Chapter 15
Human Health Risk Assessment of Perfluoroalkyl Acids

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Abstract In this chapter, the major human health risk assessment activities that have been undertaken for human exposure to perfluoroalkyls, with emphasis on perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA), have been summarized. Margin of exposure risk assessments, risk assessments based on dietary exposure, and the establishment of regulatory levels for PFOS and PFOA concentration in drinking water are covered in detail. Although a large and robust database exists for PFOS and PFOA that covers multiple health endpoints, data are more limited for other perfluoroalkyls. A brief review of the chemical/physical properties and hazard profiles of PFOS and PFOA in the context of risk assessment and human relevance is given. It becomes apparent that the methods used to assess human health risk from exposure to perfluoroalkyls have been evolving and will likely continue to develop as new information and approaches are introduced. Perhaps the most important direction that risk assessment for perfluoroalkyls has taken has been in the use of internal dose metrics to bridge differences in pharmacokinetic elimination kinetics between species. There is a need to better inform epidemiological investigations with the understanding obtained from toxicological and pharmacokinetic investigations and principals. Translating our understanding from toxicological systems into a human context will improve our collective ability to understand whether environmental exposure to perfluoroalkyls affects human health risk.

Keywords Perfluoroalkyls • Risk assessment • Margin of exposure • Hazard determination • Drinking water

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15.1 Introduction

This chapter will focus on the human health risk assessments for populations exposed to perfluoroalkyls, with particular emphasis on assessments for exposure to perfluorooctanesulfonate (PFOS) and perfluorooctanoate (PFOA). In addition, the development of major regulatory guidelines and standards for exposure is described. The principals, methods, and influencing factors related to the assessment of human health risk from perfluoroalkyls exposure will be presented. The risk assessments that have been conducted for PFOS and PFOA have either taken into account all sources of exposure by the use of PFOS and PFOA measurements from biomonitoring studies of human populations or have addressed a specific source of exposure, such as diet or drinking water.

The term "perfluoroalkyl acid" (or PFAA) describes a group of compounds that share the characteristic of being fully-fluorinated organic acids, with carboxyl, sulfonyl, or phosphonyl functional groups. These are typically strong organic acids with low pKa values compared to their hydrogenated analogs. Thus, under most common environmental and biological conditions, they are highly dissociated and exist principally in the anionic form. Salt forms of PFAAs typically have been used in commercial applications requiring high chemical stability and strong surface tension reducing properties. Examples include the use of ammonium salt of perfluorooctanoate (C8 or APFO) as an emulsifying agent in the production of polytetrafluoroethylene (PTFE) and of potassium salt of (PFOS) as a surfactant for fire-fighting foam and acid mist suppression in electroplating operations. While occupational and environmental exposures to PFAAs can occur via these direct surfactant applications, the generation of PFAAs through environmental and metabolic degradation of other fluorochemical substances used in commerce can also lead to exposure.

Small amounts of the element fluorine had been observed in human blood in the mid 1800s (Nicklès 1856). Nonetheless, in 1968, when Taves (1968) identified an organically-bound fluorine (organofluorine) in human blood, the source, natural or anthropogenic, was not apparent. Because organofluorine was observed in human blood and not in the blood of non-human animals, Taves suggested an industrial or commercial exposure source (Taves 1971). Several years thereafter, Guy et al. (1976) reported experimental data that suggested that the organofluorine in blood was consistent with fluorinated organic acids and was likely from an industrial source. They postulated that perfluoroalkyl carboxylates, in particular perfluorooctanoate (PFOA), may be a major component of this organofluorine. Following on these reports of the presence of organofluorine with the suggestion of PFOA as a principal component, Ubel et al. (1980) reported on the health of workers exposed to fluorochemicals. In their analysis, serum organofluorine measurements were made. In a small group of employees at the 3M Company's Cottage Grove, Minnesota location (see Chap. 4), serum was also analyzed specifically for PFOA, and it was found that approximately 90 % of the organofluorine measured was accounted for by PFOA in these workers. In the same year, Griffith and Long (1980)

reported on the basic toxicological hazard profile of APFO, the ammonium salt of PFOA. Ophaug and Singer (1980) found that a dose of approximately 8 mg PFOA (as acid)/kg body weight given by gavage to female rats (2 mg/rat) was rapidly absorbed, tightly bound to serum proteins, and fully excreted within 96 h, with 89.3 ± 2.6 % recovered in urine and 14.3 ± 4.1 % recovered in feces. They also noted that PFOA did not appear to be metabolized.

In reporting on the concentrations of ionic fluoride and organofluorine in eight serum samples from an area of rural China purported to have negligible exposure to industrial sources of organofluorine, Belisle (1981) found that the organofluorine concentrations in the samples were similar to concentrations in samples reported from more industrial areas, yet somewhat lower, and concluded that there was no compelling evidence that the organofluorine in human blood was largely from anthropogenic sources. These early studies were important in that they demonstrated the presence of organofluorine in human blood bound to serum proteins, suggested natural as well as anthropogenic sources, led to the medical monitoring of workers engaged in the production of fluorochemicals, and encouraged the development of more sensitive and specific bioanalytical methods.

As analytical methodology progressed, mass spectrometry became a tool that promised highly sensitive and specific identification of certain fluorochemicals. These analytical developments led to the identification by Hansen et al. (2001) of specific fluorochemicals in human serum using ion-pair extraction and high pressure liquid chromatography (HPLC) followed by negative ion electrospray tandem mass spectrometry (LC-MS/MS). They reported that the summed serum compound-specific concentrations agreed well with reported organofluorine concentrations in the early literature. In serum samples from 65 non-occupationally exposed volunteers, PFOS was detected in all samples above the lower limit of quantitation (LOQ = 5 ng/mL), with an average of 28.4 ± 13.6 (standard deviation) ng/mL (range 6.7–81.5 ng/mL). PFOA was also detected in all samples, and perfluorohexanesulfonate (PFHxS) was detected in all but one sample. In converting the mean ng/mL concentrations of PFOS, PFOA, and PFHxS to their non-specific organofluorine equivalent ng/mL concentrations (18.4, 4.4, and 4.1 ng/mL, respectively) and summing these organofluorine concentrations, Hansen et al. found an average of approximately 27 ng/mL organofluorine for the three analytes combined, consistent with the 26 ng/mL organofluorine reported by Guy et al. (1976).

The identification and quantitation of specific perfluoroalkyls (PFOS, PFOA, and PFHxS) in human sera, and the additional report of the widespread presence of PFOS in wildlife by Giesy and Kannan in the same year using similar methodology (Giesy and Kannan 2001), led to a renewed focus on the potential health implications of exposure, not only for fluorochemical workers, but also for the general population and populations that may have unique exposure from industrial sources. As the number of perfluoroalkyls and polyfluorinated alkyls substances detected has expanded, so has the number of investigators and government bodies that are actively enhancing our understanding of the potential for human health risk that may be associated with exposures to these materials.

15.2 Basic Principals Used in Risk Assessment of Perfluoroalkyls

Assessments of human health risk have been conducted for several perfluoroalkyls by a number of governmental authorities as well as independent assessments published in the scientific literature or formally submitted to government agencies. These assessments have varied in form and methodology. All of the assessments share the property of reviewing the human health hazard information, mostly in the form of toxicological studies, to identify a critical study or studies and critical endpoint(s). Dose or exposure levels from the critical study that are not expected to produce the critical effect are chosen as the point of departure (POD) for risk assessment. Although it is typical for POD values to be based on doses administered by a given route of exposure, typically oral, in the case of perfluoroalkyls, a number of PODs have been based on serum or liver perfluoroalkyl concentrations resulting from treatment as an indication of internal dose related to total body burden. Where human serum or liver perfluoroalkyl concentration data are available, uncertainties resulting from the large differences in elimination kinetics between humans and the animal models used in toxicological studies can be reduced significantly.

Typically, either the study no observed adverse effect level (NOAEL) or a modeled benchmark dose (BMD) derived from regression modeling of the study dose-response data are chosen as a POD. Modeled BMD values are preferable where possible based on established criteria for goodness of fit, as they use all of the study data and are less sensitive to the somewhat arbitrary spacing between experimental doses or concentrations. Occasionally in toxicological studies, a dose or exposure level producing no effect is not determined, in which case either a BMD value or the lowest study dose/exposure (LOAEL) are used. When the LOAEL is used, it is typically adjusted for uncertainty to account for the lack of a NOAEL.

In risk assessment, the dose/exposure corresponding to the POD is used either directly, as in some margin of exposure (MOE) analyses, as will be described later, or is reduced by various uncertainty factors to derive an acceptable level of exposure, often referred to as a reference dose (RfD) or reference concentration (RfC), tolerable daily intake (TDI), or derived no effect level (DNEL). Uncertainty adjustments do vary, but typically include adjustments for inter-individual (within species) as well as interspecies variability (across species) with respect to both pharmacodynamic response and pharmacokinetic handling. Other considerations of uncertainty related to the critical study and critical effect(s) as well as the strength of the overall hazard identification database may also be included. As will be described in the following sections, adjustments based on differences in clearance between humans and the animal models used in toxicological studies can be made to account for the differences in accumulation potential at a given dose. After deriving an acceptable dose/exposure level, it can then be used to compare with an observed or estimated exposure of a population for potential exceedance. Such risk assessments are used in determining the need for and degree of risk management.

Several risk assessments have been based on evaluating the MOE, which is the ratio of the POD to the observed or estimated population exposure. As an example, if the POD level of exposure is 100 units and the observed or estimated population level of exposure to a compound is 1 unit, the ratio (MOE) would be 100. Ascertainment of an acceptable MOE is a matter of judgment and policy; however, in general, the larger the margin of exposure, the less concern for health risk. An understanding of the mode of action involved in effecting biological responses in experimental models and the applicability or relevance of the mode of action for humans also aids in reducing uncertainty. MOE risk assessments that are based on serum or liver perfluoroalkyl concentration allow assessment based on all potential sources of exposure and reduce uncertainty relative to interspecies differences in elimination kinetics.

15.3 Evolution of Approaches to Human Health Risk Assessment for Perfluoroalkyl Exposure

15.3.1 Influence of the Pharmacokinetic Properties of Perfluoroalkyls on the Use of External Dose Versus Internal Dose Metrics in Risk Assessment

Most traditional human health risk assessments for exposure to chemical substances in the environment have been based on derivation of acceptable levels of exposure based on the administered dose-response profile of the chemical in question with appropriate adjustments for uncertainty (e.g., RfD, TDI, DNEL) and comparison of these levels of exposure to those estimated for human populations based on their intake of the chemical from various sources of exposure. This practice requires a fair understanding of the human exposure pathways and associated doses. This external dose risk assessment paradigm also works best if the pharmacokinetic and pharmacodynamic properties of the chemical are within the margins of uncertainty which are typically used, approximate half logs (i.e., factors of approximately 3) for each of pharmacokinetic and pharmacodynamic uncertainty, both within and between species.

While there is nothing inherently wrong with this traditional approach for many chemicals, it became apparent early in consideration of potential human health risk for PFOS and PFOA that a traditional approach had significant limitations. For example, the rather rapid elimination of PFOA in female rats, as first observed by Ophaug and Singer (1980), with an elimination half-life of hours, particularly in comparison to human serum PFOA elimination rate of several years, as first reported by Olsen et al. (2007) made the direct extrapolation of female dose levels in the two-generation study of APFO in rats (Butenhoff et al. 2004b) to humans questionable, as it would be expected that steady state body burden in humans would be

proportionately greater for a given dose. Although this is perhaps the extreme example, all species used in toxicological experiments with PFOS and PFOA had significantly faster elimination rates than humans by at least a factor of 10 (Chang et al. 2012; Hundley et al. 2006; Lau et al. 2007).

