environmental defence
INSPIRING CHANGE

December 24, 2010

Mr. David Morin, Executive Director
Program Development and Engagement Division
Science and Risk Assessment Directorate
Environment Canada, Gatineau, Quebec K1A 0H3

Re: Teflon chemical PFOA – Comments on Draft Screening Assessment
Notice published in the Canada Gazette, Part I, p. 2760 on October 30, 2010

Dear Sir:

On behalf of the Environmental Working Group, a non-profit research and advocacy organization based in Washington, D.C., and Environmental Defence Canada we are submitting comments on the "Draft Screening Assessment for perfluorooctanoic acid (PFOA), its salts, its precursors" published by Environment Canada and Health Canada. Since the 1950's, numerous industries have used PFOA to manufacture everyday consumer products, among them, non-stick cookware, food packaging and clothing. PFOA has become a pervasive global contaminant because of its widespread use over many years and its extraordinary persistence and toxicity.

As demonstrated by an extensive body of research, PFOA has been linked to developmental toxicity, immunotoxicity, alterations in hormonal levels, metabolic disturbances and an elevated risk of cancer. Environment Canada and Health Canada are right to give PFOA regulatory scrutiny. Yet the section of the draft assessment entitled "Potential to Cause Harm to Human Health" does not accurately represent the weight of the scientific evidence for PFOA's potential toxicity to humans. Further, it appears to dismiss the risks of PFOA exposure to human health at pollutant levels to which the general population is typically exposed.

The assessment's scientific analysis ignores at least 12 key epidemiological and laboratory studies of PFOA. As a result, the risk to human health may be up to 100 times greater than the assessment's estimate. The assessment suggests that the dose of PFOA that causes adverse effects in laboratory animals is more than 2000 times greater than the PFOA contamination found in people by recent biomonitoring studies. However, a review of the most sensitive animal studies suggests that lab animals show damage at doses that are just 20 times greater than concentrations detected in humans. This number is much smaller than the 1000-fold margin of safety typically recommended by Health Canada for toxic pollutants. If these false assumptions are not remedied, Canada's PFOA assessment will undermine ongoing and much-needed efforts to reduce PFOA pollution in people and the environment. We urge you to address the shortcomings of the current draft assessment, as outlined in our detailed comments attached.

Sincerely,

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Attachment: Detailed Comments on the PFOA Draft Screening Assessment

In its current version, the draft assessment suffers from a number of shortcomings, ignoring key studies and drawing reassuring but false conclusions as a result. These gaps should be remedied in order to assure public health protection. Specifically,

- The draft claims that "*Epidemiology studies have not identified a causal relationship between PFOA exposure and adverse health effects in humans*." This off-hand assertion ignores the basic scientific fact that epidemiological research can offer legitimate inference about a possible cause, even though definitive proof of causality may be hard to attain. The agencies use the flawed claim to dismiss a sizable body of human epidemiological data on PFOA toxicity. The claim should be removed from the draft, and replaced with a full and accurate assessment of the range of health impacts associated with PFOA in published epidemiology studies.

- The draft fails to mention findings from at least 12 key epidemiology and laboratory studies, including research finding higher levels of PFOA linked to decreased sperm count in men; preeclampsia in pregnant women; birth defects in babies with higher exposures; immune system changes indicating compromised immune function; changes in mammary gland development; adverse effects on the thyroid; and troubling findings of metabolic and liver function alterations and elevated cholesterol levels in both children and adults (Joensen 2009; Melzer 2010; Nelson 2010; Son 2009; Stein 2009; White 2009; Zhao 2010). The list of the missing studies is provided in the Appendix of our letter.

- The draft does not take into account PFOA's tendency to build up in the bodies of people, and to accumulate rapidly in the bodies of breastfed infants (Emmett 2006; Fromme 2010). Unlike laboratory animals such as mice and rats, human beings eliminate PFOA from their bodies much slower, with half-lives of PFOA on the order of years (Olsen 2007). PFOA's persistence in the human body indicates a much longer duration of exposure (Loccisano 2011), with a potential to trigger chronic effects even at lower levels observed in the general population (Nelson 2010).

