ADDITIONAL COMMENTS OF 3M COMPANY

TO THE EPA SCIENCE ADVISORY BOARD

PFOA REVIEW PANEL

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3M appreciates the opportunity to provide additional comments to the members of the U.S. EPA Science Advisory Board (SAB) Perfluorooctanoic Acid Risk Assessment review panel. These comments address specific issues that arose during the Panel's discussions at the February 2005 public meeting.[1] The SAB staff has advised us that the Panel would be willing to entertain such comments.

In these comments, we briefly address the issues of mammary tumors in rats, the overall cancer descriptor, pituitary weights in rats, mitochondrial effects of PFOA, ataxia and other neurotoxic endpoints, and characterization of the epidemiologic data.

1. Mammary Gland Tumors in Rats

The incidence of mammary gland fibroadenomas in the 3M cancer study with ammonium PFOA in female Sprague Dawley (SD) rats (Sibinski 1983) was 22%, 42%, and 48% at dietary treatment levels of 0, 30, and 300 ppm ammonium PFOA diet, respectively. There was no apparent difference in incidence over a ten-fold dose range. The authors of this study concluded that the mammary tumor data did not reflect an effect of treatment with ammonium PFOA due to the high background incidence of this tumor type in female SD rats: "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 1983, p. 22.)

The latter point notes the effect of combining the incidence of fibroadenomas and adenomas on evaluation of the mammary tumor data. Mammary tumors in rats present as a continuum from benign to malignant. They range from tumors of primarily epithelial cells to various degrees of connective tissue involvement. From a biological perspective, both adenomas and fibroadenomas are classified as benign fibroepithelial tumors. It is appropriate to combine adenomas, adenofibromas, and fibroadenomas of the mammary gland of the rat, and this has long been used as a guideline for evaluation of tumor data (Van Zwieten, 1984; McConnell et al., 1986).

Although the laboratory conducting the study, Riker Pharmaceuticals, did not have an adequate historical control database at the time the chronic study was done in

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[1] 3M, and Drs. Jack Moore and Joe Rodricks at our behest, provided written comments to the Panel prior to the meeting and testimony at the meeting. In addition, we have provided the Panel with a copy of our published risk assessment, which references many additional publications. Butenhoff et al., "Characterization of Risk for General Population Exposure to Perfluorooctanoate," in *Regulatory Toxicology and Pharmacology* 39:363-380 (2004). We also distributed to the panel during the meeting a pre-publication copy of our reply to the Environmental Working Group's Letter to the Editor responding to this publication.

1983, two historical control databases exist for female SD rats which suggest that the incidences of mammary fibroadenoma observed in the 3M study were well within the experience for female SD rats in chronic studies from 1984 – 2002. Historical control data for CRL:CD® (SD) female rats from 31 studies initiated or reported between 1989 and 2002 (http://www.criver.com/techdocs/documents/toxdata_2004.pdf) shows that the mean mammary fibroadenoma incidence is 38% with standard deviation of 13% and a range of 13 – 62%. In addition, historical control data is available from 13 chronic toxicity/oncogenicity studies conducted at DuPont Haskell Laboratory from 1984-87. These DuPont data provided 947 control female rats of the same strain (SD) and from the same supplier (Charles River) as the 3M study, and included female rats which were on test for at least one year (scheduled sacrifice at two years). Statistical evaluation of the incidence of fibroadenomas in the 3M ammonium PFOA-treated groups versus the Haskell Laboratory historical controls was not significant ($p = 0.3$). The incidence of fibroadenomas in the 13 reference Haskell Laboratory studies ranged from 24 to 54% with a mean of 37%. In the 3M study, the control group incidence (22%) is on the lower end (Charles River data) or below (DuPont Haskell data) these historical control ranges, and the test group incidences (42% and 48%) are within the standard deviation of the mean for the Charles River data and clearly lower than the maximum values.

The combined tumor (fibroadenoma and adenoma) as well as the historical control data demonstrate that the fibroadenoma incidences observed in female rats treated with ammonium PFOA in the 3M study were within the normal bounds for female SD rats and should not be interpreted as representing potential human cancer risk.

