ATTACHMENT 8

Memo

Date: April 4, 2007

To: Tim Scherkenbach
Assistant Commissioner
Minnesota Pollution Control Agency

From: John Linc Stine, Division Director
Environmental Health Division
Minnesota Department of Health

Subject: **Hazard Determination of PFOA and PFOS**

This memorandum is in response to your question regarding the potential for perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) to pose a substantial present or potential hazard to human health.

The Minnesota Department of Health (MDH) has determined that the chemicals are toxic in studies of laboratory animals and that the toxicity observed in these studies is relevant to humans. The health effect found in monkeys, rats and mice at the lowest doses that produce toxicity was increased liver weight along with clinical symptoms and histological evidence of liver toxicity (Butenoff et al. 2002; Sibinski 1987; Seacat et al., 2002; and other papers documented in the attachment). At similar doses or higher doses these chemicals also alter thyroid hormone levels and affect development in animals exposed during gestation (Seacat et al., 2002; Lau et al, 2003 and 2006; Wolf et al., 2007, Thomford 2001). Additional effects occur at higher levels: PFOA exposure to mice during gestation reduces pup survival and mammary gland development (White et al., 2007; Lau et al, 2006; Wolf et al., 2007) and PFOS exposure to mice affects the immune system (Peden-Adams et al., 2006). The MDH based the risk assessment for these chemicals primarily on the results of monkey studies, in part because the chemicals' biological mechanisms in monkeys are likely to be most similar and relevant to humans.

Rats exposed to high levels of either chemical develop tumors in the liver and other sites. The tumor sites occur in the same organs that are the most sensitive to the health effects noted above. Prevention of these sensitive, precursor effects will protect against the subsequent development of tumors. In addition, humans are not as sensitive as rats to what is believed to be the major mechanism action for inducing liver tumors.

The MDH has used the toxicity studies, information about the accumulation of each chemical in humans compared to animals, and standard risk assessment procedures to develop an oral reference dose for each chemical.

The reference dose is combined with an appropriate water intake (encompassing 95 percent of the population) to develop Health Based Values for drinking water, which are described in the attached memos. The values (0.5 ug/L for PFOA and 0.3 ug/L for PFOS) represent a level at which no health effects to humans are anticipated. The findings and resources used to develop these findings are listed in the attachments.

PFOS has been found in some fish samples. The MDH issued fish consumption advice recommending limiting meals of certain fish in order to keep the public's exposure to PFOS from fish below the 2002 provisional reference dose. The MDH will use the 2007 oral reference dose for PFOS to reevaluate fish tissue concentrations. The MDH anticipates that future fish consumption advice will be more stringent (a lower PFOS level in fish fillets will trigger advice to limit consumption of fish).

PFOA and PFOS have been found in drinking water in Lake Elmo and Oakdale. When well results exceeded MDH guidelines or Health Based Values the MDH issued well advisories that recommended that the residents should not drink the water or use it for cooking. The MDH recommended that the residents should use an alternative source of drinking water. This advice has also been shared with the Minnesota Pollution Control Agency in order to guide investigation and remediation, and to provide alternative water supplies to citizens.

In summary, we believe these compounds pose a substantial present or potential hazard to human health.

Attachments:
PFOA Health Based Value memo with attachment
PFOS Health Based Value memo with attachment

cc: Larry Gust, MDH
Pam Shubat, MDH
Rita Messing, MDH
Paul Hoff, MPCA
Doug Wetzstein, MPCA

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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(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.

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

Andersen, ME, et. al., 2006 Pharmacokinetic Modeling of Saturable, Renal Resorption of Perfluoroalkylacids in Monkeys – Probing the Determinants of Long Plasma Half-Lives. Toxicology (on-line) doi:10.1016/j.tox.2006.08.004

Austin et al., Neuroendocrine Effects of Perfluorooctane Sulfonate in Rats. Env Health Perspect 111(12)1485-1489, 2003

Bondy G, I Curran, L Coady, C Armstrong, M Parenteau, V Liston, L Hierlihy, J Shenton. Immunomodulation by perfluorooctanesulfonate (PFOS) in a 28-day rat feeding study. The Toxicologist, Abstract #101, 2006.

