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3M Specialty Materials

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3M

Dr. Oscar Hernandez
U.S. Environmental Protection Agency
EPA East, Room 4410
1201 Constitution Avenue, NW.
Washington, D.C. 20460

VIA FEDERAL EXPRESS

Re: Draft Hazard Assessment of PFOA and its Salts

Dear Dr. Hernandez:

3M has previously provided comments on portions of EPA's February 20, 2002 "Draft Hazard Assessment of Perfluorooctanoic Acid and Its Salts." In this letter, we would like to provide some additional comments, with particular emphasis on the human studies. We appreciate the effort EPA has put into the draft assessment, and hope these comments will facilitate the agency's efforts.

Our comments fall into three categories. First, we identify important data that needs to be added to the draft assessment -- both new information and data that were available but omitted. Second, we discuss some substantive issues regarding EPA's discussion of the Cottage Grove mortality study. Finally, we note a number of specific comments on the draft assessment, covering human health issues, the status of 3M's phaseout of certain fluorochemistry, and other issues.

I. **ADDITIONAL DATA FOR THE ASSESSMENT**

The February review draft needs to be supplemented, both with subsequent information, and also with information that was previously available but not referenced in the document.

A. **New Data**

First, we note that 3M has submitted a number of additional studies since the draft assessment was prepared, and the document needs to be updated. In particular:

1. **Human Health**

- a. **Individual Blood Samples for Children, Adults and Elderly**

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3M's March 13, 2002 submission provided final reports on the studies of individual blood samples for children,¹ adults² and the elderly.³ Preliminary data presented on page 18, paragraph 2, and in the table on page 19, in EPA's draft should be replaced with these new data.

b. Half-Life in Human Serum

The Executive Summary on page 2, and six paragraphs on pages 20-21 of the draft assessment, discuss Interim Report # 1 on the retiree half-life study. Interim Report #1 was entirely superseded by Interim Report #2,⁴ submitted on March 13, 2002.

Accordingly, these paragraphs in the draft assessment should be replaced with the new information. In the second interim report, the mean serum half-life for PFOA was 4.4 years (SD = 3.5; range 1.5-13.5). While these data are also still interim values from an ongoing study, they should replace the obsolete values from the earlier report. The second interim report addresses many of the concerns noted in the existing text about the first interim report, and presents individual data for the nine study subjects who had triplicate analyses of PFOA measured for each collection time period.

2. Toxicology

a. Two Generation Reproductive Study

As EPA is aware, data from the two-generation study rat reproductive study of PFOA are now available. We assume the agency plans to add these data to the assessment.

b. Final Monkey Study

3M submitted the final laboratory report on the 26-week capsule study in cynomolgus monkeys on January 30, 2002. The assessment should reflect these data as well.

¹ Olsen GW, Burris JM, Lundberg JK, Hansen KJ, Mandel JH, Zobel LR. Identification of fluorochemicals in human sera. III. Pediatric participants in a Group A Streptococci clinical trial investigation. St. Paul (MN): 3M Company, February 25, 2002.

² Olsen GW, Burris JM, Lundberg JK, Hansen KJ, Mandel JH, Zobel LR. Identification of fluorochemicals in human sera. I. American Red Cross adult blood donors. St. Paul (MN): 3M Company, February 25, 2002.

³ Olsen GW, Burris JM, Lundberg JK, Hansen KJ, Mandel JH, Zobel LR. Identification of fluorochemicals in human sera. II. Elderly participants in the Adult Changes in Thought Study, Seattle, Washington. St. Paul (MN): 3M Company, February 25, 2002.

⁴ Burris JM, Lundberg JK, Olsen G, Simpson C, Mandel J, Interim Report #2, Determination of serum half-lives of several fluorochemicals. St. Paul (MN): 3M Company, January 11, 2002.

B. Missing Data

1. Published Literature

There is an extensive body of published literature on PFOA that the draft assessment does not reference. Much of this literature has been listed in bibliographies provided to EPA with 3M submissions. Appendix A to this letter provides a list of approximately 70 articles 3M has listed in its bibliographies that do not appear in the EPA draft, covering both toxicology and environmental effects. While not all of these articles are of equal significance, it is important to the credibility of the assessment to indicate that the published literature has been reviewed.

2. Available 3M Data Not Cited

We also note specifically some omissions of 3M data:

a. Medical Surveillance Data

An entire page (pp. 35-36) is devoted to the Gilliland and Mandel (1993) publication that measured total organic fluorine concentrations in Cottage Grove workers in 1990, without any mention of three subsequent medical surveillance examinations (1993, 1995 and 1997) which specifically analyzed for serum PFOA and the same clinical chemistries. These results were reported by Olsen, et al., in *Drug Chem Toxicol* 23:603-620 (2000).