- The draft presents a faulty calculation of the margin of exposure, or MOE, the magnitude of the ratio between the dose at which toxicity is observed in studies conducted in animals and the upper-bound estimated (or measured) level of human exposure (Health Canada 2004; U.S. EPA 2009). The MOE of 2,200 estimated by the draft assessment may be at least 10 times higher and possibly 100 times higher than the real margin of exposure suggested by the most sensitive animal studies (Abbott 2007; Hines 2009).

- Finally, the draft uses the faulty MOE calculations to assert that "*the resulting margins of exposure are adequately protective of human health.*" This statement must be retracted and replaced with a conclusion that is consistent with the full range of available science demonstrating little to no margin of exposure for the general population.

Details and the rationale for our comments are provided below.

1. The draft dismisses the growing body of human epidemiological data on PFOA toxicity. Latest research studies have reported adverse health effects at the levels of PFOA found in the general population, such as adverse effects on the thyroid, elevated cholesterol levels, reproductive problems in women and men (Fei 2009; Frisbee 2010; Joensen 2009; Melzer 2010; Nelson 2010; Steenland, Tinker, Frisbee 2009). Thus, the statement in the draft's section "Human Health", page *v*: "*Epidemiological studies have not identified a causal relationship between PFOA exposure and adverse health effects in humans*," mischaracterizes and discounts the significant body of peer-reviewed scientific literature that finds adverse health effects in people linked to PFOA.

While it is frequently challenging to infer unambiguous causality from human epidemiological studies of chemical exposures, these studies can be effectively used as valuable indicators of adverse effects in people (Goldman 2001; IARC 2006; Weed 2002). So far scientists do not know what internal concentration of PFOA may be without adverse effects. The above-referenced sentence in the current draft creates an appearance of safety that contradicts the latest research.

The discussion of human epidemiological data should be strengthened in the areas of developmental/reproductive effects and prenatal/postnatal exposure to perfluorinated compounds (PFCs); serum lipids and other serum parameters as indicators of metabolic effects of PFCs; PFC impact on the immune response; and cancer, as described in the following sections.

Developmental/reproductive effects of PFOA

- The draft should include a reference to the study by Danish scientists associated PFOA with lower sperm quality in otherwise healthy young men (Joensen 2009). This study included 105 Danish men (median age 19 years) from the general population; the median levels of PFOA in this population were 4.9 ppb. Researchers observed that men with high levels of perfluoroalkyl acids (PFAAs) had a median of 6.2 million normal spermatozoa in their ejaculate compared to 15.5 million normal spermatozoa counts among men with low PFAA levels. The authors of the study suggested that "high levels of PFAAs may contribute to the otherwise unexplained low semen quality seen in many young men" (Joensen 2009).

- The draft should present a comprehensive characterization of the study conducted by the Mount Sinai School of Medicine scientists that reported a link of PFOA with hypertension during pregnancy and birth defects (Stein 2009). The Stein study is quoted in the draft, but only one finding of the study is mentioned, the reported absence of association between PFOA and low birth weight, while other key findings of the study are not cited. In this research, analysis of 1,845 pregnancies found that preeclampsia was weakly associated with PFOA (adjusted odds ratio = 1.3, 95% confidence interval: 0.9, 1.9). Birth defects were weakly associated with PFOA exposures above the 90th percentile (adjusted odds ratio = 1.7, 95% confidence interval: 0.8, 3.6) (Stein 2009). This is the first study that reported an association between PFOA and preeclampsia, a dangerous pregnancy complication. When considered together with another study that

linked PFOA with infertility in women (Fei 2009) and data from animal studies, this research highlights the potentially significant adverse effect of PFOA on human reproduction.

