Health Risk Limits for Perfluorochemicals

Report to the Minnesota Legislature 2008

Minnesota Department of Health

Final Report
January 15, 2008

MINNESOTA MDH DEPARTMENT OF HEALTH

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Health Risk Limits For Perfluorochemicals

Executive Summary

The Minnesota Legislature directed the Minnesota Department of Health to report on the department's progress toward determining the health effects of perfluorochemicals and progress toward developing health risk limits for perfluorochemicals.

Perfluorochemicals (PFCs) are substances that were manufactured by the 3M Company in Cottage Grove, Minnesota (in Washington County) from the 1950s to 2002. The chemicals have unique properties, which made them ideal for use in products that resist heat, oil, stains, grease and water. Wastes from the production process were placed in several disposal sites in Washington County.

PFCs have been found in the groundwater in areas of Washington and Dakota Counties, and in surface water and waste water effluent in other parts of the state. PFCs have also been found in some fish in the greater metropolitan area.

Health Risk Limits (HRLs) for PFCs are concentrations in water (in ug/L or parts per billion) that pose little or no appreciable risk to a person drinking the water. HRLs are values that are proposed and adopted as rules by the state following a public rule making process.

On August 27, 2007, the department established HRLs by good cause exemption for the perfluorochemicals perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS). On December 28, 2007, the department published new draft values for these PFCs on the department website as part of the department's HRL rules revision process. These draft rules will be proposed as rules in 2008 and subject to public comment. Until the time that new rules are adopted, the August 27 rules remain in effect.

The department has based its December draft HRL values for the revision on the following:

- The health effects of concern for PFOS are effects on the liver and thyroid.
- The health effects of concern for PFOA are effects on the liver and slowed development of fetuses, reduced number of red blood cells, and changes to the immune system.
- Doses of concern are based on the level of PFC in the blood (serum) of animals that is associated with health effects.
- The exposure value for water intake encompasses 95 percent of the United States population averaged from birth through the age at which the PFC level in blood remains stable.
- PFOA and PFOS each have a HRL value of 0.3 ug/L in drinking water.

The department has acquired and is reviewing data on the toxicity of perfluorobutanoic acid (PFBA).

- The toxicological data indicates that PFBA is less toxic than PFOA and PFOS, and unlikely to accumulate in the human body.
- The department intends to use the available toxicity information to develop guidance for PFBA.

- The department will not include PFBA in the upcoming HRL rules revision, but guidance in the form of health-based values will be available.

A department review of the available studies on other PFCs indicates that other PFCs are no more toxic than PFOA or PFOS. There are no immediate plans to develop guidance or HRLs for additional PFCs.

The department provides instructions in the current and draft HRL rules on a Hazard Index approach to assess risks from exposures to multiple chemicals. The department will continue to advise the use of a hazard index with HRL values to assess risks when multiple PFCs are present. Only PFCs with HRL values or other risk-based guidance will be included in the hazard index approach.

The department has compared the current HRL value (0.5 ug/L) and the new draft HRL (0.3 ug/L) for PFOA developed in Minnesota to the PFOA values established by New Jersey and North Carolina. The current and draft Minnesota values are based on toxicity observed in a monkey study, an estimated human equivalent dose, a 30-fold uncertainty factor, and a time weighted average drinking water intake of 0.053 liters water per kilogram body weight per day. In comparison to the Minnesota toxicity evaluation:

- The New Jersey value (0.04 ug/L) was based on a different species (rat) and divided the serum level in the rat study by 100 to estimate a safe dose for humans. The primary differences between the New Jersey value and the Minnesota value is due to a larger uncertainty factor (100-fold) used by New Jersey and the use of the adult intake of 2 liters water per 70 kilograms body weight per day, which is about half of the water intake rate used by Minnesota.
- The North Carolina value (0.63 ug/L) was based on the monkey study and modeled the serum level to estimate a safe dose in humans. The difference between the North Carolina value and the Minnesota value is primarily due to the difference in drinking water intake. North Carolina used the adult intake rate of 2 liters per day and 70 kilograms, which is about half of the water intake rate used by Minnesota.

Introduction

The Minnesota Legislature requested a report from the commissioner of health on legislation (Minnesota Session Laws 2007, Chapter 37) requiring Health Risk Limits for perfluorochemicals in groundwater. The Minnesota Department of Health (MDH) provided the legislature with an interim report on September 30, 2007. This report fulfills the requirement for a final report by January 15, 2008.

The legislature asked that the report describe the department's progress toward determining the health effects of perfluorochemicals and progress toward developing health risk limits for perfluorochemicals. In particular, the report was to include

1. The health effects and health risk limits adopted for perfluorooctanoic acid and perfluorooctane sulfonate;
2. The health effects and the need to develop health risk limits for perfluorobutanoic acid and other perfluorochemicals;
3. The health effects and the need to develop health risk limits for combinations of perfluorochemicals; and
4. A comparison of health-based values for perfluorochemicals established in Minnesota and the values established for those chemicals in other states including the state of New Jersey.

The Health Risk Assessment Unit (within the Division of Environmental Health's Environmental Surveillance and Assessment Section) prepared the following report to answer these requests for information. The Health Risk Assessment Unit is responsible for developing Health Risk Limits and providing technical support on the toxicity evaluation of perfluorochemicals.

I. The health effects and health risk limits adopted for perfluorooctanoic acid and perfluorooctane sulfonate

Perfluorochemicals

Perfluorochemicals (PFCs) are substances that were manufactured by the 3M Company (3M) in Cottage Grove, Minnesota (in Washington County) from the 1950s to 2002. The chemicals have unique properties, which made them ideal for use in products that resist heat, oil, stains, grease and water. Common uses included nonstick cookware, stain-resistant carpets and fabrics, fire-fighting foam, and other industrial applications. Wastes from the production process were placed in several disposal sites in Washington County.

The chemical structures of PFCs make them extremely resistant to environmental actions (e.g., heat, sunlight, bacterial action) that break down large molecules into smaller molecules. The intact chemicals have been found in water, wildlife, and humans around the world. How these chemicals move from locations where they are made, used, or disposed to remote areas is an area of active scientific research.

The chemicals that concerned the legislature and state agencies include perfluorooctane sulfonate (PFOS; C8F17SO3), perfluorooctanoic acid (PFOA; C8F15O2H), and perfluorobutanoic acid (PFBA; C4F7O2H). Each of these chemicals has been found in groundwater in Washington and Dakota Counties in Minnesota. PFOS has also been found in fish collected from some lakes in Washington County, other lakes in the St. Paul and Minneapolis metropolitan area, and sections of the Mississippi River. PFCs have also been found in surface water and in water discharged from waste waster treatment plants (http://proteus.pca.state.mn.us/hot/pfc.html).

The health effects (that is, the toxicity) of PFCs is another area of active scientific research. Many toxicity studies on laboratory animals (rats, mice, and monkeys) have been conducted with a few PFCs, such as PFOS and PFOA, while other PFCs, such as PFBA, have not been as extensively studied. In laboratory animal studies, high concentrations of PFOA and PFOS cause harmful changes in the liver and other organs. Developmental problems (for example, delays in growth and maturation) have been seen in the offspring of rats and mice that were exposed to PFCs while pregnant. The ways in which the chemicals cause health effects is not fully understood, but toxicologists assume that these health effects might also occur in humans exposed to high concentrations of the chemicals. PFOA in high concentrations over a long period of time also causes cancer in rats by a process that has been studied and is arguably unlikely to occur in humans.

There are a few studies of health effects in people. 3M studied the health of 3M workers exposed to PFCs during manufacturing and found no apparent harm to worker health. Two studies have been conducted to determine if there is a relationship between the health of newborn babies and PFC levels in the mother's blood. Each study found a small decrease in birth weight or other measures of growth with increasing PFC levels in the mother. A health study of 70,000 people exposed to PFOA in drinking water in Ohio and West Virginia is underway. In general, these studies show that the levels of PFCs in the environment may be linked to changes in the body, but the studies have not shown that the PFCs have harmed people. Therefore, toxicologists have relied on animal studies to determine whether an exposure to PFCs may be harmful.

An area of active research is the length of time that PFCs may be retained in the body ("half-life"). Scientists need to understand how humans and animals compare in eliminating PFCs from the body. PFCs circulate through the body in the blood, and are slowly removed by the kidneys and gut to be eliminated in urine and feces. 3M has studied the length of time that it takes for serum levels of PFCs to decrease once occupational exposures end. The results of these studies suggest that it may take more than five years for even one-half of a single exposure to certain PFCs to leave the human body. In contrast, some animals eliminate these PFCs in a few hours to a few weeks. Most scientists studying PFC toxicity believe that the PFC that circulates in the blood is responsible for harmful effects so that the fact that humans eliminate PFCs very slowly must be taken into account when animal toxicity studies are used to determine a safe exposure for people.

Since early in 2007, department staff have heard (in scientific meetings, in conversations with EPA scientists, and in recent scientific publications) a growing scientific consensus that serum levels, which represent a measure of internal dose, are a better predictor of toxicity in animal studies than administered dose. There are large species differences in the amount of PFC that

must be given (administered dose) to an animal to produce toxicity (for example, some measure of liver damage). But when dose is expressed as a serum level the relationship between the serum level and toxicity is much more consistent across studies and species. Using serum level as a measure of internal dose within the dose-response assessment results in a more consistent relationship between the measure of dose and the health effects observed. As the weight of evidence regarding the importance of serum levels has increased, scientists have called for researchers to report not only administered dose (mg/kg-d) but serum (ug/L) and tissue levels (ug/g) at which responses are observed. As a result, over the past year more serum level information is now available for evaluation.

The use of a biologically relevant dose is consistent with EPA guidance and practice. Use of biologically relevant dose is also consistent with how the department conducts risk assessments and develops health-based drinking water values. Since use of a biologically relevant dose is highly specific to the species tested and the chemical being evaluated, decisions on how to extrapolate the animal data to human exposures are also highly specific to the chemical and specific studies. In the case of PFCs, scientists need to convert the serum level to an intake for humans. Carefully controlled studies of exposure from water and resulting serum levels would be the most desirable data for this calculation. In absence of such studies, the relationship between intake and serum level can be estimated using data regarding uptake, distribution within the body and elimination of PFCs from animal and human studies.

PFC Risk Assessment

Information on toxicity and exposure is used to determine an exposure to humans that does not cause harmful effects. The risk assessment work that the department conducted on PFOA and PFOS in 2006 and early 2007 was extensive. The risk assessment led to guidance in February 2007 (Appendices A and B) on water concentrations (called "Health Based Values" or HBVs). The February HBVs were promulgated as Health Risk Limits (HRLs) in August 2007 by the good cause exemption rule making process. Since that time, new assessments led to draft Health Risk Limits (draft HRLs) published in December 2007 (Appendices C and D).

HBVs and HRLs are water concentrations that are safe for people to drink. The department also develops guidance for fish tissue concentrations that are safe for people to eat. In order to calculate a drinking water value, the department divides the safe dose of chemical (the "reference dose," expressed as milligrams chemical per kilogram body weight per day) by a water intake rate (liters of water per kilogram body weight per day). There may be many other sources of exposure (for example, eating sport fish contaminated with PFOS or exposure through other foods). The water value is set low enough to account for the possibility of these other exposures. Each of the steps involved in calculating a water value is described below.

The water concentrations are expressed as parts per billion (ppb, which is the same as micrograms per liter of water or ug/L), and are used to make decisions on whether exposures need to be reduced when PFOA and PFOS are measured in drinking water wells. Similarly, the fish concentrations are expressed in ppb or micrograms PFOS per gram of fish (ug/g) and are used to make decisions on whether fish advisories are needed when PFOS is measured in the edible portion of fish. PFOA is not detected in fish or is at levels too low to prompt an advisory.

Most of the research of department scientists is focused on evaluating toxicity studies and developing appropriate reference doses. Department scientists search the literature, talk to scientists who are conducting studies, and participate in scientific forums where studies are discussed. Staff toxicologists select appropriate studies and doses relevant to different life stages, make adjustments to account for human variability and uncertainties in the data, and compare the resulting doses of interest from the different studies. The result is a daily dose (the "reference dose") that is unlikely to cause health effects over either a short or very long period of time.

The research on health risks from exposure to these chemicals and the calculation of the water levels associated with no anticipated health effect is carried out by toxicologists in the department with many years of experience in laboratory research and risk assessment. This work is reviewed by supervisors and managers with experience in toxicology, risk assessment, and public health policy. In addition, many researchers in government, academia, and industry have been consulted concerning the specifics of the toxicity studies and water intake data, and the appropriate interpretation of dosing, serum levels, elimination of PFCs, and time to reach equilibrium in the body. In particular, the department has relied on 3M scientists for much of the data on PFC toxicity (see Appendix E) and on federal investigators who study these chemicals. The department also relied on advice from exposure scientists from EPA and the state of California for assistance on appropriate drinking water intakes.

PFOA Reference Dose

The PFOA reference dose was based on a study in monkeys in which some of the animals dosed with 3 milligrams per kilograms per day (3 mg/kg-day) had increased liver weights, which appeared to be reversible when dosing stopped. At higher doses the animals showed other effects (indicating liver damage and changes in thyroid) and some animals died. Studies in rats showed that doses comparable to the dose given to the monkeys had similar effects on the livers of the rats and also showed that additional health effects may be a concern (slowed development of rat fetuses, reduced number of adult red blood cells, and changes to the adult immune system).