In order to provide the US EPA with more assurance in supporting this conclusion, 3M and DuPont have recently commissioned an independent pathology working group to review the mammary tissues from the 3M study. Completion of this review will occur within the next three months.

2. Cancer Weight-of-Evidence Descriptor

The Science Advisory Board was charged with providing its opinion on the appropriate cancer weight-of-evidence descriptor based on the EPA's draft Cancer Risk Assessment Guidelines. EPA has since published its final Cancer Risk Assessment Guidelines (CRAG). 70 Fed. Reg. 17765 (April 7, 2005).

On examination of the final guidelines for choosing the cancer weight-of-evidence descriptor, 3M believes that the examples given by the CRAG for the descriptor "Suggestive Evidence of Carcinogenic Potential" provide the closest fit to the database on PFOA . The "Suggestive Evidence of Carcinogenic Potential" category descriptor is defined on page 2-56 of the final guidelines (70 Fed. Reg. page 17793) as follows: "This descriptor of the database is appropriate when the weight of evidence is suggestive of carcinogenicity; a concern for potential carcinogenic effects in humans is raised, but the data are judged not sufficient for a stronger conclusion."

The final guidelines provide four examples of database attributes to illustrate when this descriptor may be appropriate. See the Appendix to these comments for further discussion of how PFOA fits these illustrations.

3. F1-Generation Female Rat Pituitary Weights

Absolute and relative pituitary weight parameters were apparently decreased with statistical significance relative to controls in F_1-generation female rats administered 3 mg/kg and above (Table 1).

Table 1. Absolute and Relative Pituitary Weights in F_1-Generation Females

Dose Group (mg/kg)	**0**	**1**	**3**	**10**	**30**
Number	28	28	28	28	29
Body weight (g)	323 ± 23	322 ± 24	329 ± 22	325 ± 24	316 ± 21
Pituitary weight (g)	0.017 ± 0.004	0.016 ± 0.003	0.015 ± 0.003*	0.015 ± 0.002*	0.015 ± 0.003**
% PW to BW • 10^3	5.462 ± 1.605	4.976 ± 0.861	4.648 ± 0.860*	4.715 ± 0.898*	4.749 ± 1.028*

* $p<0.05$
** $p<0.01$

These decreases were not considered treatment-related, for a number of reasons.

- First, there is no difference in pituitary weights at 3, 10 and 30 mg/kg/day -- despite spanning a ten-fold range in dose.
- The pituitary weights for individual animals in the higher dosage groups were within the range of values for study controls (data not shown).
- No microscopic changes were seen in the pituitary in either sex of either generation.
- A similar pattern of pituitary weight changes was not observed in the P-generation female rats.
- Pituitary weight changes were not observed in either generation of male rats, which are typically more sensitive than females to PFOA-induced effects.
- Historical control values for F_1-generation female rats of the same strain and from the same laboratory in the time spanning the date of the conduct of the study demonstrate that the pituitary weights in PFOA-treated F_1-generation females were within the range of normal control mean values (Table 2 below).

Table 2. Pituitary Weights (in grams) in Control F_1-Generation Female Crl:CD®(SD)IGS BR VAF/Plus® Rats from Multi-generation Studies: Historical Control Data from Charles River Laboratories, Argus Division, Horsham, Pennsylvania

Date Range [a]	No. of Studies	Mean of Means	Minimum Mean	Maximum Mean
1992 – 2002	14	0.016	0.013	0.018
1997 – 2002	6	0.017	0.016	0.018
1997 – 2004	7	0.016	0.014	0.018

[a] The dosing period of two-generation study with ammonium perfluorooctanoate (Argus study 418-020) was from November 13, 2000 through July 9, 2001, and the study was reported on March 26, 2002.

For all of these reasons, it is unlikely that the statistically-significant observation of slightly reduced F_1-generation female rat pituitary weights represents a meaningful biological response. The data shown in Table 1 simply do not suggest any meaningful adverse effect.

4. Mitochondrial Effects

There was some discussion during the SAB Panel's meeting concerning non-PPAR alpha-mediated effects, and particularly mitochondrial effects of PFOA.

