

February 7, 2006



Science Advisory Board
In care of Mr. Thomas O. Miller, Designated Federal Officer
U. S. Environmental Protection Agency, Room 1400F
1200 Pennsylvania Avenue, NW.
Washington, DC 20460
via e-mail: miller.tom@epa.gov.

Re: SAB Review of Draft PFOA Panel Report

Dear Members of the Chartered Science Advisory Board:

3M appreciates the opportunity to comment on the draft PFOA panel report, and we appreciate the efforts of the chartered SAB to review the panel's draft report on such short notice. Careful review of the panel's draft report is particularly important in this instance, because the draft fails to meet the requirement of being "clear and logical."¹

Before making comments of a technical nature, 3M wishes to note important procedural inconsistencies. The panel has selectively relied on unpublished data, despite statements in the January 20, 2006 draft transmittal letter that the panel considered "only peer-reviewed published evidence." The first page of the Executive Summary in the draft report asserts: "It is important to note that all of the key findings and recommendations from the Panel deliberations were based on currently available peer-reviewed, published data." This is not the case. The panel has considered unpublished data in a number of cases, and excluded it in others.

We note four particular areas in which the draft report falls short of being clear, logical, objective:

- **Mammary Tumors.** One of the two cancer studies on which the panel relies heavily² is unpublished (Sibinski 1987). We appreciate there is unpublished data the panel *should* consider in its review, either because EPA has quality reviewed the data or because other

¹ According to the meeting notice and under SAB literature, the chartered SAB is to consider whether: (i) the charge to the review panel has been adequately addressed in the draft report, (ii) the draft report is clear and logical, and (iii) the conclusions drawn or recommendations made in the draft report are supported by the body of the report.

² The published Biegel et al. single-dose study of male rats found liver, pancreatic acinar cell and Leydig cell tumors at 300 ppm in diet. The Sibinski study used male and female rats, and doses of 30 and 300 ppm. The study found an increase in Leydig cell tumors at the high dose in the male rats, but did not find excess liver or pancreatic tumors. The study showed mammary tumors in female rats at essentially the same incidence over the ten-fold dose range and within the bounds of historical control data.

indicia of reliability including peer review are present. Our concern is that the panel failed to consider a pathology working group review of mammary tumors in the Sibinski study. The report of an independent pathology working group review of mammary tumors was provided to the Panel in writing and then orally at the July 2005 meeting. The review found no excess of benign or malignant mammary tumors associated with PFOA. This is consistent with the conclusion of the original study authors, who concluded that the mammary tumors that occurred in the study were not causally related to PFOA treatment. Yet, the draft panel report reads as if the pathology review does not even exist. At the very least, the panel should acknowledge the existence of the pathology review, and discuss the potential impact of this review on the cancer classification. By reaching a different conclusion from EPA and the study authors, and failing to consider or even acknowledge the pathology review, the panel has treated PFOA as a multi-gender and multi-site tumorigen in the Sibinski study, when in fact, only testicular Leydig cell tumors were causally associated with PFOA treatment in that study.

- **Cancer Classification.** Consideration of both the unpublished Sibinski study and the pathology working group review of mammary tumors eliminates the issue of cancer in female rats. PFOA is not a “multi-gender” carcinogen, as the proposed SAB transmittal letter to the Administrator (p. ii) asserts. There are no longer two studies showing PFOA to be a multi-site carcinogen. The “predominant” view of the panel that PFOA should be classified as a “likely human carcinogen” then rests on the multi-site tumor incidence in one study -- the single-dose Biegel study -- not replicated in the Sibinski study using the same route of administration and dose, as well as the same gender, species, strain, and supplier of rats. The panel agrees the liver tumor incidence in the Biegel study “likely results from a PPAR-alpha MOA” (draft report p. 1), but some members believe that the weight of evidence supporting a PPAR- α mediated mode of action in the case of Leydig cell and pancreatic acinar cell tumors is not strong enough to support any conclusion on the human relevance of these two tumor types (draft report p. 2), even though these tumors are extremely rare in humans.

The panel was divided over the cancer classification for PFOA at the public meetings, even with the erroneous assumption that PFOA is a multi-study, multi-site, multi-gender tumorigen in animals. The panel focused exclusively on a mechanical reading of EPA’s cancer classification guidelines, and was unable to achieve consensus on an appropriate category under the guidelines. Regardless of the descriptor used, however, the draft report fails to meaningfully describe the weight of the evidence as to PFOA’s potential carcinogenicity. The EPA guidelines require narrative description as well as a shorthand descriptor. In this case, the draft report lacks any context enabling the reader to understand the meaning of the cancer classification or the overall weight of the evidence, as evidenced by literally hundreds of press reports misconstruing the draft report’s findings.

