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Delivered by email

Dear Ministers Ujjal Dosanjh and Stéphane Dion:

Subject: Comments on the Draft Screening Level Risk Assessment Report for Perfluorooctane sulfonate (PFOS)

The signatories to this letter are submitting the following comments to respond to the findings outlined in the Draft Screening Level Risk Assessment Report for Perfluorooctane sulfonate (PFOS), announced in the Canada Gazette Notice, Part I (Vol. 138, No. 40 — October 2, 2004) by Health Canada and Environment Canada.

This letter is intended to support and expand on several specific comments submitted by a number of not for profit environmental organizations on these draft assessment reports dated December 22, 2004.

The main thrust of this submission is to present evidence and rationale to Health Canada and Environment Canada that would support a conclusion for PFOS to be CEPA toxic under Section 64(c). Three gaps and deficiencies have been identified in the draft assessment report prepared by Health Canada.

A. Uncertainties about the screening level risk assessment scope and timeframe
B. The absence of consideration of other members of perfluorinated chemicals.
C. The available data supports a designation of “toxic” even if you consider PFOS by itself.
D. Consideration of carcinogenicity data is absent from the assessment report.

Based on the rationale presented below, the signatories firmly recommend that Environment Canada and Health Canada make the conclusion that PFOS is “toxic” under CEPA Section 64(c). The final report should include the approach and information provided below.

A. Uncertainties about the screening level risk assessment scope and timeframe

The general goal of screening level risk assessments (SLRA) was to shorten the timeframe required by Health Canada and Environment Canada to identify substances of concern and those that required a full risk assessment. The length of time needed to complete and release the findings from the assessment on PFOS and previously on the seven polybrominated diphenyl ethers are being is worrisome. We are concerned that similar time delays will occur on current and future SLRAs if a transparency and accountability to the public are not applied to these processes. To address these current gaps in the approach, Environment Canada and Health Canada should develop a list of criteria that will outline the timeframe required to complete SLRAs and the conditions that will trigger a full risk assessment of a substance.

Recommendation: We strongly recommend that Environment Canada and Health Canada jointly design guidelines, timetable, and set of criteria which will outline the length of time required for a SLRA and clearly define the conditions that will trigger a full risk assessment for substances.

B. Cumulative risk assessment of PFOS and other perfluorinated acids (PFAs)

PFOS is a member of a family of chemicals that should be considered in this assessment. Past assessments, including the risk assessment conducted on chlorinated dioxins and furans considered the family.

1. Background for cumulative risk assessments:

The toxicity of chemicals acting through a common mechanism of toxicity is usually additive (Broderius 1992; Broderius *et. al.* 1995; De Wolf *et. al.* 1988; Mileson et. al. 1998; McCarty and Mackay 1993; Deneer *et. al*. 1988; Hermens *et. al.* 1985). The US EPA recognizes this and the fact that having safety limits for each chemical in a cumulative class may not be protective when a subject is exposed to several of the chemicals, promulgated guidelines for cumulative risk assessment (US EPA 1999; US EPA 2002a; Mileson *et. al*. 1998). Health Canada has implicitly recognized the need for performing cumulative risk assessments when they assessed chlorinated dioxins and furans as a cumulative class. The following is a rationale for applying a cumulative risk assessment for PFOS as part of the PFA class:

a) *Structurally similarity of PFOS and other PFAs*

On a molecular scale PFAs are almost identical. They are essentially rigid electronegative rods with a negatively charged end. The electropositive carbons are completely shielded from interacting with other molecules by the electronegative fluorines. The similarities can be seen whether we look at space filled, electronic or atom connection depictions of the structures. For instance PFOS and PFOA:

$$FCF_2CF_2CF_2CF_2CF_2CF_2CF_2CF_2SO_3^-$$

$$FCF_2CF_2CF_2CF_2CF_2CF_2CF_2CO_2^-$$

Their homologs appear the same. The only difference is that the length varies.
Many properties of PFOS and PFOA and the homologs that have been tested and are found to be similar, including:

- surfactants at less than a monolayer concentration,
- resistant to thermal degradation,
- resistant to chemical degradation,
- extremely low pKa, and
- oleophobic (Personal communications with 3M scientists, www.daikin.co.jp/chm/en/index.html, www.dupont.com/zonyl/pdf/genbrochure.pdf, www.dupont.com/zonyl/flash.htm.)

b) *Occurrence of PFAs in products*

Most all PFA precursors have similar uses and are found in similar products. Substances that break down to homologs of PFOS such as PFHS and PFBS are used in products. All these substances are not pure and contain other perfluorinated sulfonate homologs with chain lengths

C3-C10. Substances that break down to PFOA also break down to other perfluorinated carboxylates with chain lengths from C4 to C20. Precursors to PFOS, other perfluorinated sulfonates, PFOA and other perfluorinated carboxylates are used in the same type of products: fabric/upholstery protector, carpet protector, leather protector, paper protector, food packaging**,** specialty surfactants, cleaning applications, electroplating baths, insecticides, paints, inks, photographic solutions, floor polishes, and fire extinguishing foam concentrates.

c) *PFAs and precursors listed on the DSL*

There are more than 100 substances on the DSL than can break down into perfluoro sulfonates and more than 60 that can degrade to perfluoro carboxylates (Dimitrov et. al. 2004). These numbers indicate many exposures to precursors of PFOS and other PFAs.

d) *Occurrence of PFAs in humans and the environment*

PFAs can be detected in all media. PFAs have been found in surface water (Berger *et. al.* 2004;Boulanger *et. al.* 2004; Muir *et. al.* 2002; Hansen *et. al.* 2002; Battelle 2001; Giesy and Newsted 2001), drinking water (Battelle 2001), sediment (Battelle 2001; Giesy and Newsted 2001), food (Battelle 2001), and in wildlife tissues (Berger *et. al.* 2004; Kannan *et. al.* 2001a, Kannan *et. al.* 2001b, Kannan *et. al.* 2001c, Giesy and Kannan 2001a; Hansen 1999a; Hansen 1999b; Giesy and Kannan 2001b; Giesy and Kannan 2001c; Giesy and Kannan 2001d; Giesy and Kannan 2001e; Giesy and Kannan 2001f; Smithwick *et al*. 2004). The blood of every human tested for PFAs after 1980 contain PFAs and a wide range of PFAs have been found including PFOS, PFDS, PFHS, PFOA, PFHA, PFNA, PFDA, PFUA, PFDoA and PFTA (3M 2000; Mandel and Burris 1995; Hansen 2000; 3M 1999a; Mandel 2000; Guruge *et. al.* 2004; Hansen 1999c; Hansen *et. al.* 2000; Karrman *et. al.* 2004; Kubwabo *et. al.* 2004; Olsen *et. al.* 2002a; Olsen *et. al.* 2002b; Olsen *et. al.* 2002c). Precursors to many PFAs have been found in air (Martin 2002; Stock *et. al.* 2004). The levels of PFAs appear to have been increasing in sera of North Americans and Europeans since products containing these compounds or their precursors have been manufactured and marketed. No PFAs were found in sera samples from around 1950. Some samples from 1958 through 1971 showed relative low levels of PFAs and the rest had less than the detection limit (3M 1999a). Since 1976 all North American and European human sera samples have been found to contain PFAs (3M 1999a; Olsen *et. al.* 2002a; Olsen *et. al.* 2002b; Olsen *et. al.* 2002c, Mandel 2000).

The studies demonstrating the extent of exposure provide evidence that a more serious look at effects is necessary in the context of this assessment.

e) *PFAs have similar unique mechanism of bioaccumulation*

Few studies have been done on the bioaccumulation mechanism of PFAs, but they have been done for two substances in the class. Because of structural similarities it is expected that the other PFAs accumulate by the same relatively rare mechanism. PFOS and PFOA are concentrated in the bile and recycled by the enterohepatic recirculation system (Johnson *et. al.* 1984; US EPA OPPT AR226-0548).

