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July 12, 2006

VIA ELECTRONIC & U.S. MAIL

Joan E. Denton, Ph.D., Director
Office of Environmental Health Hazard Assessment
State of California
1001 I Street
P.O. Box 2815
Sacramento, California 95812-2815

RE: Petition for Expedited Consideration of PFOA under Proposition 65

Dear Dr. Denton:

I am writing on behalf of E. I. du Pont de Nemours and Company ("DuPont") to address the February 22, 2006 petition before your Office requesting that perfluorooctanoic acid and its salts ("PFOA") be given expedited consideration for listing as a chemical "known to the state to cause cancer" for purposes of Proposition 65. This letter summarizes some of the information that DuPont provided to you and your staff at a meeting in Sacramento on July 27, 2006, and addresses in further detail some of the issues in which your staff expressed particular interest.

SUMMARY

The enormous body of scientific studies conducted to date, which have examined thoroughly the potential health effects from exposure to PFOA, fail to establish any adverse effects to humans. The presence and persistence of PFOA in humans and the environment are legitimate concerns that deserve the attention of government agencies and the larger scientific community, as well as the many manufacturers that use PFOA in industrial and consumer products that are so important to the national and California economies. Nevertheless, the many health studies that have been conducted thus far, including those discussed in the petition, do not establish a credible link between exposure to PFOA and cancer. In light of these data, referral of PFOA to the Carcinogen Identification Committee ("CIC") is inappropriate. Rather, OEHHA should acknowledge the evaluations conducted by the US Environmental Protection Agency, the Food and Drug Administration, and the National Toxicology Program, none of which have concluded that PFOA causes cancer. Moreover, the data show that there is no meaningful

exposure to PFOA from the consumer and industrial products that are manufactured from or with PFOA, and that exposure to PFOA from other sources appears to be declining. Thus, although concerns other than cancer are not relevant to a decision whether to consider listing PFOA under Proposition 65, OEHHA can be confident that such concerns are being addressed adequately by the aggressively pro-active measures that are being undertaken by PFOA manufacturers and users, in cooperation with the US EPA.

The abundant health effects data on PFOA do not support listing the chemical under Proposition 65. There is an enormous volume of scientific data assessing the known and potential toxicological effects of PFOA. Many of the studies are published in peer-reviewed scientific journals, and most of the studies, including those relevant to the petition, are available to the public from the dockets maintained by the US EPA.¹ The database presently includes approximately 200 toxicological studies, and several epidemiological studies analyzing data from humans exposed to PFOA over extensive periods of time at sites where PFOA has been manufactured or used.

Epidemiological studies show no evidence of cancer in humans. Epidemiological studies have been conducted on human populations of significant size including manufacturing workers with prolonged exposure to PFOA at levels significantly higher (in many cases several orders of magnitude higher) than the potential exposures to the general public. One of the more extensive studies was a mortality study of approximately 4000 workers, who were exposed to PFOA for approximately 108,000 person-years. These epidemiological studies did not show any evidence of carcinogenicity in humans.

Animal studies do not support listing. PFOA is not genotoxic. Furthermore, none of the animal studies show a statistically significant increase in malignant tumors in any species exposed to PFOA. Although data show significant increases in *benign* tumors in the liver, pancreas and testes, in one sex of one species (the rat), it is generally recognized in the study of cancer that an increase in the rate of benign tumors is not evidence of cancer in the absence of a statistically significant increase in the rate of *malignant* tumors. Moreover, animal testing data show that PFOA causes "peroxisome proliferation," an adaptive response to which rats are uniquely susceptible. This mechanism is recognized to cause tumors in rats, but generally does not do so in humans. Therefore, the studies indicating that PFOA is a peroxisome proliferator further call into question the relevance of studies showing benign tumors observed in rats, when assessing the effects of PFOA in humans.

US EPA has not concluded that PFOA is a carcinogen. Some of the present controversy regarding PFOA appears to arise from a misunderstanding of an ongoing evaluation

¹ Information on the EPA's PFOA research activities, including how documents may be accessed from EPA's several PFOA-related electronic dockets, is available through the EPA PFOA website at www.epa.gov/oppt/pfoa/. Information on the nature and structure of PFOA Enforceable Consent Agreement meetings is available on that website at www.epa.gov/oppt/pfoa/meetings/meetings.htm.