The draft report says the panel was “unwilling to assign a probability value” to the likelihood of cancer. This does not adequately communicate the weight of the evidence,

which suggests PFOA is unlikely to cause cancer in humans. The panel should include all relevant considerations in a weight-of-evidence approach in its report. PFOA is a weak, non-genotoxic, tumorigen in rodents, known to be a PPAR α agonist, associated in a single study (Biegel et al. 2001) with a triad of primarily benign tumors (liver, Leydig cell and pancreatic acinar cell) known to be associated with other PPAR α agonist compounds. In the Sibinski study, only Leydig cell tumors can be reasonably associated with PFOA treatment, even though the 300 ppm dietary dose, gender, species, strain, and supplier were in common between the Biegel and Sibinski studies. There is no evidence of increases in any of these tumors in PFOA production workers who are exposed at levels roughly three orders of magnitude above the general population.

Moreover, if the tumors were relevant to humans, a published risk assessment³ not cited by the panel is reassuring. In that publication, EPA methodology was used to develop a benchmark dose for the Leydig cell adenomas in the Sibinski study, the only tumor endpoint on which dose-response data are available. The LBMD₁₀ of 100 ppm in diet for a lifetime conservatively equated to a PFOA serum concentration (LBMIC₁₀) of 125 ug/mL as a point of departure. Comparing this to the 95 % upper confidence limit of the estimate of the 95th percentile general population serum concentration of PFOA (0.014 ug/mL) produced a Margin of Exposure of 8900.

- **Human Health and Exposure Data.** There was not a charge question to the Panel related to the human health data, and the panel did not review the epidemiology data. Accordingly, any characterization of a large, complex data set not reviewed by the panel has no place in the panel's report. For example, the draft report asserts that there is evidence that cholesterol and triglycerides are altered in fluorochemical production workers and may be related to a possible increased risk of cerebrovascular mortality. Such a conclusion is not supported by the authors of either the medical monitoring studies or the mortality studies (published or unpublished), nor is the draft report's statement consistent with the weight of the evidence.

In referring to "highly exposed" non-occupational populations, the draft report also takes at face value unpublished human exposure biomonitoring data collected and submitted to the panel by a personal injury attorney, unaccompanied by any analytical method information or QA/QC data.

- **Reduction in Uncertainty from Use of Serum Concentrations for Risk Assessment.** The draft report acknowledges the reduced uncertainty in this risk assessment due to the use of internal serum comparisons rather than administered dose. It seems inconsistent for the draft transmittal letter and report to suggest the panel recommends retention of a default uncertainty factor for cross-species extrapolation while acknowledging that

³ Butenhoff, J.L., David W. Gaylor, John A. Moore, Geary W. Olsen, Joseph Rodricks, Jeffrey H. Mandel, and Larry R. Zobel, "Characterization of risk for general population exposure to perfluorooctanoate," *Regulatory Toxicology and Pharmacology* 39:363–380 (2004).

uncertainty is reduced. The panel did not reach a conclusion on the toxicodynamic factor, but said that the interspecies toxicokinetic uncertainty factor would be between 1 and 3, rather than the default factor of 3.

DISCUSSION

1. Evaluation of Mammary Tumors

The unpublished Sibinski study (available in EPA's AR-226 docket and reviewed by EPA) observed mammary gland fibroadenomas in the female rats, with no difference in incidence over the ten-fold dose range used in the study. The authors of this study concluded that the mammary tumor data did not reflect an effect of treatment: "Although the incidence of fibroadenomas in the high-dose females was significantly greater than that for the control females, the incidence was similar to that reported for untreated aging rats. In addition, when the incidence of benign mammary gland tumors (adenoma and fibroadenoma) are combined, the tumor incidence in the high-dose group is no longer statistically significant." (Sibinski, p. 22) The combined incidence of these benign tumors has long been used as the appropriate criterion for classification of mammary tumors. (Van Zwieten, 1984; McConnell et al., 1986)

Comments previously provided to the SAB panel by the 3M Medical Department (Drs. John Butenhoff, Geary Olsen and Larry Zobel, April 18, 2005) detailed the rationale that combined tumor (fibroadenoma and adenoma) as well as the historical control data demonstrated that the fibroadenoma incidence in the Sibinski study should not be interpreted as representing a treatment-related effect. The panel is silent as to evaluating the benign adenomas and fibroadenomas together, but its draft report "deemed inappropriate" EPA's decision to use historic controls in this particular case (draft report p. 6). The draft report concludes that benign mammary fibroadenomas were elevated in the study, and hence that PFOA is a multi-gender carcinogen. Thus, the panel, after only brief discussion, reached a different conclusion from EPA, the study authors, and a pathology working group.