Another limitation of the traditional approach was the lack of knowledge regarding the human environmental sources and related intakes from those sources. The amounts of PFOS and PFOA used directly in commercial applications were limited; however, the degradation of what came to be called precursor compounds to form these perfluoroalkyls by either metabolic or environmental processes was not fully understood. Time and the insightful work of numerous investigators increased our understanding of potential sources and associated amounts of exposure, but voluntary manufacturing phase outs and regulatory restrictions as well as *de novo* or increased manufacturing in some areas, e.g., China, have changed patterns of exposure over the last decade. Sometimes a point source of exposure can be identified, as in Hochsauerland in Germany (Kraft et al. 2007) and the mid Ohio River valley (Emmett et al. 2006) between West Virginia and Ohio, but this is generally not the case for most populations. These examples illustrate the limitations of the traditional approach to human health risk assessment for perfluoroalkyls that have poor elimination characteristics in humans once absorbed as compared to the species used in toxicological investigations.

Because the widespread environmental presence of certain perfluoroalkyls, in particular PFOS, PFHxS, and PFOA, was discovered through the development of bioanalytical methodology, particularly blood-based analyses, the early biomonitoring, medical surveillance, and toxicological investigations included measurement of perfluoroalkyls in blood matrices. At the same time, it became increasingly apparent that serum or plasma concentrations of perfluoroalkyls were strongly correlated with administered dose in toxicological studies for PFOS, PFOA, and PFHxS (Andersen et al. 2008). In fact, serum PFOS concentrations were strongly correlated with cumulative administered dose under dosing conditions that did not reach saturation and steady state (Seacat et al. 2002). The rather low serum elimination rates for PFOS, PFHxS, and PFOA in humans (Olsen et al. 2007) suggested that cumulative exposures from all sources would be directly reflected on a proportional basis in their serum concentrations, as a measure related to total body burden. This was supported by the observation that volumes of distribution for those perfluoroalkyls for which pharmacokinetic parameters had been reported were consistent with predominant extracellular distribution (approximately 0.2 L/kg body weight, or 14 L for a 70 kg person). As a result, this property of the perfluoroalkyls circumvented the need for a detailed understanding of exposure sources in order to assess risk for the general population in cases where a known source of exposure was not a factor. The early MOE health risk characterizations for general population exposure to PFOS (3M 2003; Health Canada 2006) and PFOA (Butenhoff et al. 2004a; USEPA 2005) thus relied on population serum/plasma biomonitoring data as an indicator of exposure, comparing the serum perfluoroalkyls concentrations observed in the population to those serum perfluoroalkyl concentrations observed or estimated in toxicological studies at no effect or benchmark doses.

In cases where an external dose has been necessary, such as in setting risk levels for exposure to perfluoroalkyls in drinking water, the doses derived from toxicological studies have been either: (1) used in a traditional approach to set risk levels (UKDWI 2009); (2) have been adjusted with a correction for pharmacokinetic differences between the experimental model and humans (USEPA OW 2009); or (3) have been based on a serum perfluoroalkyl concentration associated with an effect level and adjusted for uncertainty followed by derivation of an external dose using a pharmacokinetic model or relationship (MDH 2009a; NCSAB 2012; Post et al. 2009; Tardiff et al. 2009). Incorporating the concept of internal dose, as represented by serum concentration of the perfluoroalkyls, significantly reduces if not obviates the pharmacokinetic component of uncertainty. However, in less than steady-state conditions, care should be taken to understand the relationship between increasing cumulative dose with repeated exposures and pharmacodynamic response. The majority of risk levels that have been developed using the concept of internal dose have eliminated the approximately half-log (approximately 3) pharmacokinetic component of interspecies uncertainty from the derivation.

The discussion above has concerned perfluoroalkyls for which the elimination rate in humans is significantly lower compared to the species used in toxicological studies. For smaller perfluoroalkyls with fewer perfluorinated carbons for which the human elimination rate approximates that for the species used in toxicological studies, pharmacokinetic adjustments to external dose may not be as necessary. For example, the serum elimination half-lives for PFBA in mice and rats were reported to range from approximately 1–16 h depending on species, dose, and sex versus approximately 40 h for male and female cynomolgus monkeys and approximately 75 h for male and female humans (Chang et al. 2008a). The State of Minnesota Department of Health (MDH) did use pharmacokinetic adjustments in their derivation of a Health Risk Level for PFBA in drinking water (MDH 2011b).

15.3.2 Default Assumptions Regarding Source Contribution for Populations with Known Sources of Exposure

Relative source contribution factors (RSCs), which attribute the proportion of total daily intake of a compound to a specific source, have historically been 10 or 20 % for drinking water by default. Although this default assumption often may be justified in circumstances where exposure sources are not well-characterized, it is notable that Maine has recognized that the availability of robust data representative of environmental background levels of exposure to PFOA in the form of the serum PFOA analyses from the United States Centers for Disease Control (CDC) National Health and Nutrition Examination Survey (NHANES) allowed for a data-driven estimation of RSC in the derivation of Maine's Maximum Exposure Guideline (MEG) for PFOA in drinking water (MEDHHS 2014). After adjusting the external dose POD based on the ratio of human clearance to clearance in species used in toxicological testing in order to derive a lower human equivalent dose (HED) and

then applying an uncertainty factor to the HED to derive a RfD, Maine calculated the estimated steady state serum PFOA for humans associated with the RfD. In so doing, Maine also derived a serum PFOA-based reference concentration (RfC). Subtracting the 95th percentile value from an NHANES data table from this serum PFOA-based RfC and dividing that value by the RfC yielded the proportion of the RfC that would be independent of general population background exposure to PFOA from all sources, which Maine rounded off to 60 %. Maine reasoned that, if a situation did occur where exposure to PFOA was present via a drinking water source in Maine, 60 % of the additional exposure at the RfD would be attributable to the drinking water source.

A similar approach could be taken in situations where biomonitoring data is available for populations with known exposures via drinking water sources as well as for the representative general population. Examples include the mid Ohio River Valley, the east metropolitan area near Saint Paul, Minnesota, and the Hochsauerland in Germany. It could be argued reasonably that the increased serum PFOA in these populations from their specific drinking water source relative to the general population serum PFOA reflects a larger proportion of intake from the drinking water source than suggested by the default assumption of 20 % that usually is applied.

15.3.3 Potential Use of Toxic Equivalency Factors or Hazard Index to Assess Risk from Exposure to Multiple Perfluoroalkyls

It has become evident from biomonitoring studies that humans potentially are exposed to multiple perfluoroalkyls and that these exposures, when represented as measured serum concentrations, are often correlated with each other (Olsen et al. 2003a). Few risk assessments have accounted for these multiple exposures, perhaps, in part, because of limited availability of hazard data for all but a few perfluoroalkyls. Borg et al. (2013) have recently published a risk assessment for the Swedish general population and an occupationally-exposed group of professional ski waxers using a hazard index (HI) approach. Their assessment, which will be described in more detail later, included 17 polyfluoroalkyl compounds by extrapolating hazard data from five of the 17 compounds. Although the hazard index (HI) approach may have value, available data for perfluoroalkyls as well as the broad assumptions used in read-across bring into question the robustness and appropriateness of this methodology.

Scialli et al. (2007) and Peters and Gonzalez (2011) have considered the possibility of combining exposure levels of perfluoroalkyls for risk assessment in a scaling system akin to the Toxic Equivalency Factors (TEFs) which have been developed for polychlorinated biphenyls, polychlorinated dibenzo-p-dioxins, and polychorinated dibenzofurans. Scialli et al. (2007) evaluated similar same-species studies performed with different perfluoroalkyls for concordance. They found discordance in endpoints measured for PFOS, PFOA, perfluorobutanesulfonate (PFBS), and perfluorodecanoic acid (PFDA). In addition, pairs of similar rat studies for PFOS,

PFOA, and PFBS, for which dose-response curves could be modeled for the concordant endpoints, did not provide consistent values within an order of magnitude for the same compound. They concluded that available data did not support the combining of perfluoroalkyls exposures in risk assessment.

Peters and Gonzalez (2011) used the analogy of the TEFs to evaluate the suitability of combining exposures of perfluoroalkyls in risk assessment. The TEF system for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and TCDD-like chemicals assigns an order of magnitude estimate for the toxicity of a compound relative to TCDD (Van den Berg et al. 2006). They noted that the conditions required to justify a TEF approach for TCDD and dioxin-like compounds are: (1) demonstration of a toxic response similar to TCDD; (2) a mechanism of toxicity that occurs via interaction with a common receptor (Ah receptor in the case of TCDD); and, (3) substantial experimental evidence showing additive effects of the agents within a factor of about 2. Peters and Gonzalez (2011) noted that data for the perfluoroalkyls likely precludes the use of TEFs, citing the following factors:

> (1) lack of conclusive evidence demonstrating that a single receptor is required to mediate the toxicities of perfluoroalkyl chemicals; (2) the potential influence of species differences in the response to PPARα ligands that would significantly limit this approach; (3) inconsistent toxicities observed with different perfluoroalkyl chemicals; and (4) a limited toxicological database for a number of perfluoroalkyls chemicals (e.g., perfluorinated sulfonamide polymers and perfluorinated sulfonamide-based phosphate fluorosurfactants).

To date, a TEF approach for perfluoroalkyls acids has not been developed and validated for use in risk assessment.

15.4 An Overview of Factors Influencing the Hazard Determination Process as They May Affect Risk Assessment

15.4.1 Toxicological Database for Perfluoroalkyls and Basic Properties Affecting Biological Interactions

The traditional first step in any human health risk assessment is the identification of potential health hazards. Since the confirmation of the widespread presence of perfluoroalkyls in biological samples from non-occupationally exposed human populations in the late 1990s, significant advancements have been made in our understanding of the biological interactions of perfluoroalkyls. Although the majority of investigations have focused on PFOS and PFOA, the range of perfluoroalkyls that have come under study has continued to increase. Moreover, the number and global distribution of investigators has increased correspondingly, resulting in rapid growth of the scientific literature. Toxicological studies with PFOS and PFOA have covered a range of endpoints, including: oncogenesis; hepatotoxicity; metabolic function; immune function; reproduction; development; hormonal changes; neurological effects. A number of mechanistic or mode-of-action studies has been published. It is not the intent of this

chapter to provide a review for all toxicological areas of investigation, which are covered in detail elsewhere in this book and in several reviews (Andersen et al. 2008; DeWitt et al. 2012; Kennedy et al. 2004; Lau et al. 2004, 2007). However, a brief overview in the context of risk assessment can be helpful. In the following discussion, it should be noted that the effects observed are in experimental systems where the doses or concentrations used typically vastly exceed those present in the environment.

By nature, perfluoroalkyls are exceptionally stable and non-reactive under physiological conditions. In fact, this is a property of these compounds that has been exploited in commercial applications (Kissa 2001). Although perfluoroalkyls, in particular, perfluorocarboxylates, resemble free fatty acids, they are not known to be metabolized or enter into the biochemical reactions that use fatty acids (Johnson et al. 1984; Kuslikis et al. 1992; Lau et al. 2007; Ophaug and Singer 1980). However, despite this lack of reactivity, perfluoroalkyls may present themselves as similar to fatty acids in their interactions with ionic binding sites, membranes and membrane transport processes, and interactions with regulators of metabolic processes. With respect to membranes, there may be effects on fluidity (Han et al. 2009; Hu et al. 2003; Starkov and Wallace 2002) and gap junction communication (Hu et al. 2002) at high enough concentrations. Some perfluoroalkyl carboxylates have been demonstrated to utilize membrane transport processes (Nakagawa et al. 2009; Weaver et al. 2010; Yang et al. 2010) and potentially affect the induction and expression of transporters.

