Chemical Classes of Concern:
I. Highly Fluorinated Chemicals

What Are They and How Are They Used?
The perfluorinated and polyfluorinated chemicals are a class of highly fluorinated substances referred to as fluorochemicals for short. They include chemicals that contain one or more carbon atoms whose carbon-hydrogen bonds are replaced by carbon-fluorine bonds. Carbon-fluorine bonds are the shortest and strongest chemical bonds. When multiple numbers (abbreviated as "n") of fully-fluorinated carbons are linked together they are known as a "C_n" perfluorinated group. Fluorochemicals have many different structures and the perfluorinated group gives them unique properties They are used in a variety of consumer products, including cookware, clothing, carpeting, and food packaging materials, to provide an oil or water resistant finish.[1,2] Fluorochemicals are also used as surfactants in products such as firefighting foams that are used to extinguish fuel-based fires at airports, military bases, and refineries.[3]

Which Fluorochemicals Are Of Concern?
Two C_8 fluorochemicals, perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS), are well studied and are associated with a range of adverse health effects. In response to concerns about these two compounds, in 2009 the U.S. EPA issued Provisional Health Advisories recommending maximum safe exposure concentrations in drinking water for PFOS and PFOA.[4] PFOS is also a restricted chemical under the Stockholm Convention and the European Union's REACH chemical legislation.

In the U.S. and Europe, production of PFOS, PFOA, and other molecules containing a C_8-perfluorinated group has largely ceased since 2002; however, production likely continues elsewhere. Some substitutes for C_8-based products contain C_6 and C_4 perfluorinated groups;[5,6] the health effects of these replacement compounds are not well studied.

Many fluorochemicals available in commerce are precursors to PFOS, PFOA, and analogous shorter compounds because they transform to these compounds in the environment[7,8] and animals.[9] They are detected in surface waters[10-12] and groundwater[13] that could be used as drinking water sources and are also found in consumer products such as food packaging materials. Thus, these precursor compounds may contribute indirectly to exposure to PFOS, PFOA, and their shorter analogs and may themselves be harmful.

Why Are They A Concern?
PFOS, PFOA, and their shorter-chain analogs are very persistent: they are inert to most natural breakdown processes[14] and persist in humans, biota, and the environment for decades. Fluorochemicals, and especially PFOS and PFOA, are detected in Arctic animals such as polar bears and seals several thousand miles from manufacturing sources.[15] They are also detected in humans all over the world.[16]

Migration of fluorochemicals out of consumer products and into food[17] and household dust[18,19] is well documented. Fluorochemicals are also widely detected in food that does not come in contact with a fluorochemical-containing packaging material.[20] Breast milk also contains fluorochemicals and is thought to be the primary source of exposure of these compounds for most infants.[21] Transplacental transfer of fluorochemicals occurs between mother and fetus, with transfer potential increasing for the shorter-chain fluorochemicals.[22]

PFOS and other fluorochemicals with an 8-carbon perfluorinated chain bioaccumulate in humans.[23] The oleophobic and hydrophobic properties of fluorochemicals lead to their partitioning in protein-rich compartments of the body, including blood and the liver.[24,25] Twenty-two different fluorochemicals were recently detected in the blood of fifty non-occupationally exposed Americans ranging in age and gender;[26] for at least half of those compounds, there is no toxicological information publicly available.

Adverse human health effects are associated with blood concentrations of PFOS and PFOA in industrially exposed populations and the general population. A study of adults living near a fluoropolymer manufacturing facility found positive associations between the highest PFOA blood levels and testicular and kidney cancers[27] as well as positive associations between blood PFOA concentrations and a biomarker of liver malfunction.[28] In the same manufacturing-exposed region, women experienced early menopause,[29] children demonstrated an increased susceptibility to hypothyroidism[30], and both boys and girls experienced reduced hormone levels and delayed puberty[31] in relation to PFOA or PFOS concentrations in blood. PFOA concentrations in blood and total cholesterol are positively associated in both fluorochemical-manufacturing workers[32] and the general U.S. population.[33] In the general population, prenatal exposure concentrations of PFOS or PFOA are negatively associated with abdominal circumference and birth length of infants,[34] negatively associated with concentrations of vaccine antibodies in vaccinated children,[35] and positively associated with obesity in women at age 20.[36]