In February of 2007, the department calculated a human equivalent dose of concern that took into account the slow elimination of PFOA in the human body compared to the monkey. The department made this calculation based on a 70-fold difference in elimination between humans and monkeys. Over a long period of time, a human daily dose of 0.043 mg/kg-d would result in the same dose inside the body as the 3 mg/kg-d dose of concern from the monkey study because the chemical accumulates to a greater extent in humans than in monkeys. Adjustments were also made for human variability, uncertainty about differences between monkeys and humans in sensitivity to the chemical, and the fact that an effect on the liver was observed at the lowest dose tested (which meant that the true dose without any effect was likely lower). The total adjustment was a factor of 300. The human equivalent dose of 0.043 mg/kg-d was divided by 300 and the result was a reference dose of 0.00014 mg/kg-day.

In December of 2007, the department updated the risk assessment for PFOA by calculating a human equivalent of the dose in the monkey study using measures of the level of PFOA in the serum of blood. This new evaluation was a result of the department's interest in using serum

concentrations as an improvement to the PFC risk assessments. A liver effect level of minimal concern, called the benchmark dose, was estimated to occur at a level of 23 ug/mL PFOA in serum. A human equivalent dose of 0.0023 mg/kg-d was estimated based on the update, distribution within the body, and elimination of PFOA by humans (simple first order kinetics). Adjustments were also made for human variability (10-fold factor) and uncertainty (3-fold factor) about differences between monkeys and humans in sensitivity to the chemical. The total adjustment was a factor of 30, which is less than the uncertainty factor used in February 2007, and indicates that the department believes that there is greater certainty about the dose associated with minimal toxicity using this method of estimating dose. The human equivalent dose of 0.0023 mg/kg-d was divided by 30 for a resulting reference dose for PFOA of 0.000077 mg/kg-day (this is the same as 77 ng/kg-d). This value is almost identical to a value of 86 ng/kg-d developed by a consultant at CIIT Centers for Health Research and reported at a national meeting. The CIIT consultant recommended a slightly different value, 90 ng/kg-d, to the state of North Carolina. The department has not been able to duplicate the calculation performed by the consultant and cannot evaluate whether the model used by the consultant is preferable to the model used by the department.

In contrast to the February 2007 calculated reference dose of 0.00014, the reference dose calculated in December 2007 for PFOA (0.000077) is about 2-fold lower. While the older reference dose was based on less certainty about the dose of concern in monkeys compared humans, the newer reference dose shows that the cruder estimate was remarkably close to the improved calculation. The department found that in the case of PFOA, the 70-fold adjustment for the difference in monkey and human half-life and the various uncertainty factors, which were both used in the older calculation, were warranted and produced a value that was very close to the new value developed with more data and certainty.

PFOS Reference Dose

Similar steps were taken to develop a reference dose for PFOS. The reference dose for PFOS was also based on a study in monkeys. In this study a dose of 0.15 mg/kg-day caused liver effects (increased liver weight) and changes in levels of thyroid hormone, cholesterol, and high-density lipoprotein.

In February 2007, the department adjusted the dose for the slower elimination of PFOS by humans (a 20-fold difference compared to monkeys). The department estimated that a human daily dose of 0.0075 mg/kg-d would result, over time, in the same dose inside the body as the 0.15 mg/kg-d dose of concern in monkeys. Adjustments were also made for human variability, uncertainties about the true no effect level, and uncertainties about the differences between monkeys and humans in sensitivity to the chemical. The total adjustment was a factor of 100. The human equivalent dose of 0.0075 mg/kg-d was divided by 100. The result was a reference dose for PFOS of 0.000075 mg/kg-day.

In December of 2007, the department updated the risk assessment for PFOS by calculating a human equivalent of the dose in the monkey study using measures of the level of PFOS in the serum of blood. A liver weight and cholesterol effect level of minimal concern, the benchmark dose, was estimated to occur at a level of 35 ug/mL PFOS in serum. A human equivalent dose of

0.0025 mg/kg-d was calculated based on the update and elimination of PFOS by humans. Adjustments were also made for human variability (10-fold factor) and uncertainty (3-fold factor) about differences between monkeys and humans in sensitivity to the chemical. The total adjustment was a factor of 30, which is less than the uncertainty factor used in February 2007, and indicates that the department believes that there is greater certainty about the dose associated with minimal toxicity using this method of estimating dose. The human equivalent dose of 0.0025 mg/kg-d was divided by 30 for a resulting reference dose for PFOS of 0.00008 mg/kg-day.

In contrast to the February 2007 calculated reference dose of 0.000075, the reference dose calculated in December 2007 for PFOS (0.00008) is slightly higher. The 20-fold adjustment for the difference in monkey and human half-life and the various uncertainty factors, which were both used in the older calculation, were warranted and produced a value that was almost identical to the new value developed with more data and certainty.

Drinking water intake data

The department calculates drinking water values using data on how much tap water people of different ages drink each day. The drinking water intake (in liters of water per kilogram body weight per day) that was selected for each of the PFC risk assessments is an amount of water greater than what the average person drinks. The selected values encompass the drinking water intake of 95 percent of the population and are averaged over time according to different life stages and the length of time over which the chemical accumulates in the body.

The department gave careful consideration to who is exposed through drinking water, at what life stages exposure may be the greatest, and the relationship between a daily exposure and the accumulation of PFCs in the body. Human data show that a fraction of the PFCs in the body is eliminated each day, but not all of the PFCs, so the PFCs accumulate slowly over time. There is a point, however, when the amount taken into the body is equal to the amount eliminated by the body. The time period necessary to reach this “steady state” of uptake and elimination can be estimated based on measurements of PFCs in blood. For PFOA the time period is approximate 19 years and for PFOS the time period is approximately 27 years. The department averaged drinking water exposure over each period (starting from birth) using data from national studies of large numbers of people. Intake (using the 95^{th} percentile of intake) over the first 19 years of life is 0.053 L/kg-d and intake over the first 27 years of life is 0.049 L/kg-d.

As a result of consultation with exposure scientists and epidemiologists at the US EPA and state of California, an error in an EPA table of drinking water intakes was identified. The EPA had mislabeled a table, and instead of reporting summary data for only consumers that drank tap water, the data in the table included individuals that drank other sources of water. The EPA provided the department with a revised table with the correct data. The corrected values were used to calculate the draft HRLs in December 2007. The department has posted the corrected table on the department web site at (http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/table4_4.pdf).

Accounting for multiple pathways of exposure

The reference dose represents a safe daily dose of a chemical and is the basis of the calculation for a drinking water value. Drinking water standards that are set by the federal government and states take into consideration the possibility that there are other sources of exposure (for example, food, air, or soil) to the chemical besides drinking water. Drinking water standards are calculated so that the dose that would come just from drinking water is only a portion (20 percent) of the reference dose. In other words, the drinking water standard is lower, by five-fold, than a value that could be calculated if drinking water was clearly the only source of exposure to the contaminant. This 20 percent adjustment is a well-established factor called the relative source contribution factor. The factor is not based on a careful estimate of all potential exposures, rather it is a default assumption used because other sources of exposure are not well characterized. The department has not investigated other exposures to PFCs. However, since PFCs are found in the blood of the US population, and it is unlikely that the US population is drinking contaminated tap water, the department is certain that there are other sources of exposure in addition to the plume of ground water contamination in Washington County and has retained the 20 percent relative source contribution factor.

Drinking water calculations

The reference dose, the drinking water intake rate, and the relative source contribution factor were used to calculate drinking water concentrations of PFOA and PFOS. In February 2007, these health-based values (HBVs), 0.5 ug/L for PFOA and 0.3 ug/L for PFOS, were described in memoranda dated February 26, 2007 (Appendices A and B). The values were used for making decisions on whether exposures needed to be reduced when PFOA or PFOS were measured in drinking water. Similar steps were taken in 2007 to calculate a PFOS fish tissue concentration for eating fish. These values were placed in rule in August 2007 (as described in the next section of this report).

In December 2007, new draft values were calculated using the serum-level based reference doses. The new draft reference doses, 0.000077 and 0.00008 mg/kg-d, for PFOA and PFOS, respectively; the corresponding drinking water intake rates of 0.053 and 0.049 L/kg-d; and a relative source contribution factor of 0.2; were used in the HRL equation (below).

$$\text{HRL} = \frac{(\text{Reference dose}) \times (\text{relative source contribution factor})}{(\text{water intake rate})}$$

The values were converted to the appropriate units of ug/L. The result was that both PFOA and PFOS had drinking water values of 0.3 ug/L.

These new calculations do not replace the current HRL rules for PFOA and PFOS of 0.5 and 0.3 ug/L, respectively. However, the calculations and results (Appendices C and D) are draft HRL values for the HRL rules revision anticipated in 2008 (as described in the next section of this report). The PFOS fish tissue concentrations used for department fish advisories was also recalculated in December and will be used in future fish advisories.

Promulgation of Health Risk Limits for Perfluorochemicals

The department met the need for PFC water values in 2007 by calculating HBVs. These calculations used scientific data and risk assessment procedures available in February 2007. HBVs are not rules but are offered as advice to agencies in the form of a memo.

Minnesota Session Laws 2007, Chapter 37, instructed the department to adopt by rule Health Risk Limits for PFOS and PFOA according to Good Cause Exemption and specified the use of clause 1: "the rules address a serious and immediate threat to public health, safety, or welfare" (Minnesota Statutes, section 14.388, subdivision 1, clause 1, found at http://ros.leg.mn/bin/getpub.php?type=s&num=14.388&year=2007). The session language was signed into law on May 3, 2007 and the department was given a deadline of August 1, 2007 to adopt the rules.

The department prepared all of the necessary paperwork to adopt rules through good cause exemption. The rule language was drafted and sent to the office of the revisor on June 18. The department executive office was briefed for approvals on July 11. The preliminary proposal form was given to the Governor's office on July 23. On August 1, 2007, the rules were sent to the Office of Administrative Hearings and notice was given to the public that the rules were proposed for adoption. This notice followed department and state guidelines for public comment on rule making by good cause exemption. During the mandatory five-day comment period four sets of comments were sent to the Office of Administrative Hearings.

All of the comments were critical of the rules, suggesting (variously) that: the comment period was too short or otherwise inadequate (e.g., no statement of need and reasonableness), the HRL values were underprotective, alternative studies should be used as the basis of the reference dose, specific uncertainties should be (variously) used or not used, an equation used in 1993 should be used to calculate the HRL, the slow elimination of the chemical should not be factored into the reference dose, and different exposure inputs into the equation should be used.

The administrative law judge approved the rules for adoption on August 17, 2007. The department received a report from the law judge concerning the comments that had been submitted. In the report the judge said that the consideration that the department gave in developing the HRL values was reasonable, and that the commentators did not show that the department had been unreasonable (Appendix F).

The HRLS for PFOA and PFOS became effective August 27, 2007, when they were published in the State Register (Volume 32, Number 9, page 373). The final version of the rule, received from the revisor's office on August 27, 2007, is attached (Appendix G).

The current rules for PFOA and PFOS (HRLs of 0.5 and 0.3 ug/L, respectively) are temporary rules that can only be in place for two years. As described on pages 6 through 8 of this report and in Appendices C and D, the department has drafted a new analysis of the data that updates the basis of both HRL values and results in a new draft value of 0.3 ug/L for PFOA. The department intends to include the updated analyses for PFOA and PFOS in a revision of the entire HRL rules that is currently underway.

A notice soliciting comment on the possible revision of the HRL rule was published in the State Register on September 10, 2007 (although PFCs were not specifically mentioned). Other necessary steps (drafting the rules, drafting the Statement of Need and Reasonableness, and preparing notifications) are in progress. Individuals interested in following the rules revision process are encouraged to subscribe to the HRL Rules Revision Gov Delivery service available through the department web site (http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/index.html). Notice of announcements, meetings, and new materials posted on the web site are sent out to subscribers by email. The public is encouraged to comment on the posted draft HRLs, Rules and SONAR. When comments are received they are posted at: http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/comment/index.html.

Multiple public meetings to inform the public about the department's draft of a rules revision have been held. A public meeting held on September 13, 2007, focused on the draft rules and draft SONAR released September 10, 2007. A meeting on October 11, 2007, focused on four examples of chemicals that would be included in the rules. Information about meetings is published on the rules revision web site, http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/meetings.htm.

The draft HRLs for PFOA and PFOS were published to the department rules revision web site on December 28, 2007. An announcement concerning the new values was distributed to the email list of interested stakeholders on the same date. The department welcomes comments on the PFOA and PFOS draft HRL from interested persons at any time. A formal comment period will be part of the rule making procedures in 2008 following publication of the proposed rules in the State Register.

II. The health effects and the need to develop health risk limits for perfluorobutanoic acid and other perfluorochemicals

The department assembled literature for other PFCs based on literature reviews and contacts with the EPA and 3M. Staff talked with toxicologists and risk assessors in other states to determine if there may be additional studies and data to review. The data for perfluorobutanoic acid (PFBA) are limited, but as of now the quality of the data appear adequate for developing a Health Based Value. Staff scientists recently acquired additional data (such as serum level values for PFBA studies) and are preparing the assessment that the department will use to establish a Health Based Value.