Association of these relatively small, rigid, highly electronegative fatty acid-like molecules with ionic binding sites for proteins such as albumin and liver fatty acid binding protein has been demonstrated (Butenhoff et al. 2012d; Han et al. 2003; Jones et al. 2003; Luebker et al. 2002; Ophaug and Singer 1980). Several perfluoroalkyls have also been shown to either directly or indirectly activate nuclear receptors involved in controlling aspects of intermediary metabolism (Bjork et al. 2011; Bjork and Wallace 2009; Elcombe et al. 2010, 2012a; Haughom and Spydevold 1992; Maloney and Waxman 1999; Permadi et al. 1993; Shipley et al. 2004; Sohlenius et al. 1993; Vanden Heuvel et al. 2006; Wolf et al. 2008). Although the lack of metabolism can simplify risk assessment by eliminating the potential for interspecies differences in intermediary metabolism, the potential of perfluoroalkyls to compete for binding and transport with natural substrates and effect the activation of various metabolic processes via nuclear receptors can lead to species differences that affect extrapolation to humans (Andersen et al. 2008).

15.4.2 Species and Sex Differences in Pharmacokinetic Handling and the Role of Organic Anion Transporters

Another important example of the effect of species differences in biological interaction serves as a segue into the topic of pharmacokinetics and can be observed in reviewing the large differences in elimination kinetics that have been observed between species, and by age or sex within species, for PFOA (Hinderliter et al.

2006; Kennedy et al. 2004). While this is discussed elsewhere in this book, species, age, and sex differences in the expression of organic anion transporters most certainly are involved in the different pharmacokinetic profiles that have challenged risk assessors (Andersen et al. 2008; Han et al. 2012). The relatively rapid serum PFOA elimination of the female rat as compared to the male rat has been attributed to a sex-determined expression of renal proximal tubular transporters (Kudo et al. 2002), and data suggest that the male rat, on sexual maturation, has increased expression of a resorption transporter (Hinderliter et al. 2006), thus recapturing PFOA excreted in the urine filtrate (Loccisano et al. 2011, 2012). This resorption process has also been identified for humans as a likely explanation for the relatively long serum elimination half-life of PFOA, but the transporters involved may differ from those in the rat (Han et al. 2012; Yang et al. 2009, 2010). It is also apparent that these processes may be saturable, thus resulting in changes in kinetic parameters at higher levels of exposure (Andersen et al. 2006; Kemper 2003; Kudo et al. 2007).

When considering a series of perfluoroalkyls, for example, perfluoroalkyl sulfonates or perfluoroalkyl carboxylates, large within-species differences in elimination kinetics are observed between the smaller molecules with fewer carbons versus their larger homologs (Lau et al. 2007). Several factors may influence this, including binding affinity to serum carrier proteins and affinity for the key transport processes (Weaver et al. 2010). Branching in the carbon chain for materials manufactured by electrochemical fluorination (ECF) may also affect the elimination kinetics, as has been shown for PFOS in rats (Benskin et al. 2009; De Silva et al. 2009), PFOA in monkeys (3M Company, unpublished data), and PFBA in rats (Ehresman et al. 2007). Most risk assessments have not distinguished between branched and linear forms, and, indeed, much of the available toxicological and pharmacokinetic literature has reported on studies in which mixed linear and branched isomers were present. For PFOS and PFOA made by ECF, the linear content has been approximately 60–70 % of the total for PFOS and approximately 75–80 % for PFOA.

These isomeric differences could also affect target tissue bioavailability and response from differences in transporter affinity, membrane and intercellular binding, and receptor activation characteristics. Because isomeric forms are typically not separately analyzed and reported for pharmacokinetic samples from experimental investigations and in biomonitoring studies used in risk assessment, the impact of this variation in the kinetics of isomeric forms of perfluoroalkyls on risk assessments may not be fully appreciated. In a landmark study, Loveless et al. (2006) compared the effects of dosing mice and rats with linear, linear/branched, and highly branched ammonium PFOA. They were able to conclude from their study that "…the toxicological database developed primarily from testing linear/branched APFO is applicable to linear APFO."

Even though the elimination kinetics vary widely among the perfluoroalkyls that have been studied, although differences exist, there are general similarities in the absorption, distribution, and metabolism. As noted elsewhere, the perfluoroalkyls are resistant to non-metabolic and metabolic degradation pathways relevant to humans. In addition, for those PFAAs studied, the volumes of distribution are in a range that suggests a higher proportion of the body burden being distributed to

extracellular space (Andersen et al. 2008). The association with serum albumin and other carrier proteins in blood appears to constitute a principal distribution sink. As Jones et al. have suggested (Jones et al. 2003), this may have a protective effect at concentrations that do not physiologically impair with the function of natural substrates for these carriers.

Another factor to consider is the bioavailability of perfluoroalkyls to target tissues, such as liver. For example, when comparing the concurrent serum and liver concentrations of PFOS between rats, monkeys, and humans, rats appear to have proportionately higher liver-to-serum PFOS concentration ratios (Chang et al. 2012). Kudo et al. (2007) reported that biliary excretion of PFOA was affected by dose in rats, with lower doses resulting in uptake and distribution to membrane fractions with little biliary excretion, and higher doses resulting in proportionately higher biliary excretion. The concentration of PFBA in liver on dosing of rats with the ammonium salt has been shown to be consistent with predominant distribution in the blood serum contained in the liver (Butenhoff et al. 2012a; Chang et al. 2008a; Das et al. 2008; Foreman et al. 2009). Only two of the PFOS risk assessments that will be discussed attempted a MOE analysis based on liver concentration (3M 2003; Health Canada 2006). While it makes sense to perform MOE based on the target tissue concentration, lack of human-specific data on liver concentration for most perfluoroalkyls precludes meaningful analysis without making assumptions based on experimental studies with laboratory animals.

15.4.3 Activation of Nuclear Receptors

An important example can be taken in the species differences between rodents and humans in the pleiotropic effects resulting from activation of nuclear receptors involved with intermediary metabolism (Bjork et al. 2011; Bjork and Wallace 2009; Corton 2010; Corton et al. 2014; Elcombe et al. 2010, 2012a, 2014; Klaunig et al. 2012; Peters and Gonzalez 2011; Rosen et al. 2009). Several perfluoroalkyls have been shown to be capable of activating both human and rodent peroxisome proliferator activated receptor α (PPARα) (Bjork and Wallace 2009; Vanden Heuvel et al. 2006; Wolf et al. 2008). The activation of liver PPARα in rodent models is typically associated with a hypertrophic and hyperplastic response, while the hyperplastic component of that response appears to absent when the human forms of these receptors are activated (Elcombe et al. 2014). While the lack of the hyperplastic response in human liver has been explained at a molecular level (Gonzalez and Shah 2008), the hypertrophic response, which involves the up regulation of fatty acid metabolism, expansion of the smooth endoplasmic reticulum and, particularly in rodents, the proliferation of peroxisomes, appears to be less pronounced in humans, perhaps due to the known lesser amount of PPARα in human liver. The majority of effects of PFOA in rodents have been attributed to PPARα activation (Rosen et al. 2008b), the constitutive androstane receptor (CAR) and pregnane X receptor (PXR) also appear to be involved (Elcombe et al. 2010; Rosen et al. 2008a).

15.4.4 Enlargement of the Liver as a Critical Effect

Increases in absolute and/or relative liver weight are typical and sensitive responses observed in toxicological investigations of PFAAs in rodents. Because increased absolute or relative liver weight is often the most sensitive finding in toxicological studies with PFOA, many of the examples of risk assessment activity related to PFOA discussed later in this chapter have based the POD on increased liver weight in either rodents or monkeys. The hepatic hypertrophic response to PFAA exposure in rodents is now believed to be due, in large part, to activation of PPARα and CAR/PXR (Bijland et al. 2011; Bjork et al. 2011; Elcombe et al. 2010, 2012a; Foreman et al. 2009; Klaunig et al. 2012; Rosen et al. 2013). PFOA has also been found to increase proliferation of mitochondria in rats and monkeys (Butenhoff et al. 2002; Cai et al. 1996; Walters et al. 2009). Although the use of liver weight increase alone, without indications of overt liver pathology, may be questioned as an appropriate POD for risk assessment (Hall et al. 2012), the relative refractivity of human liver to PPARα activation as compared to the rodent should be considered as a mitigating factor (Corton et al. 2014).

15.4.5 Changes in Serum Lipids as a Critical Effect

Reductions in serum lipids have been noted in toxicological investigations with PFAAs and have been attributed, in large part, to activation of PPARα. The ability of rather specific PPARα agonists, such as the fibrate class of drugs, to reduce low density lipoprotein (LDL) cholesterol (often referred to as bad cholesterol) while maintaining or increasing high-density lipoprotein (HDL) cholesterol (often referred to as good cholesterol), has resulted in the therapeutic use of PPARα agonists. However, some PFAAs have been shown to reduce both LDL and HDL cholesterol. PFOS reduced serum concentrations of both LDL and HDL in experimental studies with monkeys (Seacat et al. 2002) and APOE*3.Leiden.CETP transgenic mice (Bijland et al. 2011), a model developed for atherosclerosis research. This effect has been used by the United States Environmental Protection Agency Office of Water (USEPA OW) and State of Minnesota Department of Health (MDH) as a critical effect in establishing drinking water PFOS concentration values (MDH 2009b; USEPA OW 2009). The hypolipidemic effects of PFOS and PFHxS with respect to LDL and HDL cholesterol can be ascribed to PPARα- and PXR-mediated changes in the formation and clearance of lipoproteins (Bijland et al. 2011). Because serum HDL is involved in reverse cholesterol transport, sustained clinically significant reductions in serum HDL could be considered as potentially adverse. It is interesting to note that, when dosed with ammonium PFOA, no significant change in serum lipids was observed in male monkeys (Butenhoff et al. 2002), decreases in total and HDL cholesterol were noted in mice and rats (Loveless et al. 2006), and decreases in non-HDL cholesterol were noted in human cancer patients involved in a phase I

clinical trial (MacPherson et al. 2011). These observations suggest that care must be taken in evaluating changes in serum lipids as a result of exposure to PFAAs as endpoints for use in risk assessment.

15.4.6 Reproduction and Development as Critical Effects

Effects on reproduction and development have been considered as critical effects in risk assessments. Several perfluoroalkyls have been studied for their potential to disturb reproduction and development (Lau et al. 2004). Overt effects on reproductive function in male and female rats generally have not been observed. Increased early full-liter resorption is one effect noted in female rodents dosed with PFOA during gestation (Lau et al. 2006); however, this may be more the result of an effect on the maintenance of pregnancy in the rodent than an embryotoxic effect (Lau et al. 2005). Because there are significant differences between humans and rodents in the maintenance of pregnancy, it is important to develop a better understanding of this observation.

Since the first observation of perinatal mortality in a multi-generation study of PFOS in rats (Luebker et al. 2005a), there have been numerous developmental studies undertaken to increase understanding of the potential developmental toxicity of perfluoroalkyls (Lau et al. 2007). The prenatal developmental effects of these compounds largely are unremarkable (Case et al. 2001; Lau et al. 2004). Postnatal mortality and developmental delays have been the major focus of research.

A principal role for PPARα in mediating the developmental effects of PFOA in mice has been discovered (Abbott et al. 2007), and the human relevance of these effects in mice requires additional insight and discussion. In the case of PFOS, postnatal developmental effects appear to be either not mediated by PPARα or at least largely independent of PPARα (Abbott et al. 2009), and reduced neonatal survival did not appear to be the result of reductions in lipids, glucose utilization, or thyroid hormones (Luebker et al. 2005b). Potential interference with the functional properties of pulmonary surfactant at birth has been and continues to be a leading hypothesis for the basis of PFOS postnatal mortality (Grasty et al. 2005).

15.4.7 Changes in Serum Concentrations of Thyroid Hormones as a Critical Effect

PFOS-induced hypothyroxinemia in rats appears to be the result of increased displacement from serum carrier proteins and increased uptake and elimination by the liver and kidney as opposed to a direct effect on the hypothalamic-pituitary-thyroid axis (Chang et al. 2007, 2008b; Lau et al. 2003; Yu et al. 2009). Again, differences between rats and humans in the specificity of serum carrier proteins for thyroxine,

with resulting differences in plasma half-life of the hormones, suggest that humans should be less sensitive to this displacement binding effect of PFOS (Capen 1997; Curran and DeGroot 1991; Mendel et al. 1986), a widely-recognized factor in thyroid research that risk assessors should consider.