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of the substance that is being conducted by US EPA. In order to correct misimpressions regarding the US EPA proceedings and the status of the federal Agency's present conclusions, we have summarized them below.

PFOA became the subject of US EPA scrutiny in June 2000, as a result of findings that the chemical was present at very low levels in blood samples of the general population. In late 2002, EPA initiated a priority review of PFOA, which led to a public process to develop new data on the substance and reduce scientific uncertainties surrounding pathways of human exposure and potential risks. That process, formally begun in April 2003, included the release of a preliminary risk assessment; the solicitation of letters of intent from fluoropolymer and fluorotelomer manufacturers to provide data on a range of topics involving processes, releases, production volumes and toxicity; and the development of formal Enforceable Consent Agreements ("ECAs") and Memoranda of Understanding under the authority of Section 4 of the federal Toxic Substances Control Act. The Agency's preliminary hazard assessment did not include a cancer risk assessment, because the Agency's Office of Prevention, Pesticides and Toxic Substances ("OPPTS") had questions concerning the potential significance to humans of the rodent data discussed above.

In conjunction with this review, fluoropolymer and fluorotelomer manufacturers also cooperated in developing voluntary research activities surrounding toxicity, degradation and direct and indirect precursors. Further information developed under this process is available in the public docket referred to in footnote 1.

In January 2005, US EPA released a draft risk assessment that preliminarily categorized PFOA as "suggestive" of carcinogenicity. This opinion was based on the view that human studies on the effects of exposure to PFOA do not support a conclusion that the chemical is carcinogenic, as well as uncertainties on the part of OPPTS regarding quantitative differences between rats and humans and consequent questions regarding the relevance of tumor data in rats in determining whether the chemical is carcinogenic in humans.

Soon after the 2005 draft risk assessment was released, US EPA established an independent panel of outside scientific experts under the supervision of the Agency's Scientific Advisory Board ("SAB") to peer-review the document. This panel, referred to herein as the "SAB Panel" or "Panel", was charged with ensuring that assumptions used in the Agency's 2005 draft risk assessment were scientifically sound and could be used effectively to determine potential risks and to identify appropriate risk-management actions. The SAB Panel deliberated on the questions charged to it during meetings on February 22 and 23, 2005. On July 6, 2005, the Panel met by telephone conference call to discuss the text of a draft report. Among the issues for discussion were the Panel's interpretation of studies conducted on mammary gland tissues, and which "descriptor" of hazard potential should be used to describe PFOA under the Agency's new 2003 Guidelines for Carcinogen Risk Assessment ("Cancer Guidelines").

Incidences of mammary tumors played an important part in the SAB Panel's deliberation, and were critical in the eventual recommendation of a descriptor. Due to uncertainties, the Panel

recommended that the Agency “consider new information that has been verified and peer-reviewed prior to use in their revision of the [2005] Draft Risk Assessment” and that an “independent, appropriately-designed histopathology review of . . . female mammary glands from the [1987] Sibinsky study be conducted to re-analyze the resulting tumor incidence data.”

As a result, an independent Pathology Working Group (PWG) was convened to reevaluate the mammary tissues collected from the 1987 Sibinski study. Experimental Pathology Laboratories, Inc. (“EPL”) was selected to administer the PWG, which was chaired by EPL’s president, Dr. Jerry F. Hardisty, Diplomate, A.V.C.P. Dr. Hardisty was responsible for selecting the other members, compiling the findings, and drafting the report for concurrence and signature.² The other PWG panelists were Dr. Gabrielle Wilson, FRC Path., Dr. W. Ray Brown, Diplomate, A.C.V.P., and Dr. Ernest E. McConnell, Diplomate, A.V.C.P., D.A.B.T. The panelists all have extensive experience in the microscopic evaluation and interpretation of lesions observed as a result of chronic toxicity and bioassay studies conducted in rodents.