f) *PFAs demonstrates common mechanism of action*

Uncoupling of oxidative phosphorylation is apparently the primary molecular mechanism of toxicity (Langley 1985; Schnellmann 1990; Wallace and Starkov 1998; Starkov and Wallace 2002; Thomford 1998). Poor food conversions to energy and body mass gain are frequently symptoms of the uncoupling of oxidative phosphorylation. In most all toxicity studies of PFAs on

a variety of species, loss of weight, poor growth, or poor food conversion efficiency to body mass is reported (Haughom *et. al.* 1992; Goldenthal *et. al.* 978a; Goldenthal *et. al*. 1978b; Langley and Pilcher 1990; Thomford 1998; Covance 2000; Case 1999a; York *et. al.* 1999; 3M 1987; Campbell et. al. 1993a; Campbell *et. al.* 1993b; Cook *et. al.* 1992; Borges 1992; George *et. al.* 1986).

g) *PFAs may exhibit similar toxic effects*

Similar effects on tissues are observed across this class of chemicals. Thymus atrophy, thyroid hormone or mass changes are seen when looked for, and liver enlargement is usually seen (Goldenthal *et. al.* 1978a; Goldenthal *et. al.* 1978b; Seacat and Hansen 2001; Covance 2000; Van Rafelghem *et al*.1987a; Van Rafelghem *et al.*1987b; Van Rafelghem *et al.*1987c; Langley *et. al.* 1985; Belisle 1978; Metrick and Marias 1977; Case 1999b; Hansen 1999c). Chemicals acting by the same mechanism of toxicity usually damage the same tissues in similar ways. Thus the tissue effects seen for the PFAs studied are consistent with the same mechanism of toxicity which is required for doing a cumulative risk assessment.

h) *Cumulative toxicity conclusions*

The evidence support that PFOS is a cumulative toxin with other PFAs. Given the nature of its use and presence of other perfluorinated acids, the risk assessment of PFOS should be conducted as a cumulative risk assessment. At a minimum, PFAs should be assessed by Health Canada and Environment Canada with specific focus on the cumulative effects of PFOS.

Recommendation: Perfluorinated acids should be included in the assessment of PFOS to address the cumulative effects of chemicals.

C. Deficiencies in the risk assessment of addressing PFOS alone

1. No Observable Effects Level (NOEL) versus Lowest Observable Effects Level (LOEL)

In Health Canada's draft SRLA the LOEL was presented. Usually a risk assessment is done on the NOEL because there can be effects at concentrations lower than the LOEL. Health Canada's guidance document, Human Health Risk Assessment for Priority Substances, says it is preferable to use the NOEL. In Health Canada's Assessment of diisononyl phthalate in vinyl children's product, the NOAEL (no observed adverse effects level) was used (Health Canada 1998). In this assessment report, Health Canada does not provide sufficient rationale for deviating from this approach. The use of the NOEL by Health Canada is necessary to fully protect the public. The use of the NOEL should be reflected in the final assessment for PFOS.

2. *The Monkey Study did not apply a NOEL*

Similar to the point presented in #1, no NOEL was found in the monkey study Health Canada presented in the draft assessment. The level at which PFOS causes effects could be many times lower than the LOEL presented.

3. *Sex differences in observable effects*

In the assessment Health Canada presented the average LOEL for both sexes in the rat study. Male rats were affected at lower sera levels than the females, However, the level considered does not consider the effect observed in the more susceptible subpopulation, in this case the male rats. The NOEL for male rats should be presented and used in the assessment. The

same sex difference could be fact in humans. Any assessment should consider the most susceptible subpopulation.

4. *Infants and toddlers*

Uncertainty about infants and toddlers being the most sensitive age group was not addressed. It has been shown that PFAs pass from mother to child in the womb and through mothers milk (Mylchreest 2003).

Infants and toddlers are more highly exposed because they do a lot of touching and licking of hands. PFAs are put on surfaces children contact most: floors and walls (3M 1999b; 3M 2000). PFAs are used to treat carpets and they are used in paints and floor waxes. In addition children suck on their clothes. PFAs are used to treat clothes. Thus infants and toddlers are probably the most highly exposed age group in the population.

Infants are also likely to be the most sensitive age group to the toxic effects of PFOS and other PFAS. In the first year many immunological characteristics of an individual are established. PFAs suppress the immune response (Yang *et. al.* 2002; Nelson 1992).