The department's advice for using drinking water supplies contaminated with PFBA has been based on a guidance value of 1 ug/L. This value was used for PFOA prior to February 2007 (when the revised Health Based Values were established) and used for any other PFC that is a carboxylic acid form. At the time that the PFOA Health Based Value was established, the department was aware that animal studies showed that PFBA was less toxic than PFOA. The department believed that the toxicity and half-life information meant that PFBA would be less toxic to humans than PFOA. However, the information was inadequate to determine a guidance

value specific for PFBA. The department continued to use the guidance value of 1 ug/L for PFBA after the PFOA Health Based Value of 0.5 ug/L was established.

The PFBA animal toxicity studies that the department has reviewed were conducted by the EPA, by an independent contract laboratory on behalf of 3M, and by other researchers. The studies include four 5-day to 14-day studies in male rats and mice that assessed liver effects, a 28-day study in male and female rats, a 90-day study in male and female rats, and a developmental study (dosing during gestation) in female mice. The department reviewed short summaries (from poster presentations at scientific meetings) on the comparative pharmacokinetics (half-life information) of PFBA in rats, mice, and monkeys. The department has also received reports on half-life in humans (workers) from 3M.

The department has made the process of acquiring PFBA data and reviewing the data for quality and consistency a high priority. Assuring the toxicity data are reproducible (that is, accurate) is beyond the capacity of the department, but this assurance is part of the current toxicity work of the EPA and such assurance will continue as additional scientists replicate the toxicity work of both 3M and the EPA. The department is discussing the PFBA data with EPA scientists, 3M scientists, toxicologists in other states, and independent researchers in academia. Department staff have attended scientific meetings at which PFC toxicology and risk assessment is discussed and in this way the department learns who is conducting and interpreting PFC research. To date, the department has no reason to doubt the accuracy of the PFBA toxicity data. The department is currently asking academic and government researchers in Minnesota and other states specific questions concerning how to interpret the scientific data. For example, the department has asked researchers whether the specific thyroid hormone assays that 3M conducted can be used to support 3M hypotheses concerning thyroid function. This constant monitoring of the science is necessary in order to determine which studies and which health endpoints should be used as the basis for risk assessments.

The PFBA studies that appear most useful for risk assessment are the 28- and 90-day studies in rats. In these studies, changes in liver, serum cholesterol and thyroid hormone levels were found at low doses. The department intends to use this information to develop a Health Based Value in the next two months. Staff intend to base a PFBA health based calculation on toxicity data specific to PFBA, half-life information for a human equivalent dose, and intake rates reflecting the shorter half life of PFBA. New data on PFBA toxicity are expected in the future, and any Health Based Value could change within the next few years. The department will consider all of the available data in calculating a value and take into account the uncertainty around any lack of data.

There are few studies on other PFCs, but staff conducted a cursory review of the available studies to compare the toxicity of the PFCs. This initial review showed that other PFCs are likely to be no more toxic than PFOA or PFOS. The department has listed known studies in Appendix H. There are no plans at the present time to develop Health Based Values for other PFCs.

III. The health effects and the need to develop health risk limits for combinations of perfluorochemicals

The legislature asked for information on the need to develop HRLs for mixtures of perfluorochemicals. The preferred scientific approach is to base a risk assessment for a particular exposure on the results of a toxicity study that perfectly duplicates the exposure. This means that a study might be done with the exact mixture found in a well. This type of mixtures work has not been done with perfluorochemicals and has rarely been done with other chemical mixtures. Even when toxicity studies have been completed with mixtures, the results are difficult to apply to the results of environmental sampling because the ratio of chemicals found in each water sample may not be the same as the ratio of chemicals used in the toxicity study. Mixtures in the environment can be very different across different geographic locations and may change over time, so there might be an endless number of unique toxicity studies that would need to be conducted to accurately assess a complex or changing mix of chemicals.

Since toxicity data on mixtures is rarely available, the department offers rules and advice on developing a risk assessment when multiple chemicals are present. The department's recommendation is to consider the combined effects of chemicals when two or more chemicals in a mixture affect the same tissue, organ, or organ system. The methods in the HRL rule for considering risks from multiple chemicals did not change with the adoption of the PFC rules, and these methods will continue to be recommended by the department for PFCs as well as other chemicals. This guidance is well accepted nationally (US EPA 2000) and within the state as a simple yet protective procedure. The department provides instructions in the current and draft HRL rules on a Hazard Index approach to assess risks from exposures to multiple chemicals. The department will continue to advise the use of a hazard index with HRL values to assess risks when multiple PFCs are present. Only PFCs with HRL values or other risk-based guidance will be included in the hazard index approach (PFBA is not included at this time because no risk-based guidance has been established by the department).

In order to consider the combined health risk of multiple chemicals, the department advises the risk assessor to first compare the measured water concentration of each chemical to the corresponding HRL value. The result is a "hazard quotient." For example, a water concentration of 1.2 ug/L water compared to the corresponding HRL of 3 ug/L results in a hazard quotient of 0.4 (see Table 1). A hazard quotient of 1 or less shows that the HRL has not been exceeded and that the exposure is not harmful.

Table 1. Examples of hazard quotient calculations for three chemicals found in a single water sample.

Chemical	Amount detected in water ug/L)	HRL (ug/L)	Hazard Quotient*	Health Effects
A	1.2	3	1.2/3 = 0.4	Liver, Developmental Effects
B	150	500	150/500 = 0.3	Liver, Blood
C	0.48	0.6	0.48/0.6 = 0.8	Developmental Effects

* The Hazard Quotient is the ratio of the amount detected in water and the HRL value (that is, the water concentration divided by the HRL value). The resulting quotient is unitless because each value has the same units of micrograms per liter (ug/L).

To determine the health risks when multiple chemicals are present, the hazard quotients for each health effect are added together. A sum of hazard quotients is called the "hazard index." In the example in Table 1, a hazard index for liver effects and a hazard index for developmental effects should be calculated when chemicals A, B, and C are present in a sample of drinking water.

The hazard index for liver effects is calculated by adding the hazard quotients for chemicals A and B (0.4 + 0.3 = 0.7). The hazard index for developmental effects is calculated by adding the hazard quotients for chemicals A and C (0.4 + 0.8 = 1.2).

The risk assessor advises the risk manager of the resulting hazard index. A hazard index that exceeds one (as is the case with the hazard index for developmental effects in the example above) indicates that an intervention to reduce exposure may be needed. For example, the well owner may be advised to use bottled water until a filter is installed.

The department decides which health endpoints should be included in the risk assessment for a mixture based on an understanding of the toxicity of each of the chemicals. The health endpoints (there may be more than one) for each HRL chemical are included in the HRL rule. The health endpoints for PFOS are the liver and thyroid. The health endpoints for PFOA are liver, the hematologic (blood) system, developmental effects, and the immune system. These are effects that the department believes occur at similar doses across the different studies that have been conducted in animals. These are also effects that the department believes are appropriate groupings. For example, the department believes that various liver effects (for example, abnormal liver cells and increased serum liver enzymes) should be considered together even if the effects are not identical or caused by the same toxic action in the organ.

This procedure not only addresses the potential combined effects of PFOS and PFOA on the liver (a shared health endpoint of concern), it also addresses the combined effects of any other chemicals that are analyzed for and found in the water. For example, the potential harmful effects of the pesticides alachlor and simazine on the blood system should be added to the potential for harmful effects of PFOA on the blood system if all three are found in a water sample.

The department uses the hazard index approach to assess potential health risks when multiple chemicals are present in a drinking water sample. As described above, a hazard index of greater than one indicates that public health action to reduce exposure may be needed, and the

department makes such recommendations to risk managers. For example, when the hazard index has exceeded one, the department has sent letters to residents with PFC contaminated wells alerting residents that the concentrations of PFCs present a health risk and that the water should not be used for drinking and cooking. The letters also inform the well owner that Minnesota Pollution Control Agency staff will be contacting the household about delivery of bottled water or installation of a water filter.

The procedures described above are not the only approach for considering the potential risks from the presence of multiple chemicals. Other approaches use the hazard index approach (that is, adding the health quotients from two or more contaminants), but only when the mechanism of action of two substances is the same. This alternative tends to result in a lower hazard index (that is, less likely to exceed a hazard index of 1 and therefore less likely to be considered a risk of concern) compared to the practice of the department. Other approaches may add the hazard quotients of all substances present in the water sample, regardless of the health endpoint. This alternative tends to be result in a higher hazard index (that is, more likely to exceed a hazard index of 1 and more likely to be considered a risk of concern) than the approach used by the department. Another approach for considering the co-occurrence of PFCs is to add the risks using a toxic equivalency factor (Scialli et. al., 2007). Such methods are under investigation, but are not likely to be useful for some time.

At this time, the department is not including PFBA in the approach of adding hazard quotients for PFCs found in a water sample. The department has used 1 ug/L as a decision point for giving guidance to homeowners on reducing exposure. This value was not based on a specific health endpoint from a toxicity study. Once a health-based value for PFBA is derived, PFBA will be included in the hazard index approach along with PFOS and PFOA.

IV. A comparison of health-based values for perfluorochemicals established in Minnesota and the values established for those chemicals in other states including the state of New Jersey.

Two states have developed health protection values for PFOA contamination of drinking water. The states of New Jersey and North Carolina published values of 0.04 ug/L and 0.63 ug/L, respectively, in 2007. The department is not aware of any other values developed by any other states. The EPA derived an action value of 0.50 ug/L for PFOA as part of a Consent Order for the DuPont Washington Works facility (http://www.epa.gov/opptintr/pfoa/index.htm). The United Kingdom and Germany have also developed values for PFOA or PFOS that range from 0.1 to 5 ug/L and higher (Appendix I).

The New Jersey Water Value

The State of New Jersey based their preliminary risk assessment for PFOA on an analysis of the serum level in animal studies and a factor to convert a human equivalent serum level to a water level (Post, 2007). New Jersey used information from a 2005 EPA draft risk assessment of PFOA (US EPA 2005) to determine a no effect level of PFOA in the serum of tested female rats (1,800 ug/L serum). Default uncertainty and variability factors (totaling 100) were used to divide

the no effect serum level in female rats to a serum level of 18 ug/L that would be unlikely to harm humans. In comparison, a recent study at the US Centers for Disease Control and Prevention (CDC) found that the level of PFOA in the general population does not reach this concentration (Calafat et. al., 2007). Fifty percent of the more than 2,000 randomly selected people in the CDC study had serum concentrations of 4.0 ug/L and 95 percent of those tested had a serum level of 9.8 ug/L or less.

New Jersey next calculated a drinking water concentration that would result in an accumulation of 18 ug/L PFOA in the serum. New Jersey scientists felt that the appropriate conversion or mathematical relationship between serum and water was a factor of 100. The factor of 100 came from a study of individuals who drank from a contaminated water supply in Little Hocking, Ohio. The median serum concentration among the 371 subjects in the Little Hocking study was 354 ug/L and the average PFOA concentration in Little Hocking system distribution water was 3.55 ug/L (Emmett, et. al, 2006a; 2006b). A simple comparison between the two values is the ratio of 354/3.55 or 100. The 100-fold factor does not distinguish between exposures from the water supply and other exposures. However, New Jersey used a relative source contribution factor of 0.2 in the same way that the department took into account other sources of exposure.

New Jersey used the factor of 100 to calculate drinking water values from seven animal toxicity studies. The seven results were compared and the lowest water concentration, 0.04 ug/L, was selected as the health-based drinking water guidance for the state. Details of the analysis of data and calculations that were used are at http://www.state.nj.us/dep/watersupply/pfoa_dwguidance.pdf.

The North Carolina Water Value

The State of North Carolina calculated an interim value of 2 ug/L for PFOA in water in November 2006 followed by a Public Health Goal of 0.63 ug/L in June 2007. The first calculation (the interim value of 2 ug/L) was calculated by the North Carolina Division of Water quality (http://h2o.enr.state.nc.us/csu/documents/IMACBasisC8.pdf) and was based on a reference dose from a rat study. The more recent calculation (the Public Health Goal of 0.63 ug/L) was calculated by the North Carolina Division of Public Health (Williams, L.C., and Rudo, K., 2007) and was based on a reference dose from a monkey study. The Public Health Goal (PHG) was reviewed by a state Science Advisory Board in February 2007 (http://www.ncair.org/toxics/risk/sab/proceed/121.pdf).

The PHG calculation was based on a reference dose recommended by researchers at CIIT Centers for Health Research in Research Triangle Park, NC (now known as the Hamner Institutes for Health Sciences); a relative source contribution factor of 0.2; an intake rate of 2 L/day; and a body weight of 70 kg. The reference dose calculated by researchers at CIIT was based on the same monkey study and health effect selected by the Minnesota Department of Health. The CIIT researchers used the benchmark dose based on serum level developed by 3M (23 ug/ml). The CIIT researchers used a pharmacokinetic model developed in monkeys but scaled to humans to estimate that an oral dose (in ug/kg-d) is about 0.12 times the serum level (in ug/mL). Uncertainty factors (totaling 30) were used to reduce the human equivalent dose from the calculation to a reference dose. The resulting reference dose was 0.00009 mg/kg-d

(Appendix J). Although the details of the pharmacokinetic model are not published, North Carolina described the calculation as equivalent to multiplying the target serum level (in this case, 23 ug/ml) by a factor of 0.12, and dividing by the total uncertainty factor of 30. Prior to the development of the North Carolina value, the CIIT researchers had developed a reference dose of 0.000086 mg/kg-d, which they presented at the 2006 annual meeting of the Society of Risk Analysis.