Changes in serum concentrations of hormones related to thyroid function, namely decreased triiodothyronine (T3) and increased thyrotropin (TSH), observed in a 6-month capsule dosing study in monkeys (Seacat et al. 2002) have been considered as co-critical endpoints by USEPA OW and MDH in establishing risk levels for PFOS in drinking water. The small magnitude of the changes relative to the natural variability of these endpoints and the lack of corresponding histological changes in the thyroid gland led the authors of that study to conclude that any actual change in serum thyroid-related hormones likely was due to non-thyroidal illness syndrome, and, as such, secondary to treatment-related stress.

15.4.8 Genotoxicity and Oncogenicity as Critical Endpoints

With respect to cancer risk, a combination of genotoxicity studies, chronic bioassays, and mechanistic studies is presently available for PFOS and PFOA. Perfluoroalkyls do not possess the chemical/physical properties typically associated with directly genotoxic agents and, in general, have not been found to be genotoxic in the various screening assays used to detect point mutations and chromosomal aberrations (Butenhoff et al. 2014; Lau et al. 2007). At the present time, three Sprague Dawley rat dietary toxicological studies are available that inform us about the oncogenic potential of PFOS and PFOA, two for ammonium PFOA (Biegel et al. 2001; Butenhoff et al. 2012c) and one for PFOS (Butenhoff et al. 2012b). None of these studies has shown a statistically significant increase in any type of malignant tumor. An increase in benign liver tumors was observed in one PFOA study (Biegel et al. 2001) and with PFOS. Based on several mechanistic studies, the origin of liver tumors from exposure of rats to PFOA and PFOS is currently believed to be the result of a combined activation of the xenosensor nuclear receptors, PPARα, CAR, and PXR (Elcombe et al. 2010, 2012a). As discussed above, recent advances in our understanding of differences between rodents and humans with respect to the proliferative response to activation of these receptors allows valuable perspective for human risk assessment in that human PPARα and CAR/PXR support the hepatic hypertrophic response but not the hepatic hyperplastic response, which is necessary for tumor formation (Corton et al. 2014; Elcombe et al. 2014). Pancreatic acinar cell tumors were also increased in one PFOA study (Biegel et al. 2001), and testicular Leydig cell tumors were increased in both PFOA studies. Insights have been gained as to the etiology of these two additional tumor types (Klaunig et al. 2012). It has been reported in secondary sources that female rat mammary tumors were increased by PFOA; however, this was not the conclusion of the study authors, and the lack of an increase in mammary tumors has been confirmed

after a complete audit of the study followed by a pathology working group review (Hardisty et al. 2010). PFOS increased benign thyroid follicular cell tumors (adenomas) only in males for whom dosing was suspended after 1 year and not for males dosed for 2 years. In a follow-up mechanistic studies, PFOS did not increase the S-phase labeling index or decrease apoptotic index of male Sprague Dawley rat thyroid follicular epithelial cells, suggesting that the original observation may have been a chance finding (Elcombe et al. 2012a, b).

To date, risk assessments have treated PFOS and PFOA as non-genotoxic, threshold "carcinogens". Butenhoff et al. (2004a) and Tardiff et al. (2009) used increased incidence of benign testicular Leydig cell adenoma in Sprague Dawley rats as a critical effect in performing MOE analysis and developing RfD values, respectively. No authoritative body has treated PFOS or PFOA as non-threshold carcinogens in risk assessment at this time.

15.4.9 Immunotoxicity

A number of rodent immunotoxicology studies have been published on PFOA and PFOS (DeWitt et al. 2009, 2012). In general, these studies have provided evidence of effects on inflammatory responses, production of proteins involved in immune responses, lymphoid organ weights, and antibody synthesis. Reported findings have been somewhat inconsistent, and have varied with dose, strain, and dosing methodology. Although observed responses have been shown to be driven, in part, by PPARα, the need to study the role of PPARα-independent processes and other factors that may affect the nature of observed responses has become clear (DeWitt et al. 2009).

15.4.10 Neurotoxicity

There have been a number of studies that have incorporated neurotoxicological endpoints (Mariussen 2012). As noted by Mariussen (2012) in a recent review of the neurotoxicological effects of PFAAs:

> Most of the studies that have showed neurobehavioral effects are on prenatally or neonatally animals exposed to doses that have caused other serious effects, such as increased mortality reduced growth and maturation, and birth defects. These effects may lead to the assumption that other toxicological endpoints are of higher importance. The observed neurobehavioral effects also appear subtle and inconclusive.

In general, neurological effects have not been singled out as PODs for risk assessment.

15.4.11 Epidemiological Investigations

The epidemiology of perfluoroalkyls is covered elsewhere in this book. The intention of this section is to comment on the use of epidemiological data in the risk assessment of perfluoroalkyls. To date, risk assessments of perfluoroalkyls have not been based primarily on the results of epidemiological studies.

Identification of organofluorine in human blood, the suggestion of an industrial source, and early results focused on perfluorinated carboxylates as a principal component of blood-borne organofluorine led to early reports on the health of workers at 3M Company engaged in the manufacture of fluorochemicals (Ubel et al. 1980). Until the mid 1990s, 3M Company's medical surveillance of its fluorochemical production workers included periodic measurement of non-specific total organofluorine at three fluorochemical manufacturing plant sites. Beginning in the mid 1990s, medical surveillance at these sites included serum measurements of PFOS and PFOA by high-performance liquid chromatography followed by mass spectrometry (HPLC-MS/MS) methodology. Similarly, such analytical advancements resulted in the speciation of PFOA at the DuPont Company Washington Works plant site in West Virginia, where the ammonium salt of PFOA (C8 or APFO) was used as an emulsifier in the polymerization of tetrafluoroethylene (TFE) to make polytetrafluoroethylene (PTFE) (Woskie et al. 2012). Most of the published articles on occupational fluorochemical biomonitoring (see Chap. 4) and occupational epidemiology (see Chap. 13) have related to the 3M Company and DuPont Company workforces. Although these occupational studies represent the highest known exposures to PFOS and PFOA, the use of these occupational data is rare for the purpose of human health risk assessment for non-occupationally exposed populations. The occupational studies would add valuable context to human health risk assessment.

Similarly, non-occupational epidemiological studies have not been used in health risk assessment of perfluoroalkyls. This is because many of the epidemiological studies of the general population or populations with known local sources of exposure have been cross-sectional in nature, therefore incapable of drawing conclusions with regard to causality. The distribution of perfluoroalkyls to serum carrier proteins and the slow elimination from serum of PFOS and PFOA in humans, likely due to renal proximal tubular resorption, can confound interpretation of cross-sectional epidemiological investigations that make associations between serum/plasma PFOS or PFOA concentrations and various serum clinical measures. Uncontrolled confounding factors that may affect the concentrations of PFOS and PFOA in serum through changes in processes that affect elimination or retention of these compounds, *e.g.*, filtration rate, plasma volume, blood loss, may lead to non-causal associations, especially at low perfluoroalkyls concentrations. An example is the cross-sectional association of serum PFOS and PFOA with subfecundity (as measured by time to pregnancy) in the Danish National Birth Cohort, first reported by Fei et al. (2009). Stratification by parity, taking into account nulliparous births, weakened some of the associations (Fei et al. 2012). Similarly, Whitworth et al.

(2012) found higher odds ratios for subfecundity in the fourth quartile of serum PFOS and PFOA concentrations in parous women of the Norwegian Mother and Child (MoBa) cohort associated with both PFOS (2.1 (95 % CI 1.2–3.8)) and PFOA (2.1 (95 % CI 1.0–4.0)) than among primiparous women (0.7 (95 % CI 0.4–1.3) and 0.5 (95 % CI 0.2–1.2), respectively). Transfer of body burden in prior pregnancies and re-equilibration with the environment in parous women were speculated to contribute to non-causal associations of serum PFOS and PFOA with subfecundity, as no associations were observed in primiparous mothers.

Integration of occupational and non-occupational epidemiological investigations with careful consideration of clinical, mechanistic, and pharmacokinetic factors is necessary. In the authors' opinion, much needs to be done to achieve a framework in which to integrate the toxicological, pharmacological, and epidemiological observations in the context of human health risk assessment for exposure to perfluoroalkyls.

15.4.12 Summary

In summary, there is an expanding understanding of the molecular, biological, metabolic, and physiological bases of responses observed in laboratory toxicological studies. Between and within species differences in the pharmacokinetic and pharmacodynamic properties of perfluoroalkyls have been investigated actively and are important factors to consider and incorporate into the health risk assessment process. Increased liver weight has been used frequently as a critical effect in developing acceptable levels of exposure for risk assessment, yet this is not necessarily reflective of an adverse outcome and may be overly conservative as an endpoint. It is important to incorporate an understanding of epidemiological investigations to gain perspective on the toxicological data; however, due to potential confounding with factors that affect clearance of perfluoroalkyls, care must be taken in interpretation of epidemiological observations, particularly from cross-sectional studies, that associate blood concentrations of perfluoroalkyls with health outcomes. Translating understanding from toxicological systems into a human context will improve our collective ability to understand potential human-health risk from environmental levels of exposures to these agents.

15.5 Perfluoroalkyl Risk Assessment for Non-occupationally Exposed Populations

Although the health status of occupational cohorts exposed to perfluoroalkyls has continued to be followed and updated (Raleigh et al. 2014; Steenland and Woskie 2012), increasing attention has been drawn to potential general population health

risks from background environmental levels of exposure to perfluoroalkyls as well as populations with potential exposure from point sources of exposure from industrial activity. These non-occupational epidemiological investigations are covered in detail in Chap. 13. Following the initial identification of PFOS as the major component of organofluorine in the samples from volunteers non-occupationally exposed to fluorochemicals as reported in 2001 (Hansen et al. 2001), the Organization for Economic Cooperation and Development (OECD) released a hazard profile of PFOS and its salts in which it was recommended that exposure information and risk assessments may be warranted based on widespread occurrence in the environment (OECD 2002).

In the same year, USEPA issued a significant new use rule (SNUR) that restricted the manufacture, use, sale, and importation of PFOS and related precursor materials as well as releasing a revised draft hazard assessment of PFOA and its salts (USEPA 2002). Several actions followed on the OECD hazard profile for PFOS. The UK concluded that PFOS met criteria as persistent, bioaccumulative, and toxic (PBT) (Brooke et al. 2004). The Swedish Chemical Inspectorate recommended a ban under the Stockholm Convention in 2005 (http://www.pops.int/documents/meetings/poprc/meeting_docs/en/POPRC1-INF9-b.pdf). In 2008, Canada banned the manufacture, use, sale, offering for sale or importation of PFOS and its salts as well as compounds containing the perfluorooctanesulfonamide moiety except in certain proscribed exceptions (Canadian Government Department of the Environment 2008). In 2009, PFOS and its precursor compound, perfluorooctanesulfonyl fluoride (POSF) were added to Annex B of the Stockholm Convention (http://chm.pops.int/Implementation/NewPOPs/TheNewPOPs/tabid/672/Default.aspx). This new attention focused on the environmental presence of perfluoroalkyls resulted in a surge of risk assessment activity focused on non-occupationally exposed populations, including populations with potential exposure to perfluoroalkyls via commercial and agricultural sources. This activity is the focus of the remainder of this chapter.