Butenhoff et al, Perfluorooctane Sulfonate-Induced Perinatal Mortality in Rat Pups is Associated with a Steep Dose-Response. The Toxicologist 66(1): 25 (Abstract 120), 2002.

Butenhoff et al, Thyroid hormone status in adult female rats after an oral dose of perfluoroctanesulfonate (PFOS). The Toxicologist, Abstract #1740, 2005.

Curran et al., Perfluorooctanesulfonate (PFOS) Toxicity in the Rat: A 28-Day Feeding Study. The Toxicologist Abstract #102, 2006

Fan YO, Jin YH, Ma YX, Zhang YH 2005. [Effects of perfluorooctane sulfonate on spermiogenesis function of male rats] [Article in Chinese] Wei Sheng Yan Jiu. Jan;34(1):37-9. (accessed at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15862018)

Food Standards Agency, Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Second Draft Working Paper on the Tolerable Daily Intake for Perfluorooctane Sulfonate (May 2006).

Food Standards Agency (a United Kingdom Government Agency), Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Minutes of the July 11, 2006 meeting.

Food Standards Agency, Committee on Toxicity (COT) of Chemicals in Food, Consumer Products and the Environment. COT Statement on the Tolerable Daily Intake for Perfluorooctane Sulfonate (November 2006).

Fuentes S, MT Colomina, J Rodriguez, P Vicens, JL Domingo. Interactions in developmental toxicology: concurrent exposure to perfluorooctane sulfonate (PFOS) and stress in pregnant mice. Toxicology Letters 164:81-89, 2006.

German Ministry of Health Drinking Water Commission. Provisional evaluation of PFT in drinking water with the guide substances perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) as examples. July 13,2006. http://www.umweltbundesamt.de/uba-info-presse-e/hintergrund/pft-in-drinking-water.pdf

Grasty et al, Critical Period for Increased Neonatal Mortality Induced by Perfluorooctane Sulfonate (PFOS) in the Rat. The Toxicologist 66(1): 25 (Abstract 118), 2002.

Grasty et al., Perfluorooctane Sulfonate (PFOS) Alters Lung Development in the Neonatal Rat. The Toxicologist, Abstract # 1916, 2004.

Hu Wen yue, PD. Jones, W DeCoen, L King, P Fraker, J Newsted and JP Giesy 2003. Alterations in cell membrane properties caused by perfluorinated compounds. Comparative Biochemistry & Physiology Part C 135:77-88.

Hu Wen yue, PD. Jones, T Celius and JP Giesy 2005. Identification of genes responsive to PFOS using gene expression profiling. Environmental Toxicology and Pharmacology Jan (Vol 19, Issue 1): 57-70.

Johansson, N, et al., 2006. Neonatal exposure to perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) causes deranged behaviour and increased susceptibility of the cholinergic system in adult mice. The Toxicologist Abstract # 1458

Keil DE, T Mehlman, L Butterworth, MM Peden-Adams. Gestational exposure to PFOS suppresses immunological function in F1 mice. The Toxicologist Abstract #882, 2005.

Lau, et al., 2003. Exposure to Perfluorooctane Sulfonate during Pregnancy in Rat and Mouse. II. Postnatal Evaluations. Tox Sci 74: 382-392.

Lau, et al., 2004. The developmental toxicity of perfluoroalkyl acids and their derivatives. Tox Appl Pharm 198:231-241.

Lau et al, 2006. Evaluation of Perfluorooctane Sulfonate (PFOS) in Rat Brain. The Toxicologist Abstract #576.