Comparisons to the Minnesota Department of Health Value

A risk assessment is based on toxicity studies, and the selection of the appropriate toxicity study and analysis is a fundamental decision for PFC risk assessments. The New Jersey assessment used toxicity data from a chronic feeding study of rats. However, New Jersey relied upon serum levels of concern estimated by EPA using a pharmacokinetic model based on an acute (one single dose) study with female rats. In this short-term study, the half-life for the chemical in the female rats was shorter than the dosing interval used in the study. The department is concerned that the model may not be adequate for estimating serum levels in chronic studies. When serum level data from toxicity studies are compared, the PFOA serum levels of concern tend to be more consistent in studies of animals with longer half-lives, such as monkeys. The results of this pharmacokinetic model were applied to a chronic rat feeding study to estimate a PFOA serum level that caused chronic health effects. In addition, serum levels were not actually measured in the rat study used by New Jersey (New Jersey scientists had to rely on modeled serum data for rats).

The Minnesota Department of Health used the monkey study due to the half-life considerations, the potential greater similarities between humans and monkeys, and because researchers measured PFOA serum levels in the monkey study. The department believes that measured serum levels in monkeys are more reliable than modeled data from female rats.

Another important consideration in risk assessment is the selection of uncertainty and variability factors. Both the type of uncertainty and the magnitude of uncertainty are important considerations in evaluating studies and comparing the results. New Jersey's supporting documentation for their water value shows that New Jersey scientists also derived a water value based on the same monkey study selected by the department. The New Jersey water value based on the monkey study was ten-fold lower than the value derived by the department. The reason for the difference is explained by the selection of uncertainty factors. New Jersey used a ten-fold uncertainty factor for the possibility that a longer study conducted with lower doses (the monkey study lasted six-months) would result in a lower dose of concern. The department made the determination that the critical effects at low doses in all of the PFOA studies occurred at similar human equivalent dose levels and took a minimal period of time to develop, and the department did not use a subchronic-to-chronic uncertainty factor.

The approach of using serum levels as a basis for deriving references doses and HRLs is of great interest and utility, but there may be many approaches to describing the relationship between the oral dose in humans and the resulting human blood serum level of PFOA. New Jersey used a very simplistic ratio of human serum and water concentration from the study by Emmett. The Emmett study did not take into account additional sources of exposure besides water; the length

of time individuals had been drinking the water; changes in water concentration; or the amount of water each person drank. Emmett presented data that indicated the potential for wide variation in the relationship between water concentration and serum level. For example, six people drinking from a contaminated private well as the only source of residential drinking water exhibited ratios ranging from 142 to 855 (Emmett 2006a).

During scientific meetings and in conversations with EPA the department learned that serum levels represent the best measure of body burden and are a better choice than administered dose for PFC risk assessments. The department used serum level data in an approach similar to that used by North Carolina. The department developed a reference dose of 0.000077 that was very similar to the value of 0.00009 mg/kg-d developed by North Carolina. The department has not received detailed analysis from North Carolina to determine the difference in methods. However, North Carolina depended on a relationship (exposures to PFOA, in ng/kg-day, can be estimated as 0.12 times the plasma concentration in ng/mL) calculated by CIIT scientists based on a pharmacokinetic model developed in monkeys but scaled to humans. The pharmacokinetic model used by Minnesota resulted in a nearly identical relationship (exposures to PFOA in ng/kg-day are approximately 0.1 times the plasma concentration in ng/mL). A presentation the CIIT made to the North Carolina scientists suggests that elimination at high doses does not follow a simple one-compartment model of elimination. However, given the slight difference in the exposure to serum relationships derived by CIIT and MDH, it appears that at low doses the simple one-compartment model used by MDH adequately approximates the relationship.

Each of the reference doses described above (from the department, CITT, or North Carolina) yields the same HRL of 0.3 ug/L when used in the department's HRL equation.

The other difference between the drinking water calculations made by North Carolina, New Jersey, and Minnesota is the water intakes. Minnesota used a time-weighted average water intake rate (0.053 L/kg-day) based on new exposure data analyzed by the EPA. The result is a higher intake because the greater intake during childhood is included in the calculation. The other states used the default drinking water intake for adults based on 2 L per day for 70 kg adults (approximately 0.029 L/kg-day). This 2-fold difference between adult intake and a time-weighted average intake accounts for the difference between the department HRL calculation and the North Carolina public health goal calculation.

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US EPA 2006. Child-Specific Exposure Factors Handbook 2006 (External Review Draft). EPA/600/R-06/096A. Online: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=56747

Williams, LK and Rudo, K. 2007. North Carolina Public Health Goals. Memorandum June 20, 2007.

Web References in Text

Corrected drinking water intake table:
http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/table4_4.pdf

Minnesota Statute for Good Cause Exemption:
http://ros.leg.mn/bin/getpub.php?type=s&num=14.388&year=2007

MDH rule revision web pages:

General information about the rules
http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/index.html
Comments on rules received by the department
http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/comment/index.html.
Information about public meetings
http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/meetings.htm.

EPA action value for the DuPont Washington Works facility:
http://www.epa.gov/opptintr/pfoa/index.htm

New Jersey drinking water value:
http://www.state.nj.us/dep/watersupply/pfoa_dwguidance.pdf

North Carolina Division of Water quality interim drinking water value:
http://h2o.enr.state.nc.us/csu/documents/IMACBasisC8.pdf

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Proceedings of the February 22, 2007 Meeting
http://www.ncair.org/toxics/risk/sab/proceed/121.pdf

List of Appendices

Appendix A

PFOA Health Based Value Memo

Memo

Date: February 26, 2007

To: John Stine, Environmental Health Division Director

Via: Larry Gust, Environemental Surveillance and Assessment Section Manager
Pamela Shubat, Health Risk Assessment Unit Supervisor

From: Helen Goeden, Health Risk Assessment Unit staff

Subject: Health Based Values for Perfluorooctanoic acid (PFOA)

In 2002 the Minnesota Department of Health (MDH) developed a HBV of 7 ppb for PFOA. Since 2002 additional toxicity data, toxicokinetic data, and reviews of preexisting data have been produced. After a careful review of this information the Health Risk Assessment Unit staff recommends that the HBV for PFOA be lowered to 0.5 ug/L (ppb).

The following information was utilized in generating the revised HBV:

Chemical	CAS #	Endpoint	RfD (mg/kg-d)	HBV (ug/L)	Source
PFOA	335-67-1	hepatic (liver) system, hemotopoietic (blood) system, developmental, and immune system	0.00014	0.5	MDH 2007

More detailed information, supporting the development of the HBV, is attached. Please be advised that, although we believe that this number will provide an adequate level of protection, there is a degree of uncertainty associated with all HBVs, and they should be considered provisional. Professional judgment should be used in implementing this HBV. MDH will review this HBV if and when additional studies have been conducted.

The MDH's authority to promulgate health risk limits under the Groundwater Protection Act is limited to situations where degradation has already occurred. Similarly, health-based values, which are un-promulgated exposure values, serve as interim advice issued for specific sites where a contaminant has been detected. As such, neither health risk limits nor health-based values are developed for the purpose of providing an upper limit for degradation.

cc: Larry Gust, MDH
Pam Shubat, MDH
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ATTACHMENT

DATA FOR DERIVATION OF GROUND WATER HEALTH BASED VALUE (HBV)

Chemical Name: Perfluorooctanoic Acid (PFOA)
CAS: 335-67-1(acid)
3825-26-1 (ammonium salt, APFO)
2395-00-8 (potassium salt)
335-95-5 (sodium salt)

Non-Cancer Health Based Value (HBV) = 0.5 ug/L

$$= \frac{\text{(toxicity value, mg/kg/d) x (relative source contribution) x (1000 ug/mg)}}{\text{(intake rate, L/kg-d)}}$$

$$= \frac{\text{(0.00014 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.053 L/kg/day)}}$$

$$= \textbf{0.5 ug/L}$$

Toxicity value:	0.00014 mg/kg-d (Cynomolgus monkeys)
Source of toxicity value:	MDH 2007 (RfD derived by MDH)
Point of Departure:	LOAEL, 3 mg/kg-d
Dose Metric Adjustment:	70 (to adjust for half-life duration of 3.8 years in humans versus 20 days in male Cynomolgus monkeys)
Total uncertainty factor:	300
UF allocation:	3 interspecies toxicodynamic differences, 10 intraspecies variability; and 10 LOAEL-to-NOAEL (for lack of a no effect dose in the critical study)
Critical effect(s)*:	Increased relative liver weight
Co-critical effect(s)*:	Reduced number of erythrocytes, reduced body weight and body weight gain, developmental effects (decreased weight gain, delayed developmental progress, hypoactive response in nicotine-induced behavior test), suppressed IgM titers
Additivity endpoint(s):	Hepatic (liver) system, hematopoietic (blood) system, developmental, immune system
Secondary effect(s)*:	Decreased postnatal survival, increase in the incidence of full litter resorptions, altered mammary gland development, decreased thyroid hormones (T4 & T3), disruption of spontaneous behavior, changes in the adrenal cortex

* for explanation of terms see Glossary located at: http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/glossary.html

Cancer Health Risk Limit (HRL) = N/A

Volatile: No

Summary of changes since 2002 HBV:
Toxicity Value (RfD):
Improved toxicokinetic (e.g., half-life) information allowed for the incorporation of a 70-fold dose-metric adjustment based on half-life differences between humans and monkeys and a 10-fold decrease in the total UF. In 2002 a 30-fold factor (3 interspecies extrapolation + 10 subchronic-to-chronic) was used to address uncertainties around toxicokinetics.

Intake rate:
PFOA, unlike most ground water contaminants, has a long half-life and therefore will accumulate in the body if repeated exposure occurs over long-periods of time. Eventually the internal concentration of PFOA will reach a plateau (steady-state). The length of time to reach steady state conditions is equivalent to approximately 5 half-lives. In the case of PFOA the time to steady-state would be approximately 19 years (5 x human half-life of 3.8 years). The intake rate selected for the revised HBV was a time-weighted average intake of an upper-end consumer over the first 19 years of life (0.053 L/kg-d). This intake rate incorporates the higher intake rates early in life (i.e., infants and children) as well as the accumulation of the chemical over time.

Consideration of Sensitive Populations:
Delayed development and growth deficits in the offspring of females mice exposed during pregnancy have been reported at dose levels similar to the LOAEL of the critical study (3 mg/kg-d). Studies have shown that the developmental effects are mainly due to exposure during pregnancy rather than after birth. Possible HBVs, based on protection of a pregnant woman and her fetus, were also calculated. Two scenarios were evaluated: 1) a long-term exposure – exposure to the mother from birth to age 19 years, and 2) a short-term exposure – exposure to an infant. The long-term exposure scenario incorporated accumulation over time and utilized a time-weighted intake rate 0.053 L/kg-d. The short-term exposure scenario did not incorporate accumulation over time but did utilize a young infant intake rate of 0.221 L/kg-d. The resulting potential HBVs for both scenarios were higher than the HBV based on the selected critical study in monkeys.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Sec. Observations[1]	Yes	Yes	Yes	Yes
Effects?	Yes	Yes[2]	Yes[3]	Unclear[4]	Yes[5]

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect may be available from studies conducted for other purposes. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:

[1] Hormonal perturbations (e.g., decreased thyroxine (T4) and triiodothyronine (T3) levels) have been observed in laboratory animals at dose levels approximately 3-fold higher than the LOAEL and have been identified as secondary effects.

[2] Short-term immunotoxicity studies have shown that PFOA exposure suppresses humoral immunity and may adversely affect cell mediated immunity at doses similar to the critical study LOAEL. These effects have been identified as co-critical effects.

[3] Developmental delays, lower body weight/weight gain and behavior in offspring have been observed at dose levels similar to the LOAEL. These effects have been identified as co-critical effects. At doses 3-fold higher than the LOAEL additional developmental effects (decreased pup viability, delays in eye opening, increased incidence of full-litter resorption, alterations in mammary gland development) are observed. Effects occurring at doses approximately 3 fold higher have been identified as secondary effects.

[4] The results of the 2-generational study indicate that fertility is not affected by treatment. Full-litter resorption was observed at dose levels 3-fold higher than the LOAEL, however, it is unclear whether this resulted from maternal toxicity or a direct effect on the developing organism. Altered mammary gland development during the lactational period was observed in mice exposed to dose levels slightly higher than the critical study LOAEL during pregnancy. Increased incidence of full-litter resorption and alterations in mammary gland development have been identified as a secondary effects.

[5] Hypoactive response to nicotine has been observed in neonatal mice and has been included in the list of co-critical effects. A dose-related increase in ataxia in the female rats was reported in the chronic 2 year study at dose levels greater than the LOAEL, however, this effect was not observed in males with higher body burdens or in 90 day studies utilizing higher doses. Disruption of spontaneous behavior following acute neonatal exposure to doses approximately 3-fold higher than the critical study LOAEL have been observed and are identified as a secondary effect. The SAB has recommended additional neurological testing.