- The section on human exposure to PFOA from breast milk (p. 39 of the draft) should be expanded to include the study conducted by the scientists at the Bavarian Health and Food Safety Authority (Munich, Germany) that found a dramatic increase in the body burden level of PFOA during the first months of infant life (Fromme 2010). This is the first study that reported longitudinal data on the PFOA levels in mothers, fetuses (via cord blood testing) and infants, as well as in breast milk samples. While the number of mother-child pairs enrolled in the study was small (53 pregnant women participated), the results of this pilot study are very powerful, demonstrating that mean PFOA levels increase by 4.7-fold in the first 6 months of a child's life. At this sensitive point during early postnatal development, the infant's PFOA levels are also 4.7 times greater than the mother's PFOA body burden. Infants in the study were primarily breast-fed, suggesting that the rise in PFOA levels is primarily due to transfer via breast milk (Fromme 2010). Although the study did not assess health consequences of this intense early-life exposure to PFOA, these findings are an essential contribution to the knowledge of PFOA toxicity and exposure patterns, since PFOA effects tend to be more pronounced in younger humans or laboratory animals (Frisbee 2010; Hines 2009)

Metabolic effects of PFOA

The current draft does not discuss any of the data on the association of PFOA with various biochemical parameters measured in human serum that indicate adverse effects of PFOA on various aspects of metabolism and liver function. Most recently, publications from a multi-year study of 69,000 West Virginians and Ohioans whose drinking water was contaminated by a fluorochemical manufacturing plant in Washington, W.Va., along the Ohio River (Frisbee 2009) raise the same health concerns for PFOA exposure as has been previously reported by occupational exposure studies (Sakr 2007). Some of these studies are listed in the Appendix of the draft assessment. However, their cumulative weight of evidence should be considered in the main text of the assessment.

Specifically, elevated cholesterol levels observed in association with PFOA in adults and children can lead to potentially serious consequences such as an increased risk of cardiovascular disease and diabetes (Frisbee 2010; Steenland, Tinker, Frisbee 2009). PFOA has also been significantly associated with elevated levels of uric acid in serum, a risk factor for hypertension that may be associated with stroke and diabetes (Heinig 2006; Steenland, Tinker, Shankar 2009). Of note, elevated mortality from diabetes and ischemic heart disease has been observed in occupational studies of PFOA, confirming the connection between metabolic effects of PFOA and chronic health problems (Leonard 2008; Sakr 2009).

Immune system effects of PFOA

Adverse effects on the immune system have been reported in human and laboratory animal studies (Dewitt 2009; Frisbee 2008). Increased PFOA levels in serum have been linked with

immune system changes such as a significant decrease in serum levels of two immune defense proteins, immunoglobulins IgA and IgE (C8 Science Panel 2009).

PFOA association with cancer

The draft assessment devotes several pages (44-46) to discounting animal carcinogenicity data for PFOA as not relevant to humans because of involvement of peroxisome proliferation response in PFOA toxicity response for rodents, a process that is believed to be less important in humans. However, a thoughtful analysis of animal carcinogenicity data indicates that the development of two types of tumors observed in PFOA-exposed animals, Leydig cell tumors and pancreatic acinar cell tumors, is less likely to be dependent on peroxisome proliferation (U.S. EPA SAB 2006). Thus, their relevance for human cancer risk remains a concern. Furthermore, PFOA toxicity in various species, including rodents, is not exclusively dependent on peroxisome proliferation (Dewitt 2009). Rather, significant toxicity effects, such as adverse effects on mammary gland development, are independent of the peroxisome proliferator-activated receptor alpha (PPARa) activation, and thus would be highly pertinent to human health (Minata 2010; Zhao 2010).

In their 2006 assessment, majority of the members of the U.S. EPA's Science Advisory Board (SAB) considered PFOA to be "likely carcinogenic" to humans, on the basis of the fact that PFOA is a multi-site carcinogen in rats (U.S. EPA SAB 2006). Two out of three different types of tumors, Leydig cell tumors and pancreatic acinar cell tumors that develop in PFOA-exposed rats, may be relevant to humans (U.S. EPA SAB 2006).

The animal carcinogenicity findings are all the more of concern because of cancer findings in occupational studies. In the current draft, human cancer data are referenced only in the Appendix. Instead, this analysis should be included in the main text, keeping in mind the following points:

- The draft Appendix references Leonard et al. 2008 study, stating that "*the number of deaths due to liver, pancreatic and testicular cancers were less than expected for the US population*" (p. 83). This quote misrepresents the focus of the Leonard 2008 publication, which was not to compare the cancers in the study population to the general U.S. population, but to compare these numbers to the appropriate reference worker population. Because of the "healthy worker effect", a phenomenon well studied in epidemiology (Baillargeon 2001), lower incidence of various diseases is expected in many occupational cohorts (Burns 2010). The study abstract states that their study "demonstrates the utility of comparing occupational cohorts with a similar worker population in order to reduce bias associated with the healthy worker effect" (Leonard 2008).

