed, the weight of evidence makes concluding a relationship between PFOA exposure and the increase in mammary gland tumors scientifically untenable based on the facts that the mammary gland incidence in the test groups was only marginally higher (and not

statistically significantly) than that of the concurrent controls and the incidence in the test groups was well within expected ranges for rats of this strain.

3. Cancer classification

DuPont does not believe that the weight of scientific evidence supports the descriptor of “likely to be carcinogenic” for the following reasons:

- PFOA is non-genotoxic
- PFOA does not cause an increase in mammary gland tumors or any other tumor types in female rats, hence it is not a multi-gender carcinogen
- PFOA produces benign tumors (tumor triad) in rats at the high dose tested. The previous assessment by experts in this area concluded that this tumor triad is mediated via PPAR- α .

Because of the significant toxicodynamic differences between the rat and human, it is unlikely that a carcinogenic response induced via the proposed MOAs for liver, Leydig-cell, and pancreatic acinar-cell tumorigenesis in rodents would occur in humans following exposure to PFOA, assuming that the proposed MOAs for Leydig-cell and pancreatic acinar-cell tumors are affirmed with additional investigation (Klaunig JE, et. al., 2003).

This previous conclusion is consistent with the EPA review where the SAB has stressed that there is an incomplete understanding of the MOA. However, the full mechanism of tumor induction is not known for any animal or human tumor and risk assessment decisions are and must be based on the weight of evidence from existing data. Hypothetical possibilities such as activation of the Kupffer cell need to be kept in perspective. The SAB notes that the full cascade of cellular effects leading to a carcinogenic response needs to involve cellular proliferation. We have commissioned and have preliminary (no final report) information that an early burst of cell proliferation occurs on Day 2 and 7 in rats fed PFOA. Decision on mode-of-action must be based on available data and a weight-of-evidence analysis.

Klaunig, JE, Babich, MA, Baetcke, KP, Cook, JC, Corton, JC, David, RM, DeLuca, JG, Lai, Dy, McKee, RH, Peters, JM, Roberts, RA, and Fenner-Crisp, PA. 2003. PPAR-alpha agonist-induced rodent tumors: modes of action and human relevance. Critical Reviews in Toxicology, 33:655-780.

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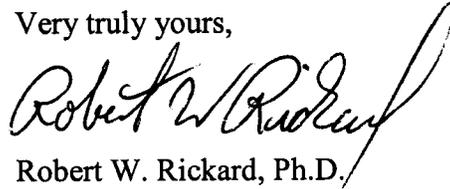
- *The PFOA primate study was conducted at an MTD and did not alter the key end-points identified in rats studies for the liver, testis, or pancreas, consistent with the conclusion that these events are unlikely to occur in humans. (Klaunig JE, et. al., 2003).*
- Epidemiology studies published to date, indicate no known health effects in workers at exposure level approximately 1000X the levels in the general population.

Although the MOAs for the tumor triad is not proven, the weight of evidence and conclusions expressed in the published, peer-reviewed literature indicates that PFOA probably is not a cancer risk to humans.

We recommend that this critical issue be thoroughly reviewed by the Oversight SAB given that the prevalent SAB panel opinion is inconsistent with the views of an expert panel published in the peer-reviewed literature.

In conclusion, we realize the challenge of reviewing a risk assessment for a compound with an extensive database that is growing rapidly. Throughout this review process, we provided scientific comments and new data from DuPont, as well as outside experts, to address gaps expressed by the SAB panel. We encourage the Oversight SAB to ensure that relevant scientific information that meets your quality standards receive appropriate attention and are adequately reflected in the final SAB report. We continue to support the SAB review process and will provide additional comments as requested.

Very truly yours,



Robert W. Rickard, Ph.D.
Science Director
Haskell Laboratory

RWR:jhh