15.5.1 Margin of Exposure Health Risk Characterizations Based on Comparison of Serum or Liver Concentrations Associated with Effect to Those Observed in Biomonitoring Studies

15.5.1.1 Margin of Exposure Health Risk Characterization for PFOS (3M 2003)

In August of 2003, 3M Company submitted an "Environmental and Health Assessment of Perfluorooctane Sulfonic Acid and Its Salts" to the USEPA (3M 2003) that included a MOE characterization of risk. In 2003, the database available for human health risk characterization included a large number of toxicological studies as well as medical surveillance and epidemiological investigations of

exposed workers. The toxicological studies included: subchronic studies in rodents and monkeys; a two-year dietary chronic toxicity and cancer bioassay in rats; an extensive array of genotoxicological tests; reproduction/developmental studies in rats and mice, including a multigeneration reproduction study in rats; fetal developmental studies in rats and rabbits; pharmacokinetic data; and, various investigations into the mode of action of PFOS. In addition, 3M had conducted medical surveillance of fluorochemical production workers for over 25 years. Medical surveillance and epidemiological investigations in workers potentially exposed to PFOS included: medical surveillance of fluorochemical production workers at 3M plants in Decatur, Alabama and Antwerp, Belgium; a mortality study of the Decatur plant workers; a hypothesis-generating study of episodes of medical care based on medical insurance claims from Decatur plant employees. At the time of the MOE analysis, there were no epidemiological studies of the general (non-occupational) population (see Chap. 13). However, based on the biomonitoring data available for the general population, it was reasonable to assume that 3M fluorochemical production workers had the highest level of human exposure to PFOS at the time of the MOE assessment (see Chap. 4).

A unique feature of the MOE analysis was the use of serum/plasma and liver concentrations of PFOS as a measure of internal dose or internal exposure. The use of serum or liver PFOS concentrations as a measure related to integrated exposure to PFOS for risk characterization offered several distinct advantages. Foremost of these was overcoming the uncertainty involved in attempting quantitative estimates of external PFOS exposure from a variety of sources, routes of exposure, and exposure pathways that were not well-characterized at the time. Another important advantage was the ability to compare NOAELs or calculated BMDs, both expressed as the serum or liver PFOS concentration, between studies and species, thus reducing uncertainty in interspecies extrapolation. In the MOE analysis, it was possible to compare human exposure to PFOS as represented by serum or liver PFOS concentration to the serum and liver PFOS concentrations associated with NOAEL or BMD values from toxicological studies. Serum PFOS concentration was used as an integrated measure of exposure over time and related to the probability of toxic response, regardless of source or pathway of exposure. The overall potential variability in using serum PFOS concentrations in risk analysis is likely to be much less than attempting to estimate external exposures to humans from various sources. The MOE analysis was facilitated by the availability of serum/plasma PFOS concentration data in both fluorochemical production workers and the United States general population as well as serum/plasma PFOS measurements made during the course of toxicological investigations. Reported serum PFOS levels in fluorochemical production workers averaged 1,000–2,000 ng/mL, and the highest measured serum PFOS concentration in a worker approached 13,000 ng/mL (Olsen et al. 1999).

3M scientists, in collaboration with others, were able to survey PFOS serum concentrations in the United States general population in four separate studies. (These studies also provided PFOA concentration data used in a similar MOE health risk characterization (Butenhoff et al. 2004a), which is discussed below). Three of

Table 15.1 Geometric mean serum PFOS concentration (ng/mL), range, and upper bound estimate of 95 % tolerance limit in biomonitoring studies of children, adults, and elderly from the general United States population that were used for the 3M (2003) margin-of-exposure health risk characterization

Population (study)	N	Year(s) sampled	Geometric mean (95 % CI)	Range	Upper bound of 95 % tolerance limit estimate
Children (Olsen et al. 2004a)	598	1994–1995	38 (36–39)	7–515	97
Adults (Olsen et al. 2003a)	645	2001	35 (33–37)	<5[a]–1,645	100
Elderly (Olsen et al. 2004b)	238	2001	31 (29–33)	<3[a]–175	104

Tabulated data are adapted from Table 4.4 of 3M (2003)
[a]Analytical method limit of quantitation

these studies provided reasonably good estimates of serum PFOS concentration in the United States across age groups, including: (1) children (N = 598) involved in a Group A Streptococcal clinical trial across 23 states (Olsen et al. 2004a); (2) adult American Red Cross blood donors (N = 645) from six regional collection centers (Olsen et al. 2003a); and, (3) dementia-free elderly (N = 238) from a prospective study of cognitive function (Olsen et al. 2004b). These sample data revealed that approximately 95 % of individual serum PFOS concentrations were less than 100 ng/mL, and the average serum PFOS concentrations in these cohorts ranged between 30 and 40 ng/mL (Table 15.1). The fourth included study serum and/or liver samples from organ donors (N = 31) of which 23 serum and liver samples were paired (Olsen et al. 2003b). The paired organ donor liver and serum PFOS concentration data were valuable in providing insight into the ratio of liver-to-serum PFOS concentration, which allowed for extrapolation to estimate liver concentration in the biomonitoring studies for which only serum PFOS values were available.

Critical effect dose levels were based on either the highest study dose at which the critical effect was not observed (no observed adverse effect level, or NOAEL) or on the modeled benchmark dose (BMD) for the critical effect. The serum and liver PFOS concentrations associated with these dose levels were obtained by direct measurement or through estimation based on pharmacokinetic data and principals. The term benchmark internal concentration (BMIC) was used to represent a serum PFOS concentration corresponding to a BMD value based on administered dose.

The endpoints used for the serum PFOS MOE analysis are presented in Table 15.2 along with the serum PFOS concentration used as the POD for the MOE. For serum comparisons, the lower 95 % CL of the BMIC for a 5 % response ($LBMIC_5$) in reduced post-natal rat pup weight gain during lactation was chosen for the POD. This $LBMIC_5$ value was 31,000 ng/mL. While reduced pup weight gain was the most sensitive endpoint, comparisons were also made for other endpoints. For liver response, the male rat NOAEL for liver effects yielded a serum PFOS-based POD of 44,000 ng/mL PFOS. For liver tumors (benign adenoma) in male and female rats,

Table 15.2 Margins of exposure (MOE) from 3M (2003) health risk characterization based on human serum PFOS concentration in the United States general population

Critical endpoint	POD[a] (ng PFOS/mL serum)	MOE at estimated geometric mean[b] (40 ng PFOS/mL serum)	MOE at estimated upper bound[c] (100 ng PFOS/mL serum)
Pup weight gain	31,000	775	310
Liver effects, rats	44,000	1,100	440
Liver tumors, rats	62,000	1,550	620

Tabulated data are adapted from Table ES-1 of 3M (2003)
[a]Point of departure
[b]Value estimate from Table 15.1
[c]Estimated upper 95 % confidence limit at 95 % tolerance limit from Table 15.1

Table 15.3 Margins of exposure (MOE) from 3M (2003) health risk analysis based on estimated human liver PFOS concentration in the United States general population

Critical endpoint	POD[a] (ng PFOS/g liver)	MOE at estimated geometric mean (68 ng PFOS/g liver)[b]	MOE at estimated upper bound[c] (170 ng PFOS/g liver)[b, c]
Liver effects, monkeys	59,000	868	341

Tabulated data are adapted from Table ES-1 of 3M 2002
[a]Point of departure
[b]Conservative human liver PFOS concentration estimated from serum PFOS concentration in Table 15.1, assuming a liver-to-serum ratio of 1.7:1, which was the upper 95 % CL of liver-to-serum PFOS concentration ratios among 23 paired liver and serum samples from organ donors as reported by Olsen et al. (2003b)
[c]Estimated upper 95 % confidence limit at 95 % tolerance limit from Table 15.1

the $LBMIC_{10}$ (10 % response rate) was associated with a serum PFOS value of 62,000 ng/mL. Thus, the value for pup weight gain in lactation was considered to be protective of liver effects as well.

The serum-based MOE values used estimates of general population serum PFOS at the geometric mean and upper bound 95 % tolerance limit. Based on the data from Table 15.1, 40 and 100 ng PFOS/mL serum were chosen to represent the geometric mean and upper bound 95 % tolerance limit, respectively. MOE values were obtained by dividing the serum PFOS-based POD for an effect by these estimated serum concentrations for the general population (Table 15.2). At the geometric mean for the general population, MOE values ranged from 775 based on reduced rat pup weight gain to 1,550 based on benign liver tumors in rats, and, at the upper bound, MOEs ranged from 310 to 620, respectively.

In estimating the MOE based on liver PFOS concentration (Table 15.3), a POD of 59,000 ng PFOS/g liver was chosen. This liver concentration value corresponded to the study NOAEL for male cynomolgus monkeys in a 6-month oral toxicity study of PFOS (Seacat et al. 2002). Liver concentrations for the general population were conservatively estimated by multiplying the geometric mean and upper bound estimates for serum PFOS by a factor of 1.7, which was the maximum value of the liver-to-serum concentration ratio obtained from the 23 paired organ donor liver and

serum samples (Olsen et al. 2003b). MOE values of 868 and 341 were obtained for the geometric mean and upper bound estimated general population liver PFOS.

15.5.1.2 MOE for United States General Population Exposure to PFOA (Butenhoff et al. 2004a)

Butenhoff et al. (2004a) published a MOE risk characterization for United States general population exposure to PFOA. Measured general population serum PFOA concentrations were obtained from the biomonitoring studies that were used for the PFOS MOE risk characterization discussed previously (3M 2003). Serum concentrations of PFOA averaged approximately 5 ng PFOA/mL with an upper bound of the 95th percentile estimate approximating 11–14 ng PFOA/mL (Table 15.4). The MOE estimates for several endpoints were based on an upper bound 95 % tolerance limit estimate for serum PFOA of 14 ng PFOA/mL serum (Tables 15.4 and 15.5). Dose-response data from toxicological studies were used to estimate serum PFOA concentrations associated with a 10 % benchmark response (BMR) for several key endpoints (Table 15.5). The lower 95 % confidence limits of these benchmark internal concentrations ($LBMIC_{10}$) were then used as a basis for comparison with general population serum PFOA concentrations.

At the time of the assessment, the toxicological database included developmental toxicity, reproductive toxicity, immunotoxicity, genotoxicity, carcinogenicity, pharmacokinetic, and various mode-of-action studies (Kennedy et al. 2004). A review of the toxicological database for PFOA was conducted in order to select studies that covered a variety of endpoints, were sufficiently robust, and provided good dose-response data. The endpoints and associated studies chosen are presented in Table 15.5. Sensitive indicators of response that were chosen for the determination or estimation of $LBMIC_{10}$ were post-natal developmental effects in rats, liver-weight increase in monkeys (not considered by the authors to be an adverse effect in and of itself), body-weight change in monkeys, and increased incidence of benign testicular Leydig cell adenoma in rats. Serum PFOA concentrations for the $LBMIC_{10}$ were based on: (1) measured serum PFOA concentration at presumed steady state; (2) pharmacokinetic estimates of steady-state; or, (3) 24-h mean serum PFOA concentration (24-h area under the curve divided by 24 h). The POD $LBMIC_{10}$ values

Table 15.4 Upper bound estimate of 95 % tolerance limit for serum perfluorooctanoate (PFOA) in biomonitoring studies of children, adults, and elderly from the general United States population that were used for the Butenhoff et al. (2004a) margin-of-exposure health risk characterization

Population (study)	N	Year(s) sampled	Upper bound of 95 % tolerance limit estimate (ng PFOA/mL serum)
Children (Olsen et al. 2004a)	598	1994–1995	11
Adults (Olsen et al. 2003a)	645	2001	14
Elderly (Olsen et al. 2004b)	238	2001	11

Tabulated data are adapted from Table 1 of Butenhoff et al. (2004a)

Table 15.5 Margins of exposure (MOE) from the Butenhoff et al. (2004a) health risk analysis based on estimated upper bound 95 % tolerance limit for human serum perfluorooctanoate (PFOA) concentration (14 ng PFOA/mL serum) in the United States general population

Critical effect	POD (ng PFOA/mL serum)[a]	Margin of exposure[a]
Post-natal effects, rats	29,000[b]	2,100
Liver weight: brain weight ratio[c], monkeys	23,000	1,600
Body-weight change, monkeys	60,000	4,300
Benign leydig cell tumors, rats	125,000	8,900

Tabulated data are adapted from Table 10 of Butenhoff et al. (2004a)

[a]The margin of exposure was calculated by dividing the lower 95 % CL estimate of the benchmark internal concentration (serum concentration associated with the benchmark dose) for a 10 % response ($LBMIC_{10}$ (ng/mL)) by the general population serum PFOA concentration representing the upper 95 % confidence limit of the estimate of the 95th percentile general population serum PFOA (14 ng/mL)

[b]The serum [PFOA] in post-weaning rat pups were estimated conservatively based on adult female rat AUC at the $LBMD_{10}$ value of 22 mg/kg/day for post-natal effects using the relationship of AUC to administered oral dose.