The following sources were reviewed in the preparation of the HBV:

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Appendix B

PFOS Health Based Value Memo

Memo

Date: February 26, 2007

To: John Stine, Environmental Health Division Director

Via: Larry Gust, Environemental Surveillance and Assessment Section Manager
Pamela Shubat, Health Risk Assessment Unit Supervisor

From: Helen Goeden, Health Risk Assessment Unit staff

Subject: Health Based Values for Perfluorooctane Sulfonate (PFOS)

In 2002 the Minnesota Department of Health (MDH) developed a HBV of 1 ppb for PFOS. Since 2002 additional toxicity data, toxicokinetic data, and reviews of preexisting data have been produced. After a careful review of this information the Health Risk Assessment Unit staff recommends that the HBV for PFOS be lowered to 0.3 ug/L (ppb).

The following information was utilized in generating the revised HBV:

Chemical	CAS #	Endpoint	RfD (mg/kg-d)	HBV (ug/L)	Source
PFOS	1763-23-1	hepatic (liver) system and thyroid	0.000075	0.3	MDH 2007

More detailed information, supporting the development of the HBV, is attached. Please be advised that, although we believe that this number will provide an adequate level of protection, there is a degree of uncertainty associated with all HBVs, and they should be considered provisional. Professional judgment should be used in implementing this HBV. MDH will review this HBV if and when additional studies have been conducted.

The MDH's authority to promulgate health risk limits under the Groundwater Protection Act is limited to situations where degradation has already occurred. Similarly, health-based values, which are un-promulgated exposure values, serve as interim advice issued for specific sites where a contaminant has been detected. As such, neither health risk limits nor health-based values are developed for the purpose of providing an upper limit for degradation.

cc: Larry Gust, MDH
Pam Shubat, MDH
Rita Messing, MDH
Cathy Villas-Horns, MDA
Shelley Burman, MPCA
Paul Hoff, MPCA
Doug Wetzstein, MPCA

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http://www.health.state.mn.us

ATTACHMENT

(Corrected March 9, 2007)

DATA FOR DERIVATION OF GROUND WATER HEALTH BASED VALUE (HBV)

Chemical Name: Perfluorooctane Sulfonate (PFOS)
CAS: 1763-23-1 (acid)
29081-56-9 (ammonium salt)
70225-14-8 (diethanolamine salt)
2795-39-3 (potassium salt)
29457-72-5 (lithium salt)

Non-Cancer Health Based Value (HBV) = 0.3 ug/L

$$= \frac{\text{(toxicity value, mg/kg/d) x (relative source contribution) x (1000 ug/mg)}}{\text{(intake rate, L/kg-d)}}$$

$$= \frac{\text{(0.000075 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.048 L/kg/day)}}$$

$$= \textbf{0.3 ug/L}$$

Toxicity value:	0.000075 mg/kg-d (Cynomolgus monkeys)
Source of toxicity value:	MDH 2007 (RfD derived by MDH)
Point of Departure:	minimal LOAEL, 0.15 mg/kg-d
Dose Metric Adjustment:	20 (to adjust for half-life duration of 5.4 years in humans versus 110 - 132 days in Cynomolgus monkeys)
Total uncertainty factor:	100
UF allocation:	3 interspecies toxicodynamic differences, 10 intraspecies variability; and 3 LOAEL-to-NOAEL (a value of 3 was applied to the study LOAEL rather than using the NOAEL or the default UF of 10 because the effect observed at the LOAEL was considered to be of minimal severity)
Critical effect(s)*:	Decreased HDL and T3
Co-critical effect(s)*:	None
Additivity endpoint(s):	Hepatic (liver) system, Thyroid (E)
Secondary effect(s)*:	Developmental (decreased body weight/weight gain, decreased total T4), decreased gestation length, immune system alterations

* for explanation of terms see Glossary located at: http://www.health.state.mn.us/divs/eh/groundwater/hrlgw/glossary.html

Cancer Health Risk Limit (HRL) = N/A

Volatile: No

Summary of changes since 2002 HBV:
Toxicity Value (RfD):
Improved toxicokinetic (e.g., half-life) information allowed for the incorporation of a 20-fold dose-metric adjustment based on half-life differences between humans and monkeys and a 10-fold decrease in the total UF. In 2002 a 30-fold factor (3 interspecies extrapolation + 10 subchronic-to-chronic) was used to address uncertainties around toxicokinetics.

Intake rate:
PFOS, unlike most ground water contaminants, has a long half-life and therefore will accumulate in the body if repeated exposure occurs over long-periods of time. Eventually the internal concentration of PFOS will reach a plateau (steady-state). The length of time to reach steady state conditions is equivalent to approximately 5 half-lives. In the case of PFOS the time to steady-state would be approximately 27 years (5 x human half-life of 5.4 years). The intake rate selected for the revised HBV was a time-weighted average intake of an upper-end consumer over the first 27 years of life (0.048 L/kg-d). This intake rate incorporates the higher intake rates early in life (i.e., infants and children) as well as the accumulation of the chemical over time.

Consideration of Sensitive Populations:
Growth deficits, alterations in thyroid hormone levels (T4 and T3), increased liver weights, and delays in development have been reported in offspring exposed during development. These effects were observed at doses approximately 3 to 7 times higher than the critical study minimal LOAEL. Potential health-based values based on protection of a pregnant woman and her fetus were evaluated. Two scenarios were evaluated: 1) a long-term exposure – exposure to the mother from birth to age 27 years, and 2) a short-term exposure – exposure to an infant. The long-term exposure scenario incorporated accumulation over time and utilized a time-weighted intake rate 0.048 L/kg-d. The short-term exposure scenario did not incorporate accumulation over time but did utilize a young infant intake rate of 0.221 L/kg-d. The resulting potential HBVs for both scenarios were not lower (i.e., more restrictive) than the HBV based on the selected critical study in monkeys.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Sec. Observations[1]	Yes	Yes	Yes	Yes
Effects?	Yes	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect may be available from studies conducted for other purposes. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:
[1] Thyroid hormonal perturbations have been observed in laboratory animals at dose levels similar to the critical study LOAEL. Alterations in thyroid hormone levels have been identified as critical effect.
[2] Short-term immunotoxicity studies have shown that PFOS exposure alters several immunologic parameters (suppression of SRBC-specific IgM production and T-cell proliferation, increased natural killer cell activity) at levels below the critical study LOAEL. The biological significance of these effects

is not entirely clear. Further study is needed to determine whether PFOS poses potential health risks to humans as a result of alterations in immune function, however, the MDH will include immune system as a secondary effect at this time.

[3] Lower body weight in offspring, decreased T4, increased sternal defects and decreased gestation length have been reported at levels approximately 3-fold higher than the critical study LOAEL. These effects have been identified at secondary effects. At doses approximately 10-fold higher than the LOAEL additional developmental effects (decreased pup viability, developmental delays) are observed.

[4] A male reproductive study reported decreases in sperm count and increases in sperm deformities at levels 10-fold higher than the critical study LOAEL.

[5] Hypoactive responses to nicotine has been observed in neonatal mice acutely exposed to levels 75-fold higher than the critical study LOAEL but these effects were not observed at levels 5-fold higher. Convulsions, severe rigidity and body trembling have been observed in Rhesus monkeys subchronically exposed to levels approximately 30-fold higher than the critical study LOAEL.

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Appendix C

PFOA Draft Health Risk Limit December 2007

Chemical Name: Perfluorooctanoic Acid

Synonyms: PFOA

CAS: 335-67-1(free acid)
335-66-0 (acid fluoride)
3825-26-1 (ammonium salt, APFO)
2395-00-8 (potassium salt)
335-93-3(silver salt)
335-95-5 (sodium salt)

The perfluorooctanoate anion does not have a specific CAS number.

Serum concentrations appear to be the best dose-metric for extrapolating to humans. At the present time the information necessary to estimate less than chronic doses (i.e., acute, short-term or subchronic) that would result in a given serum concentration is not available. Additional uncertainty exists regarding toxicokinetics in early life. Therefore, acute, short-term and subchronic HRLs will not be derived at this time.

Draft Acute Non-Cancer Health Risk Limit (HRL) = Not Derived (Insufficient Data)

Draft Short-term Non-Cancer Health Risk Limit (HRL) = Not Derived (Insufficient Data)

Draft Subchronic Non-Cancer Health Risk Limit (HRL) = Not Derived (Insufficient Data)

Draft Chronic Non-Cancer Health Risk Limit (HRL) = 0.3 ug/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(chronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.000077 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.053* L/kg-d)}}$$

$$= 0.29 \text{ rounded to } \mathbf{0.3\ ug/L}$$

* Intake rate used corresponds to the time-weighted average 95th% intake rate over first 19 years of life. Nineteen years represents the estimated duration to achieve steady-state serum concentration, based on a half-life of 3.8 years.

Reference Dose:	0.000077 mg/kg-d(Cynomolgus monkeys)
Source of toxicity value:	MDH
Point of Departure:	23 mg/L serum concentration (serum $BMDL_{10}$) (Thomford et al 2001 and Butenhoff et al 2002)

Human Equivalent Dose Adjustment: 0.0023 mg/kg-d	
	[Dose mg/kg-d = (Ln2/1387 day half-life$_{human}$) x 23 mg/L x 0.2 L/kg (Vd)]
Total uncertainty factor:	30
UF allocation:	3 interspecies extrapolation for potential differences in toxicodynamics and 10 intraspecies variability
Critical effect(s):	increased relative liver weight
Co-critical effect(s):	increased liver weight with histopathological changes, decreased total serum cholesterol and triglycerides, developmental delays (e.g., altered body weight gain, delayed physical development, hepatocellular hypertrophy) in offspring, altered immune function
Additivity endpoint(s):	Development (body weight, delayed development), Hepatic (liver) system, Immune system
Secondary effect(s):	Increased incidence of full litter resorption, additional developmental delays (e.g., sexual maturation), increased pup mortality, altered mammary gland development, additional immune system effects, increased kidney weight, hematological effects, decreased thyroid hormone (TT4, T3) serum levels, increased serum estradiol levels, increased incidence of benign hepatocellular adenomas, testicular Leydig-cell tumors and pancreatic acinar-cell adenoma/carcinomas

Proposed Cancer Health Risk Limit (HRL) = Not Applicable

Volatile: No

Summary of changes since 1993/1994 HRL promulgation:
No 1993/94 HRL value exists for PFOA. The draft chronic HRL (0.3 ug/L) is ~1.7-fold lower than the Good-cause exception HRL (0.5 ug/L) adopted August 1, 2007 as the result of using serum levels as the dose metric rather than administered dose.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Sec. Observations[1]	Yes	Yes	Yes	Yes
Effects?	Yes	Yes[2]	Yes[3]	Unclear[4]	Yes[5]

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect may be available from studies conducted for other purposes. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:
Note – comparisons based on HED LOAEL or HED BMDLs are associated with higher uncertainty than comparisons based on serum levels.

[1] Changes in serum thyroid hormone (e.g., decreased thyroxine, T4 and triiodothyronine, T3) and estradiol levels have been observed in some animal studies but not in others. These changes were observed at estimated human equivalent dose (HED) levels higher but within 3-fold of the critical study HED LOAEL and are therefore identified as secondary effects.
[2] Short-term immunotoxicity studies have shown that PFOA exposure suppresses humoral immunity and may adversely affect cell mediated immunity at HED doses similar to the critical study HED LOAEL. These effects have been identified as co-critical effects.
[3] Developmental delays and body weight/weight gain changes in offspring have been observed at serum and HED dose levels similar to the serum and HED LOAEL of the critical study. These effects have been identified as co-critical effects. At HED doses 3- fold higher than the critical study HED LOAEL additional developmental effects (decreased pup viability, delays in eye opening, increased incidence of full-litter resorption, and alterations in mammary gland development) are observed. Effects occurring at doses approximately 3 fold higher have been identified as secondary effects.
[4] The results of the 2-generational study indicate that fertility is not affected by treatment. Full-litter resorption was observed at HED dose levels 3-fold higher than the critical study HED LOAEL, however, it is unclear whether this resulted from maternal toxicity or a direct effect on the developing organism. Altered mammary gland development during the lactational period was observed in pregnant/lactating mice exposed to dose levels slightly higher than the critical study LOAEL during pregnancy. Increased incidence of full-litter resorption and alterations in mammary gland development have been identified as a secondary effects.
[5] Hypoactive response to nicotine has been observed in neonatal mice given a single dose at 10 days of age. No serum level information was reported in this study and it is not possible to extrapolate from a single dose to a HED dose. The additional neurological testing has been recommended by the EPA PFOA draft Risk Assessment Science Advisory Review Board.

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Appendix D

PFOS Draft Health Risk Limit December 2007

Chemical Name: Perfluorooctane Sulfonate
Synonym: PFOS
CAS: 1763-23-1 (acid)
29081-56-9 (ammonium salt)
70225-14-8 (diethanolamine salt)
2795-39-3 (potassium salt)
29457-72-5 (lithium salt)

Serum concentrations appear to be the best dose-metric for extrapolating to humans. At the present time the information necessary to estimate less than chronic doses (i.e., acute, short-term or subchronic) that would result in a given serum concentration is not available. Additional uncertainty exists regarding toxicokinetics in early life. Therefore, acute, short-term and subchronic HRLs will not be derived at this time.