Health effects associated with fluorochemicals other than PFOS and PFOA are not as extensively studied. However, a few studies indicate that shorter-chain fluorochemicals also result in adverse human health effects. Shorter chain fluorochemicals, including the C_4 and C_6 perfluorinated carboxylates and the C_4 and C_6 perfluorinated sulfonates, are observed to activate a nuclear receptor protein called a peroxisome proliferator that can induce liver tumors in mouse and human cells.[37] The C6 analog of PFOA, can interact with drug binding sites at lower concentrations than ibuprofen and may interfere with drug delivery.[38] The concentrations of the C_4 and C_6 perfluorinated sulfonates have risen in some human blood samples as PFOS and PFOA have declined,[39] despite reports that the C4 and C6 analogs lack the potential to bioaccumulate.[23]

Do We Need Them?

The presence of fluorochemicals in a wide array of consumer products has fostered an expectation that many everyday products should exhibit enhanced stain resistance and oil and water repellence. For products such as high altitude mountaineering clothing, they may provide an important safety factor. However, in light of what is known about the harmful effects of fluorochemicals, the desirability of their use in consumer products such as food packaging materials, everyday apparel, carpeting, and cookware could be questioned. In products where the performance provided by fluorochemicals has come to be expected, the tendency has been to replace PFOS and PFOA with very similar substitutes. Instead of moving from one fluorochemical to the next, the challenge for manufacturers is to innovate and develop more benign alternatives through materials innovation and green chemistry.

References

[1] Key, B.D.; Howell, R.D.; Criddle, C.S. Fluorinated organics in the biosphere. *Environ. Sci. Technol.* **1997**, *31*, 2445-2454.

[2] Paul, A.G.; Jones, K.C.; Sweetman, A.J. A first global production, emission, and environmental inventory for perfluorooctane sulfonate. *Environ. Sci. Technol.* **2009**, *43*, 386-392.

[3] Place, B.J.; Field, J.A. Identification of novel fluorochemicals in Aqueous-Film Forming Foams used by the U.S. military. *Environ. Sci. Technol.* **2012,** *46*, 7120-7127.

[4] U.S. EPA. Provisional Health Advisories for Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS). **2009.**

[5] Ehresman, D.J.; Froehlich, J.W.; Olsen, G.W.; Chang, S-C.; Butenhoff, J.L. Comparison of human whole blood, plasma, and serum matrices for the determination of perfluorooctane sulfonate (PFOS), perfluorooctanoate (PFOA), and other fluorochemicals. *Env. Res.*, **2007**, *103*, 176-184.

[6] Telomer Research Program Update. Presentation to the U.S. EPA, November 25, 2002. Public Docket AR226-1141; Washington, DC, November 25, **2002**.

[7] Houtz, E.F.; Sedlak, D.L. Oxidative conversion as a means of detecting precursors to perfluoroalkyl acids in urban runoff. *Environ. Sci. Technol.* **2012**, *46*, 9342-9349.

[8] Rhoads, K.R.; Janssen, E.M.-L.; Luthy, R.G.; Criddle, C.S. Aerobic biotransformation and fate of N-ethyl perfluorooctane sulfonamidoethanol (*N*-EtFOSE) in activated sludge. *Environ. Sci. Technol.* **2008**, *42*, 2873-2878.

[9] Plumlee, M.H.; McNeill, K.; Reinhard, M. Indirect photolysis of perfluorochemicals: hydroxyl radical-initiated oxidation of N-ethyl perfluorooctane sulfonamido acetate (*N*-EtFOSAA) and other perfluoroalkanesulfonamides. *Environ. Sci. Technol.* **2009**, *43*, 3662-3668.

[10] Tomy, G.T.; Tittlemier, S.A.; Palace, V.P.; Budakowski, W.R.; Braekevelt, E.; Brinkworth, L.; Friesen, K. Biotransformation of N-ethyl perfluorooctanesulfonamide by rainbow trout (Onchorhnchus mykiss) liver microsomes. *Environ. Sci. Technol.*, **2004**, *38,* 758-762.