- Comparing the cohort of PFOA-exposed workers to the closest reference population, DuPont Region 2 workers, researchers found mortality from various cancers, for example lymphatic and hematopoietic cancers, to be higher than expected (Leonard 2008). Similarly, another occupational cohort study found elevated risk for prostate cancer (Lundin 2009). While detailed statistical analysis of elevated cancer incidence may be difficult with the currently available cohorts, these studies clearly demonstrate that PFOA

carcinogenicity is not a laboratory animal-only effect, contrary to the viewpoint advanced by the draft assessment.

In light of both human and laboratory animal cancer studies, we urge Health Canada and Environment Canada to reconsider their review of PFOA cancer data and remedy the gaps outlined above.

2. The calculated margin of exposure should be based on the most sensitive animal studies

Margin of exposure approach, which compares the levels of chemical that elicit adverse effects in laboratory animals with current human exposures, is a reasonable method for estimating risks due to substance in question (Barlow 2010). However, human PFOA toxicity studies outlined above clearly demonstrate that chronic PFOA exposure is associated with the type of health effects that may be easily missed in short-term animal studies, such as the effects on the immune system, metabolism, and fertility, as well as increased risk of cancer. In people these effects would lead to long-term, chronic health problems that carry a heavy burden of suffering as well as high financial costs. Thus, it is essential to ensure that appropriate, most sensitive animal studies are used for calculating margin of exposure.

Unfortunately, one of the main conclusions of the current draft: "*Comparison of the PFOA serum levels associated with adverse effects in laboratory animals (13–77 µg/mL) with the serum levels found in non-occupationally exposed adults and in children (0.0034–0.010 µg/mL) results in margins of exposure of ≥1 300*" (page v) is based on a departure point for toxicity observed in animal studies that is higher than that determined by the most sensitive studies in the literature. Furthermore, the studies that provide departure point for the above calculations are short-term, subchronic studies (14 days exposure in rats or mice or 26 week-exposure in monkeys), which all fall short of the necessary chronic study duration. None of the chosen studies identified a No Adverse Effect Level (NOAEL) and the margin of exposure has been calculated from the lowest dose tested in those studies, which may be high above the actual lowest level of PFOA that would elicit toxic effect under a comparable study design.

Recent publications that could provide more sensitive departure points for estimating margin of exposure for PFOA include:

- Study finding changes in liver weights in pups of dams dosed with PFOA during pregnancy, starting with the dose of 0.1 mg/kg-bw/day, which is three times lower than the lowest departure point identified in the draft assessment (Abbott 2007).

- Study finding significant dose-dependent increases in young female mice that were exposed to as little as 0.01 and 0.1 mg PFOA/kg-bw/day during gestation (Hines 2009).

- Study finding immune changes in the spleens of mice exposed to the lowest PFOA dose tested, 2 ppm of PFOA administered in drinking water (Son 2009).

On page 47 of the draft, a mouse pregnancy dosing study (Lau 2006) was used to compare a LOAEL of 1 mg/kg-bw day to a PFOA body burden of ~10 μg/ml (parts per billion or ppb), the 95% exposure bracket reported for adults and children in the U.S. population tests (Calafat 2007; Olsen 2004). Based on this study, the draft suggested that a margin of exposure of ~2200 exists between adverse developmental effects in mouse development and human exposures.

In contrast to this assumption, if the true point of departure, as suggested by the Abbott 2007 and Hines 2009 studies, is at 0.1-0.01 mg/kg-bw/day, the margin of exposure may be 10-100 times smaller than estimated by the draft. The real margin of exposure may be as small as 22, a finding in agreement with human epidemiological studies that find adverse reproductive and developmental effects at the current levels of exposure in the general population.