PFOA does not demonstrate classic uncoupling of mitochondrial oxidative phosphorylation. *In vitro* experiments have demonstrated that PFOA is not a classic protonophoric uncoupler of oxidative phosphorylation (Starkov and Wallace, 2002) and does not induce the mitochondrial permeability transition (O'Brien and Wallace, 2004). However, at concentrations that are relatively high compared to effective concentrations of classic uncoupling agents in *in vitro* systems involving isolated mitochondria, PFOA causes a non-specific uncoupling, likely due to increased non-selective permeability of the mitochondrial inner membrane (Starkov and Wallace, 2002).

PFOA has been shown to increase the mitochondrial content of hepatocytes. After intraperitoneal injection of 100 mg PFOA/kg body weight in male rats, PFOA caused an increase in mitochondrial DNA and a decrease in cytochrome oxidase activity but did not alter mitochondrial cytochrome content (Berthiaume and Wallace, 2002). A decrease in mitochondrial image profile size and an increase in the number of mitochondrial profile images per liver cell has been reported after treatment with PFOA (Kawashima et al., 1995). An increase in hepatocellular mitochondrial content as evidenced by an increase in the mitochondrial enzyme, succinate dehydrogenase, was also observed in male cynomolgus monkeys treated orally with ammonium PFOA (Butenhoff et al. 2002) and may explain, in part, the increase in liver weight observed in monkeys.

5. Ataxia and Other Neurotoxicity

There was discussion among the Panel as to whether EPA needed to address ataxia. The subjective observation of ataxia was only reported in females (and not males) from the two-year dietary chronic study with ammonium PFOA (Sibinski et al., 1983). Ataxia was not observed in another chronic study, two subchronic studies, or the two-generation reproductive study.

The incidence of ataxia in female rats from the chronic study was 3, 18, and 23 percent respectively at treatment levels of 0, 30, and 300 ppm APFO in diet, and the observations were primarily in moribund rats. The incidence in male rats was 6 percent in the control animals and 10 and 3 percent in the 30 and 300 ppm dose groups respectively. Female rats excrete PFOA very rapidly as compared to males. Thus, males have a higher body burden at steady state. The lack of a dose-related increase in ataxia in male rats, which have a higher body burden of PFOA, suggests that the subjective observation of incidence of ataxia in female rats is not related to treatment.

Neither ataxia, other neurotoxic signs, nor evidence of neurological damage in non-moribund animals treated with PFOA have been reported in the many other studies that have been conducted. A second two-year dietary bioassay of male rats (Biegel et al., 2001) did not report increased ataxia at 300 ppm ammonium PFOA in diet. Two additional 90-day dietary studies, one in which male rats were treated with up to 100 ppm in diet (Palazzolo, 1993) and another in which male and female rats were treated with up to 1,000 ppm in diet (Goldenthal, 1978), failed to note ataxia as a finding. Lastly, a two-generation reproduction study was conducted in rats with ammonium PFOA at oral gavage doses up to 30 mg/kg/day without any indications of ataxia as a treatment-related effect (Butenhoff *et al*., 2004). Thus, we do not consider the observation from the Sibinski (1983) study to be a treatment-related finding.

There is also evidence that distribution of PFOA to brain or fat tissue is not significantly different between male and female rats to the extent that differences in distribution may explain differences in presentation of the symptom of ataxia. Indeed, the Kemper (2003) study showed that tissue distribution of PFOA at C_{max} and $C_{max/2}$ with respect to brain and fat does not differ significantly between males and females after a single oral doses of ^{14}C-labelled PFOA.

6. Characterization of Epidemiologic Data

The SAB was asked to comment on the human biomonitoring data by addressing question #9, "Please comment on the adequacy of the human exposure data for use in calculating a MOE." In its charge from the Agency, the SAB Panel was not asked to review the occupational epidemiologic studies beyond that of the biomonitoring data. The SAB Panel, however, has commented on the occupational epidemiology data in its draft response to question #9. The occupational epidemiology data have been inaccurately characterized in this draft. In particular, the data do not indicate the occurrence of "certain adverse effects (cancer, heart disease, blood chemistries)". Below, we briefly

explain why this characterization of the occupational epidemiology data is not correct, and present pertinent data for the panel's consideration. The data cited are from references in the EPA Risk Characterization for PFOA.

a. Cancer

We agree the highest serum levels of PFOA that have been reported in the published literature have occurred among employees at 3M's Cottage Grove, Minnesota facility. PFOA has also been measured at lower levels among workers at 3M's Decatur, Alabama facility.