[11] Meyer, T.; De Silva, A.O.; Spencer, C.; Wania, F. Fate of perfluorinated carboxylates and sulfonates during snowmelt within an urban watershed. *Environ. Sci. Technol.* **2011,** *45*, 8113-8119.

[12] Nguyen, V.T.; Reinhard, M.; Karina, G.Y.-H. Occurrence and source characterization of perfluorochemicals in an urban watershed. *Chemosphere* **2011**, *82*, 1277-1285.

[13] Murakami, M.; Kuroda, K.; Sato, N.; Fukushi, T.; Takizawa, S.; Takada, H. Groundwater pollution by perfluorinated surfactants in Tokyo. *Environ. Sci. Technol.* **2009,** *43*, 3480-3486.

[14] Vecitis, C.D.; Park, H.; Cheng, J.; Mader, B.T. Treatment technologies for aqueous perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA). *Front. Environ. Sci. Eng. China* **2009**, *3*, 129-151.

[15] Houde, M.; De Silva, A.O.; Muir, D.C.G.; Letcher, R.J. Monitoring of perfluorinated compounds in aquatic biota: an updated review. *Environ. Sci. Technol.* **2011**, *45*, 7962-7973.

[16] Houde, M.; Martin, J.W.; Letcher, R.J.; Solomon, K.R.; Muir, D.C.G. Biological monitoring of polyfluoroalkyl substances: a review. *Environ. Sci. Technol.* **2006**, *40*, 3463-3473.

[17] Begley, T.H.; Hsu, W.; Noonan, G.; Diachenko, G. Migration of fluorochemical-paper additives from food-contact paper into foods and food simulants. *Food Additives & Contaminants: Part A* **2008**, *25*, 384-390.

[18] Trudel, D.; Horowitz, L.; Wormuth, M.; Scheringer, M.; Cousins, I.T.; Hungerbühler. Estimating consumer exposure to PFOS and PFOA. *Risk Anal.* **2008**, *28*, 251-269.

[19] Björklund, J.A.; Thuresson, K.; de Wit, C.A. Perfluoroalkyl compounds (PFCs) in indoor dust: concentrations, human exposure estimates, and sources. *Environ. Sci. Technol.* **2009**, *43*, 2276-2281.

[20] Vestergren, R.; Berger, U.; Glynn, A.; Cousins, I.T.; Dietary exposure to perfluoroalkyl acids for the Swedish population in 1999, 2005, and 2010. *Environ. Int.* **2012**, *49*, 120-127.

[21] Haug, L.S.; Huber, S.; Becher, G.; Thomsen, C. Characterization of human exposure pathways to perfluorinated compounds – comparing exposure estimates with biomarkers of exposure. *Env. Int.* **2011**, *37*, 687-693.

[22] Gutzkow, K.B.; Haug, L.S.; Thomsen, C.; Sabaredzovic, A.; Becher, G.; Brunborg, G. Placental transfer of perfluorinated compounds is selective – A Norwegian mother and child sub-cohort study. *Int. J. Hygient and Environ. Health*. **2012**, *215*, 216-219.

[23] Conder, J.M.; Hoke, R.A.; De Wolf, W.; Russell, M.H.; Buck, R.C. Are PFCAs bioaccumulative? A critical review and comparison with regulatory criteria and persistent lipophilic compounds. *Environ. Sci. Technol.* **2008,** *42*, 995-1003.

[24] Olsen, G.W.; Huang, H.Y.; Helzlsouer, K.J.; Hansen, K.J.; Butenhoff, J.L.; Mandel, J.H. Historical comparison of perfluorooctanesulfonate, perfuorooctanoate and other fluorochemicals in human blood. *Environ Health Perspect.* **2005**. *113*, 539-545.

[25] Bischel, H.N.; MacManus-Spencer, L.A.; Luthy, R.G. Noncovalent interactions of long-chain perfluoroalkyl acids with serum albumin. *Environ. Sci. Technol*. **2010**, *44*, 5263-5269.