Lieder PH, PE Noker, GS Gorman, SC Tanaka, JL Butenhoff. 2006. Elimination Pharmacokinetics of a Series of Perfluorinated Alkyl Carboxylate and Sulfonates (C4, C6 and C8) in Male and Female Cynomolgus Monkeys. Poster presentation at the 2006 European SETAC meeting in Den Hague, Netherlands.

Logan MN, JR Thibodeaux, RG Hanson, M Strynar, A Lindstrom, C Lau. 2004. Effects of perfluorooctane sulfonate (PFOS) on thyroid hormone status in adult and neonatal rats. The Toxicologist Abstract #1917

Luebker, D. et al., Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. Toxicology 215:126-148, 2005a.

Luebker, D. et al., Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats: Dose-response, and biochemical and pharmacokinetic parameters. Toxicology 215:149-169, 2005b.

Karrman A, I Ericson, B van Bavel, PO Darnerud, M Aune, A Glynn, S Lignell and G Lindstrom. 2006. Exposure of Perfluoroinated Chemicals through Lactation – Levels of Matched Human Milk and Serum and a Temporal Trend, 1996 – 2004, in Sweden. EHP Online November 2006.

Maras, M et al., 2006. Estrogen-like properties of fluorotelomer alcohols as revealed by MCF-7 breast cancer cell proliferation. Env Hlth Perspec 114(1):100-105.

Olsen et al, 2005 Evaluation of the half-life (t1/2) of elimination of perfluorooctanesulfonate (PFOS), perfluorohexanesulfonate (PFHS) and perfluorooctanoate (PFOA) from human serum. FLUOROS: International Symposium on Fluorinated Alky Organics in the Environment, TOX017)

Organization for Economic Co-operation and Development (OECD) Nov. 21, 2002. Hazard Assessment of Perfluorooctane Sulfonate (PFOS) and Its Salts.
http://www.oecd.org/document/58/0,2340,en_2649_37465_2384378_1_1_1_37465,00.html#3
(Accessed Nov. 2002)

Peden-Adams, et al., Oral Exposure to PFOS for 28 Days Suppresses Immunological Function in B6C3F1 Mice. The Toxicologist Abstract #573, 2006.

Seacat et al., Subchronic Toxicity Studies on Perfluorooctanesulfonate Potassium Salt in Cynomolgus Monkeys. Tox Sci 68:249-264, 2002

Takacs ML and BD Abbot. 2007. Activation of Mouse and Human Peroxisome Proliferator–Activated Receptors (α, β/δ, γ) by Perfluorooctanoic Acid and Perfluorooctane SulfonateToxicological Sciences 95(1), 108–117.

Tanaka et al., 2005. Thyroid hormone status in adult rats given oral doses of perfluorooctanesulfonate. FLUOROS: International Symposium on Fluorinated Alky Organics in the Environment, TOX018)

Tanaka, S, et al. 2006 Effects of Perfluorooctanesulfonate on 125I Elimination in Rats after a Single Intravenous Dose of 125I-Labeled Thyroxine. The Toxicologist Abstract #573

Thayer, K. 2002. Environmental Working Group: Perfluorinated chemicals: Justification for inclusion of this chemical class in the national report on human exposure to environmental chemicals.
http://www.ewg.org/reports/pfcworld/pdf/EWG_CDC.pdf

Thibodeaux, et al., Exposure to Perfluorooctane Sulfonate during Pregnancy in Rat and Mouse. I. Maternal and Prenatal Evaluations. Tox Sci 74: 369-381, 2003.

Thomford, P. 2002 Final Report: 104 Week Dietary Chronic Toxicity and Carcinogenicity Study with Perfluorooctane Sulfonic Acid Potassium Salt (PFOS: T-6295) in Rats. (Abstract only).
3M 2002. Personal communication from Dr. John Butenhoff. Nov 25, 2002. Benchmark doses from the 6-month oral dosing study in monkeys developed by Dr. Gaylor.