Table 3 provides data from the most recent retrospective cohort mortality studies conducted at the Cottage Grove and Decatur facilities (Alexander 2001a; 2001b). The Alexander 2001a studied workers at 3M's Cottage Grove plant where PFOA was manufactured for over forty years. Neither study's data suggest an indication of an adverse health effect for all malignant neoplasms (i.e., cancer), as inferred in the SAB draft response to question #9.

Table 3 also presents the mortality data for liver, pancreas and prostate cancers at each facility.[2] There are few deaths for these outcomes and none of the SMRs for these specific cancers is statistically significant.

Thus, a reference in the SAB report to the epidemiologic studies as presenting "indications" of cancer is inappropriate.

[2] An excess of bladder cancer mortality was reported in the Decatur study, but was not confirmed by a subsequent incidence study (Alexander 2004).

Table 3. Observed, Expected, Standardized Mortality Ratio and 95% Confidence Intervals for the Cottage Grove and Decatur Retrospective Cohort Mortality Studies

	High (ever)*				High (min 1 yr)**				Low or High (min 1 yr)***			
	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
Cottage Grove (Alexander 2001a)												
All malignant neoplasms	11	13.79	0.80	0.40 – 1.43	4	6.33	0.63	0.17-1.62	68	77.33	0.88	0.68-1.11
Liver	0	0.30	0.00	0.00-12.12	0	0.14	0.00	0.00-26.38	1	1.70	0.59	0.01-3.27
Pancreas	1	0.75	1.34	0.03-7.42	0	0.35	0.00	0.00-10.67	6	4.17	1.44	0.53-3.13
Prostate	1	0.77	1.30	0.03-7.20	1	0.38	2.63	0.07-14.62	6	5.19	1.16	0.42-2.52
All heart disease	17	15.69	1.08	0.63-1.73	7	7.28	0.96	0.39-1.98	68	90.90	0.75	0.58-0.95
Cerebrovascular disease	5	1.94	2.58	0.84-6.03	3	0.89	3.36	0.69-9.82	11	13.03	0.84	0.42-1.51
Decatur (Alexander 2001b)												
All malignant neoplasms	18	21.54	0.84	0.50-1.32	14	16.67	0.84	0.46-1.41	19	28.45	0.67	0.40-1.04
Liver	1	0.50	2.00	0.05-11.10	1	0.39	2.57	0.06-14.26	2	0.65	3.08	0.37-11.10
Pancreas	0	0.86	0.00	0.00-4.30	0	0.67	0.00	0.00-5.52	0	0.15	0.00	0.00-3.21
Prostate	0	0.49	0.00	0.00-7.53	0	0.40	0.00	0.00-9.26	0	0.88	0.00	0.00-4.21
All heart disease	14	24.78	0.56	0.31-0.95	12	19.52	0.61	0.32-1.07	19	32.73	0.58	0.35-0.91
Cerebrovascular Disease	2	2.76	0.72	0.09-2.62	2	2.14	0.93	0.11-3.37	4	3.79	1.05	0.29-2.70

* "High" defined in the Cottage Grove mortality study was "definite (high) PFOA exposure." "High" defined in the Decatur mortality study was "high potential workplace exposure to perfluorooctanesulfonyl fluoride-based fluorochemcials (includes cell operators, chemical operators, maintenance workers, mill operators, waste operators and crew supervisors." These individuals would also have had the highest PFOA levels (Olsen 2003).