The PWG conducted its review in accordance with US EPA guidelines (US EPA PR Notice 94-5), and reexamined all mammary gland tissues microscopically, without identifying their treatment groups to the pathologists. Using the diagnostic criteria and nomenclature recommended by the Society of Toxicologic Pathologists, the PWG concluded that there were no statistically-significant increases in incidence of mammary tumors, of total benign neoplasms, or total malignant neoplasms, and no increase in tumor multiplicity. The PWG also concluded that the incidence of mammary gland neoplasms observed in the study was similar to the historical control incidence.

In May 2006, the SAB issued its report and noted a split among Panel members with regard to the hazard descriptor used to indicate the potential for carcinogenicity. To explain, this Panel was the first to apply the Agency’s new Cancer Guidelines. Thus, as noted above, there was considerable discussion among the Panel members as to how the new descriptors articulated in the Guidelines should be interpreted and utilized. The SAB reported that one-quarter of the Panel agreed with EPA’s January 2005 draft assessment, and the use of the descriptor “suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential.” Three-quarters of the Panel chose the hazard descriptor “likely to be carcinogenic.” As a result, the SAB report strongly “urge[d] the Agency to strengthen its risk assessment by considering verified and peer-reviewed new information found to be relevant and critical to the assessment.” Thus, although the PWG was convened in response to the SAB Panel’s recommendation, the results of the pathology review were not available in time for the Panel’s consideration. As a result, the recent conclusions of the SAB Panel process do not incorporate these key findings regarding the mammary glands.

² Dr. Hardisty is an expert in conducting pathology peer reviews. EPL is the largest independent pathology contract laboratory in the world, providing hazard identification services to governmental agencies and industry in support of human risk assessment programs. Dr. Hardisty advises both EPA and FDA on pathology issues.

Obviously, it is essential that any determination of cancer risk include the most current information. Therefore, US EPA declined to reach any conclusions regarding the SAB Panel report. Referring to the new data and the SAB process on its website, US EPA states that “[s]ome of this new research may impact the Panel’s assessment of PFOA. For this reason, *it is premature to draw any conclusions on the potential risks, including cancer, from PFOA until all of this new testing is complete and the data are integrated into the risk assessment.*” (Emphasis added.)

US EPA Administrator Stephen Johnson similarly has stated his concern about the Agency’s need to consider completely the most recent information. In his June 20, 2006 letter to the Panel co-chairs acknowledging receipt of the SAB report, Mr. Johnson states that “[i]t has been “nearly two years since the package of information that the Panel reviewed was compiled, and since that time, a considerable amount of research has been completed . . . or is presently underway.” The Administrator adds that the Agency intends to “integrate this new toxicity testing and mechanistic data into the risk assessment as it becomes available.”

As it stands now, US EPA has not revised its 2005 draft risk assessment or its preliminary adoption of the “suggestive” descriptor. The Agency has said it will seek a second SAB review upon completion of its final risk assessment. Thus, on June 8, 2006, the Agency announced in a public PFOA Information Forum updating the process that “*EPA has no information linking current levels of PFOA in the blood of the general public to any adverse health effects in people.* Additional study is still needed to understand these persistent chemicals. While information is being developed, EPA is taking the prudent step of seeking to reduce possible sources now, to avoid potentially larger future problems.” (Emphasis added.)

PFOA does not meet any of the criteria for listing under Proposition 65. The data summarized above demonstrate that PFOA is not a legitimate candidate for listing under Proposition 65, under any of the criteria set forth in the statute, implementing regulations, or policy documents.

First, PFOA has not been identified as a carcinogen by an “authoritative body” within the meaning of the Act, even though the petition may imply otherwise. Citing implementing regulations at 22 Cal. Code Regs, *tit.* 22, § 12306(e)(2), the petition recites that a chemical should be listed as a carcinogen under Proposition 65 if “studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (*e.g.*, with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site, or type of tumor, or age at onset.” Obviously, PFOA would not meet any of these criteria, base on the data summarized above.

