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An Office of the Department of Health and Human Services
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Memorandum

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From: Andrew E. Smith, SM, ScD, State Toxicologist, Maine Center for Disease Control and Prevention
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Re: Action levels for PFOS in cow's milk

Summary

The Animal Health Program of the Department of Agriculture, Conservation and Forestry requested that the Maine Center for Disease Control and Prevention (Maine CDC) provide assistance in an ongoing evaluation of localized contamination of cow's milk with perfluorooctane sulfonate (PFOS). Specifically, Maine CDC was asked to determine a level of PFOS in cow's milk that would guide recommendations on whether to allow a dairy farm's milk to be blended with other milk and allowed to enter the commercial market.

There are currently no action levels or tolerance limits for PFOS in milk or food available from the U.S. Food and Drug Administration (FDA). The U.S. Environmental Protection Agency (U.S. EPA) recently published a drinking water health advisory level for PFOS of 70 nanograms per liter (ng/L). Maine CDC derived action levels for PFOS in cow's milk following standard risk assessment methodology using the U.S. EPA's recently published toxicity information for PFOS, and daily milk consumption rates for high-end consumers on a body weight basis. After accounting for additional background sources of PFOS exposure, the action levels for PFOS in cow's milk are as follows:

Action levels for PFOS in cow's milk

	Age group (years, male and female combined)				
	1-2	3-5	6-11	12-19	20+
Action level (nanograms/Liter, ng/L)*	210	400	710	1,510	2,700

*Calculated values rounded to nearest 10.

These action levels are not legally enforceable standards. Rather, they are intended as guidance to determine whether a dairy farm's milk should be considered adulterated with PFOS, and therefore should neither be sold or delivered for sale in accordance with Title 22 MRS §2155-A, nor blended with uncontaminated milk to obtain PFOS levels less than the action levels as per FDA policy[1]. These action levels are not intended to establish permissible levels of PFOS in cow's milk at the commercial market level.

Derivation of action levels for PFOS

General method

Action levels for PFOS in cow's milk were derived following standard health risk assessment methods, and calculated using the following equation:

$$PFOS\ action\ level\ (ng/L) = \frac{Reference\ dose\ (ng/kg\ body\ weight/day)}{Daily\ milk\ comsumption\ (g/kg\ body\ weight/day)} \times RSC \times CFs \quad (Equation\ 1)$$

In Equation 1 the reference dose (RfD), a term commonly used by the U.S. EPA, is a toxicity value that represents an estimate of an oral daily dose of a chemical below which there is likely to be minimal risk of any deleterious health effects. Other agencies (e.g., the U.S. Food and Drug Administration (FDA), the European Food Safety Agency) refer to this threshold toxicity value as a tolerable or allowable daily intake. The denominator in Equation 1 is an exposure-related term; in this case, daily milk consumption, often referred to as intake, on a body weight basis. The relative source contribution (RSC) factor is a term which is used to account for other sources of exposure that are unrelated to milk consumption. The RSC factor is used when other exposures to a contaminant are expected and there is a risk management goal to ensure that total estimated exposure does not exceed the reference dose. The CFs term in Equation 1 represents two conversion factors, i.e., one CF of 1000 g/kg to convert ng/g to ng/kg and a second CF of 1.03 kg/L, which is the approximate density of cow's milk, to convert ng/kg to ng/L. Specific values for the RfD, daily milk intake and RSC used in the present analysis, and the basis for their selection, are discussed below.

Specific inputs

A. Reference dose

Maine CDC selected a RfD for PFOS of 20 nanograms per kg body weight per day (ng/kg/day)[2]. The U.S. EPA recently developed this PFOS RfD to derive a lifetime health advisory for PFOS in drinking water[3]. The basis for this RfD is a developmental toxicity study in rats where there was an observed decrease in rat pup body weight in pups born to dams exposed to PFOS for six weeks prior to mating and throughout mating, gestation, and lactation (USEPA, 2016). In deriving the PFOS RfD, the U.S. EPA selected a 'no observable adverse effect level' (NOAEL), from this study. The NOAEL is the dose at which there is no corresponding health effect in the animal; in this case, the level at which there was no observed decrease in pup body weight.