When the panel expressed concerns about mammary tumors and concurrent controls in its initial meeting based on arguments presented by an Environmental Working Group presenter who was not a pathologist, 3M and DuPont commissioned an independent pathology working group to review all of the mammary tissues from the Sibinski study conducted in 1983 using modern pathology criteria. Four board-certified veterinary pathologists convened and examined the mammary tissues from the study, without knowledge of treatment group.⁴ The report from this pathology working group was presented to the panel on June 27, 2005 with a cover letter from Dr. Zobel of 3M. Dr. Jerry Hardisty of Experimental Pathology Laboratories (EPL) presented the findings to the PFOA review panel at its teleconference on July 6, 2005.

⁴ The reviewing pathologist was Dr. Gabrielle Willson. Dr. Jerry Hardisty convened the review panel of Dr. Willson, Dr. E. Eugene McConnell, and Dr. Ray Brown. They applied diagnostic criteria and nomenclature of the Society of Toxicological Pathologists (Mann et al. 1996).

The existence of this pathology working group report is never mentioned in the panel's draft report. Instead, the draft report (at page 17) urges that a pathology working group be conducted to address both liver and mammary tumors. This is inexplicable. While we recognize the pathology working group report is as yet unpublished, it does represent a peer review of the original pathologist's diagnoses from the study, which is also unpublished.

The EPL report concluded:

[T]he incidence of mammary gland neoplasms in the study was not affected by chronic dietary administration of PFOA. The morphologic appearance, overall incidence, and distribution of the neoplasms observed in the treated and control animals were similar."

Furthermore:

- There were no statistically significant differences in the incidence of fibroadenoma, adenocarcinoma, total benign neoplasms or total malignant neoplasms between control and treated animals using Fisher's Exact Test for pairwise comparison (page 11 of report).
- Combining benign and malignant neoplasms was not recommended. However, even if combined, there was no significant difference between control and treated groups. (page 11 of report)
- None of the tumor types or combinations of tumor types exhibited statistically significant survival-adjusted dose-response trends. (page 20 of report)
- There was no increase in tumor multiplicity or incidence with dose between control and treated groups. (page 11 of report)

Despite calling for a pathology working group review, and being provided with a pathology working group review of the mammary tumors, the panel's draft report states that "many panel members therefore believe that the elevated tumor rates observed in female rats in the Sibinski (1987) study raise concerns for neoplastic effects induced by PFOA in the mammary gland that should not be dismissed." However, neither EPA, the original study authors, nor the pathology working group members who have actually reviewed the tissues attributed a significant increase in mammary tumors to PFOA. The panel concluded otherwise without reviewing the tissues or the pathology criteria for mammary tumors.

2. Cancer Classification

a. Impact of the Mammary Tumor Data on the Cancer Classification

The selective consideration of available data has significant ramifications for the substantive conclusions of the panel's report, not just the fairness and objectivity of the SAB process.

Page ii of the draft transmittal letter to be signed by the chartered SAB states:

The predominant Panel view was that the experimental weight of evidence regarding the human carcinogenic potential of PFOA was more consistent with the Agency's descriptor of "likely to be carcinogenic" as described in the EPA Guidelines for Carcinogen Risk Assessment since laboratory studies in rats show that PFOA is a multi-site and multi-gender carcinogen. (Emphasis added.)

Had the panel not disregarded the available data, the report would have reached a different conclusion regarding the evidence for carcinogenicity in female rats, and may well have reached a different conclusion regarding the appropriate classification of PFOA under EPA's guidelines. Removing the multi-gender issue, the "predominant" view of the panel rests on the multi-site tumor incidence in the single-dose Biegel study, not replicated in the Sibinski study in the same strain of male rats at the same dose. And, the panel agrees that the liver tumors are "likely due to PPAR alpha MOA" (draft report p. 1).