Nor is there any mention of the 2000 medical surveillance -- either the cross-sectional analyses for PFOA among Antwerp and Decatur employees,⁵ nor the 1994-2000 longitudinal analysis of PFOA among a subset of Antwerp and Decatur employees.⁶ These 3M final reports were submitted to EPA in December 2001, and corrected versions were provided with our March 13, 2002 submission.

We urge these paragraphs include these reports that are specific to PFOA and which provide considerably more data than currently cited.

⁵ Olsen GW, 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, 3M Company, October 11, 2001.

⁶ Olsen GW, 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, 3M Company, October 11, 2001.

b. Measurement of PFOA in Workers

Along the same lines, the last sentence of the fifth paragraph on page 3 states, "PFOA was not measured directly" in the medical surveillance exams. This is not correct. In fact, page 17 of the assessment, in paragraph 3, provides worker serum data from the medical surveillance.

Total organic fluorine in the serum was measured in Cottage Grove workers in 1990, but PFOA was measured in the serum for Cottage Grove employees in 1993, 1995 and 1997, and statistically analyzed in relation to their clinical chemistry values (including liver function tests) and various reproductive-related hormones (in 1993 and 1995) and CCK in 1997. In addition, serum PFOA concentrations were measured and analyzed in conjunction with clinical chemistry data for Antwerp and Decatur employees in 2000. As noted above, all these data have been submitted to EPA.

c. CCK Data and Confounders

Page 34, paragraph 2, notes that the 3M Report on the 1997 medical surveillance did not report data on the relationship between CCK and PFOA adjusted for confounders. These data can be found in Figure 1 and Table II in Olsen, et al., *Drug Chem Toxicol* 23:603-620 (2000).

In sum, there is a great deal of additional information available. While we commend EPA for its efforts in reviewing a large amount of data already, we hope these comments will assist the agency in ensuring that the hazard assessment is complete.

II. **COMMENTS ON MORTALITY STUDY**

Mortality experience at the Cottage Grove plant where 3M manufactured and processed PFOA was studied in 1992 by Gilliland as his Ph.D. dissertation. That study was subsequently published as Gilliland and Mandel (1993). The study used duration of employment in the "Chemical Division," meaning the entire Cottage Grove facility and not just the PFOA production buildings within that complex, as an (inexact) surrogate for exposure, and did not include any actual exposure data. The mortality study was recently updated by Dr. Bruce Alexander of the University of Minnesota; Alexander looked specifically at fluorochemical workers within the Chemical Division, using an improved measure of exposure and with the benefit of published serum data for the workforce.

We have several concerns about the presentation of the data on mortality in the draft assessment.

A. Difference in Exposure Information in Original and Subsequent Studies

The retrospective cohort mortality study by Gilliland and Mandel examined employment duration in the "Chemical Division," referring to the entire Cottage Grove facility. PFOA production occurred in only certain areas within the much larger Chemical Division operations. The investigators did not construct a PFOA exposure matrix. Accordingly, we suggest that the opening statement in the fourth paragraph of page 3 should read, "A retrospective cohort mortality study demonstrated a weak association between prostate cancer mortality *and employment duration in a chemical facility where PFOA was manufactured only in certain areas of the facility.*"

The data from the updated study should also be cited in the Executive Summary, particularly given that the exposure classifications became specific for PFOA in the updated study. We recommend the following sentences be added to this paragraph: "In the updated study by Alexander, an exposure matrix was developed to identify calendar-year specific departments and jobs where PFOA exposure occurred. Prostate cancer mortality was not significantly associated with definite or probable PFOA exposure categories."

On pages 3 and 32, the draft assessment notes that Alexander in his report to 3M did not provide an analysis by exposure duration. Such analysis will be provided in Dr. Alexander's forthcoming publication of the study. The manuscript states, "Categorized by duration of exposure in PFOA definite or probable jobs, observed to expected prostate cancer mortality ratios were (in parentheses) 0-<1 year (0/0.01), 1-<5 years (2/1.42), 5 - < 10 years (0/0.82) and ≥ 10 years (4/2.95). The SMR was 1.36 (95% CI 0.37-3.48) for prostate cancer mortality in the ≥ 10 year duration category." In short, there was no clear pattern with duration of exposure, and the 95% confidence interval around the SMR for prostate cancer mortality workers exposed longer than ten years included the null value.