Draft Acute Non-Cancer Health Risk Limit (HRL) = Not Derived (Insufficient Data)

Draft Short-term Non-Cancer Health Risk Limit (HRL) = Not Derived (Insufficient Data)

Draft Subchronic Non-Cancer Health Risk Limit (HRL) = Not Derived (Insufficient Data)

Draft Chronic Non-Cancer Health Risk Limit (HRL) = 0.3 ug/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(chronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.00008 mg/kg/d) x (0.2) x (1000 ug/mg)}}{\text{(0.049* L/kg-d)}}$$

$$= 0.327 \text{ rounded to } \mathbf{0.3\ ug/L}$$

* Intake rate used corresponds to the time-weighted average 95th% intake rate over first 27 years of life. Twenty-seven years represents the estimated duration to achieve steady-state serum concentration, based on a half-life of 5.4 years.

Reference Dose: 0.00008 mg/kg-d (Cynomolgus monkeys)
Source of toxicity value: MDH
Point of Departure: 35 mg/L serum concentration (BMDL) (Thomford et al 2002 as cited by OECD 2002 and Seacat et al 2002)
Human Equivalent Dose Adjustment: 0.0025 mg/kg-d
[Dose mg/kg-d = (Ln2/1971 day half-life$_{human}$) x 35 mg/L x 0.2 L/kg (Vd)]

Total uncertainty factor:	30
UF allocation:	3 interspecies extrapolation for potential differences in toxicodynamics and 10 intraspecies variability
Critical effect(s):	decreased HDL cholesterol, decreased total T3, increased TSH
Co-critical effect(s):	decreased body weight and body weight gain in offspring
Additivity endpoint(s):	Development (body weight/weight gain), Hepatic (liver) system, Thyroid (E)
Secondary effect(s):	changes in immune function, delayed development (e.g., body weight gain, eye opening), decreased adult body weight gain & loss of fat tissue, increased severity of liver effects (e.g., histological changes), disruption of estrus cycle, decreased sperm count & increased sperm deformities, decreased serum leptin levels, increased incidence of neoplasms (e.g., liver, thyroid, mammary gland), increased mortality (offspring and adults)

Proposed Cancer Health Risk Limit (HRL) = Not Applicable

Volatile: No

Summary of changes since 1993/1994 HRL promulgation:
No 1993/94 HRL value exists for PFOS. The draft chronic HRL (0.3 ug/L) is the same as the Good-cause exception HRL (0.3 ug/L) adopted August 1, 2007.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Sec. Observations[1]	Yes	Yes	Yes	Yes
Effects?	Yes	Yes[2]	Yes[3]	Yes[4]	Yes[5]

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect may be available from studies conducted for other purposes. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:
Note – comparisons based on HED LOAEL or HED BMDLs are associated with higher uncertainty than comparisons based on serum levels.

[1] Thyroid hormonal perturbations have been observed in laboratory animals at serum levels and human equivalent dose (HED) levels similar to the critical study point of departure (serum BMDL) and HED-LOAEL. Alterations in thyroid hormone levels have been identified as a critical effect.
[2] Short-term immunotoxicity studies have shown that PFOS exposure alters several immunologic parameters (suppression of SRBC-specific IgM production and T-cell proliferation, increased natural killer cell activity) at HED levels below the critical study HED LOAEL. The biological significance of these effects is not entirely clear. Further study is needed to determine whether PFOS poses potential health risks

to humans as a result of alterations in immune function, however, the MDH will include immune system as a secondary effect at this time.

[3] Lower body weight, decreased total T4 and free T4, and increased relative liver weight have been reported at serum levels similar to the critical study point of departure (serum BMDL). These effects have been identified at co-critical effects. At serum levels approximately 2-fold higher than the critical study point of departure additional developmental effects (decreased pup viability, developmental delays) are observed. These additional effects are listed as secondary effects.

[4] Increased incidence of abortions was noted in female rabbits at serum levels ~ 2-fold higher than the critical study point of departure (serum BMDL), however, these were associated with significant loss in body weights. Disruption of estrus cycling in female rats has also been noted at serum levels ~ 2-fold higher than the critical study BMDLserum levels. A male reproductive study in rats reported decreases in sperm count and increases in sperm deformities at HED levels 3-fold higher than the critical study HED LOAEL. Disruption of estrus cycling and spermatozoal effects are listed among the secondary effects.

[5] Increased norepinephrine concentrations in the paraventricular nucleus of the hypothalamus have been reported in female rats at serum levels ~2-fold higher than the critical study point of departure (serum BMDL). These effects have been noted as secondary effects.

Hypoactive responses to nicotine has been observed in neonatal mice acutely exposed to HED levels > 30-fold higher than the critical study HED LOAEL, however, these effects were not observed at levels 3-fold higher. Convulsions, severe rigidity and body trembling have been observed in Rhesus monkeys exposed to HED levels approximately 30-fold higher than the critical study HED LOAEL.

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Appendix E

3M Fluorochemical Research Report for December 2007

3M Perfluorochemical Studies In Progress

December 2007

Study	Submitted to MDH	Research Organization	3M Internal Research	Contract Research	Grant	Collaboration	Status
PFOS TOXICOLOGY							
Developmental Neurotoxicity	Copy of TSCA 8(e) letter sent to MDH 6/6/2007.	WIL Research		X			Audited draft final report received. Both analytical final report (3M in-house laboratory) and limited RT-PCR final report for PPARα-regulated genes (Univ. MN) studies had been forwarded to WIL Research to be incorporated in the final report. Report finalization expected in January 2008. Letter summarizing aspects of the study submitted to EPA TSCA 8(e) docket in June, 2007.
Rat Liver and Thyroid Response, Mode-of-Action		CXR Biosciences		X			Draft report was prepared by CXR Biosciences and reviewed by 3M. Finalization of reports expected by first quarter, 2008.
^{35}S-PFOS Synthesis		Stockholm University			X		On-going. This project is funded as a non-restricted gift. There is no requirement for the investigator to prepare a report for 3M. ^{35}S-PFOS has been produced, and improvements to yield are being pursued.

Fetal/Neonatal Distribution and Retinoids		Karolinska Institute			X		On-going. This project is funded as a non-restricted gift in support of a Ph.D. candidate and his major advisor. There is no requirement for the investigator to prepare a report for 3M. 3M has provided tissues from studies to investigators.
28-day oral study in rats with extensive follow-up to investigate the relationship of toxicokinetics on repeat dosing to thyroid hormone status.	ICT Poster provided July 26, 2007	3M Toxicology Lab	X				In-life complete. Data presented as poster in Montreal at the ICT meeting in July. Some detailed pharmacokinetic analyses still outstanding. A manuscript will be prepared from the data. Due to other priorities, detailed pharmacokinetic analyses have not been undertaken, but are planned for fourth quarter 2007. Work on the manuscript may begin in January 2008.
PFOS-exposed rat brain study		3M and EPA/ORD/NHEERL				X	On-going (analysis pending). Analytical results are expected in first quarter, 2008. Manuscript will eventually be prepared.
Pharmacokinetics in rats		3M	X				On-going. In life phases are largely completed. Analysis of samples has not begun. Completion of analyses and report expected by first quarter, 2008.
Interaction thyroid hormone transporters and other transporters		University of Minnesota, Duluth			X		On-going. This project is funded as a non-restricted gift. There is no requirement for the investigator to prepare a report for 3M.
PFOA TOXICOLOGY							
Study Material Audit of 3M 2-Year Study and Pathology Peer Review of Mammary Tumors and Publication of Review		EPL		X			On-going. Peer review was completed and has been available on USEPA docket. Audit completed and reported received. Manuscript to be prepared. Not possible to provide completion date for manuscript at this time. Target for 2008.
Humanized PPAR-		Pennsylvania State			X		Funded. On-going. This project is funded as a

αSv129 Wild Type Mice developmental study		University					non-restricted gift. There is no requirement for the investigator to prepare a report for 3M.
Mechanisms of Rat Liver and Pancreatic Acinar Tumor Production and Rat Liver Hypertrophy		CXR Biosciences, joint study through Association of Plastics Manufacturers of Europe;				X	Two proposals in consideration: 1) additional bioinformatics on existing transcriptional data from previous reports; and 2) effects of PFOA on guinea pig liver
Cholesevelam HCL Enhancement of Elimination		Southern Research Corporation		X			On-going. In-life completed. Analytical completed. Pharmacokinetic analyses completed. Report pending.
Pharmacokinetics in Rats		3M	X				On-going. Completion by first quarter 2008.
PFBA TOXICOLOGY							
5-Day Oral in Rats		3M	X				On-going. In-life completed. Analyses of tissue samples by RT-PCR are expected by early fourth quarter 2007. To be reported as manuscript. Manuscript submission targeted for January 2008.
28-Day Oral in Rats	Final report from NOTOX provided to Dr. Helen Goeden on 6/28/07	NOTOX		X			Contract laboratory final report received. Tissue analyses by RT-PCR completed. Manuscript in preparation. Completion of manuscript targeted for January 2008.
90-Day Oral in Rats	Protocal provided to Dr. Helen Goeden on 4/03/07	NOTOX		X			On-going. 90-day terminal sacrifice was conducted July 12 and 13. 25-day recovery sacrifice was conducted on August 6. Amendments made to accommodate evaluation of ocular tissues by Dr. Donald Fox, University of Houston. Unaudited draft report received 10-19-2007. Final report expected by December 2007.

Pharmacokinetics in Rats	2007 SOT CCT poster provided on 2/28/2007 ICT Poster provided July 26, 2007	3M	X				Completed. Manuscript titled "Comparative Pharmacokinetics of Perfluorobutyrate (PFBA) in Rats, Mice, Monkeys, and Humans and Relevance to Human Exposure via Drinking Water" is currently in-preparation and will circulate for reviews by co-authors by December 2007. Branched versus linear poster given at ICT meeting in Montreal in July.
Pharmacokinetics in Mice	2007 SOT CCT poster provided on 2/28/2007	EPA/ORD/NHEERL				X	Completed. Manuscript in-preparation (see above) with targeted completion by end of 2007 (part of overall pharmacokinetic manuscript).
Developmental Toxicity in Mice		EPA/ORD/NHEERL				X	On-going. Manuscript is in-preparation by EPA.
PPARα-null vs. Sv129 WT vs. CD-1 dose-response study		EPA/ORD/NHEERL				X	On-going. In-life completed. EPA to write manuscript or report.
Humanized PPAR-α□Sv129 Wild Type Mouse Liver Response		Pennsylvania State University			X		Funded. On-going. This project is funded as a non-restricted gift. There is no requirement for the investigator to prepare a report for 3M. Licenses from NIH were finalized in early October 2007. In-life phase was completed on October 23 2007 for the first experiment.
PFBA drinking water palatability		3M	X				In-life phase completed; report in-preparation
STUDIES INVOLVING MULTIPLE CHEMICALS							
Toxicokinetic Modeling		Hamner Insititute		X			On-going from existing data. Additional proposals in development.
Lipid Homeostasis, Hypothalamic Saity Regulation		Stockholm University			X		Funded. On-going. This project is funded as a non-restricted gift. There is no requirement for the investigator to prepare a report for 3M. Chemicals evaluated are: PFOA and PFOS.

Thyroid Hormone Homeostasis		3M	X				On-going with assistance from Mayo Medical Laboratories, NHPP-UCLA, EPA, Fairview University Hospital. Chemicals evaluated are: PFOA and PFOS.
Pulmonary Surfactant Interaction	Poster presented at SOT CCT in Arlington, VA in February, 2007	University of Calgary			X		Funded. On-going. This project is funded as a non-restricted gift. There is no requirement for the investigator to prepare a report for 3M. Chemicals evaluated are: PFBS, PFHS, PFOS, and PFOA.
Cholesterol Synthesis and Metabolic Effects Research	MDH staff invited to and attended presentation on completed work on April 17, 2007	TNO		X			Chemicals evaluated were: PFBS, PFHS, and PFOS. Reports issued. Additional work in proposal stage. Manuscripts will be prepared.
Comparative Molecular Responses of Human and Rodent Liver Cells		University of Minnesota, Duluth			X		Funded. On-going. This project is funded as a non-restricted gift. There is no requirement for the investigator to prepare a report for 3M.
Short-Chain Perfluoroalkyl Acid Comparative Pharmacokinetics in Rats		3M	X				On-going. Some in-life completed. Analyses pending. Completion targeted in first or second quarter 2008.
Biochemical Toxicology		Stockholm University			X		Funded. On-going. This project is funded as a non-restricted gift. There is no requirement for the investigator to prepare a report for 3M. Two manuscripts have been submitted.
BIOMONITORING AND/OR EPIDEMIOLOGY							
PFBS human, monkey and rat half-life study		3M	X				Manuscript in-preparation Goal Q407
American Red Cross 2006 Biomonitoring study		3M / American Red Cross				X	Manuscript submitted for publication consideration. Poster presented at ISEA October 2007 meeting. Results presented at British Society of Toxicology meeting in November 2007.