The Hines et al (2009) study highlights that early-life exposures to small amounts of PFOA could lead to significant adverse consequences later in life, such as obesity, a finding that is in agreement with metabolic and cholesterol effects of PFOA. This research also indicates that the actual margin of exposure for the general population is much smaller than calculated by the draft. Finally, PFOA accumulation and persistence in the human body (Emmett 2006; Olsen 2007; Steenland, Jin 2009) exposes humans to long-term risks that mice and rats, with much faster PFOA elimination, might not experience.

3. The draft fails to consider PFOA's tendency to build up in the bodies of people.
As demonstrated by a study from the University of Pennsylvania, PFOA ingested with drinking water builds up in the human body to levels 100-fold higher than found in the contaminated water source (Emmett 2006). As a result of this build up, the half-life of PFOA in the human body is on the order of 4 years (Olsen 2007). The Emmett study is mentioned in the draft, but its most critical finding, namely, the accumulation of PFOA in humans and its implication for the PFOA human health risk assessment, is not discussed anywhere in the document.

The conventional definitions of bioaccumulation developed for persistent chlorinated organic pollutants that partition to the adipose tissue miss the ability of substances such as PFOA to build in the human body (OECD 2007). The draft agrees with this viewpoint, stating that the current bioaccumulation criteria *"do not account for the bioaccumulation of PFOA that is preferentially partitioning in the proteins of liver, blood and kidney in terrestrial and marine mammals*" (p. 16). Further, the draft states that PFOA "*may be considered to bioaccumulate and biomagnify in terrestrial and marine mammals*" (p. 21).

The revised assessment needs to discuss the scientific, regulatory and human health implications of the fact that PFOA builds up in the bodies of humans. Specifically, following improvements are urgently needed:

- The Human Health sections of the final document should include latest research on the build up of the PFOA in people (Emmett 2006; Seals 2010; Steenland, Jin 2009).

- The Emmett publication data should be added to the Table 5, Summary of bioaccumulation data (p. 19-20). Currently, this table includes studies on fish, turtles, and marine mammals, but misses the crucial human study.
- The margin of exposure discussion needs to be revised in the light of PFOA accumulation in the human body.

These changes and additions would greatly strengthen the scientific validity of the human risk assessment and help protect public health from the adverse effects of PFOA exposure.

Conclusions

In summary, various and multiple shortcomings of the human health risk assessment of the draft negate the conclusion that "*the resulting margins of exposure are adequately protective of human health*" (p. 51). We urge Health Canada and Environment Canada to revise the current assessment by incorporating the suggestions outlined above and by taking a firm stand to protect the health of the Canadian people from PFOA and related fluorinated compounds.

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Appendix: Epidemiology and laboratory studies that need to be added to the assessment

1. DeWitt JC, Copeland CB, Strynar MJ, Luebke RW. 2008. Perfluorooctanoic Acid–Induced Immunomodulation in Adult C57BL/6J or C57BL/6N Female Mice. Environ Health Perspect 116(5): 644-50.

Scientists from the University of North Carolina, Chapel Hill and the U.S. Environmental Protection Agency reported that IgM antibody production, an important marker of the immune system function, was suppressed by PFOA exposure in laboratory mice.

2. Frisbee S, Shankar A, Knox SS, Steenland K, Savitz D, Fletcher T, et al. 2010. Perfluorooctanoic Acid, Perfluorooctanesulfonate, and Serum Lipids in Children and Adolescents: Results From the C8 Health Project. Arch Pediatr Adolesc Med 164(9): 860-69.

A study of 12 476 children and adolescents in the C8 Health Project, led by the scientists from the West Virginia University School of Medicine, found that PFOA was significantly associated with increased total cholesterol and low-density lipoprotein, factors that are associated with obesity and heart disease.

3. Fromme H, Mosch C, Morovitz M, Alba-Alejandre I, Boehmer S, Kiranoglu M, et al. 2010. Pre- and Postnatal Exposure to Perfluorinated Compounds (PFCs). Environ Sci Technol 44(18): 7123-29.

Research by the Bavarian Health and Food Safety Authority (Germany) found that the body-burden levels of PFOA in infants rise rapidly in the first 6 months of life due to PFOA transfer from mother to infant via breast milk.