3M provided a discussion of the criteria and examples from EPA's classification guidelines, and an analysis of how they apply to PFOA, in comments submitted to the panel on April 18, 2005 at Appendix A. That discussion is re-printed as Appendix A to these comments.⁵

b. Clarity with Regard to Weight of the Evidence

In evaluating the appropriate cancer descriptor for PFOA, the Panel was unable to reach consensus on how to apply the guidelines. While the panel belabored how to apply a cancer descriptor, it lost sight of the overall weight of the evidence.

On page 19, the draft report acknowledges that the panel understands that a shorthand descriptor alone is not adequate to communicate the weight of the evidence:

The meaning of terms such as "suggestive evidence of carcinogenic potential" or "likely to be carcinogenic to humans" may differ among some in the general public and the EPA because of differences in perception and intent. Hence, EPA recommends a weight-of-evidence narrative that explains the complexity of issues

⁵ We note that the examples in the EPA guidelines are just that - examples, not to be applied by rote. EPA has classified other compounds as having "suggestive" evidence even with evidence of multiple tumors in multiple species, sexes and studies. See, e.g., compounds such as Fluazinam and Ziram classified as having "Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential" on EPA's Office of Pesticide Program's List of Chemicals Evaluated for Carcinogenic Potential (7/19/04).

influencing an agent's carcinogenic potential in humans. . . . EPA also cautions that terms such as "likely," when used as a weight-of-evidence descriptor, do not correspond to a quantifiable probability.

The draft report states that those panel members favoring classification of PFOA as a "likely human carcinogen" "were not willing to ascribe an associated probability value to the potential for PFOA-induced carcinogenicity." (p. 6; see also page 23) However, this is simply too cryptic a statement to convey to readers that the overall evidence does not lead experts to conclude that PFOA is likely to cause cancer in humans at actual exposure levels. Laypersons, and even trained scientists not steeped in EPA's classification guidelines, have and will misinterpret whatever shorthand descriptor is applied without clarification as to the overall weight of the evidence. This is evidenced by hundreds of headlines reporting that the panel has branded PFOA as "likely" to cause cancer in humans -- in the ordinary sense of the word "likely."⁶ At the February public meeting, the panel appeared to agree that they did not intend the classification based on animal data to imply that PFOA is actually likely to cause cancer in humans, in the sense of "more likely than not." This is a distinction the press and public cannot apprehend from the language of the draft report.

EPA's guidelines stress the importance of a narrative description to explain the weight of the evidence. Given the significant attention focused on PFOA and on this SAB review, the report needs to provide meaningful context for whatever descriptor is selected.

In short, all the following considerations bear on the question whether PFOA really is a "likely human carcinogen":

- PFOA is not genotoxic. It is a known PPAR α agonist.

⁶ See, e.g., *United Press International* (multiple outlets), 30 June 2005 ("A chemical DuPont Co. uses to make the non-stick covering Teflon is likely to cause cancer, an independent panel concluded."); *The Philadelphia Inquirer*, 29 June 2005 ("A mysterious chemical is linked to the coatings on take-out food cartons and raincoats is "likely" to cause cancer in humans, according to a draft report by a panel of an independent advisory board to the U.S. Environmental Protection Agency."); *The Washington Post*, 29 June 2005 ("The Environmental Protection Agency's own scientific advisory panel has identified perfluorooctanoic acid, a chemical compound used to make Teflon, as a "likely carcinogen" in a report it plans to submit to the agency next month."); *Associated Press* (multiple outlets), 30 January 2006 ("A chemical used in the manufacture of Teflon and other nonstick and stain-resistant products should be considered a "likely" carcinogen, according to an independent scientific review panel advising the Environmental Protection Agency."); *The Wall Street Journal*, 31 January 2006 (Yesterday, an EPA advisory group issued a statement, saying the majority of its members agree that the main chemical under review -- perfluorooctanoic acid, or PFOA -- is a "likely" cancer-causing agent.)