3M 2003. Environmental and Health Assessment of Perfluorooctane Sulfonic Acid and Its Salts.

UK Environmental Agency 2004. Environmental Risk Evaluation Report: Perfluorooctanesulphonate (PFOS).

U.S. EPA 2003. Toxicological Review of Perfluorooctane Sulfonate (PFOS) In Support of Summary Information on the Integrated Risk Information System (IRIS). September 2003. External Peer Review Draft.

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
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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:

Andersen, ME, et. al., 2006 Pharmacokinetic Modeling of Saturable, Renal Resorption of Perfluoroalkylacids in Monkeys – Probing the Determinants of Long Plasma Half-Lives. Toxicology 227:156-164.

Abbott B,CJ Wolf, KP Das, CS Lau. 2007. Role of peroxisome proliferator activated receptor-alpha (PPARα) in mediating the developmental toxicity of perfluorooctanoic acid (PFOA) in the mouse. The Toxicologist (submitted for the 2007 annual SOT meeting).

ACGIH Documentation of TLVs 2001. Ammonium Perfluorooctanoate.

Butenhoff, et al., 2002. Toxicity of Ammonium Perfluorooctanoate in Male Cynomolgus Monkeys After Oral Dosing for 6 Months. *Toxicological Sciences* 69:244-257.

Butenhoff JL, et al., 2004a. Pharmacokinetics of perfluorooctanoate in Cynomolgus monkeys. Toxicological Sciences 82: 394-406

Butenhoff, et al., 2004b. The Reproductive Toxicology of Ammonium Perfluorooctanoate (AFO) in the Rat. Toxicology 196: 95-116.

Butenhoff et al, 2004c. Characterization of risk of general population exposure to perfluorooctanoate. Reg Tox and Pharm 39:363-380.

Butenhoff et al., 2005. Response to letter to the editor. Reg Tox and Pham 42:146-147.

CATT 2002. West Virginia Department of Environmental Protection (DEP). August 2002. Final Ammonium Perfluorooctanoate (C8) Assessment of Toxicity Team (CATT) Report.

Clewell HJ, Tan YM, Andersen ME. Society of Risk Analysis presentation Dec. 2006. Application of Pharmacokinetic Modeling to Estimate PFOA Exposures Associated with Measured Blood Concentrations in Human Populations. Abstract M2-C.1.

DeWit JC, CB Copeland and RW Luebke. 2007. Dose-response of perfluorooctanoic acid-induced immunomodulation in adult C57BL/6 mice. The Toxicologist (submitted for the 2007 Annual SOT meeting).

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Memo

MINNESOTA MDH DEPARTMENT OF HEALTH

Date: November 20, 2002

To: Douglas Wetzstein
Dave Douglas

From: Helen Goeden, Health Risk Assessment Unit

Phone: (651) 215-0874

Subject: Response to Request for Health Based Values and interim Soil Reference Values

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This memorandum is in response to a request by the Minnesota Pollution Control Agency (08/21/02) for Health Based Values (HBVs) and interim Soil Reference Values (SRVs) for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS).

There is limited published information on the toxicity of PFOA and PFOS. The MDH relied heavily on readily available toxicity summary information provided by 3M, EPA and the West Virginia Department of Environmental Protection. After reviewing this information the MDH modified the RfD and RfC values proposed by 3M.

Health Based Values (HBVs)

Chemical	CAS #	Endpoint	RfD (mg/kg/d)	HBV µg/L
PFOA	3825-26-1	Liver	0.001	7
PFOS	2795-39-3/ 1763-23-1	Liver	0.0002	1

Soil Reference Values (SRVs)

Chemical	CAS#	Endpoint	RfD (mg/kg/d)	RfC (mg/m^3)	Residential SRV (mg/kg)	Industrial SRV (mg/kg)
PFOA	3825-26-1	Liver	0.001	2E-5	30	200
PFOS	2795-39-3/ 1763-23-1	Liver	0.0002	2E-5	6	40

Toxicity Value Sources: See Attachment II.