[c]The authors noted that liver-weight increase was not necessary reflective of an adverse effect, as this is a normal adaptive response when other clinical and histological manifestations of liver toxicity are absent. This endpoint was used by the authors as a sensitive indication of biological response in a non-human primate

ranged from 23,000 ng PFOA/mL serum for liver-weight-to-brain-weight ratio increase in monkeys to 125,000 ng PFOA/mL serum for Leydig cell adenoma in rats (Table 15.5).

The MOE values shown in Table 15.5 were estimated by dividing the $LBMIC_{10}$-based POD by the upper bound 95 % tolerance limit estimate of the general population serum PFOA concentration (14 ng/mL). These MOE values ranged from 1,600 for increased liver-weight-to-brain-weight ratio in monkeys to 8,900 for Leydig cell adenoma in rats. The authors noted that MOEs based on the geometric mean serum PFOA (approximately 5 ng PFOA/mL serum) would be approximately three times higher.

15.5.1.3 United States Environmental Protection Agency Preliminary PFOA Health Risk Characterization (2003) and Draft PFOA Risk Assessment (2005)

In 2003, a preliminary MOE risk assessment was released by USEPA (2003), which presented a range of MOE values for developmental toxicity based on comparisons of human serum concentrations of PFOA and the serum concentrations in samples taken from rats involved in a two-generation reproduction and development study that was submitted to USEPA and later published by Butenhoff et al. (2004b). For

this preliminary assessment, USEPA used the adult American Red Cross blood donor and children studies published by Olsen et al. (2003a, 2004a) that were also used in the previously discussed MOE assessments for PFOS (3M 2003) and PFOA (Butenhoff et al. 2004a). USEPA used the mean and geometric mean serum PFOA concentrations for both sexes combined from the American Red Cross blood donor and children biomonitoring studies for MOEs calculated for women of childbearing age and children, respectively. Because there were no effects on reproductive parameters in the parental (F0) and F1 generation in rats, endpoints related to development were considered relevant for the preliminary risk assessment. These included significant mean body weight reductions with respect to controls during the lactation period, with the additional and likely related observation of post-weaning mortality and delayed sexual maturation. The study LOAEL for developmental effects was given as 10 mg/kg/day with a study NOAEL of 3 mg/kg/day.

Mean serum PFOA concentrations of the parental male and female rats from the two-generation reproduction and development study at 10 mg/kg/day dose group (51,100 ng/mL and 370 ng/mL, respectively) were used as POD values for calculating the MOEs. For women of childbearing age, the ranges of MOEs based on arithmetic mean and geometric mean serum PFOA were 66–9,125 and 80–11,109, respectively. For children, the ranges of MOEs based on the arithmetic and geometric mean serum PFOA were 66–9,125 and 75–10,429, respectively. However, the USEPA cautioned that the MOE values in their preliminary assessment should not be considered to represent the range of possible MOE values for general populations because of uncertainties resulting from the lack of appropriate pharmacokinetic data in weanling rats and their relationship to human serum levels of PFOA:

> It is important to note that MOEs that were calculated from the serum levels in the F0 female and male rats provide a means to bracket the low and high ends of experimental animal exposures. This is an unusual situation in that MOE estimates, which typically represent point estimates, are described here as a range of potential values due to uncertainties in the rat serum data. This situation arises from the fact that the available data do not allow selection of a particular departure point for the MOE calculations. It is likely that MOEs calculated using the F0 female rat serum level are lower than what would be anticipated in the human population, and it is likely that MOEs calculated using the F0 male rat serum level are higher than what would be anticipated in the human population. As uncertainty around the rat serum values decreases the end brackets are likely to shift towards the middle of the current range. Therefore, MOE values presented in this document should not be interpreted as representing the range of possible MOEs in the US population. It is likely that when more extensive rat kinetic data are available, the resultant, refined estimated range of MOEs will constitute a narrower subset of the range presented here. Interpretation of the significance of the MOEs for ascertaining potential levels of concern will necessitate a better understanding of the appropriate dose metric in rats, and the relationship of the dose metric to the human serum levels.

The USEPA followed with a draft risk assessment in 2005 (USEPA 2005). The 2005 draft risk assessment also derived MOE values but has not been finalized to date.

Table 15.6 Margins of exposure based on serum PFOS concentrations at the mean and 95th percentile for Canadian adults and United States children from the Health Canada (2006) screening health risk characterization

Critical effect(s), species	Point of departure (ng/mL serum)	Margin of exposure			
		Adults		Children	
		Mean (28 ng/mL)	95th percentile (63.1 ng/mL)	Mean (37.5 ng/mL)	95th percentile (97 ng/mL)
Histological changes in liver, ♂ and ♀ rats[a]	13,900	496	220	371	143
Multiple effects, monkeys[b]	14,500	578	230	387	149

Tabulated data are adapted from Health Canada (2006)
[a]Based on data from a 104-week dietary study of potassium PFOS in Sprague Dawley rats (Butenhoff et al. 2012b; Seacat et al. 2002)
[b]Thymic atrophy (♀), reduced serum high density lipoprotein (♂), cholesterol (♂), triiodothyronine (♂) and total bilirubin (♂). Based on a 6-month capsule dosing study of potassium PFOS in cynomolgus monkeys (Seacat et al. 2002)

15.5.1.4 Health Canada Screening Level Health Assessments for PFOS (Health Canada 2006)

In January, 2006, Health Canada released a "State of the Science Report for a Screening Health Assessment" of PFOS and its salts and precursors containing the perfluorooctanesulfonyl or perfluorooctanoate moiety (Health Canada 2006). In this screening MOE assessment, mean and 95th percentile serum PFOS values from a pilot biomonitoring study of Canadian adults (Kubwabo et al. 2004) and United States children (Olsen et al. 2004a) were used to represent the Canadian population (Table 15.6). Mean and 95th percentile serum PFOS values in ng/mL were 28 and 63.1 for adults, respectively, and 37.5 and 97 for children, respectively. In addition, the mean liver PFOS concentrations in a group of 30 organ donors from the United States (Olsen et al. 2003b) (18.8 ng PFOS/g liver) was used to estimate MOEs based on liver concentration data associated with the critical effects.

Two toxicological studies were chosen to assign critical endpoints and obtain associated serum and liver PFOS concentration data for use as PODs. These were a 104-week dietary study of potassium PFOS in Sprague Dawley rats (Butenhoff et al. 2012b; Seacat et al. 2003) and a 6-month capsule dosing study of potassium PFOS in cynomolgus monkeys (Seacat et al. 2002). Microscopic changes in the livers of male and female rats were chosen as the critical endpoint from the chronic dietary study, and combined average male and female serum and liver PFOS concentrations associated with this effect were used as the POD values for serum (13,900 ng PFOS/mL serum) and liver (40,800 ng PFOS/g liver). From the monkey study, thymic atrophy in females, and, in males, reductions in serum high density lipoprotein cholesterol, total cholesterol, triiodothyronine, and total bilirubin were considered as critical effects. Serum and liver concentrations associated with these effects were 14,500 ng/mL and 19,800 ng/g, respectively. Margins of exposure

based on serum PFOS are presented in Table 15.6 and varied from 371 to 578 at the mean values for serum PFOS for Canadian adults and United States children and from 143 to 230 at the 95th percentile serum PFOS values for these two groups.

The MOE values obtained based on liver PFOS concentration were 2,170 and 1,053 when comparing mean liver PFOS from the 30 organ donor samples to the liver PFOS concentration associated with the critical effects in the rat chronic dietary study and the monkey six-month capsule dosing study, respectively. In a footnote to the table displaying the MOE values, Health Canada noted that the MOEs based on the highest liver PFOS among the 30 donor samples (57 ng/g) would be 716 and 347 based on POD values from the rat and monkey studies, respectively.

In considering potential risk based on the MOE values obtained, Health Canada concluded:

> These margins are considered adequate to address elements of uncertainty, including intraspecies variation, interspecies variation and biological adversity or severity of the effects considered critical here. These margins will also be protective for the increased incidence of tumours observed in the chronic study of PFOS in rats, since the tumours were observed only at doses of PFOS that were higher than those that induced non-neoplastic effects and since the weight of evidence indicates that PFOS (and its precursors) are not genotoxic. While the margins for blood levels in children are somewhat less (approximately 145 for the 95th-percentile values), more appropriate margins for comparison with the effect level from long-term studies are those for adults (approximately 225 for the 95th-percentile values), since they are exposed for a greater portion of their life span. In addition, the critical lowest-observed-effect levels selected for development of these margins of exposure are very conservative, being about an order of magnitude less than values in other studies (i.e., for effects observed in reproductive studies with rats).

15.5.1.5 Health Canada Screening Level Health Assessment for PFOA (Health Canada 2012)

The screening assessment for PFOS was followed in 2012 by a screening level MOE assessment for exposure of Canadians to PFOA (Table 15.7). This assessment was also based on a MOE comparison of serum PFOA concentrations associated with toxicological studies with serum or plasma PFOA concentrations observed in adults, infants, and children. Adult geometric mean and 95th percentile plasma PFOA was based on results of the Canadian Health Measures Survey Cycle 1 (2007–2009) (Health Canada 2010). Geometric mean and maximum PFOA values for Inuit children in Canada aged 12–54 months were from a contaminant nutrient interaction study (Turgeon-O’Brien et al. 2010). Median and 95th percentile serum PFOA values for 6-month-old infants in Munich, Germany from samples collected between the years 2007–2009 were also used.

Serum PFOA concentrations associated with lowest observed effect levels for several critical endpoints were used as the reference POD for the MOE analyses. These are summarized in Table 15.7, and include increased liver weight in mice, changes in serum lipids in rats, increased liver weight in pregnant mice as well as developmental effects in their offspring, and increased liver weight in monkeys. These serum PFOA-based PODs varied from 13,000 to 77,000 ng/mL. Resulting

Table 15.7 Margins of exposure based on either geometric mean (GM), 95th percentile (95th %tile), maximum (MAX), or median (MED) serum PFOA concentrations for Canadian adults, Inuit children (12-months old), and German infants (6 months old) from the Health Canada (2012) screening health risk characterization

		Margin of exposure					
		Canadian adults (20–79 years old)		Inuit children (12–54 months old)		German infants (6-months old)	
Critical effect(s) sex and species	Point of departure (ng/mL)	GM 2.52	95th %-tile 5.50	GM 1.62	MAX 11	MED 6.9	95th %-tile 19.5
↑ Liver weight, ♂ mice[a]	13,000	5,159	2,364	8,024	1,182	1,884	667
Serum lipids, ♂ rats[a]	20,000	7,937	3,636	12,346	1,818	2,899	1,026
↑ Liver weight, ♀ mice, and development, ♂ mice[b]	21,900	8,690	3,982	13,519	1,991	3,174	1,123
↑ Liver weight, ♂ monkeys[c]	77,000	30,556	14,000	47,531	7,000	11,159	3,949

Tabulated data are adapted from Table 8 Health Canada (2012)
All PFOA concentrations are in ng/mL
[a]Based on the 14-day gavage study of Loveless et al. (2006)
[b]Increased liver weight (♀ mouse dams) and delayed fetal ossification and early puberty in male mouse pups from Lau et al. (2006)
[c]Based on the 6-month capsule dosing study of Butenhoff et al. (2002)

MOE values ranges from 1,884 to 30,556 at the central estimates and from 667 to 14,000 at the upper bound (Table 15.7). Health Canada concluded from these MOE data that:

> Based on the available information on the potential to cause harm to human health and the resulting margins of exposure, it is concluded that PFOA and its salts are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

15.5.2 Health Risk Characterizations Based on Dietary Intake of Perfluoroalkyls

Dietary sources represent an exposure pathway for PFOS and PFOA as reviewed by Domingo (2012); however, the proportion of total exposure to PFOS and PFOA that is contributed by diet may vary. Some authors have suggested diet as a principal source of exposure for the general population unaffected by point sources of exposure from industrial or agricultural activity. It is likely that there are regional

differences. Three examples of risk assessments based on estimated dietary intake follow.