- The only PFOA-treatment-related increase in tumors found in both studies was in testicular Leydig cell tumors, and there was a statistically significant increase only at the high dose in the Sibinski study.
- A margin of exposure of 8900 was derived for Leydig cell tumors based on the lower 95% confidence limit of the benchmark internal concentration for Leydig cell tumors from the Sibinski study compared to the upper bound estimate of the 95th percentile general population serum PFOA concentration.⁷
- Leydig cell and pancreatic acinar cell tumors are extremely rare in humans. Aging rats are prone to Leydig cell tumors, but “The incidence of Leydig cell tumors in human patients, in comparison to rodents, is extremely rare, something on the order of 1 in 5 million. . . . Ninety or more percent of Leydig cell tumors in humans are benign. . . .” Casarett & Doull’s Toxicology, 6th edition (2001), page 741.
- All panel members acknowledge the evidence is strong (if not absolutely definitive) that PFOA-induced liver tumors seen only in one of two studies at the same dose occurred through a mode of action likely not relevant to humans. There is no other known mode of action, as the panel acknowledges.
- The tumor triad including liver, pancreatic acinar cell and Leydig cell tumors is often found in studies of peroxisome proliferators in rodents.⁸
- The mode of action for Leydig and pancreatic tumors in rodents has not been fully elucidated, but they appear to involve a non-genotoxic mechanism which may be linked to PPAR- α activation and is unlikely to operate at human exposure levels.⁹
- The draft report fails to note the absence of any significantly increased cancer risk in the worker mortality studies of any of these types of tumors.

The chartered SAB would serve the public interest by adding clarification as to the meaning of EPA’s descriptors versus the overall weight of the evidence, particularly in light of the splintered panel and the extent to which the draft report has already been misconstrued.

3. Human Studies

a. Human Health Endpoints

There was no charge question asking the panel to comment on the human data on PFOA, which includes over 25 years of medical monitoring data on 3M’s PFOA

⁷ Butenhoff, J.L., David W. Gaylor, John A. Moore, Geary W. Olsen, Joseph Rodricks, Jeffrey H. Mandel, and Larry R. Zobel, “Characterization of risk for general population exposure to perfluorooctanoate,” *Regulatory Toxicology and Pharmacology* 39:363–380 (2004).

⁸ See Table 35, page 750 of Klaunig, et al., PPAR alpha agonist-induced rodent tumors: modes of action and human relevance, *Critical Reviews in Toxicology* 33:655-780 (2003).

⁹ There is evidence supporting the hypothesis that the Leydig cell tumors stem from a sustained low-level increase in estradiol resulting from PFOA-induced PPAR α -mediated induction of aromatase, as proposed by Liu et. al., *Fund. & App. Tox.* 30:220-228 (1996).

production workers, along with multiple mortality studies. The panel nonetheless characterizes the human data in its discussion of endpoints, without having engaged in a rigorous review of those studies.¹⁰ Certainly all these reports warrant review by EPA, and it is legitimate for the SAB to suggest that EPA carefully consider the entire human data set. But any characterization of a complex data set not fully studied or discussed by the panel has no place in the panel's report.

For example, page 24 of the draft report states: "the evidence showing increases in cholesterol and triglyceride values in worker cohorts suggest increased risk of cerebrovascular disease [stroke] mortality." This statement is a vast oversimplification of an extensive dataset on lipid levels. Such a conclusion is not supported by the authors of either the medical monitoring studies or the mortality studies (published or unpublished), nor is the draft report's statement consistent with the weight of the evidence.¹¹ While the draft panel report provides no

¹⁰ The minutes of the July 6, 2005 teleconference of the panel (p. 8) note that "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."

¹¹ Medical monitoring studies addressing lipid levels in 3M production workers include

- Gilliland & Mandel, *Am.J Ind. Med.* 29:560-568 (1996) (reporting 1990 Cottage Grove monitoring);
- Olsen, et al., "Plasma Cholecystokinin and Hepatic Enzymes, Cholesterol and Lipoproteins in Ammonium Perfluorooctanoate Production Workers," *Drug and Chemical Toxicology* 23:603-620 (2000) (reporting 1993, 1995, 1997 Cottage Grove monitoring);
- Olsen, et al., "Assessment of Lipid Hepatic and Thyroid Function in Relation to an Occupational Biologic Limit Value for Perfluorooctanoate," EPA Docket AR226.1351 (reporting 2000 monitoring of Cottage Grove workers);
- Olsen, et al., "An Epidemiologic Investigation of Clinical Chemistries, Hematology and Hormones in Relation to Serum Levels of Perfluorooctanesulfonate in Male Fluorochemical Production Employees" (1998) EPA Docket AR226-0030;
- Olsen, et al., "A Cross-sectional Analysis of Serum Perfluorooctanesulfonate (PFOS) and Perfluorooctanoate (PFOA) in Relation to Clinical Chemistry, Thyroid Hormone, Hematology and Urinalysis Results from Male and Female Employee Participants of the 2000 Antwerp and Decatur Fluorochemical Medical Surveillance Program" (2001), EPA Docket AR226-1087;
- Olsen, et al., "A longitudinal analysis of serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) levels in relation to lipid and hepatic clinical chemistry test results from male employee participants of the 1994/95, 1997, and 2000 fluorochemical medical surveillance program" (2001), EPA Docket AR-226-1048.
- Olsen, et al., "Epidemiologic assessment of worker serum perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA) concentrations and medical surveillance examinations," *Journal of Occupational and Environmental Medicine* 45:260-270 (2003).