Based on information currently available we feel that the above values will provide an adequate level of protection from exposure to PFOA and PFOS in drinking water and direct exposure to PFOA or PFOS in soil; however, there is a degree of uncertainty associated with the HBVs and SRVs, and they should be considered provisional. The above criteria do not address impacts to groundwater as a result of soil leaching, food chain impacts or ecological impacts.

Please note that carcinogenicity studies in the rat have shown PFOA and PFOS to be potentially carcinogenic. However, at this time the available data are not sufficient to determine relevance to humans or for development of cancer potency values.

The data utilized in the derivation of the HBVs is provided in Attachment I. Standard assumptions of a 70 kilogram person with a drinking water ingestion rate of 2 liters per day, and a relative source contribution of 20 percent were used to calculate these values.

MDH is in the process of revising its Health Risk Limits for groundwater rule. The MDH is likely to recommend that the standard assumptions of 70 kilograms and 2 liters/day be replaced by a body weight and an intake rate more appropriate for children. If this recommendation is accepted and promulgated as rule, HBVs would likely decrease by a factor of 3 to 4.

The data utilized in the derivation of the SRVs is provided in Attachment II. The default exposure scenarios and target risk values presented in the MPCA's Draft Guidelines for the Soil-Human Health Pathway, Technical Support Document (Working Draft, January 1999) were utilized to calculate these values.

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

cc: Larry Gust, MDH
Anne Kukowski, MDH
Jim Kelly, MDH
Gerry Smith, MDH
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Luke Charpentier, MPCA
Mary Dymond, MPCA
Laura Solem, MPCA
Michael Santoro, 3M
John Butenhoff, 3M

ATTACHMENT I

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

Compound Name: **Perfluorooctanoate (PFOA)**
CAS #: **3825-26-1** (Oct. 16, 2002 personal communication with Dr. John Butenhoff, 3M)

LOAEL *(ingestion)*: **3 mg/kg/day**
Uncertainty Factor: **3000** (3 - interspecies; 10 - intraspecies; 10 subchronic-to-chronic; 10 LOAEL-to-NOAEL)
Modifying Factor: **1**
RfD*: **0.001 mg/kg/day**

Health effect: **Liver**

Relative Source Contribution (RSC): **20%**

Oral Slope Factor: **NA**
Applied Risk Level: **NA**

$$\text{HBV} = \frac{(\text{RfD, mg/kg/d})\,(\text{RSC})\,(1000\ \mu\text{g/mg})}{\text{Intake Rate (2 L per day/70 kg)}}$$

$$= \frac{(0.001\ \text{mg/kg/d})\,(0.2)\,(1000\ \mu\text{g/mg})}{0.029\ \text{L/kg/d}} = \mathbf{7\ \mu g/L}$$

Data Sources:

1. EPA Revised Draft Hazard Assessment of Perfluorooctanoic Acid and Its Salts (Nov 4, 2002);
2. EPA Draft Hazard Assessment of Perfluorooctanoic Acid and Its Salts (Feb 2002);
3. 3M Lifetime Drinking Water Health Advisory for Perfluorooctane sulfonate (April 2002);
4. 3M Soil Screening Guidelines for PFOS (May 2002);
5. Subchronic Toxicity Studies on Perfluorooctanesulfonate Potassium Salt in Cynomolgus Monkeys. Seacat et al., Toxciological Sciences 68:249-264, 2002; and
6. 3M Soil Screening Guidelines for PFOA (March 2002).

* Carcinogenicity studies in the rat have shown PFOA to be carcinogenic. However, at this time the available data are not sufficient for a quantitative assessment. Reproductive and developmental effects, based on studies in rats and rabbits, occur at levels higher than doses causing liver toxicity. However, due to rapid elimination in female rats (serum half-life of 1 day) it is unclear to what degree the fetuses and neonates were exposed. Ovarian tubular hyperplasia has also been observed in female rats at doses as low as 1.6 mg/kg/d (note: a NOAEL was not determined for this effect since effects were observed at the lowest dose evaluated). Women do not appear to have the same active secretory mechanism that exists in the female rat.