** "High (min 1 yr)" defined as above for workers employed for at least one year in a "High" exposure job.

*** "Low" defined in the Cottage Grove mortality study as probable exposure to PFOA. "Low" defined in the Decatur mortality study was "low potential workplace exposure to POSF-based fluorochemicals (includes such jobs as engineers, quality control technicians, environmental, health and safety workers, administrative assistants and managers)." These individuals would also have had lower PFOA levels than those categorized as high potential workplace exposure (Olsen 2003).

b. Heart disease

The data in Table 3 do not indicate excess heart disease mortality. Overall, the findings are generally within the range expected for the healthy worker effect. As shown in Table 3, there were 5 deaths from cerebrovascular disease compared to 1.94 expected in the Cottage Grove mortality study among those who had ever worked in a definite exposure job.

This finding generated two dose-response analyses by Alexander in his report, which are shown in Tables 4 and 5 below. Table 4 restricts the analysis to years of PFOA exposure in only the definite PFOA exposure group of workers, whereas Table 5 provides a more comprehensive cumulative exposure analysis by weighting duration of employment (days) by an exposure factor based on the job. Observed cerebrovascular deaths are less than expected (11 v. 16.25) for weighted exposure of less 10,000, and above expected (but not statistically significant) when the weighted exposure exceeds 10,000 (4 v. 1.21). From 5,000 and above for weighted exposure, the observed deaths equal expected (5 v. 5.29).

Summarizing these data, Alexander concludes: "At this time a causal association cannot be drawn between exposure to PFOA and death from cerebrovascular disease." (Alexander 2001a, p.15).

Table 4. Observed and expected deaths from cerebrovascular disease with SMRs and 95% CI by years of employment in jobs with definite PFOA exposure.

YEARS OF PFOA EXPOSURE	OBS	EXP	SMR	95% CI
<1	2	1.05	1.91	0.22-6.91
1-<5	0	0.46	0.00	0.0-8.02
5-<10	3	0.19	15.03	3.02-43.91
>= 10	0	0.23	0.0	0.0-15.17
TOTAL	5	1.94	2.58	0.83-6.03

Table 5. Observed and expected deaths from cerebrovascular disease with SMRs and 95% CI by cumulative exposure

Weighted Exposure[a]	Obs	Exp	SMR	95% CI
>0-2499	8	9.67	0.83	0.36-1.63
2500-4999	2	2.80	0.71	0.08-2.58
5000-7499	1	2.32	0.43	0.01-2.40
7500-9999	0	1.76	0.00	0.0 – 2.08
10000 & over	4	1.21	3.31	0.89-8.46
TOTAL	**15**	**17.75**	**0.85**	**0.47-1.39**

[a] Duration of employment (days)*exposure weighting factor

c. Blood chemistries

There was also mention in the SAB Panel's discussions about whether PFOA may increase cholesterol in occupationally exposed individuals. In these discussions, there was no reference to the fact that PFOA was found *not* to statistically significantly affect total cholesterol in several analyses of workers at 3M's Cottage Grove facility that occurred in 1990 (Gilliland and Mandel 1996), 1993, 1995, 1997 (all presented in Olsen 2000) and 2000 (Olsen 2003b).

In one instance in which a weak positive association was observed among 3M's Decatur and Antwerp plant employees, who generally have lower PFOA levels than the Cottage Grove PFOA production workers, the finding was attributed to 21 Antwerp employees whose Body Mass Index increased at the same time their cholesterol and triglycerides also increased over a six-year period (Olsen et al. 2003a). We are aware of data (fewer than 50 workers per year tested for four years) from Miteni, reported to the Agency, that were suggested to show a slight increase in total cholesterol in relation to PFOA. The PFOA/cholesterol associations were not statistically significant consistently from year to year in these workers, and many individuals participated in more than one year of analysis.

In summary, the epidemiological data is not properly represented in the panel response to charge question #9. If the Panel is to characterize the epidemiologic data, all of these data would need to be reviewed carefully, with appropriate opportunity for input.

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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 doses 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 tmors.) 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 PPARα agonist, and there is evidence that a number of PPARα 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 PPARα 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 PPARα-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 PPARα 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 PPARα 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 PPARα 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* <u>*or*</u> *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 μg 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 PPARα-mediated modes of action in the observed rat tumors together with the low expression of PPARα in humans and lack of proliferative response to WY-14643 in PPARα-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."