Studies addressing cerebrovascular effects include Alexander, "Mortality study of workers employed at the 3M Cottage Grove facility," U.S. EPA docket AR-226- 1030a018 (2001); Alexander, et al., "Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility" *Occup Environ Med* 60:722-29 (2003) (Decatur mortality study); and Olsen, et al.,

references with respect to cerebrovascular [stroke] mortality, we believe the panel refers to a single, unpublished report on 3M Cottage Grove plant workers (Alexander, 2001, EPA AR-226 docket 1030a018). Interestingly, the Alexander data were discussed in our April 18, 2005 letter to the panel, which was written in part to respond to the panel's first draft report that suggested PFOA was linked to cancer and heart disease as well as cerebrovascular disease. We note the panel has wisely stricken from its current draft the reference to human cancer and heart disease associations with PFOA. Nevertheless, the draft report still refers to cerebrovascular disease mortality while ignoring the dose-response analyses in that report that cast doubt on such an association. In fact, Dr. Alexander, the University of Minnesota author of that study, concludes that: "a causal association cannot be drawn between exposure to PFOA and death from cerebrovascular disease." (p.15, emphasis added).

b. Assertions about Human Exposure

The mammary tumor pathology peer review and the human health evidence are not the only instances in which the panel selectively used data. It appears that unpublished blood serum data on PFOA levels in a West Virginia/Ohio community submitted to the panel by a personal injury attorney without any accompanying quality control information or analytical validation *was* used by the panel.

The draft report states: "Many Panel members agreed that existing subpopulations of the general public are more highly exposed than those studied. . . ." (p. 7; see also page 29). The draft report provides no reference in support of the assertion that there are "highly exposed" non-occupational populations. However, the June 2005 draft panel report at page 6 expressly referred to reliance on public presentations for this information, although that acknowledgement no longer appears in the current draft panel report. Thus, the panel did rely on *some* information submitted during the public comment period.

After the panel's June 2005 draft report referred to highly exposed subpopulations, in August 2005, NIH-funded University of Pennsylvania researchers released data showing blood levels in the West Virginia/Ohio community are elevated above general population levels (they do not exceed 3M's occupational levels). The independent University of Pennsylvania researchers found no adverse health effects associated with PFOA exposure, and no elevation in cancer rates in the affected counties. See www.lhwc&study.org (PowerPoint slides; manuscript forthcoming).

We leave to EPA whether its draft general population risk assessment is the appropriate place for a site-specific evaluation of a local source. EPA does not typically conduct those two exercises together, and the two issues are analytically distinct.

4. Cross-species Uncertainty Factor

"Analysis of Episodes of Care in a Perfluorooctanesulfonyl Fluoride Production Facility,"
Journal of Environmental Medicine 46:837-46, 2004.

Finally, we note a fundamental internal inconsistency with respect to the uncertainty factor applied to address cross species extrapolation. The standard default factor is ten, consisting of a three-fold factor for differences in delivered dose to target organ if different species are given the same administered dose (toxicokinetics) and a three-fold factor for differences in inherent risk/susceptibility (toxicodynamics). The panel commends EPA for the use of internal serum concentration for risk assessment, and notes that, “[t]his new approach reduces the need to include uncertainties introduced by the use of administered or ambient doses as measures of exposure.” (draft report, p. 27) The report continues:

The internal dose analysis used in this document is considered by the Panel to be a significant step toward reducing uncertainty related to cross species extrapolation. Although reduced, however, cross species toxicokinetic uncertainty is not eliminated. . . . While it is difficult to assign a quantitative value to the magnitude of this uncertainty reduction, it can be stated that the toxicokinetic uncertainty value for PFOA would fall within the range of one to three, based on the customary scale of a value of 3 for each aspect of cross species extrapolation, pharmacokinetics and pharmacodynamics. (p. 27)

Nevertheless, the recommendation in the draft transmittal letter (p. ii) says that knowledge gaps “merit retention of the default uncertainty value” for cross-species extrapolation. (In fact, there are data available addressing some of the gaps to which the panel refers in the report.) It seems inconsistent to acknowledge that the use of internal concentration reduces uncertainty, to suggest that toxicokinetic uncertainty is within the range of 1 and 3, but then to conclude that the default uncertainty factor should be retained.