Compound Name:	**Perfluorooctanesulfonate (PFOS)**
CAS #:	**2795-39-3 (potassium salt)** **1763-23-1 (free salt)** (Oct. 16, 2002 personal communication with Dr. John Butenhoff, 3M)
LOAEL *(ingestion)*:	**0.15 mg/kg/day**
Uncertainty Factor:	**1000** (3 - interspecies; 10 - intraspecies; 10 subchronic-to-chronic; 3 LOAEL-to-NOAEL)
Modifying Factor:	**1**
RfD*:	**0.0002 mg/kg/day**
Health effect:	**Liver**

Relative Source Contribution (RSC): **20%**

Oral Slope Factor:	NA
Applied Risk Level:	NA

$$\text{HBV} = \frac{\text{(RfD, mg/kg/d) (RSC) (1000 µg/mg)}}{\text{Intake Rate (2 L per day/70 kg)}}$$

$$= \frac{\text{(0.0002 mg/kg/d) (0.2) (1000 µg/mg)}}{\text{0.029 L/kg/d}} = \mathbf{1\ µg/L}$$

Data Sources:

1) EPA Hazard Assessment and Biomonitoring Data on Perfluorooctane Sulfonate – PFOS (July 2000);
2) 3M Lifetime Drinking Water Health Advisory for Perfluorooctane sulfonate (April 2002);
3) 3M Soil Screening Guidelines for PFOS (May 2002);
4) Subchronic Toxicity Studies on Perfluorooctanesulfonate Potassium Salt in Cynomolgus Monkeys. Seacat et al., Toxciological Sciences 68:249-264, 2002; and
5) 3M Comments on Interspecies Uncertainty in Risk Assessment for PFOS.

*Carcinogenicity studies in the rat have shown PFOS to be carcinogenic. However, at this time the available data are not sufficient for a quantitative assessment. Reproductive and developmental effects, based on studies in rats and rabbits, occur at levels higher than doses causing liver toxicity.

Date (Prepared or Modified): November 14, 2002
Prepared by: H. Goeden

ATTACHMENT II

DATA FOR DERIVATION OF SOIL REFERENCE VALUE (SRV)

Compound Name:	***Perfluorooctanoate* (PFOA)**
CAS #:	**3825-26-1** (Oct. 16, 2002 personal communication with Dr. John Butenhoff, 3M)
LOAEL *(ingestion)*:	**3 mg/kg/day**
Uncertainty Factor:	**3000** (3 - interspecies; 10 - intraspecies; 10 subchronic-to-chronic; 10 LOAEL-to-NOAEL)
Modifying Factor:	**1**
RfD*:	**0.001 mg/kg/day**
RfC**:	**2E-5 mg/m^3**
Dermal Absorption:	**10% (MPCA Default for organic compounds)**
Health effect:	**Liver**
Hazard Quotient:	**0.2 (MPCA target risk value)**
Oral Slope Factor:	**NA**
Inhalation Unit Risk:	**NA**

Residential SRV: **30 mg/kg**
Industrial SRV: **200 mg/kg**

Data Sources:

1) EPA Revised Draft Hazard Assessment of Perfluorooctanoic Acid and Its Salts (Nov 4, 2002);
2) EPA Draft Hazard Assessment of Perfluorooctanoic Acid and Its Salts (Feb 2002);
3) 3M Lifetime Drinking Water Health Advisory for Perfluorooctane sulfonate (April 2002);
4) 3M Soil Screening Guidelines for PFOS (May 2002);
5) Subchronic Toxicity Studies on Perfluorooctanesulfonate Potassium Salt in Cynomolgus Monkeys. Seacat et al., Toxciological Sciences 68:249-264, 2002; and
6) 3M Soil Screening Guidelines for PFOA (March 2002).