[1] CPG Sec. 555.200 Adulterated Food Mixed with Good Food: https://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074551.htm

[2] U.S. EPA typically presents RfDs in units of milligrams/kg-body weight/day. 20 ng/kg/day = 0.00002 mg/kg/day.

[3] The U.S. EPA PFOS lifetime health advisory for drinking water is for both PFOS and perfluorooctanoic acid (PFOA). When both chemicals are present in a drinking water source the combined total should not exceed 70 ng/L. If only one of the perfluorinated chemicals is detectable in a drinking water source than its concentration should not exceed 70 ng/L (https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos).

The U.S. EPA utilized a pharmacokinetic model to calculate an average PFOS serum level in the rat dams at the corresponding NOAEL (USEPA, 2016). The average serum level in rats at the NOAEL was translated to an oral human equivalent dose based on steady state clearance calculated from a PFOS-specific volume of distribution and a human half-life for PFOS (USEPA, 2016). The U.S. EPA then applied a 10-fold uncertainty factor for intraspecies variability, to account for any human populations that may be more sensitive to PFOS exposure, and a 3-fold uncertainty factor for extrapolating from animals to humans. Use of these uncertainty factors is a standard risk assessment practice when extrapolating laboratory animal data to human populations. Applying the 30-fold cumulative uncertainty factor to the human equivalent dose resulted in a 20 ng/kg/day RfD.

As the 20 ng/kg/day RfD for PFOS is derived from a developmental endpoint based on exposure to pregnant and lactating animals, there is uncertainty regarding the use of this developmental toxicity value to derive action levels for other populations (e.g., young children or adults). However, the U.S. EPA derived a candidate RfD from a 14-week exposure study in adult male rats based on changes in liver and kidney function. This subchronic adult exposure RfD was 40 ng/kg/day, which is only 2-fold higher than the selected RfD based on developmental effects and is well within the uncertainty surrounding an estimated RfD. The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) has developed an intermediate Minimal Risk Level (MRL), which is the same type of toxicity value as a subchronic RfD, for PFOS of 30 ng/kg/day based on liver effects in adult cynomolgus monkeys exposed to PFOS for 26 weeks (ATSDR, 2015). The ATSDR intermediate MRL has only been published for public comment and to date has not been finalized (ATSDR, 2015). While the use of the developmental RfD may be slightly conservative for assessing non-fetal/infant exposures, it is of similar magnitude to an RfD based on liver effects in adult animals following subchronic exposure (USEPA, 2016 and ATSDR, 2015).

B. Milk intake

Maine CDC calculated values for daily milk intake on a body weight basis using fluid milk consumption and body weight data from U.S. Centers for Disease Control and Prevention's (U.S. CDC) National Health and Nutrition Examination Survey (NHANES) and the U.S. Department of Agriculture (USDA) Food Patterns Equivalents Database (FPED) (USCDC, 2017a and USDA, 2016a). NHANES is a nationally representative sampling of the population of the United States, and provides food consumption data collected using 2 day, 24-hour recall surveys. NHANES also provides demographic and body measures data including age, gender, and body weight for individuals that participated in the dietary recall surveys. The USDA's FPED provides the daily amount of various foods, including fluid milk consumed, for each individual participating in the NHANES dietary recall surveys.