[26] Lee, H.; Mabury, S.A. A pilot survey of legacy and current commercial fluorinated chemicals in human sera from United States donors in 2009. *Environ. Sci. Technol.* **2011**, *45*, 8067-8074.

[27] Vieira, V.M.; Hoffman, K.; Shin, H.M.; Weinberg, J.M.; Webster, T.F.; Fletcher, T. Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: A geographic analysis. *Environ. Health Perspect.*, **2013**, *121*, 318-323.

[28] Gallo, V.; Leonardi, G.; Genser, B.; Lopez-Espinosa, M.; Frisbee, S.J.; Karlsson, L.; Ducatman, A.M.; Fletcher, T. Serum perfluorooctanoate (PFOA) and perfluorooctane sulfonate (PFOS) concentrations and liver function biomarkers in a population with elevated PFOA exposure. *Environ. Health Perspect.*, **2012**, *120*, 655-660.

[29] Knox, S.S.; Jackson, T.; Javins, B.; Frisbee, S.J.; Shankar, A.; Ducatman, A.C. Implications of early menopause in women exposed to perfluorocarbons. *Endocrine Resarch*, **2011**, *96*, 1747-1753.

[30] Lopez-Espinosa, M.; Mondal, D.; Armstrong, B.; Bloom, M.S.; Fletcher, T. Thyroid function and perfluoroalkyl acids in children living near a chemical plant. *Environ. Health Perspect.* **2012**, *120*, 1036-1041.

[31] Lopez-Espinosa, M.; Fletcher, T.; Armstrong, B.; Genser, B.; Dhatariya, K.; Mondal, D.; Ducatman, A.; Leonardi, G. Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with age of puberty among children living near a chemical plant. *Environ. Sci.Technol.* **2011**, *45*, 8160-8166.

[32] Sakr, C.J.; Kreckmann, K.H.; Green, J.W.; Gillies, P.J.; Reynolds, J.L.; Leonard, R.C. Cross-sectional study of lipids and liver enzymes related to a serum biomarker of exposure (ammonium perfluorooctanoate or APFO) as part of a general health survey in a cohort of occupationally exposed workers. *J. Occup. Environ. Med.* **2007**, *49*, 1086-1096.

[33] Nelson, J.W.; Hatch, E.E.; Webster, T.F. Exposure to polyfluoroalkyl chemicals and cholesterol, body weight, and insulin resistance in the general U.S. population. *Environ. Health Perspect.* **2009**, *118*, 197-202.

[34] Fei, C.; McLaughlin, J.K.; Tarone, R.E.; Olsen, J. Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. *Environ. Health Perspect.* **2007**, *115*, 1677-1682.

[35] Grandjean, P.; Wreford Andersen, E.; Budtz-Jorgensen, E.; Nielsen, F.; Molbak, K.; Weihe, P.; Heilmann, C. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *J. American Med. Assoc.* **2012***, 307*, 391-397.

[36] Halldorsson, T.I.; Rytter, D.; Smastuen, H.; Hammer Bech, B.; Danielsen, G.B.; Henriksen, T.B.; Olsen, S.F. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective cohort srtudy. *Environ. Health Perspect.* **2012**, *120*, 668-673.

[37] Wolf, C.J.; Takacs, M.L.; Schmid, J.E.; Lau, C.; Abbott, B.D. Activation of mouse and human peroxisome proliferator – activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. *Toxicol. Sci.* **2008,** *106*, 162-171.

[38] D'Eon, J.C.; Simpson, A.J.; Kumar, R.; Baer, A.J.; Mabury, S.A. Determining the molecular interactions of perfluorinated carboxylic acids with human sera and isolated human serum albumin using nuclear magnetic resonance spectroscopy. *Environ. Toxicol. Chem.*, **2010**, *29*, 1678-1688.

[39] Glynn, A.; Berger, U.; Bignert, A.; Ullah, S.; Aune, M.; Lignell, S.; Darnerud, P. O. Perfluorinated alkyl acids in blood serum from primiparous women in Sweden: serial sampling during pregnancy and nursing, and temporal trends 1996−2010. *Environ. Sci. Technol.* **2012**, *46*, 9071−9079.