Moreover, this regulation applies in addressing “Chemicals Formally Identified by Authoritative Bodies” pursuant to Cal. Code Regs., *tit.* 22., § 12306. As OEHHA is aware, no “authoritative body” has designated PFOA as a carcinogen. To elaborate, the US EPA, the U S FDA, the International Agency for Research on Cancer, the National Toxicology Program, and

the National Institute of Occupational Health are “authoritative bodies” for purposes of Proposition 65. *None of these organizations has identified PFOA as a carcinogen.* Thus, PFOA is not a candidate for listing through the “authoritative bodies” mechanism.

Second, PFOA does not meet the criterion for listing by the CIC. In the words of the statute and its implementing regulations, PFOA has not been “clearly shown through scientifically valid testing according to generally accepted principles to cause cancer.” Cal. Health & Safety Code § 25249.8(b); Cal. Code Regs., *tit.* 22, § 12305(a)(1). As discussed above, PFOA is not genotoxic, and the animal data show that the chemical produces only benign tumors and (even then) only in one sex of one species (the male rat). Moreover, the fact that PFOA is a peroxisome proliferator raises questions about the relevance to humans of the benign tumors observed in male rats. Finally, there is no evidence of carcinogenicity in humans, even in populations with historically high exposures to PFOA.

The CIC’s own listing criteria further demonstrate that PFOA is not a legitimate candidate for listing. The CIC’s “Guidance Criteria for Identifying Chemicals for Listing as ‘Known to the State to Cause Cancer’” states that “if the weight of evidence *clearly shows* that a certain chemical causes *invasive cancer* in humans, or that it causes *invasive cancer* in animals (unless the mechanism of action has been shown not to be relevant to humans), the committee will normally identify that chemical for listing.” (Emphasis added) The term “invasive cancer” refers to malignant tumors (*i.e.*, tumors that metastasize), as opposed to benign tumors. No study of PFOA has shown any statistically significant increase in “invasive cancer.” The weight of the scientific evidence, therefore, does not support listing PFOA as a chemical that is “known to the State” to cause cancer.³

EPA has not concluded that exposure to PFOA results in any adverse health effects in humans. In opposing the consideration of PFOA for listing, DuPont does not ignore or discount the evidence showing that PFOA has been shown to be present in human blood, and that the presence of the material in so many people in so many places cannot presently be explained. To the contrary, DuPont, other companies that manufacture and use PFOA, and the US EPA are investigating diligently to determine the sources of exposure and to reduce exposure. Nevertheless, the scientific evidence gathered thus far does not show any adverse effects to humans.

US EPA has confirmed this on several occasions within the past year. In a press release on December 14, 2005, Susan Hazen, Acting Administrator of the EPA’s OPPTS, stated that: “*The agency has information based on animal studies and toxic effects in animals, [but] we have no information at this point that would lead us to believe there is a significant human health impact.*” Although EPA has continued to gather data and study the matter diligently, the

³ The fact that NTP is proposing to conduct a 2-year bioassay of PFOA is further evidence that it has not been “clearly shown” to cause cancer. NTP would not spend millions of dollars on such a study if it were clear that PFOA causes cancer.

Agency's conclusion has not changed. On January 25, 2006, Administrator Johnson announced that "[a]lthough our risk assessment activities are not complete and new data may change the current picture, to date *EPA is not aware of any studies specifically relating current levels of PFOA exposure to human health effects.*" Finally as recounted above, the Agency announced at its June 8, 2006 PFOA Information Forum on that "*EPA has no information linking current levels of PFOA in the blood of the general public to any adverse health effects in people.*" (Emphasis added in all quotations.)

There is no meaningful exposure to PFOA from consumer articles on the market. A comprehensive scientific study confirmed that consumer articles made with or using DuPont materials are safe to use and would not result in quantifiable exposure to PFOA. The independent, peer-reviewed study was published in 2005 in *Environmental Science & Technology* (vol. 39, pp. 3904-3910). DuPont initiated the study, which was conducted by ENVIRON, an independent research firm, to enhance the understanding of the potential for consumer exposure and to determine what potential risks, if any, might result from exposure to PFOA.