NHANES 2009-2010 and 2011-2012 demographic and body measures data were combined with corresponding 2009-2010 and 2011-2012 FPED individual food consumption data and used to derive age group-specific mean and 90th percentile fluid milk intake per kg body weight[4]. Fluid milk intake was calculated for individual's that reported consuming milk on either day 1 or day 2 or both days of the dietary recall survey. Milk intake was

[4] NHANES 2009-2010 and 2011-2012 datasets:
https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Demographics&CycleBeginYear=2009
https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Examination&CycleBeginYear=2009
https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Demographics&CycleBeginYear=2011
https://wwwn.cdc.gov/nchs/nhanes/search/datapage.aspx?Component=Examination&CycleBeginYear=2011
USDA FPED 2009-2010 and 2011-2012 datasets:
https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/food-surveys-research-group/docs/fped-databases/

averaged over the two days and divided by the participant's body weight to derive a daily milk intake on a body weight basis. Total fluid milk intake in the FPED is presented as cup equivalents per day, which was converted to grams/day with one cup of fluid milk equal to 244 grams (USDA, 2016b). Mean and 90th percentile fluid milk intakes (grams of fluid milk/kg body weight/day) were calculated for age groups with similar intakes (Table 1)[5].

Maine CDC used the 90th percentile consumer-only milk consumption rate to represent daily milk intake for a high-end milk consumer. Using a 90th or 95th percentile for an exposure scenario is a common practice in human health risk assessment. For example, for the PFOS/PFOA drinking water health advisory, the U.S. EPA used the 90th percentile consumer-only estimate for water ingestion on a body weight basis for lactating women (USEPA, 2016). The FDA typically uses the 90th percentile of a daily intake to represent a high-end consumer (FDA, 2006).

Table 1. Consumer-only mean and 90th percentile daily fluid milk intakes in grams/kg bw/day.

Age group (years)	**Sample size**	**Mean** (95% confidence interval)	**90th Percentile** (95% confidence interval)
1-2	872	40.3 (37.5-43.0)	76.7 (69.6-83.7)
3-5	969	21.4 (19.8-22.9)	41.1 (34.8-47.3)
6-11	1,972	11.8 (11.0-12.6)	23.1 (21.4-24.8)
12-19	2,012	4.9 (4.4-5.4)	10.9 (9.0-12.8)
20+	8,741	2.7 (2.6-2.8)	6.1 (5.8-6.4)

C. Relative source contribution

The purpose of the RSC factor is to account for additional sources of PFOS, aside from milk, to help ensure that the daily dose of PFOS from all sources combined does not exceed the RfD. It is clear from U.S. CDC biomonitoring programs that exposure to PFOS is ubiquitous, as it is present in the blood of most of the individuals tested in recent samplings of Americans 12 years and older (USCDC, 2017b). The presence of PFOS in the general U.S. population is the result of exposures from multiple sources, including dietary sources other than milk, house dust, drinking water, and indoor and outdoor air (Egeghy and Lorber, 2011; Gebbnik et al., 2015; Tittlemier et al., 2007; Trudel et al., 2008; USEPA, 2016). Serum PFOS levels may also reflect the contribution of exposure to PFOS precursors that have undergone *in vivo* biotransformation (Gebbnik et al., 2015 and Vestergren et al., 2008). Studies have estimated daily PFOS intake based on the amount of PFOS found in various dietary items and environmental media, and individual diet- and media-specific consumption rates. From these studies, the largest contributor to overall PFOS exposure seems to be the diet for adults, and diet and house dust for young children (Egeghy and Lorber, 2011; Tittlemier et al., 2007; Trudel et al., 2008). However, the magnitude and relative contribution of these daily intake estimates from various sources, such as diet, indoor dust or drinking water, are uncertain, and may not be entirely representative of exposures for the general U.S. population.