							Results presented at SETAC North American meeting in November 2007.
PFBA Human Half Life Study (Cottage Grove)	Report to MDH August 2007	3M	X				Manuscript in preparation.
Cottage Grove cohort mortality study - update	Report to MDH October 2007	University of Minnesota / 3M		X			Final report received; meeting arranged for October 4 2007 with MDH to present. Presentation and copy to MDH on Oct 4, 2007. Manuscript in preparation.
PFBA Human Half Life Study (Cordova)	Report to MDH October 2007		X				Manuscript in preparation.
Danish birth outcome study		International Epidemiology Institute		X			Ongoing Multi-year study; more than one publication See Fei et.al., Environmental Health Perspectives doi: 10.1289/ehp.10506
Danish case – cohort study		International Epidemiology Institute		X			Ongoing Multi-year study; more than one publication
2005 PFBA biomonitoring study	Reports to MDH August 2007 and October 2007	3M	X				Final report completed July 2007 (Cottage Grove) Final report completed July 2007 (Cordova)
Cottage Grove CPDC Employee Biomonitoring Study		3M	X				Individual results provided to employees. Final report completed December 2007.
ANALYTICAL							
European 6th Framework PERFORCE World-Wide Analytical Challenge		3M				X	On-going

OTHER							
British Toxicology Society (BTS) PFOA workshop		British Toxicology Society				X	3M participating in the organizing committee; Workshop held in November 2007

Appendix F

Report of the Administrative Law Judge

STATE OF MINNESOTA
OFFICE OF ADMINISTRATIVE HEARINGS
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August 17, 2007

Pamela Shubat
Minnesota Department of Health
Freeman Building 3C
P.O. Box 64975
St. Paul, MN 55164-0975

RE: Review of the Proposed Exempt Rules of the State Department of Health Relating to Health Risk Limits for Perfluorochemicals, Minn. R. parts 4717.7200, 4717.7500, and 4717.7650.
OAH Docket No. 70-0900-19137-1. Governor's Tracking No. AR 346.

Dear Ms. Shubat:

This is to inform you that the amendments to Minnesota Rules, parts 4717.7200, 4717.7500, and 4717.7650 have been approved as to legality on August 17, 2007, under Minnesota Statutes, sections 14.386 and 14.388, subdivision 1, clause 1. The amendments to the rule parts are exempt from the rulemaking requirements of Minnesota Rules, Chapter 14, by the direction of the Legislature in Laws of Minnesota 2007, Chapter 37, Section 1.

Further, because this Office received detailed and vigorous public comment regarding the selections made by the Department in these amendments, the undersigned ALJ has issued a brief report which details the rule review.

With the approval of the adopted rules, our office has closed this file and is returning the rule record to you so that your agency can maintain the official rulemaking record in this matter as required by Minnesota Statutes, section 14.365. Our office will file four certified copies of the rules with the Secretary of State's office. The Department may publish a copy of the amendment in the State Register pursuant to Minn. Stat. § 14.386(a)(4). The amendments will be effective upon publication.

If you have any questions, please contact Maria Lindstrom at 612/349-2527.

Sincerely,

ERIC L. LIPMAN
Administrative Law Judge

Enclosures

OAH Docket No. 70-0900-19137-1
Governor's Tracking Number AR 346

STATE OF MINNESOTA
OFFICE OF ADMINISTRATIVE HEARINGS

FOR THE MINNESOTA DEPARTMENT OF HEALTH

Review of the Proposed Exempt Rules of the State Department of Health Relating to Health Risk Limits for Perfluorochemicals, Minn. R. parts 4717.7200, 4717.7500, and 4717.7650.

ORDER ON REVIEW OF RULES UNDER MINN. STAT. § 14.386

The Minnesota Department of Health (the Department) is seeking review and approval of the above-entitled rules, promulgated pursuant to Minn. Stat. § 14.388. On August 3, 2007, the Office of Administrative Hearings received the documents from the Department required to be filed under Minn. Stat. § 14.388 and Minn. Rule 1400.2400.

This matter came before Administrative Law Judge Eric L. Lipman during the review for legality pursuant to Minnesota Statutes, sections 14.386 and 14.388, subdivision 1, clause 1. This legal review was undertaken because the proposed amendments to Part 4717 are otherwise exempt from the rulemaking requirements of Minnesota Rules, Chapter 14, by the direction of the Legislature in Laws of Minnesota 2007, Chapter 37, Section 1.

Based upon a review of the written submissions and filings, Minnesota Statutes, Minnesota Rules, and for the reasons set forth in the Memorandum that follows below:

IT IS HEREBY ORDERED:

1. The rules were adopted in compliance with the procedural requirements of Minn. Stat. Chap. 14 and Minn. R. Chap. 1400.

2. The amendments to Minnesota Rules, parts 4717.7200, 4717.7500, and 4717.7650 are **APPROVED**.

Dated: August 17, 2007

ERIC L. LIPMAN
Administrative Law Judge

MEMORANDUM

On May 4, 2007, Governor Tim Pawlenty signed, and deposited with the Secretary of State, Chapter 37 of the 2007 Laws of Minnesota. In addition to other requirements, this legislation directed the Commissioner of Health to:

> develop and adopt by rule, pursuant to Minnesota Statutes, section 14.388, subdivision 1, clause (1), health risk limits, as defined in Minnesota Statutes, section 103H.005, subdivision 3, for perfluorooctanoic acid, and perfluorooctane sulfonate. The commissioner shall develop and adopt the health risk limits according to Minnesota Statutes, section 144.0751, and ensure that the health risk limits are based on currently available toxicity and exposure data.[1]

Chapter 37 was effective on the day following final enactment.[2]

The legislation has a number of noteworthy features that are relevant to the later legal review of the proposed rules. First, the state legislature's directive that "the commissioner shall develop and adopt by rule" health risk limits for perfluorooctanoic acid (PFOA), and perfluorooctane sulfonate (PFOS) "pursuant to Minnesota Statutes, section 14.388, subdivision 1, clause (1)," makes two points clear: the Legislature concluded that the ordinary rulemaking procedures of Chapter 14 are "unnecessary, impracticable, or contrary to the public interest," and that the sought-after health risk limits are needed to "address a serious and immediate threat to the public health, safety, or welfare."[3] Minn. Stat. § 14.388 provides an abbreviated rulemaking procedure where an agency can show good cause for use of that provision. In this instance, however, the Legislature has determined (and specified in Chapter 37) that good cause is present.[4]

Second, section 14.388 provides that the agency must satisfy the requirements of Minn. Stat. § 14.386(a)(1)-(4) in order to adopt a rule. Under those provisions the Revisor of Statutes must approve the form of the rule, the agency head must adopt the rule, the Office of Administrative Hearings must approve the rule as to its legality and the rule must be published in the State Register.

The legality determination by OAH is governed by Minn. Rule pt. 1400.2400, subp. 3, which states that in reviewing a filing the judge must decide

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[1] *See,* 2007 Laws of Minnesota, Chapter 37, Section 1.

[2] *Id.*

[3] *See,* Minn. Stat. § 14.388 (1)(1) (2007).

[4] *Compare, e.g., In the Matter of the Adoption of Rules Governing Voter Registration, Minnesota Rules, Chapters 8200 and 8210,* OAH Docket No. 70-3500-16046-1 (2004) (http://www.oah.state.mn.us/aljBase/350016046.or.htm).

whether the rule meets the standards of part 1400.2100, Items A and D to G. Those standards of review provide as follows:

> A rule must be disapproved by the judge or chief judge if the rule:
>
> > A. was not adopted in compliance with procedural requirements of this chapter, Minnesota Statutes, chapter 14, or other law or rule, unless the judge decides that the error must be disregarded under Minnesota Statutes, section 14.15, subdivision 5, or 14.36, subdivision 3, paragraph (d);
> >
> > . . .
> >
> > D. exceeds, conflicts with, does not comply with, or grants the agency discretion beyond what is allowed by its enabling statute or other applicable law;
> >
> > E. is unconstitutional or illegal;
> >
> > F. improperly delegates the agency's powers to another agency, person or group;
> >
> > G. is not a "rule" as defined in Minnesota Statutes, section 14.02, subdivision 4, or by its own terms cannot have the force and effect of law. . . .

Minn. Stat. § 14.388, subd. 2 provides that interested parties have five business days after the date of the Notice of Adoption to submit comments to the Office of Administrative Hearings. The comment period ended on August 10, 2007 at 4:30 p.m. OAH received four timely-submitted comments regarding this rule.

Third, while the ordinary review of rules under the "good cause exemption," specifically excludes assessments of the reasonableness of the proposed rules,[5] in this instance the enabling legislation reintroduces some inquiry into the reasonableness of the Department's selections when issuing heath risk limits. Chapter 37 requires that the adoption of health risk limits for PFOA and PFOS be made "according to Minnesota Statutes section 144.0751," and so as to "ensure that the health risk limits are based on currently available toxicity and exposure data."[6] Minn. Stat. § 144.0751 further provides that:

> (a) Safe drinking water or air quality standards established or revised by the commissioner of health must:

[5] *Compare,* Minn. R. 1400.2400 (3) (2005) with Minn. R. 1400.2100 (B) (2005).

[6] *See,* 2007 Laws of Minnesota, Chapter 37, Section 1.

(1) be based on scientifically acceptable, peer-reviewed information; and

(2) include a reasonable margin of safety to adequately protect the health of infants, children, and adults by taking into consideration risks to each of the following health outcomes: reproductive development and function, respiratory function, immunologic suppression or hypersensitization, development of the brain and nervous system, endocrine (hormonal) function, cancer, general infant and child development, and any other important health outcomes identified by the commissioner.

(b) For purposes of this section, "peer-reviewed" means a scientifically based review conducted by individuals with substantial knowledge and experience in toxicology, health risk assessment, or other related fields as determined by the commissioner.[7]

In this circumstance, therefore, in order to complete an assessment of whether the proposed health care limits "exceeds, conflicts with, does not comply with, or grants the agency discretion beyond what is allowed by its enabling statute or applicable law,"[8] some inquiry into the agency's choices of data, "margins of safety" and "peer-reviewed information" is needed.

When Chapter 37 and Minn. Stat. § 144.0751 are read together, three essential requirements are presented. The Commissioner is to develop health risk limits for PFOA and PFOS that:

(1) reflects scientifically acceptable, peer-reviewed information;

(2) includes a reasonable margin of safety to protect the health of infants, children and adults from health outcomes that are specified in statute and by the Commissioner; and

(3) are based on currently available toxicity and exposure data.

Because the health risk limits developed by the Department meet each of these statutory standards, approval of the proposed rules is warranted.

At the core of the controversy over the proposed health risk limits, is a dispute over the integers that should be used in an important equation. The founding blocks of both the Department's assignment of health risk limits, and the sharp critiques of the commentators who timely responded to the proposed limits,

[7] *See,* Minn. Stat. § 14.388 (1)(1) (2007).

[8] *Compare,* Minn. R. 1400.2100 (B) and (D) (2005) with Minn. R. 1400.2400 (3) (2005).

are the numerical values that should be used to complete the following calculation:

$$\text{Health Risk Limits (in micrograms per liter)} = \frac{\text{(Reference dose) (Weight of the subject) (Relative source contribution) (1,000)}}{\text{(time weighted water intake in units of liters per kilogram of human body weight per day)}}$$

The Department's calculations for PFOA and PFOS revise and supplement the values stated in its earlier regulation "Health Risk Limits for Systemic Toxicants."[9]

Minnesota Mining and Manufacturing (3M), the Minnesota Center for Environmental Advocacy and Dr. David Gray all urge different values to be placed into the Department's health risk limit equation. Yet, the claim that another integer represents a better choice does not establish that the Department's selections fail to provide "a reasonable margin of safety," as those terms are used in Chapter 37. Particularly instructive in this regard, is the summary that Administrative Law Judge Bruce D. Campbell made on a similar question, nearly fifteen years ago. Judge Campbell observed:

> The word "reasonable" is perhaps one of the most relative and generic terms used in the law and it is difficult to formulate an adequate or all-encompassing definition. The word "reasonable" has been defined in the law as "ordinary or usual", "not immoderate or excessive", "not capricious, arbitrary, or confiscatory." When employed to describe the means which are used to achieve a legitimate end, it suggests not necessarily the best or only method but one fairly appropriate, at least under all circumstances. It has been said that conduct is reasonable if it is consistent with that of a prudent person in like circumstances. The word has also been held to be the equivalent of the words "adequate", "moderate", and "ordinary".
>
> "Reasonably", when used as a qualifying adverb likewise has many shades of meaning, depending in a particular case on the context or attendant circumstances. It is defined as meaning in a "reasonable manner", "consistently with reason", "fairly", "in moderate degree", "measurably", "moderately", "tolerably", "not extravagantly, excessively, or fully."[10]

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[9] *Compare,* Minn. R. 4717.7100 through 4717.7800 (2007) and Minn. Stat. § 103H.005 (3) (2006) with 3M's Exhibits 2 and 3 (February 26, 2007 Memoranda of Helen Goeden).

[10] *See, In the Matter of the Application of Northern States Power Company for Reissuance of the Air Emission Permit for the Allen S. King Generating Plant*, OAH Docket No. 2-2200-7921-2 (1993) (citing 75 C.J.S. 635 and 75 C.J.S. 638 omitted) (http://www.oah.state.mn.us/aljBase/22007921.93.htm).

By any fair reading of the February 26, 2007 memoranda which underlie the Department's PFOA and PFOS health risk limits, the promulgated standards are "moderate" and "consistent with reason."