Given the much more detailed exposure information in the Alexander update of the study, we do not understand why the draft assessment only discusses (at page 31, paragraph 5) the potential for exposure misclassification in the updated mortality study by Alexander, while never discussing exposure misclassification concerns regarding the Gilliland and Mandel (1993) study. Alexander developed an exposure matrix for calendar-year department- and job-specific classifications to PFOA in order to arrive at his study definitions of definite and probable PFOA exposure, while Gilliland and Mandel did not develop any PFOA-specific exposure matrix. Gilliland and Mandel utilized the non-specific exposure definition of years worked in a chemical plant that was based only employees' start and quit dates. Alexander worked from work history records that were computerized for the study and therefore allowed all jobs and departments throughout the study period to be evaluated for the potential for PFOA exposure. Industrial hygienists, plant management, production workers and retirees provided input into the exposure classifications used by Alexander. This was not done by Gilliland and Mandel.

Moreover, although not specifically stated in the report, the exposure matrix Dr. Alexander used in the updated mortality study was constructed with the benefit of the serum PFOA concentrations measured in employees at Cottage Grove since 1993, as reported by Olsen et al. in *Drug Chem Toxicol* 23:603-620 (2000). Therefore, it is inappropriate to comment on page 32, third paragraph, that "without measured exposures (serum PFOA levels), it is difficult to judge the reliability of exposure categories that were defined." Serum PFOA data are available. While the serum measurements were not used directly in the updated study, they were taken into consideration.

For all of these reasons, we believe the potential for exposure misclassification was far greater in the Gilliland study than in the Alexander study.

B. Prostate Cancer

As indicated by the preceding discussion, we believe EPA's emphasis on the earlier version of the study leads to an unfounded emphasis on prostate cancer. Prostate cancer mortality was not significantly associated with definite or probable PFOA exposure categories in the updated study, which used a far more accurate exposure classification scheme.

Indeed, in the Gilliland study, there were four prostate cancer deaths observed in Chemical Division workers, as the draft assessment notes on page 30. However, subsequent research has shown that only one of these employees worked in the PFOA production building. See *J. Occup. & Envir. Medicine* 40:614-621 (1999), at page 615, column 2.

Thus, the association between employment in the Chemical Division or length of employment in the Chemical Division and prostate cancer mortality, is not meaningful in attributing the results to PFOA.

C. Use of Confidence Intervals

In the second paragraph on page 31, discussing the results of the Alexander update, the draft states that a few SMRs were elevated for employees in the definite PFOA exposure group, but does not provide 95% Confidence Intervals (CIs) for these point estimates. The confidence intervals are critical for evaluating the extent to which the SMR's are meaningful, as the intervals all include the null hypothesis. Therefore, 95% CIs should be provided for cancer of the large intestine (SMR = 1.67, 95% CI 0.02-6.02), pancreatic cancer (SMR = 1.34, 95% CI 0.03-7.42) and prostate cancer (SMR = 1.30, 95% CI 0.03-7.20). Similarly, in the next paragraph on page 31 addressing the results in the probable exposure group, 95% CIs are provided for several endpoints, but not for the deficit of prostate cancer (CI 0.28-2.02).

D. Bladder Cancer

It is unfounded to suggest (in the second paragraph on page 32) that the Cottage Grove mortality study bladder cancer mortality results are consistent with those reported for the Decatur mortality study, or that they are of particular significance because of the

results at Decatur, where exposure is primarily to PFOS. We recommend that this paragraph discussing the bladder cancer results be deleted.

- First, there were zero bladder cancer deaths in the Cottage Grove mortality study associated with the definite PFOA exposure groups (only 0.23 expected, 95% CI 0.00-15.72) and just one bladder cancer death in the probable PFOA exposure group (1.68 expected, SMR = 0.59, 95% CI 0.02-3.30).
- Combined, the workers with a minimum of one year in definite and probable PFOA exposure job groups resulted in 1 observed and 1.47 expected deaths for bladder cancer (SMR = 0.68, 95% CI 0.02-3.79).
- The remaining 4 bladder cancer deaths (expected 1.89, SMR = 2.11, 95% CI 0.58-5.40) occurred among individuals who never worked in the chemical division at Cottage Grove.

Thus, unlike Decatur, there were no positive associations between bladder cancer mortality and fluorochemical exposures at the Cottage Grove chemical division. It is inappropriate to suggest the overall Cottage Grove results for bladder cancer mortality, with 5 cases observed where 3.83 were expected (SMR 1.31, 95% CI 0.42-3.05), are indicative of an association between PFOA and bladder cancer.