Rather than estimate intake from individual exposures sources, several research groups have applied a one-compartment pharmacokinetic model to back-calculate a daily intake based on blood PFOS levels from a general population (Egeghy and Lorber, 2011; Thompson et al., 2010; Trudel et al., 2008). U.S. EPA has

[5] Mean and percentile distribution estimates for fluid milk intake were calculated following NHANES analytic guidelines (https://www.cdc.gov/nchs/data/series/sr_02/sr02_161.pdf).

described this approach of using pharmacokinetic modeling to infer total dose from measured contaminant levels in tissues or body fluids as backward, or reconstructive, analysis (USEPA, 2013). Egeghy and Lorber (2011) utilized serum PFOS data from U.S. CDC NHANES biomonitoring efforts, which are nationally representative samplings of the U.S. population, with a one-compartment pharmacokinetic model to derive an overall daily PFOS intake. Using the geometric mean serum PFOS level for all individuals >12 years, from 2003-2004 NHANES samplings, Egeghy and Lorber (2011) estimated a daily PFOS intake for adults ranging from 1.6 to 24.2 ng/kg/day[6]. This range in estimated intake is the result of using low and high bounds for the volume of distribution parameter in the pharmacokinetic model, with the lower volume of distribution (200 mL/kg) producing an estimated intake that was similar to the total intake calculated from food, water, and dust exposure estimates for adults (Egeghy and Lorber, 2011). This method - using nationally representative serum PFOS data - has the advantage of estimating a daily PFOS intake by integrating all potential sources, which better represents overall PFOS exposure for the general U.S. population. Considering this daily intake to represent general background PFOS exposure, the remaining dose which could be allocated to other sources such as cow's milk can be calculated by subtracting the background exposure from the 20 ng/kg/day PFOS RfD. The RSC can then be derived by dividing the remaining dose by the PFOS RfD.

To derive a RSC using a background exposure estimate from serum PFOS levels, Maine CDC utilized the one-compartment pharmacokinetic model as presented in Egeghy and Lorber (2011) (Equation 2). The U.S. CDC recently updated their national biomonitoring data to include 2013-2014 NHANES sampling years. As it is U.S. EPA guidance to use central tendencies for RSC intake estimates, the geometric mean serum PFOS level for individuals 20 years and older (5.22 ng/mL) from 2013-2014 NHANES survey years was selected to represent the central tendency PFOS serum level in adults[7] (USEPA, 2000). For the volume of distribution and elimination rate parameters, values as described in the U.S. EPA's drinking water health advisory for PFOS were selected (USEPA, 2016). In deriving a PFOS RfD, U.S. EPA converted serum levels in animals to oral equivalent doses in humans assuming a linear steady state clearance calculated as volume of distribution (230 ml/kg-body weight) times the PFOS elimination rate (0.00035 days^{-1}) (USEPA, 2016).

$$Background\ exposure\ (ng/kg/day) = CP \times kP \times Vd \qquad (Equation\ 2)$$

Where:
CP = PFOS serum concentration (5.22 ng/mL)
kP = first-order elimination rate (0.00035 day^{-1})
Vd = volume of distribution (230 mL/kg-body weight)

The calculated background PFOS exposure for adults based on a recent nationally representative PFOS serum level is 0.42 ng/kg/day. For children, especially young children, this estimated background exposure for adults may underestimate a child's daily background exposure. However, U.S. CDC biomonitoring does not provide serum PFOS levels for individuals less than 12 years old. Thus, a background exposure estimate specific to children <12 years old cannot be directly calculated using this method. The Egeghy and Lorber (2011) study estimated that total intake per body weight from food, dust, and water for a typical 2-year-old child was approximately twice that of the total intake for adults. Doubling the adult background exposure of 0.42

[6] The geometric mean PFOS serum level for all individuals >12 years for 2003-2004 NHANES samplings was 20.7 ng/mL.
[7] For the 2013/2014 sampling years, the U.S. CDC quantified branched and linear PFOS isomers present in serum samples. They provided a summed value for all PFOS isomers to represent total PFOS serum levels. The value for the summed PFOS isomers was used in the RSC calculations as it is the equivalent measure to previous surveys years (USCDC, 2017b).

ng/kg/day results in an estimated background exposure of 0.84 ng/kg/day for a young child. The estimated background exposure of 0.84 ng/kg/day for young children was used to derive a RSC (Equation 3).

$$RSC = \frac{PFOS\ RfD\ (ng/kg/day) - Background\ exposure\ (ng/kg/day)}{PFOS\ RfD\ (ng/kg/day)} \times 100 \qquad (Equation\ 3)$$

Using the background exposure estimate for a young child in comparison to the PFOS RfD produces a RSC of 96%. According to U.S. EPA guidelines for drinking water, RSC values should not exceed an 80% celling, nor fall below a 20% floor (USEPA, 2000). As the calculated RSC using the background exposure estimate of 0.84 ng/kg/day is above the 80% celling, the RSC was limited to 80%. The RSC of 80% is the result of a relatively small background exposure as compared to the RfD.