* * *

In sum, we appreciate there is unpublished data that the panel *should* consider in its review, either because EPA has quality reviewed data or because other indicia of reliability including peer review are present. We do, however, take exception to a lack of objectivity by including some non-peer-reviewed or unpublished data while purposely excluding other unpublished data, including the pathology working group review of mammary tumors that peer-reviewed the original unpublished study. This selective use of data presented to the panel taints the report’s evaluation and classification of PFOA. We urge the chartered SAB to revisit the cancer classification in light of the pathology review, and to provide sufficient context for both the cancer classification and weight of the evidence so that they can be understood by readers.

We also urge that the report avoid inaccurate and conclusory characterizations of the extensive human data, which was not fully addressed by the panel and not covered by the charge questions. In addition, the logical inconsistency of the panel’s agreement that serum comparisons reduce uncertainty with its conclusion that uncertainty factors should not be reduced should be addressed.

We appreciate your consideration and the important function you play in the PFOA review.

Respectfully submitted,

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Attachment:
Appendix A from 3M's April 18, 2005 comments to the panel

Appendix A from 3M's April 18, 2005 comments to the Panel on Cancer Classification

Appendix: Cancer classification discussion

The following four examples are given in EPA's final Cancer Risk Assessment Guidelines for the "suggestive" descriptor:

1. *"A small, and possibly not significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor, "Likely to be Carcinogenic to Humans." The study generally would not be contradicted by other studies of equal quality in the same population group or experimental system..."* (p.2-56; 70 Fed.Reg. p. 17793) – An association of increased cancer risk in worker populations exposed to PFOA has not been demonstrated in epidemiology studies currently available. While one study in male Sprague Dawley (SD) rats (Biegel et al., 2001) found significant increases in hepatocellular adenoma, pancreatic acinar cell adenoma, and testicular Leydig cell adenoma at the single dose of 300 ppm ammonium PFOA in the diet, a 3M-sponsored study (Sibinski et al., 1983) did not find increases in hepatocellular adenoma or pancreatic acinar cell adenoma in male and female SD rats at the two dose levels tested, 30 and 300 ppm ammonium PFOA in diet. Thus, only Leydig cell adenomas are seen in both studies.
2. *"A small increase in a tumor with a high background rate in that sex and strain, when there is some but insufficient evidence that the observed tumors may be due to intrinsic factors that cause background tumors and not due to the agent being assessed. (When there is a high background rate of a specific tumor in animals of a particular sex and strain, there may be biological factors operating independently of the agent that could be responsible for the development of the observed tumors.) In this case, the reasons that the tumors are not due to the agent are explained."* (p.2-56; 70 Fed.Reg. p.17793) – This applies to the incidences of mammary fibroadenoma observed in female SD rats treated with ammonium PFOA in the 3M cancer study (see discussion under Section 1, "Mammary Tumors," above).
3. *"Evidence of a positive response in a study whose power, design, or conduct limits the ability to draw confident conclusion (but does not make the study fatally flawed), but where the carcinogenic potential is strengthened by other lines of evidence (such as structure-activity relationships)." (p.2-56; 70 Fed.Reg. p.17793)* – The study in male Sprague Dawley rats reported by Biegel et al. (2001) found significant increases in hepatocellular adenoma, pancreatic acinar cell adenoma, and testicular Leydig cell adenoma at the single dose of 300 ppm ammonium PFOA in the diet; however, the 3M-sponsored study (Sibinski et al., 1983) did not find increases in hepatocellular adenoma or pancreatic acinar cell adenoma in male and female Sprague Dawley rats at the two dose levels tested, 30 and 300 ppm ammonium PFOA in diet. The Biegel et al. study was limited by a single dose and single sex. Therefore, with the exception of Leydig cell adenoma, there is not consistency between the two studies with respect to tumor outcome. However, PFOA is known to be a PPAR α agonist, and there is evidence that a

number of PPAR α agonists increase incidences of hepatocellular adenoma, pancreatic acinar cell adenoma, and testicular Leydig cell adenoma in male rats.