Moreover, it is illogical to suggest that the Cottage Grove findings are somehow of particular significance because bladder cancer was elevated in the mortality study at the Decatur plant, where exposure was primarily to PFOS-related compounds. If PFOA were responsible for bladder cancer, one would expect to see that at Cottage Grove, where exposures to PFOA were higher than at Decatur. Instead, it is the Decatur study that shows bladder cancer (SMR 8.68, 95% CI 1.79-25.39 among workers with a minimum of one year exposure). The results in the two studies are not comparable.

Finally, in the discussion of bladder cancer at Decatur, the draft assessment suggests that PFOA exposures at Decatur will likely increase. This is incorrect. PFOA exposures will not increase at either the Cottage Grove or Decatur plants. PFOA production at these plants has ceased, per the 3M Company's May 16, 2000 phase-out announcement.

Thus, we urge EPA to delete the bladder cancer paragraph on page 32.

E. Effect of Missing Death Certificates

Although as noted on page 32 in the last paragraph discussing the mortality study, there were 17 death certificates (3%) that could not be located, only 6 of those missing certificates belonged to subjects who had definite exposure ($n = 0$) or probable exposure ($n = 6$). Consequently, the 17 death certificates would not "greatly change" the PFOA analyses. Only 6 death certificates could affect the analyses for the PFOA exposure categories. While we certainly agree it is important to continue analysis of the cohort, and that missing death certificates are a limitation of the study, we believe it overstates the limitation to state these death certificates could greatly change the results of the study.

III. SPECIFIC COMMENTS

A. Discussion of Human Health Studies

We offer the following editorial suggestions with regard to the presentation of human health data:

- Small Number of Study Subjects Highly Exposed. In several places, including page 4, paragraph 1; page 22, paragraph 2; and page 33, paragraphs 2 and 5, the draft assessment notes that the small number of workers with PFOA serum levels greater than 10 ppm was a limitation of a study. We suggest this sentence be rewritten to state more precisely that inferences regarding results in workers above 10 ppm PFOA in the serum would be difficult to derive due to the few subjects. However, it should be clear that the lack of statistical power in high PFOA concentration categories does not limit the ability to make inferences from lower serum PFOA concentrations where data are more numerous.
- Number of Cottage Grove Employees. The draft assessment at page 17, paragraph 3, giving worker serum data notes that the total number of employees working at the Cottage Grove plant was not reported. However, that number can be discerned from the publication reporting those data, Olsen, et al., *Drug Chem Toxicol.* 23:603-620 (2000), at page 605: "The total number of male subjects, by year, who participated in these three cross-sectional investigations were: 1993 ($n = 111$); 1995 ($n = 80$); and 1997 ($n = 74$). (There were too few female employees to include in the data analysis.) Eligible voluntary participation rates among these production workers ranged from approximately 50 (1997) to 70 (1993) percent." Thus, the eligible population ranged from 80 in 1997 to 158 in 1993.
- Table of Serum Levels. Table 1 on page 19 might be clearer if both occupational and general population levels were reported consistently in parts per million (ppm). In addition, the reference to occupational and general population exposures, referring to types of exposures, could be confusing if the reader were to infer erroneously that the table presents exposure levels rather than serum levels.
- Pancreas Findings in Episodes of Care Study. If disorders of the pancreas are to be mentioned at page 37, paragraph 5, it would be appropriate to mention the fact that in

the high exposure, long-term employment group (Table 10 in the Episodes of Care report), this association was based on one individual in the chemical plant who had 6 episodes of care for acute pancreatitis.

B. Discussion of PFOA Production

We are concerned that the document does not accurately capture the status of 3M's phase-out of PFOA. EPA on page 9 says: "In terms of on-going production, 3M has not committed publicly to a complete phase-out of PFOA and PFOA-related chemicals as it has for PFOS and PFOS-related chemicals. However, 3M has indicated that it is phasing out certain FLUORAD Brand specialty materials that contain PFOA and its salts such as FC-26, FC-118, and FC-143, FX-1001 and others (3M Company, 2000c)." To the contrary, on May 16, 2000, 3M announced the phase-out of the production of "perfluorooctanyl chemistry" and related products. This announcement includes PFOA and its salts, and it is 3M's intention to cease production for sale by the end of 2002. 3M will continue to manufacture only a small amount of the substance in Germany for internal uses within the company after that time. 3M requests that the FLUORAD brand name not be mentioned, to avoid confusion generated when relating chemistry to brand names. However, EPA can note 3M's phase-out of U.S. production and sales of PFOA-related products.