15.5.2.1 United Kingdom Committee on Toxicology (COT) Statement on the Tolerable Daily Limit (TDI) for Intakes of PFOS and PFOA

The UK Committee on Toxicity of Chemicals in Food, Consumer Products and The Environment (COT) released their "COT Statement on the Tolerable Daily Intake for Perfluorooctane Sulfonate" and their "COT Statement on the Tolerable Daily Intake for Perfluorooctanoic Acid" in October, 2006 (COT 2006a, b). In considering PFOS, the NOAEL for reduced serum triiodothyronine (0.03 mg/kg) from the six-month capsule dosing study in cynomolgus monkeys of Seacat et al. (2002) was used as the critical effect. COT considered the pharmacokinetic data available for PFOS in the cynomolgus monkey model, noting that, at study term, monkeys in the 0.03 mg/kg dose group would have been at approximately one-half steady state. Because the critical effect chosen was considered mild, an uncertainty factor for incomplete attainment of steady state was not applied, and a total uncertainty of 100 was used to derive a provisional TDI of 0.3 μg/kg (0.0003 mg/kg). Because of the accumulative properties of PFOS, COT recognized that exposures should be averaged over prolonged times for comparison with the provisional TDI. In composite samples of food from a UK 2004 Total Diet Survey, PFOS was detected above the method detection limit only in potatoes, canned vegetables, eggs, and sugars and preserves (FSA 2006).

Using the latter data, the UK Food Standards Agency (FSA) estimated the ranges of average and high adult PFOA intake from whole diet to be 0.01–0.1 μg/kg body weight and 0.03–0.2 μg/kg body weight daily, respectively, where the ranges represent lower and upper bound values. For toddlers (1.5–2.5 years old), the estimated high dietary intake was 0.1–0.5 μg/kg body weight daily. Only 10–20 % of the estimated intake was assumed to be from the four food groups. Based on estimated food intake of PFOS and the provisional TDI, the COT concluded that, "on the basis available information this provisional TDI is adequate to protect against the range of identified effects." However, COT went on to note that some groups of consumers may exceed the recommended TDI. COT further noted that there were "considerable uncertainties in the dietary intake estimates, and therefore these potential exceedances do not indicate immediate toxicological concern."

In considering PFOA, a point of departure of 0.3 mg/kg body weight daily was established based on several endpoints (hepatic, renal, hematological, and immunological). To this, a total uncertainty factor of 100 was applied to derive a TDI of 3 μg/kg body weight daily (0.003 mg/kg). The COT noted that PFOA was only detected in potatoes above the method limit of detection in the analysis of composite food group samples from the UK 2004 Total Diet Study. The FSA estimated the

ranges of average and high PFOA adult intake from whole diet to be 0.001–0.07 μg/kg body weight daily and 0.003–0.1 μg/kg body weight daily, respectfully, where the ranges represent lower and upper bound values. For toddlers, the estimated high dietary intake was 0.01–0.3 μg/kg body weight daily. An analysis based on estimated intake of PFOA from food as compared to the TDI led the COT to conclude that "the estimated intakes are not of concern regarding human health."

In 2009, at the request of the UK Drinking Water Inspectorate (DWI), COT reconsidered their TDI for PFOA and lowered this to 1.5 μg/kg body weight daily after adding an additional pharmacokinetic uncertainty factor of 2 (COT 2009). COT also reevaluated the provisional TDI for PFOS at that time, and COT came to the conclusion that a change in the PFOS TDI was not warranted.

15.5.2.2 Health Canada Health Risk Characterization for Exposure of Canadians to PFOS and PFOA from Consumption of Various Food Items (Tittlemier et al. 2007)

Tittlemier et al. (2007) reported on the analysis of 54 solid food composite samples from the Canadian Total Diet Study collected between 1992 and 2004 for PFOS and perfluorocarboxylates (PFCAs), including PFOA. Nine of the composite samples contained quantifiable amounts of perfluoroalkyl compounds, with PFOS and PFOA being detected with greatest frequency. From the 25 composite samples in 2004, only six of which had detectable perfluoroalkyls, they estimated that the dietary intake of PFCAs and PFOS to be 250 ng/day and concluded that diet was an important source, with PFOS contributing 110 ng/day and PFOA and perfluorononoate (PFNA) each contributing 70 ng/day. This was in consideration of data for estimated daily exposure via water, dust, solution-treated carpeting, treated apparel, and air, which totalled 160.3 ng/day in Table 6 of their published article.

Tittlemier et al. used their analytical data and estimates of dietary exposure to perform MOE risk characterizations for Canadians ≥12 years old for dietary exposure to PFOS and perfluorocarboxylates. For the latter, it was assumed that all perfluorocarboxylates had the same biological activity as PFOA. For the PFOS POD, the 0.03 mg/kg/day dose from the six-month capsule dosing study in monkeys (Seacat et al. 2002) was taken as the LOEL, consistent with the Health Canada screening assessment discussed previously (Health Canada 2006). The POD for the perfluorocarboxylates was based on the $BMDL_{10}$ for PFOA of 0.6 mg/kg/day for increased liver weight in rat parental and F1 offspring from the two generation study of Butenhoff et al. (2004b) as calculated by Butenhoff et al. (2004a). The calculated MOE values were greater than 1.6×10^4 and 2.7×10^5 for PFOS and PFOA, respectively. The authors noted that MOE values $\geq 1.0 \times 10^4$ were considered by the EFSA to be of low concern (EFSA 2005). The authors also noted that, for infants and children, a separate exposure evaluation involving a broader array of composites would be warranted.

15.5.2.3 European Food Safety Agency (EFSA) Scientific Panel on Contaminants in the Food Chain (CONTAM) Health Risk Characterization for PFOS and PFOA (Alexander et al. 2008; EFSA 2012)

An initial risk assessment for the exposure of the European population to PFOS and PFOA via food was published in 2008 by the European Food Safety Agency (EFSA) Scientific Panel on Contaminants in the Food Chain (CONTAM) (Alexander et al. 2008). At the time of their assessment, CONTAM had established TDI values for PFOS and PFOA of 0.15 μg/kg body weight per day and 1.5 μg/kg body weight per day, respectively.

The TDI for PFOS was based on the 6-month capsule dosing study in cynomolgus monkeys (Seacat et al. 2002), from which CONTAM identified a NOAEL of 0.03 μg/kg body weight per day as suitable for deriving the TDI. CONTAM used an overall uncertainty factor (UF) of 200, 100 for inter and intra-species differences plus an additional factor of two to compensate for uncertainties in connection to the relatively short duration of the study with respect to the internal dose kinetics, yielding a TDI of 0.15 μg/kg body weight per day for PFOS. CONTAM noted difficulties in obtaining robust estimates of daily PFOS intake and reported indicative dietary exposures of 0.060 μg/kg body weight per day based on average food consumption to 0.200 μg/kg body weight per day for higher consumption of fish. CONTAM noted that the average consumption values were below the TDI of 0.150 μg/kg body weight, but that the highest exposed people within the general population might slightly exceed this TDI.

CONTAM recognized that limited quantitative data were available for the occurrence of PFOA in food. Because serum PFOA concentrations measured in non-occupational populations in Europe were approximately three orders of magnitude lower than those associated with thresholds for effects in rats, CONTAM considered it unlikely that adverse effects of PFOA were occurring in the general population.

Importantly, CONTAM pointed out the limited availability of data on exposure via food and suggested that more data on the occurrence of polyfluoroalkylated substances (PFASs) be collected to facilitate a more accurate assessment of risk. This resulted in the European Commission's issuance of Commission Recommendation 2010/161/EU which called for member states to collect data on the occurrence and concentration of PFASs in a broad range of foods. These monitoring data were collected and assessed by EFSA, resulting in EFSA's updated risk assessment, which was published in 2012 (EFSA 2012).

For their 2012 risk assessment, EFSA had available 54,195 analytical determinations covering 27 PFASs made across 7,560 samples of food that were submitted by 13 European member states. Not all analytes were monitored in all samples. Of the 27 PFAS analytes, only 16 were present at concentrations that allowed quantitation. All analyses for the other 11 PFASs were either below the limit of quantitation or the limit of detection. Analytical determinations for PFOS (N=7,523) and PFOA (N=7,536) were most frequent. PFOS was by far the most frequently quantified

PFAS in food (29 %). Foodstuffs with the highest frequency of reported PFAS analytes were fish and other seafood, meat and meat products, with lesser frequencies in other food groups. Highest concentrations were in edible offal, especially liver. EFSA reported the range of PFOS concentrations in samples varied from a low of 0.00034 μg/L in a drinking water sample to a high of 3,480 μg/kg for wild boar liver.

In their assessment of risk from exposure via food, EFSA used lower and upper bound mean concentrations of PFASs. Because of a "very low proportion of quantified results", EFSA concluded that, with the exception of PFOS and PFOA, chronic dietary exposure to the additional 25 PFASs would be on the order of low ng/kg body weight per day or lower, and that the lack of TDI values for these 25 PFASs disallowed evaluation of the relevance of their contribution to dietary exposure to human health. The results of the EFSA risk analyses for PFOS and PFOA with respect to adults and children are shown in Table 15.8. With respect to dietary exposure to PFOS and PFOA, EFSA concluded that:

> The low proportion of quantified results prevented calculation of a more realistic dietary exposure. The upper bound result are highly overestimated, but still the exposure estimates in all age classes and for both mean and 95th percentile consumers were well below the TDIs for PFOS (150 ng/kg b.w. per day) and PFOA (1500 ng/kg b.w. per day) set by the EFSA Scientific Panel on Contaminants in the Food Chain.

15.5.3 Risk Assessment for Members of the Swedish Population Using a Hazard Index Approach

Using a hazard index (HI) approach, Borg et al. (2013) have recently reported on a risk assessment for 17 polyfluoroalkylated chemicals identified in samples from the Swedish general population as well as a group of occupationally-exposed ski waxers. RfD values for liver and reproductive (developmental) effects were established for compounds for which appropriate toxicological data existed (5 of the 17) via selection of POD values based on NOAELs where feasible and through application of assessment factors (AF = uncertainty factors) based on REACH guidelines. Read-across methodology was used to estimate the RfD values for the 12 compounds which lacked appropriate data. This involved use of an AF of three to go from shorter-chain congener to longer-chain, while no AF was used when extrapolating from longer-chain to shorter-chain congeners. Because RfD values based on serum concentration of the chemicals were derived, an AF for pharmacokinetic differences between species was not used. Hazard quotients (HQs) for "hepatotoxicity" and "reproductive toxicity" for the general population and an occupationally-exposed group were calculated for 15 of the 17 compounds by taking the ratio of the highest population serum level from 5 general population biomonitoring studies and one occupational study of ski waxers to the serum concentration-based RfD. Individual perfluoroalkyl HQ values >1.0 were considered cause for concern by the authors. These HQ values were summed to yield the HI, such that an HI value

Table 15.8 Estimated highest upper bound mean and highest 95th percentile daily dietary exposures of adults and toddlers to PFOS and PFOA in ng/kg body weight at and the corresponding percent of the TDI represented by these exposures from the EFSA (2012) risk characterization

		Highest upper bound mean daily dietary intake						Highest 95th percentile daily dietary intake					
	TDI	Adult			Toddler			Adult			Toddler		
	(ng/kg)	ng/kg	%TDI	MOE[a]	ng/kg	%TDI	MOE	ng/kg	%TDI	MOE	ng/kg	%TDI	MOE
PFOS	150	5.2	3.5	29	14.0	9.3	10.7	10.0	6.7	15.0	28.5	19.0	5
PFOA	1,500	4.3	0.3	349	16.5	1.1	90.9	7.7	0.5	194.8	31.5	2.1	48

[a]Margins of exposure based on the TDI have been calculated by the authors from the data

of >1.0 would be considered by the authors as a cause for concern for the combined exposures. PFOS was the largest individual contributor to the HI. The HIs for "hepatotoxicity" and "reproductive toxicity" for the general population did not show cause for concern, except for a small sub-population of high fish consumers. HIs for ski waxers were above 1 for "hepatotoxicity" (1.3–1.4) and "reproductive toxicity" (1.1).