* Carcinogenicity studies in the rat have shown PFOA to be carcinogenic. However, at this time the available data are not sufficient for a quantitative assessment. Reproductive and developmental effects, based on studies in rats and rabbits, occur at levels higher than doses causing liver toxicity. However, due to rapid elimination in female rats (serum half-life of 1 day) it is unclear to what degree the fetuses and neonates were exposed. Ovarian tubular *hyperplasia has also been observed in female rats at doses as low as 1.6 mg/kg/d (note:* a NOAEL *was not* determined for this effect since effects were observed at the lowest dose evaluated). Women do not appear to have the same active secretory mechanism that exists in the female rat.

** There is insufficient information on the toxicological effects of PFOA following inhalation exposure. PFOA is not considered to be a volatile chemical and therefore the inhalation exposure pathway is anticipated to be a minor pathway. 3M has suggested a RfC of 2E-5 mg/m^3 based on a generic exposure guideline for chemicals found to be carcinogenic in animals but with unknown relevance to humans. The CATT report generated a RfC of 1.1E-3 mg/m^3. In the absence of information the provisional RfC suggested by 3M will be utilized for the development of an interim Soil Reference Value.

Compound Name:	**Perfluorooctanesulfonate (PFOS)**
CAS #:	**2795-39-3 (potassium salt)**
	1763-23-1 (free salt)
	(Oct. 16, 2002 personal communication with Dr. John Butenhoff, 3M)
LOAEL *(ingestion)*:	**0.15 mg/kg/day**
Uncertainty Factor:	1000 (3 - interspecies; 10 - intraspecies; 10 subchronic-to-chronic; 3 LOAEL-to-NOAEL)
Modifying Factor:	1
RfD*:	**0.0002 mg/kg/day**
RfC**:	**2E-5 mg/m^3**
Dermal Absorption:	**10% (MPCA Default for organic compounds)**
Health effect:	**Liver**
Hazard Quotient:	**0.2 (MPCA target risk value)**
Oral Slope Factor:	NA
Inhalation Unit Risk:	NA

Residential SRV: **6 mg/kg**
Industrial SRV: **40 mg/kg**

Data Sources:

Data Sources:

1) EPA Hazard Assessment and Biomonitoring Data on Perfluorooctane Sulfonate – PFOS (July 2000);
2) 3M Lifetime Drinking Water Health Advisory for Perfluorooctane sulfonate (April 2002);
3) 3M Soil Screening Guidelines for PFOS (May 2002);
4) Subchronic Toxicity Studies on Perfluorooctanesulfonate Potassium Salt in Cynomolgus Monkeys: Seacat et al., Toxciological Sciences 68:249-264, 2002; and
5) 3M Comments on Interspecies Uncertainty in Risk Assessment for PFOS.

*Carcinogenicity studies in the rat have shown PFOS to be carcinogenic. However, at this time the available data are not sufficient for a quantitative assessment. Reproductive and developmental effects, based on studies in rats and rabbits, occur at levels higher than doses causing liver toxicity.

**There is insufficient information on the toxicological effects of PFOS following inhalation exposure. PFOS is not considered to be a volatile chemical and therefore the inhalation exposure pathway is anticipated to be a minor pathway. 3M suggested a RfCs of 2E-4 and 2E-5 mg/m^3 for PFOS and PFOA, respectively. The value for PFOA was based on a generic exposure guideline for chemicals found to be carcinogenic in animals but with unknown relevance to humans. PFOS appears to be carcinogenic in rats but it is not clear whether suggested mechanism of action is relevant to humans. In the absence of information the provisional RfC for PFOA (2E-5 mg/m^3) suggested by 3M will be utilized for the development of an interim Soil Reference Value for PFOS as well.

Date (Prepared or Modified): November 14, 2002
Prepared by: H. Goeden