Further, based on our knowledge and experience, we disagree with the speculation on page 10 of the draft assessment, which says: "Based on the physicochemical properties of the salts of PFOA, they may also have other related surfactant or emulsifier uses as a photographic chemical or in the manufacture of electronic components such as semiconductors. These same properties may lead industry to explore PFOA as a replacement chemical for PFOS in other applications in which PFOA is not currently used." While some physicochemical properties of PFOA and PFOS may be similar, these substances exhibit distinct product performance characteristics that would make direct replacement either unfeasible or very difficult.

* * *

We hope this input will assist the Agency, and we would be pleased to answer any questions. We appreciate the opportunity to provide comments.

Respectfully submitted



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APPENDIX A

PFOA-related Publications Not Cited in Draft Assessment

1. Abdellatif, A.G., V. Pr  at, J. Vamecq, R. Nilsson, and M. Roberfroid. Peroxisome proliferation and modulation of rat liver carcinogenesis by 2,3-dichlorophenoxyacetic acid, 2,4,5-trichlorophenoxyacetic acid, perfluorooctanoic acid and nafenopin. *Carcinogenesis* 11 (1990) 1899-1902.
2. An YJ, Carraway ER (2002). PAH degradation by UV/H₂O₂ in perfluorinated surfactant solutions. *Water Res.* 36:309-314.
3. An YJ, Carraway ER, Schlautman MA (2002). Solubilization of polycyclic aromatic hydrocarbons by perfluorinated surfactant micelles. *Water Res.* 36:300-308.
4. Belisle, J., and D. Hagen. A method for determination of perfluorooctanoic acid in blood and other biological samples. *Analytical Biochemistry* 101 (1980) 369-376.
5. Biegel, L.B., M.E. Hurtt, and J.C. Cook. Effects of ammonium perfluorooctanoate (C8) on Leydig cell function: In vivo, ex vivo, and in vitro studies. *The Toxicologist* 13[1] (1993) 399.
6. Biegel, L.B., R.C.M. Liu, M.E. Hurtt, and J.C. Cook. Effects of ammonium perfluorooctanoate on Leydig cell function: In vivo, ex vivo, and in vitro studies. *Toxicology & Applied Pharmacology* 134 (1995) 18-25.
7. Borjes, H.K. and R.G. Thurman. Peroxisomal proliferators inhibit Acyl CoA synthesis and stimulate protein kinase C in vivo. *Toxicology & Applied Pharmacology* 126 (1994) 233-239.
8. Clapperton, R.M., B.T. Ingram, R.H. Ottewill, and A.R. Rennie. NMR spectroscopic and neutron scattering studies on ammonium decanoate-ammonium perfluorooctanoate mixtures. In: *Mixed Surfactant Systems. ACS Symposium Series 501*, Eds.: P.M. Holland and D.N. Rubingh, American Chemical Society: Washington, DC, 1992, 268-277.
9. Cook, J.C., S.M. Murray, S.R. Frame, and M.E. Hurtt. Induction of Leydig cell adenomas by ammonium perfluorooctanoate: A possible endocrine related mechanism. *Toxicology & Applied Pharmacology* 113 (1991) 209-217.
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11. Feller, D.R. and U. Intrasukri. Mechanism of peroxisome proliferation by perfluorinated fatty acids in primary cultures of rat hepatocytes (abstract). *Toxicologist* 13 (1993) 395.

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13. Haugthorn, B., and O. Spydevold. The Mechanism Underlying the Hypolipemic Effect of Perfluorooctanoic Acid (PFOA), Perfluorooctane Sulphonic Acid (PFOSA) and Clofibrilic Acid. *Biochim. Biophys. Acta.* 1128[1] (1992) 65-72.
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15. Huang Q, and Hong CS (2000). TiO_2 photocatalytic degradation of PCBs in soil-water systems containing fluoro surfactant. *Chemosphere* 41:871-879.
16. Hurtt, M.E., S.M. Murray, S.R. Frame, and J.C. Cook. Investigation of a hormonally-mediated mechanism for ammonium perfluorooctanoate (C8)-induced Leydig cell adenomas. *Toxicologist* 10 (1990) 192.
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24. Kudo N, Bandai N, Suzuki E, Katakura M, Kawashima Y (2000). Induction by perfluorinated fatty acids with different carbon chain length of peroxisomal beta-oxidation in the liver of rats. *Chem. Biol. Interact.* 124:119-132.
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