The study examined a wide variety of ways that consumers could be exposed to PFOA from common household products such as cookware and clothing. Potential routes of exposure included exposure through the skin, in the air, and orally. All ages of consumers from infant to adult, including adult professionals, were considered. To ensure accuracy and provide the most reliable test results, dozens of consumer articles were assessed using extremely conservative exposure models. A peer-review panel, moderated by Dr. George Gray, formerly the executive director of the Harvard Center for Risk Analysis, evaluated the study to ensure its scientific rigor and validity.⁴

The margins-of-exposure (*i.e.*, ratios of estimated exposure levels in human to any relevant health benchmark from toxicological studies) for all articles tested ranged from 30,000 to over 9 billion. Aggregate margins-of-exposure also were calculated to ensure that multiple-article exposures were considered and were found to be equally substantial. The large margins-of-exposure dramatically exceed the margins-of-exposure of 100 to 1,000 typically used by regulatory agencies to judge the safety of chemicals.

For example, cookware coated with Teflon® non-stick coating underwent rigorous scientific testing designed to see if any PFOA could be detected under exaggerated or extreme cooking conditions, and no detectable levels were found. The ENVIRON risk assessment demonstrated that cookware coated with Teflon® non-stick coating and other tested articles present no meaningful risk of exposure to PFOA, and thus pose no health risks from the substance. Based on results of the study, the use of the tested products would not result in quantifiable levels of PFOA in the blood.

⁴ Dr. Gray presently is the US EPA Assistant Administrator, Office of Research and Development.

Exposure to PFOA, which apparently results from sources other than consumer articles presently on the market, appears to be declining. A study conducted from samples taken in 2000/2001 analyzed 645 human blood samples for the presence of seven fluorochemicals.⁵ Samples were obtained from six blood bank locations in the United States, which included 125 samples from Los Angeles. The median concentration of PFOA in these samples was 4.7 parts per billion ("ppb"). There were no significant differences with respect to age, gender, or geographical location. The median concentration for the samples collected from Los Angeles was 4.6 ppb. An historical comparison of fluorochemicals in human blood compared samples collected in 1974, 1989 and 2001 from a community in Washington County, Maryland.⁶ The median PFOA concentrations in samples collected in 1974, 1989, and 2001 were 2.1 ppb, 5.5 ppb, and 4.2 ppb, respectively, with each year being significantly different than the other years. Recent data submitted to the US EPA showed results of human blood concentrations of PFOA and other fluorochemicals in 36 pooled samples from locations across the United States, including samples from California.⁷ The median PFOA concentration was 3.2 ppb.

These data, taken together, indicate (1) that the population of California is not uniquely exposed to PFOA in that the blood concentrations were comparable across the United States, and, (2) that the blood levels of PFOA in the general population in the United States appear to be declining. We have enclosed copies of these references.

There is no valid reason to expedite the consideration of PFOA for listing under Proposition 65. Given that PFOA does not meet any of the criteria for listing under Proposition 65, there is no valid reason to expedite its referral to the CIC for *consideration* for listing. The recent discoveries that PFOA is present in humans and the acknowledged persistence of the chemical are valid bases for investigation. It is clear, however, that other public agencies, most notably the US FDA and US EPA, are addressing those issues vigorously and that the interests of the public are being addressed through further study and responsible product stewardship.

US EPA in particular has taken aggressive steps to reduce possible sources of human exposure through a voluntary program announced earlier this year. In January, Administrator

⁵ Olsen, G.W., Church, T.R., Miller, J.P., Durris, J.M., Hansen, K.J., Lundberg, K.J. *et al.*, Perfluorooctane Sulfonate and Other Fluorochemicals in the Serum of American Red Cross Blood Donors, *Environ. Health Perspect.* **2003A**, 111, 1892-1901.

⁶ Olsen, G. W.; Huang, H.-Y.; Helzlsouer, K. J.; Hansen, K. J.; Butenhoff, J. L.; Mandel, J. H., Historical comparison of perfluorooctanesulfonate, perfluorooctanoate, and other fluorochemicals in human blood. *Environmental Health Perspectives* **2005**, 113, (5), 539-545.