Several analyses were performed to evaluate this data-driven derivation of an RSC. There is uncertainty in the intake estimate for young children being approximately twice that of adults. However, even if the intake estimate for children was assumed to be four times greater than that of an adult, the resulting RSC would still be greater than 80%.

It may also be appropriate to consider exposure to additional perfluorinated compounds such as PFOA, which may have toxicities similar to PFOS and potentially have an additive effect. A daily intake for PFOA can be back-calculated similar to PFOS using the same one-compartment pharmacokinetic model with a volume of distribution and clearance rate specific to PFOA and NHANES 2013-2014 PFOA serum data[8]. Back-calculated adult daily intakes for PFOA at the geometric mean serum level for individuals 20 years and older is 0.28 ng/kg/day. Doubling the adult intake to estimate a young child's background PFOA exposure results in daily intake of 0.56 ng/kg/day. Combining the PFOA and PFOS background exposure estimates for children, to account for background exposure to both chemicals, the calculated RSC is 93%.

Although it is standard U.S. EPA practice to base an RSC on central estimates of exposure, there may be concern for more highly exposed populations. Highly exposed populations were evaluated by reproducing the above calculations using the 95th percentile PFOS and PFOA serum levels for all individuals 20 years and older from 2013-2014 NHANES. The calculated background exposure for adults is 1.58 ng/kg/day for PFOS and 0.79 ng/kg/day for PFOA. Doubling these high-end adult daily intakes and combining them to estimate an high-end PFOS and PFOA exposure rate for children yields an RSC of 76%. Thus, an RSC of 80% should also be protective of background PFOS and PFOA exposure for highly exposed individuals.

Discussion

Maine CDC has developed age-specific action levels for PFOS in cow's milk that range from a low of 210 ng/L for young children to 2,700 ng/L for adults, assuming 90th percentile milk consumption behavior and allowing 80% of the reference dose to come from cow's milk consumption. These action levels are not legally enforceable standards, and are established as guidance for determining whether a dairy farm's milk should be considered adulterated, and therefore should neither be sold or delivered for sale in accordance with Title 22 MRS §2155-A. Standard risk assessment methods were used to derive these levels. These levels differ from the recently published U.S. EPA health advisory for PFOS in drinking water of 70 ng/L in part because of milk

[8] Model parameters used to estimate background exposure for PFOA are volume of distribution of 170 ml/kg-body weight, and a clearance rate of 0.00083 day^{-1}. These parameters are described in the U.S. EPA drinking water health advisory for PFOA (https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_health_advisory_final_508.pdf).

versus water exposure pathways, but also because Maine CDC used a data-driven approach to derive a RSC of 80% to account for background exposure. In contrast, U.S. EPA used a lower bound default RSC value of 20%, based on its determination that sufficient information is not available to quantitatively characterize exposure to PFOS from the many different exposure pathways (USEPA, 2016). Maine CDC believes that background exposure can be reliably estimated from serum PFOS levels from a sample of the U.S. population and a pharmacokinetic model used in the peer-reviewed literature and by the U.S. EPA in deriving their PFOS toxicity value. Overall, exposure to PFOS in the general U.S. population is decreasing, as measured by U.S. CDC biomonitoring programs (USCDC, 2017b). Based on a recent small-scale sampling study of milk from areas throughout the United States, cow's milk, in general, does not appear to be a significant dietary source of PFOS (Young et al., 2012).

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