The thymus is important in the first year of life for producing immunological cells and setting the long term path of various immunological functions in the body. One of the outstanding effects observed for PFAs is thymus atrophy or involution (Yang *et. al.* 2000; Yang *et. al.* 2001; Goldenthal *et. al.* 1978a; Thomford 2001a; Thomford 2000; Goldenthal *et. al.* 1978b). In a 26-week study of Cynomolgus monkeys, 11 of the 12 dosed female monkeys given the PFA, PFOS, had atrophied thymi. This effect was not seen in the controls. The range of PFOS levels in the sera of the low dose monkeys were 11.4 to 14.8 mg/l (Thomford 2000; Seacat and Hansen 2001). No study in experimental animals to date has allowed the determination of a no-observable-effect-level (NOEL) for thymus atrophy associated with exposure to any PFAs. Damage of the thymus has been associated with immune base diseases. For instance, the health of the thymus is central in the aetiology of IDDM (insulin-dependent diabetes mellitus) also known as early onset diabetes. The size or the mass of thymic epithelium is reduced in animal models of IDDM: nonobese diabetic (NOD) mice (Savino *et. al.* 1991), athymic nude Balb/c mice (Zeidler *et. al.* 1982), and diabetes prone BB rats (Doukas *et. al.* 1994). A relatively slow rate of thymocytes proliferation in NOD mice as compared to non-autoimmune mice has been reported and has been suggested as a mechanism through which genetic propensity to diabetes can be expressed (Bergman *et. al.* 2001). The reduced mass of thymic epithelium in these animal models of IDDM can be postulated to cause the slow development of immature lymphocytes in these animal models. Thymectomy of NOD mice (Dardenne et. al.), and the PVG>RT1 strain of rats (Saoudi *et. al.* 1996) at a critical stage of development gives rise to IDDM earlier than normal for these strains demonstrating the effect of a loss of regulatory T lymphocytes. The deficiency of critical thymus tissue in the diabetes prone BB rat was demonstrated by the observation that diabetes is prevented by intrathymic islet transplantation at birth (Posselt *et. al.* 1992). Removing the thymus just after birth takes away the T lymphocytes that give rise to the autoimmune response and removing it later impairs the regulation of autoimmune cells.

IDDM can be caused by chemicals that affect thymus tissue. PFAs suppress the immune response (Yang et. al. 2002; Nelson 1992) just like the IDDM inducing chemical, cyclophosphamide (Ahmed *et. al.* 1984; ten Berge *et. al.* 1994).

Cyclophosphamide causes earlier onset of IDDM in NOD mice (Harada *et. al.* 1984; Yasunami *et. al.* 1988). It also causes decreased thymus mass in Sprague-Dawley rats (Tanaka *et. al.*

1992). The decreased thymus mass is similar to that observed in a strain of rat prone to IDDM. The diabetes prone BB rat has regions of the thymic cortex and medulla devoid of thymic epithelium (Doukas *et. al.* 1994; Rozing *et. al.* 1989). NOD mice have the same defect (Savino *et. al.*, 1991). Streptozotocin is another chemical that causes IDDM and concurrent thymus atrophy in rats (Chatamra *et. al.* 1985; Warley *et. al.* 1988). Streptozotocin also causes autoimmune diabetes in several strains of mice (Kiesel *et. al.* 1983; Herold *et. al.* 1997; Li *et. al.* 2001).

Another immunological disease of children that is tied to the thymus is asthma. Asthma usually develops in infancy. Asthmatics' ratio of t-helper cells, T1 and T2, is skewed toward Th2 (Robinson *et. al.* 1992), while non-asthmatic children and adults are have a ratio skewed toward Th1 (Adkins *et. al.* 2001). Damage to the thymus results in T-helper cell populations ratios skewed toward Th2 like asthmatics.

5. *Sex differences in sera levels*

In considering the level of PFOS in children, the assessment considered the 95th percentile of all children. But boys have higher levels than girls. Males also appear to be more vulnerable in rat studies. Therefore the assessment should consider the levels in male sera.