Moreover, in accordance with the statutory mandates, the proposed health risk limits: (1) reflect scientifically acceptable, peer-reviewed information;[11] (2) include a reasonable margin of safety to protect the health of infants, children and adults from specified health outcomes;[12] and (3) are based on currently available toxicity and exposure data.[13]

Lastly, if the commentators (or others) are not persuaded by the analyses that appear in the February 26, 2007 memoranda, and believe that other numerical values should represent the "reference dose,"[14] "relative source contribution"[15] or "intake values,"[16] their best remedy is to present these views directly to the Minnesota Legislature. Just as the Legislature directed the Commissioner of Health to render her best judgment on the question of health risk limits, and to work within specified parameters, the Legislature is at liberty to revise those directives or to substitute other health risk limits as it sees fit.

CONCLUSION

Pursuant to Minnesota Statutes, sections 14.386 and 14.388, subdivision 1, clause 1, the amendments to Minnesota Rules, parts 4717.7200, 4717.7500, and 4717.7650 are approved as to legality.

With the approval of the adopted rules, our office has closed its file and will return the rule record to the Minnesota Department of Health. Our office will file four certified copies of the rules with the Secretary of State. The Department may publish a copy of the amendment in the State Register pursuant to Minn. Stat. § 14.386(a)(4). The amendments will be effective upon publication.

[11] *See,* Attachment to 3M's Exhibit 2 at 2 through 7; Attachment to 3M's Ex. 3 at 2 through 7.

[12] *See,* Attachment to 3M's Ex. 2 at 1 through 3; Attachment to 3M's Ex. 3 at 1 through 3.

[13] *See,* Attachment to 3M's Ex. 2 at 1 through 7; Attachment to 3M's Ex. 3 at 1 through 7.

[14] *See,* Comments of 3M at 13 through 17; Comments of David Gray at 4.

[15] *See,* Comments of 3M at 12 and 13; Comments of D. Gray at 2.

[16] *See,* Comments of MCEA at 2; Comments of 3M at 11 and 12.

Appendix G

PFOA and PFOS Health Risk Limits Rules

Office of the Revisor of Statutes
Administrative Rules

TITLE: Adopted Exempt Temporary Rules Relating to Health Risk Limits for Perfluorochemicals

AGENCY: Department of Health

MINNESOTA RULES: Chapter 4717

FILED
AUG 2007
(MN) SECRETARY OF STATE

RULE APPROVED
OFFICE OF ADMINISTRATIVE HEARINGS
August 17, 2007
DATE

ADMINISTRATIVE LAW JUDGE.

The attached rules are approved as to form

Sandra Glass-Sirany
Senior Assistant Revisor

0800504

Department of Health

Adopted Exempt Temporary Rules Relating to Health Risk Limits for Perfluorochemicals

4717.7200 HEALTH RISK LIMITS FOR SYSTEMIC TOXICANTS.

Subpart 1. **Scope.** This part establishes the method for determining the health risk limit for a systemic toxicant.

Subp. 2. **Equation for systemic toxicants other than nitrate (as nitrogen), perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), or possible human carcinogens.** The equation for determining the health risk limit for a systemic toxicant other than nitrate (as nitrogen), perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), or a possible human carcinogen is:

$$HRL = \frac{(RfD)(70)(RSC)(1{,}000)}{(2)}$$

Where:

A. HRL is expressed in microgram or micrograms per liter.

B. (70) is the standard weight of an adult expressed in kilograms.

C. The RSC for substances or chemicals not listed in item D shall be 0.2.

D. The RSC for the following substances or chemicals is:

Name	CAS RN	RSC
(1) antimony	7440-36-0	0.4
(2) barium	7440-39-3	0.8
(3) cadmium	7440-43-9	0.25
(4) chromium III	16065-83-1	0.7
(5) chromium VI	18540-29-9	0.7
(6) manganese	7439-96-5	0.8

E. (1,000) is a factor used to convert the units of concentration from milligrams per liter to micrograms per liter. There are 1,000 micrograms per milligram.

F. (2) is the standard amount of water ingested by an adult expressed in liters per day.

[For text of subp 3, see M.R.]

Subp. 3a. **Equation for perfluorooctane sulfonate (PFOS).** The equation for determining the health risk limit for perfluorooctane sulfonate (PFOS) is:

$$HRL = \frac{(RfD)(RSC)(1{,}000)}{(0.048)}$$

Where:

A. HRL, RSC, and (1,000) have the meanings given in subpart 2.

B. (0.048) is the time weighted average water intake (in units of liters per kilogram human body weight per day) of an upper-end consumer (95th percentile of water intake) over the first 27 years of life; a period of time corresponding to the longer half-life of the chemical in the human body.

Subp. 3b. **Equation for perfluorooctanoic acid (PFOA).** The equation for determining the health risk limit for perfluorooctanoic acid (PFOA) is:

$$HRL = \frac{(RfD)(RSC)(1{,}000)}{(0.053)}$$

Where:

A. HRL, RSC, and (1,000) have the meanings given in subpart 2.

B. (0.053) is the time weighted average water intake (in units of liters per kilogram human body weight per day) of an upper-end consumer (95th percentile of water intake) over the first 19 years of life; a period of time corresponding to the longer half-life of the chemical in the human body.

[For text of subp 4, see M.R.]

4717.7500 TABLE OF HEALTH RISK LIMITS.

[For text of subps 1 to 70, see M.R.]

Subp. 70a. **Perfluorooctane sulfonate (PFOS).** Perfluorooctane sulfonate (PFOS):

1763-23-1	0.000075	--	0.3

Subp. 70b. **Perfluorooctanoic acid (PFOA).** Perfluorooctanoic acid (PFOA):

335-67-1	0.00014	--	0.5

[For text of subps 71 to 90, see M.R.]

4717.7650 TOXIC ENDPOINTS.

[For text of subps 1 to 57, see M.R.]

Subp. 57a. **Perfluorooctane sulfonate (PFOS).** Perfluorooctane sulfonate (PFOS), 1763-23-1, hepatic (liver) system, thyroid.

Subp. 57b. **Perfluorooctanoic acid (PFOA).** Perfluorooctanoic acid (PFOA), 335-67-1, hepatic (liver) system, hematopoietic (blood) system, developmental, immune system.

[For text of subps 58 to 69, see M.R.]

Appendix H

Studies on PFCs

Available Studies on PFCs

Chemical names:

PFBS - Perfluorobutane sulfonate C4F9SO3
PFHxS - Perfluorohexane sulfonate, C6F13SO3
PFPeA - Perfluoropentanoic acid, C5HF9O2
PFHxA - Perfluorohexanoic acid, C6HF11O2

Half-life study information that the department is aware of:

PFBS - mice NA; rats NA; monkeys (3.5 to 4 days); and humans (approximately 30 days). Manuscript for publication under preparation and anticipated to be available late 2007.
PFHxS - mice NA; rats NA; monkeys (87 to 141 days); and humans (approximately 8.7 years).
PFPeA - mice NA; rats NA; monkeys NA; and humans NA.
PFHxA - mice NA; rats 0.5 days; monkeys 0.8 - 1.45 days); and humans NA.

Toxicity study information that the department is aware of:

PFBS - 2 generation reproductive/developmental study in rats; 90 day oral study in rats; and genotoxicity data.
PFHxS - a 28 day study with a screening evaluation of developmental endpoints and genotoxicity data
PFPeA - no studies
PFHxA - screening 28 day study (only 1 dose level). Asahi Glass Company (Japan) in a presentation to EPA reported data from a 28 day study with a screening evaluation of developmental endpoints and a 90 days study. These studies have not been published. The department has a copy of the 28 day report summary but does not have access to the 90 day study report.

Appendix I

PFC Water Values from the United Kingdom and Germany

United Kingdom

The United Kingdom Drinking Water Inspectorate has developed a series of values for drinking water supplies

Tier	PFOS (ug/L)	PFOA (ug/L)
1 (monitor levels)	> 0.3	> 0.3
2 (take action to reduce levels as soon as practicable)	> 1.0	> 10.0
3 (take action to reduce levels as soon as possible)	> 10.0	> 90.0

Note: > means "greater than"

Source:
Guidance on the Water Supply (Water Quality) Regulations 2000/01 specific to PFOS (perfluorooctane sulphonate) and PFOA (perfluorooctanoic acid) concentrations in drinking water
May 2007
http://www.dwi.gov.uk/regs/infolett/2007/info0507.pdf

Germany

The Drinking Water Commission in Germany has developed maximum guidance values for evaluating composite PFOA and PFOS water concentrations.

Type of maximum value	PFOA/PFOS composite (ug/L)
Health-based precautionary value	0.1
Strictly health-based for safe lifelong exposure	0.3
Precautionary action level for infants	0.5
Precautionary action level for adults	5.0

Source:
Provisional evaluation of PFT in drinking water with the guide substances perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) as examples
Assessment of PFOA in the drinking water of the German Hochsauerlandkreis. Statement by the Drinking Water commission (Trinkwasserkommission) of the German Ministry of Health at the Federal Environment Agency
June 21, 2006/revised July 13, 2006
http://www.uba.de/uba-info-presse-e/hintergrund/pft-in-drinking-water.pdf

Appendix J

North Carolina PFOA Water Value

[Only the first page of the memo and the PFOA table entry of the memo are displayed]

December 11, 2007

TO: Requesting Parties

FROM: Dr. Luanne K. Williams, Toxicologist
Dr. Kenneth Rudo, Toxicologist
NC Occupational and Environmental Epidemiology Branch (NC OEEB)
NC Division of Public Health
NC Department of Health and Human Services

SUBJECT: North Carolina Public Health Goals (NCPHGs)

The North Carolina Public Health Goals (NCPHGs) are North Carolina Division of Public Health health-based drinking water levels. These levels are used by NC OEEB for evaluating the safety of private well drinking water. The basis for each NCPHG is provided in the table that follows. New or updated NCPHGs are also provided including the basis for the new NCPHGs. Questions regarding the calculation of the NCPHGs can be directed to the two state toxicologists, Dr. Luanne K. Williams at 919-707-5912 or Dr. Ken Rudo at 919-707-5911.

NCPHGs are not regulatory levels but provide guidance on the safety of North Carolina private wells. When NC OEEB receives private well sampling results, these results will be compared to the health-based NCPHGs to determine if the water is safe to drink. For new private wells, a "Guide for Interpreting Private Well Water Lab Results" and "Information and Recommendations for Uses of Private Well Water" will be provided to the health department responsible for collecting the private well samples. When the NCPHG is less than the practical quantitation limit, the detection of that substance at or above the practical quantitation limit, shall be considered an unsafe level.

The list of NCPHGs is subject to change and will be reviewed every year or sooner if new scientific and toxicological data become available. When a NCPHG is revised, we will send an electronic file to those that have requested to be placed on our list of individuals to receive the revised tables.

The following references shall be used in order of preference in establishing the NCPHGs.

1. US EPA Integrated Risk Information System Database http://www.epa.gov/iris/index.html
2. EPA latest Edition of the Drinking Water Standards and Health Advisories www.epa.gov/waterscience/criteria/drinking/dwstandards.html (which references a 10 fold adjustment factor in the development of the chronic oral reference dose to take into account possible human carcinogenicity by oral and/or inhalation routes).
3. US EPA Region 9 Preliminary Remediation Goals http://www.epa.gov/region09/waste/sfund/prg/files/04prgtable.pdf
4. US EPA Region 3 Risk-Based Concentration Table http://www.epa.gov/reg3hwmd/risk/human/rbc/RBCapr07.pdf
5. US EPA 1997 Health Effects Assessment Summary Tables
6. Centers for Disease Control and Prevention ATSDR chronic oral minimum risk level http://www.atsdr.cdc.gov/mrls.html and cancer risk evaluation guide for 1 x 10^{-6} excess cancer risk (CREG)
7. California EPA Public Health Goals (PHGs) http://www.oehha.ca.gov/water/phg/allphgs.html
8. National Primary Drinking Water Regulations http://www.epa.gov/safewater/mcl.html
9. Other health risk assessment data published by US EPA and states

Table entry for PFOA in the North Carolina Public Health Goals (NCPHGs) December 11, 2007 memo

NCPHG for Total PFOA and PFOS 0.00063 mg/L (reference dose 0.00009 mg/kg-day generated by CIIT at RTP based on lower bound 10% benchmark plasma concentration response for monkeys associated with increased liver weight at 23,000 ng/mL, pharmacokinetic modeling data show equivalent human administered dose is 0.12 times serum 10% lower bound effect level of 23,000 ng/mL (equal to 2,760 ng/kg-day), safety factors 3 for animal to human and 10 for human variability corresponds to equivalent human administered dose of 90 ng/kg-day or 0.00009 mg/kg-day; 0.20 relative source contribution; due to half life differences between rats of 2.8 to 202 hours and humans 38,281 hours or 4.37 years (difference of as high as 13,671). Applying traditional safety factors to an administered effect dose is not a scientifically valid approach for determining a safe dose for humans because the corresponding serum level for humans at a given administered dose would be significantly higher than for animals such as rodents. Instead, EPA, EPA's Scientific Advisory Board, CIIT, and NC DHHS recommend the use of pharmacokinetic modeling to predict safe dose in humans based on serum effect levels. Previous NCPHG was just for PFOA of 0.00063 mg/L.

Odor threshold level not available

Taste threshold level not available

IMAC 0.002 mg/L (0.0003 mg/kg-day based on decreased body weight in rats and safety factor of 3000 based on 10 animal to human, 10 human variability, 10 Lowest Observed Adverse Effect Level to No Observed Adverse Effect Level, and 3 data gaps)

MCL not available