⁷ Letter from 3M Company to US EPA, December 19, 2005, and attached analytical report, *US EPA Administrative Record AR226-3579, AR226-3580 2005*.

Johnson invited the eight fluoropolymer and telomer manufacturers to participate in a global stewardship program on PFOA and related chemicals. By March, all eight companies had agreed to participate. The program requires corporate commitments to the following goals:

- (1) To commit to achieve, no later than 2010, a 95% reduction, measured from a year 2000 baseline, in *both* facility emissions to all environmental media *and* product content levels of: PFOA, precursor chemicals that can break down to PFOA, and related higher homologue chemicals; and
- (2) To commit to working toward the elimination of PFOA, precursor chemicals that can break down to PFOA, and related higher homologue chemicals from emissions and products by five years thereafter, or no later than 2015.

All participants in the program will be required to provide regular updates on a global basis, starting with a report in October, on their progress toward achieving these goals.

The issues of presence and persistence, moreover, are largely irrelevant to the application of Proposition 65. In the absence of scientific data demonstrating that the chemical is clearly shown to cause cancer, neither the presence of the chemical nor its persistence presents a basis for listing or for an expedited review.

The expedited review process is best reserved for chemicals where there are exceptional circumstances, such as a new study that clearly shows a chemical causes cancer. The Prioritization Procedure provides the following guidance: "The Director may abbreviate or otherwise modify the process. For example, the public or a [CIC] committee member may petition the Director to abbreviate the prioritization process to respond to *new information* or an *emerging public health issue*"⁸ Obviously, these terms refer to matters that Proposition 65 is intended to address.

PFOA does not meet either of these criteria. There is no new information demonstrating carcinogenicity of PFOA. To the contrary, the two carcinogenicity bioassays of PFOA that are discussed in the petition were publicly available in 1987 and 2001, and have been the subject of continued governmental evaluation since that time. Any "new information" regarding the presence or persistence of the chemical is not related to carcinogenicity, which Proposition 65 is intended to address. Similarly, the absence of any data to support a conclusion that exposure to PFOA causes cancer prevents any conclusion that exposure presents an "emerging public health issue" that Proposition 65 is intended to address.

For these reasons, expedited referral of PFOA to the CIC is not a good use of OEHHA's resources, or those of the CIC. Referral and consideration of the chemical would occupy

⁸ OEHHA (2004) Process for Prioritizing Chemicals for Consideration under Proposition 65 by the "State's Qualified Experts," December 2004, p. 6.

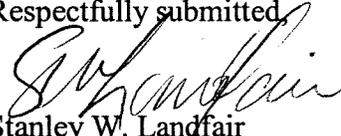
considerable staff time and resources to review scientific data, hold public hearings and examine public comments, in a process that could require several years. The scientific evidence available at this time does not warrant that diversion of resources from other chemicals already nominated for listing under OEHHA's Prioritization Procedure, pursuant to the criteria for listing established under the Statute and implementing regulations and those considerations further articulated in the Committee's policy for determining whether asserted evidence of carcinogenicity is sufficient to support a conclusion that a chemical meets those criteria.

The criteria set forth in the Prioritization Procedure bear this out: under the normal prioritization procedure, PFOA would not receive a "high" priority since it would not pass through the initial epidemiological screen. This initial screen requires: (1) "chemicals with epidemiological evidence suggesting they cause cancer" or (2) "very strong evidence from animal studies" in the absence of positive epidemiological data. PFOA meets neither of these criteria. In our view, a chemical should not receive an expedited review if it would not even receive a "high" priority under the Prioritization Procedure.

CONCLUSION

DuPont appreciates the time and resources that your Office has expended in addressing this issue, and would be pleased to provide further information if it will assist you. For all the reasons discussed above, we believe it is unnecessary and inappropriate to refer PFOA to the CIC or to consider the chemical for listing for carcinogenicity.

Respectfully submitted,


Stanley W. Landfair
Counsel for E.I. du Pont de Nemours
and Company

Enclosures (references)

cc: Carol Monahan-Cummings, Chief Counsel, OEHHA