4. *“A statistically significant increase at one dose only, but no significant response at the other doses and no overall trend.”* (p.2-57; 70 Fed.Reg.p. 17793) – The increases in hepatocellular adenoma and pancreatic acinar cell adenoma in the Biegel et al. (2001) study were observed at the only study dose of 300 ppm ammonium PFOA in diet. In the 3M-sponsored study (Sibinski et al., 1983), Leydig cell tumors were statistically significant only at 300 ppm ammonium PFOA in the diet and not at 30 ppm.

By contrast the weight-of-evidence descriptor, “Likely to be Carcinogenic to Humans,” is not appropriate. Five examples of database attributes are used to illustrate when this descriptor may be appropriate and include:

1. *“An agent demonstrating a plausible (but not definitely causal) association between human exposure and cancer, in most cases with some supporting biological, experimental evidence, though not necessarily carcinogenicity data from animal experiments.”* (p.2-55; 70 Fed.Reg. p.17793) – This is not the case for PFOA, based on the epidemiology data available to date.
2. *“An agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans.”* (p.2-55; 70 Fed.Reg. p.17793) – Although there was an increase in tumors at three sites in male Sprague Dawley rats in the Biegel et al. (2001) study at the single dose of 300 ppm diet, guidance for the descriptor, “Suggestive Evidence of Carcinogenicity,” (see above discussion for that descriptor) offers a mitigating view of the applicability of this data to the “Likely to be Carcinogenic to Humans” descriptor.
3. *“A positive tumor study that raises additional biological concerns beyond that of a statistically significant result, for example, a high degree of malignancy, or an early age at onset.”* (p.2-55; 70 Fed.Reg. p.17793) – This is not the case for PFOA.
4. *“A rare animal tumor response in a single experiment that is assumed to be relevant to humans.”* (p.2-55; 70 Fed.Reg. p.17793) – With respect to the pancreatic acinar cell tumors (Biegel et al., 2001) and the Leydig cell tumors (Biegel et al, 2001; Sibinski et al., 1983) observed in male Sprague Dawley rats, the relevance of these tumors to humans is questionable, as they are rarely observed in humans. PFOA increased cell proliferation in the acinar pancreas of male rats in the Biegel et al. (2001) study; although, at some time points, acinar cell proliferation was increased in pair-fed controls. Ohmura et al. (1997) provided data demonstrating that another ligand for the PPAR α receptor, 4-chloro-6-(2,3-xylidino)-2-pyrimidinylthio-(N-beta-hydroxyethyl) acetamide, increases acinar cell proliferation of the rat pancreas (but not ductal or islet cell) proliferation. The recent development of the PPAR α -humanized mouse model by Cheung et al. (2004) and comparison of the hepatic proliferative response with the wild-type mouse demonstrated that the level of PPAR α protein expression was similar between the humanized mouse and

the wild-type mouse, and increased peroxisomal and mitochondrial oxidation and decreased serum triglycerides were seen in both humanized and wild-type mice compared to respective controls when treated with the model potent PPAR α agonist, WY-14643. However, only the wild-type mouse responded to WY-14643 with increased hepatic cell proliferation. These differences between the humanized and wild-type mice may help to explain the apparent refractiveness of humans to liver tumors from fibrate hypolipidemic agents and PPAR α agonists in general.

5. *“A positive tumor study that is strengthened by other lines of evidence, for example, either plausible (but not definitely causal) association between human exposure and cancer or evidence that the agent or an important metabolite causes events generally known to be associated with tumor formation (such as DNA reactivity or effects on cell growth control) likely to be related to the tumor response in this case.”* (p.2-55; 70 Fed.Reg. p.17793) – There is currently no plausible causal association between human exposure to PFOA and cancer, and PFOA has not been shown to react with DNA. Other than hyperplastic areas in aging rats, increased cell proliferation was only observed in the acinar pancreas of male rats treated with 300 μ g PFOA/g diet (Biegel et al., 2001).

The database on oncogenic effects of PFOA does not provide compelling evidence that PFOA would pose a likely risk of cancer to humans. The lack of increased cancer mortality risk in occupationally-exposed populations and the potential role of PPAR α -mediated modes of action in the observed rat tumors together with the low expression of PPAR α in humans and lack of proliferative response to WY-14643 in PPAR α -humanized mice, and variable responses in two rat carcinogenicity studies all argue for the descriptor “Suggestive Evidence of Cancer Risk” rather than “Likely to be Carcinogenic to Humans.”