4. Hines EP, White SS, Stanko JP, Gibbs-Flournoy EA, Lau C, Fenton SE. 2009. Phenotypic dichotomy following developmental exposure to perfluorooctanoic acid (PFOA) in female CD-1 mice: Low doses induce elevated serum leptin and insulin, and overweight in mid-life. Mol Cell Endocrinol 304(1-2): 97-105.

Research from the U.S. Environmental Protection Agency found that in laboratory animals *in utero* exposure to low doses of PFOA predisposed animals to elevated body weight and obesity as well as elevated insulin levels in mid-life.

5. Joensen UN, Bossi R, Leffers H, Jensen AA, Skakkebæk NE, Jørgensen N. 2009. Do Perfluoroalkyl Compounds Impair Human Semen Quality? Environ Health Perspec 117(6): 923-27.

A team of Danish researchers reported an association between elevated levels of PFOA and decreased number of normal spermatozoa in young men.

6. Melzer D, Rice N, Depledge MH, Henley WE, Galloway TS. 2010. Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U.S. National Health and Nutrition Examination Survey. Environ Health Perspect 118(5): 686-92.

A team of British researchers found that higher concentrations of serum PFOA and PFOS are associated with current thyroid disease in the U.S. general adult population.

7. Minata M, Harada KH, Karrman A, Hitomi T, Hirosawa M, Murata M, et al. 2010. Role of peroxisome proliferator-activated receptor-alpha in hepatobiliary injury induced by ammonium perfluorooctanoate in mouse liver. Industrial Health 48(1): 96-107.

Scientists from the Kyoto University Graduate School of Medicine reported that PFOA-treated PPARalpha-null mice experienced significant fat accumulation in the liver, severe bile duct

disease, hepatocellular damage and cell death, indicating that many toxicity effects of PFOA are unrelated to PPARalpha and thus are would be highly relevant to human health.

8. Nelson JW, Hatch EE, Webster TF. 2010. Exposure to Polyfluoroalkyl Chemicals and Cholesterol, Body Weight, and Insulin Resistance in the General U.S. Population. Environ Health Perspec 118: 197-202.

Researchers from Boston University School of Public Health reported an association between PFOA levels in the body and elevated cholesterol in a study of 2,094 participants aged 12-80.

9. Son HY, Lee S, Tak EN, Cho HS, Shin HI, Kim SH, et al. 2009. Perfluorooctanoic acid alters T lymphocyte phenotypes and cytokine expression in mice. Environ Toxicol 24(6): 580-8.

A team of South Korean scientists found adverse effects of PFOA on the immune system of laboratory animals, even at the lowest level of PFOA tested in the study.

10. Steenland K, Tinker S, Shankar A, Ducatman A. 2009. Association of Perfluorooctanoic Acid (PFOA) and Perfluorooctanesulfonate (PFOS) with Uric Acid Among Adults with Elevated Community Exposure to PFOA. Environ Health Perspec 118(2): 229-33.

A study of 54,951 adult community residents in Ohio and West Virginia, who lived or worked in six water districts contaminated with PFOA from a chemical plant found that higher serum levels of PFOA were associated with higher levels of uric acid, a risk factor for hypertension that may be associated with stroke and diabetes.

11. White SS, Kato K, Jia LT, Basden BJ, Calafat AM, Hines EP, et al. 2009. Effects of perfluorooctanoic acid on mouse mammary gland development and differentiation resulting from cross-foster and restricted gestational exposures. Reprod Toxicol 27(3-4): 289-98.

Researchers from the U.S. Environmental Protection Agency demonstrated that developmental PFOA exposure in laboratory animals leads to early and persistent mammary gland effects, suggesting permanent consequences.

12. Zhao Y, Tan YS, Haslam SZ, Yang C. 2010. Perfluorooctanoic acid effects on steroid hormone and growth factor levels mediate stimulation of peripubertal mammary gland development in C57BL/6 mice. Toxicol Sci 115(1): 214-24.

Michigan State University scientists reported that effects of PFOA on mammary gland was observed in both PPARalpha knockout and wild-type laboratory animals, demonstrating PPARalpha independence of PFOA toxicity which would be strongly relevant to human health.