6. *Using the 95th percentile is not protective enough*

The assessment considered the 95th percentile of sera levels. That leaves 5 out of 100 children not considered. The assessment should use the highest level found in sera. All children should be safe from chemical toxicity. We realize that may not be possible when one considers millions of people, but in this case there were only about 600 child sera samples evaluated. The highest level found is probably not the highest level found in the total population. This is a screening level assessment and should therefore error on the side of safety. A more refined risk can be considered in the next level assessment. We strongly encourage Health Canada to use the highest level found in children's sera for their risk assessment.

7. *Consumers of wildlife and fish*

The assessment did not consider the subpopulation who consume lots of wildlife and fish (including First Nations communities and children). These vulnerable communities are likely to contain much higher levels of PFOS and other PFAs in there bodies. Wildlife and fish have much higher levels of PFAs (Berger *et. al.* 2004; Martin *et. al.* 2004) than food purchased at a urban grocery (Centre Analytical 2001). A method for estimating the level in this subpopulation of Canada should be incorporated into the assessment.

8. *More care required when making species-species extrapolation for assessing effects on human population*

There was no mention of uncertainty level from extrapolating toxicity responses verse sera levels from rats or monkeys to humans. The appropriate factor for the assessment was not enumerated. Thus inhibiting the transparency of the assessment. An uncertainty factor for extrapolating from rats to humans should be specified and supported.

9. *Lack of margin of exposure/safety*

The assessment fails to provide a rationale for the margin of safety used to establish effects on human health. It is critical to have a margin of safety that can be applied in these situations.

Based on the table presented on page 7 of the report, it is not transparent that the margin of exposure is set at the most protective level for human health.

10. *Apparently much more risk than assessment reports*

If the above changes are made, the margin of exposure decreases dramatically. If we start with the margin of exposure as presented in the draft of 143 for the effect of microscopic changes in liver of rats and the 95the percentile of serum PFOS level in United States children, and apply some of the above suggestions the margin of safety decreases dramatically. The margin drops to 13.5 if we consider the NOEL instead of the LOEL for male rats for the same effect (143 * 1.31ug/ml/13.9ug/ml) If we use the highest level of PFOS found in male children of the U. S. A. to represent the 99.9 percentile the margin of exposure drops to 2.6 (13.5 *0.097ug/ml / 0.515 ug/ml). This value of 2.6 was derived without a margin of safety, an uncertainty factor for children being more sensitive, an uncertainty factor for extrapolating from rats to humans, an uncertainty factor for the fact that thymus effects are seen at concentration below which are seen for effects in livers of monkeys, and an factor for subpopulation that consume large amounts of wildlife and fish. If these factors were included the margin of exposure would be much less than one and indicate a significant risk of harm to children and populations consuming wild game and fish.

If the uncertainty factor of 100 is applied as it is in Health Canada's assessment of polychlorinated dioxins and polychlorinated dibenzofurans, a margin of exposure of 0.026 is obtained. That indicates children are exposed to 40 times more PFOS than would cause no effect. We do not believe that is acceptable

It appears this chemical and others in its family pose a significant risk to Canadians and others in the world.

The gaps identified above provide support that PFOS should be considered toxic under CEPA section 64 (c).

D. Cancer

The assessment failed to take into account a recent report on finding higher than normal cancer rates among people living in proximity of a manufacturing facility that makes and uses PFAs (EPA AR226-1771). The findings of the report include the following:

- thyroid cancer was found to be 3.3 times higher in the residence of those living close to manufacturing facility than the general population. Thyroid cancer is seen in studies of PFAs.
- liver cancer was also seen in studies and it is found in the residence at levels greater than 30 times the general population.
- bladder cancer was found to be 7.6 times higher in the residence than the general population. Bladder cancer was noted in Health Canada's assessment as being higher in workers exposed to PFOS.
- cervical cancer was found to be 77 times higher in the residence than the general population.
- myeloma was 33 times higher.

This information is relevant and should have a significant impact on the findings by Health Canada.

In light of these uncertainties, we submit that sufficient evidence is available for Health Canada and Environment Canada to consider PFOS to be toxic under CEPA according to section 64(c). However, we support that PFOS as well as other members of the same chemical family should be virtually eliminated as currently proposed by Environment Canada. A determination of CEPA toxic under section 64(c) may have a significant impact on the type of tools to be discussed in the risk management process to address these substances.

Thank you for consideration of this submission. We look forward to your response.

Yours truly,

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