15.5.4 Conclusions Regarding General-Population Risk Assessments

The general populations risk assessments that have been presented in this section support a conclusion that untoward health risk is unlikely at the levels of exposure found from serum or liver biomonitoring or in diet. The MOE analyses based on serum PFOS and PFOA levels found in the general population provide a direct indication of the extent of exposure of these populations from all sources in the environment. The strength of these assessments is dependent on the degree to which the serum biomonitoring data represent the population. In the United States, the serum PFOS and PFOA biomonitoring conducted with sub-samples from NHANES is considered to be representative. Early MOE risk assessment for PFOS (3M 2003) and PFOA (Butenhoff et al. (2004a) and USEPA (2003)) used data from the biomonitoring studies of Olsen et al. (2003a, 2004a), in particular approximately 600 American Red Cross adult blood donors, approximately 100 from each of 6 regional collection centers, to estimate serum concentrations of PFOS and PFOA. Serum PFOS and PFOA distributions in the American Red Cross adult blood donor samples have tracked well with the NHANES data for concurrent time periods, and, although they are not fully representative, they are a good approximation for adults. Similarly, the Health Canada MOE risk assessment of 2012 used representative data for Canadian adults (Health Canada 2012). In all of these MOE assessments, less representative serum PFOS and PFOA data have been available for infants and children; however, the data that were available suggested that the serum concentrations in children were not greatly different than those in adults.

For the risk assessments based on dietary exposure, strength of the assessment is dependent on the representativeness of the estimates for dietary exposure. The 2012 risk assessment from EFSA provided a much broader view of the magnitude of exposure via diet for PFOS and PFOA within Europe. The composite food samples used in the UK and Canadian risk assessments were designed to be reasonably representative of diets in those regions. However, it is likely that there are regional differences that may affect exposure patterns, e.g., higher consumption of fish.

It should also be noted that the risk assessments based on dietary exposure are dependent on the methods used to establish the TDI values. The choice of critical endpoint and the POD based on the critical endpoint as well as uncertainty factors chosen can vary considerably.

15.6 Establishment of Regulatory Risk Levels for Exposure to Perfluoroalkyls via Drinking Water

Consumption of water containing PFOA, and, to a lesser extent, PFOS, has been a documented source of exposure for several populations. Most notable among these populations were communities in the mid Ohio River Valley that were exposed to PFOA in their water supplies as a result of discharges from an industrial facility that used ammonium PFOA as a processing aid in the production of polytetrafluoroethylene (PTFE). Exposure via drinking water and the resulting serum PFOA concentrations in these mid Ohio River Valley communities have been well described (Emmett et al. 2006; Frisbee et al. 2009; Steenland et al. 2009). In another circumstance, a community in the vicinity of Arnsberg in the state of North Rhine-Westphalia in Germany was also exposed to PFOA, with lesser concentrations of PFOS, in drinking water after a soil enhancer that had been mixed with industrial waste was applied to agricultural land on the upper Moehne River (Brede et al. 2010; Hölzer et al. 2008, 2009; Skutlarek et al. 2006). In 2009, the Minnesota Department of Health released the results of a pilot biomonitoring study that covered residents in an area with potential exposure via consumption of ground water containing PFOA, and lesser concentrations of PFOS, as a result of leaching from landfill waste sites (MDH 2009c). Concern for exposure to perfluoroalkyls through drinking water has prompted several jurisdictions to develop guidelines or advisories for the presence of certain perfluoroalkyls in drinking water, predominantly PFOA, but also for PFOS, and sometimes with consideration of other perfluoroalkyls. These guidelines are based on daily intake of the perfluoroalkyl(s) via consumption of water. Several approaches to the development of drinking water guidelines and advisories have been taken, with most incorporating a means of adjusting for pharmacokinetic differences between humans and the species used in the study from which the critical effect(s) and POD has been chosen. Notable examples of drinking water guidelines/advisories developed for PFOS and PFOA are presented below, and several of these are summarized in Tables 15.9 and 15.10.

15.6.1 United States Environmental Protection Agency Office of Water Provisional Health Advisories for PFOS and PFOA

In 2009, United States Environmental Protection Agency (USEPA) Office of Water (OW) derived Provisional Health Advisory (PHA) values for PFOS and for PFOA in drinking water (USEPA OW 2009), which are summarized in Tables 15.9 and 15.10, respectively. In deriving the PHA for PFOS, USEPA OW considered as critical three clinical chemistry endpoints observed in females from a 6-month capsule dosing study of potassium PFOS in male and female cynomolgus monkeys (*Macaca fascicularis*) (Seacat et al. 2002): decreased serum concentration of high-density

Table 15.9 Factors used by the United States, the State of Minnesota, and the United Kingdom in deriving guidance values for exposure to PFOS via drinking water

	United States	Minnesota	United Kingdom
	EPA OW[a]	MDH[b]	DWI[c]
Study	Seacat et al. (2002)	Seacat et al. (2002)	Seacat et al. (2002)
Species	Monkey	Monkey	Monkey
Sex	Female	Female	Female
Endpoint(s)	↓HDL, ↑TSH, ↓TT3	↓HDL, ↑TSH, ↓TT3	Multiple
Basis of POD	NOAEL (oral gavage)	BMCL10 (serum [PFOS])	NOAEL
POD	0.03 mg/kg/day	35 μg/mL	0.03 mg/kg/day
PK adjustment			
Clearance ratio	13		
HED	0.0023 mg/kg/day	Direct calculation[d]	Direct calculation
Uncertainty			
Inter-individual	10	10	10
Interspecies	3	3	10
Total uncertainty	30	30	100
RfD or TDI	0.000077 mg/kg/day	0.00008 mg/kg/day	0.0003 mg/kg/day[e]
Guideline factors			
Daily water	0.1 L/kg/day (10 kg child)	0.049 L/kg/day[f]	0.1 L/kg/day (10 kg child)
RSC	0.2	0.2	0.1
Guidance level	0.2 μg/L	0.3 μg/L	>0.3 μg/L (Tier 2)[g]

[a]Environmental Protection Agency Office of Water
[b]Minnesota Department of Health
[c]Drinking water inspectorate
[d]Based on one-compartment, first order kinetics using a human serum PFOS elimination half-life of 1,971 days (5.4 years) and a volume of distribution of 0.2 L/kg
[e]From UK FSA COT (2009)
[f]Estimated TWA 95th percentile intake rate for the first 27 years of life. For a 70 kg adult, this would be 3.4 L/day
[g]Tier 2 (DWI notes that drinking water suppliers should include PFOS in their Regulation 27 risk assessments as a minimum (Tier 1). If the value for Tier 2 is exceeded, monitoring and consultation with health authorities is required as a minimum. Tier 3 and Tier 4 values and their required actions are discussed in the text)

Table 15.10 Factors used by the United States and the States of Maine, Minnesota, New Jersey, and North in deriving guidance values for exposure to PFOA via drinking water

	United States	Maine	Minnesota	New Jersey	North Carolina
	EPA OW	DHHS	MDH	DEP	NCDENR
Study	Lau et al. (2006)	Multiple studies	Butenhoff et al. (2002)	Butenhoff et al. (2012c)	Butenhoff et al. (2002)
Species	Mouse	Mouse and rat	Monkey	Rat	Monkey
Sex	Female (maternal)	Male and female	Male	Female	Male
Endpoint(s)	↑ Liver weight	↑ Liver weight/hepatocellular hypertrophy	↑ Relative liver weight (liver: brain weights)	↓ Body weight	↑ Liver weight
Basis of POD	$BMDL_{10}$ (gavage dose)	$BMDL_{10}$[a] (gavage and dietary dose)	$BMDL_{10}$ (serum [PFOA])	NOAEL (dietary dose)	BMC_{10}[b] (serum [PFOA])
POD	0.46 mg/kg/day	0.42 mg/kg/day[c]	23 μg/mL	1.8 μg/mL[d]	40 μg/mL
PK adjustment					
PBPK					0.12 μg/kg body weight per μg/mL[e]
HEss dose[f]			Direct calculation[g]		
Clearance ratio	81	226[h]			
HED	0.0057 mg/kg/day	0.0018 mg/kg/day[a]	0.0023 mg/kg/day		0.0048 mg/kg/day
Uncertainty					
Inter-individual	10	10	10	10	10
Interspecies	3	3	3	10	3
Total uncertainty	30	300 (includes a factor of 10 for database uncertainty)	30	100	30
RfD or TDI	0.00019 mg/kg/day	0.000006 mg/kg/day	0.000077 mg/kg/day	18 ng/mL[i]	0.00016 mg/kg/day

(continued)

Table 15.10 (continued)

	United States	Maine	Minnesota	New Jersey	North Carolina
	EPA OW	DHHS	MDH	DEP	NCDENR
Guideline factors					
Daily water	0.1 L/kg/day[j]	0.029 L/kg/day[k]	0.053 L/kg/day[l]	Not used	0.029 L/kg/day[k]
RSC	0.2	0.6	0.2	0.2	0.2
Guidance level	0.4 μg/L	0.1 μg/L	0.3 μg/L	0.04 μg/L[m]	1 μg/L

[a]Geometric mean among six $BMDL_{10}$ values obtained from various gavage and dietary studies
[b]Central estimate of BMC_{10} based on serum PFOA concentration
[c]Geometric mean among six $BMDL_{10}$ values obtained from various gavage and dietary studies (individual $BMDL_{10}$ values are: 0.46, 0.4, 0.29, 0.44, 0.74, and 0.31)
[d]Based on estimate of serum PFOA concentration at NOAEL of 1.6 mg/kg/day using modelled AUC from USEPA (2005) (1.6 mg/kg/day gives AUC of 44 μg*h/mL)
[e]From Clewell et al. (2006)
[f]Human equivalent steady state dose
[g]Based on one-compartment, first order kinetics using a human serum PFOA elimination half-life of 1,387 days (3.8 years) and a volume of distribution of 0.2 L/kg
[h]Geometric mean of gavage and dietary study clearance ratios (individual values were 82, 277, 277, 277, 277, and 277)
[i]Target human blood concentration (assume serum concentration)
[j]10 kg child
[k]2 L/day, 70 kg adult
[l]Estimated TWA 95th percentile intake rate for the first 19 years of life
[m]0.18 μg/L based on observation by Emmett et al. (2006) of the relationship in Mid-Ohio Valley community samples of 1 μg/L contaminated water results in approximately 100 μg/L serum PFOA if water accounts for 100 % exposure. Applying a RSC of 20 % lowers to 0.04 μg/L.

lipoprotein (HDL) cholesterol; decreased total triiodothyronine (TT3); increased thyrotropin (thyroid stimulating hormone, or TSH). A NOAEL of 0.03 mg/kg/day was used as the POD, from which a human equivalent dose (HED) of 0.0023 mg/kg/day was obtained after a pharmacokinetic adjustment of 13 based on the monkey: human clearance ratio. To this HED, a total uncertainty factor of 30 was applied to yield a RfD of 0.000077 mg/kg/day. A water consumption rate of 1 L/day based on a 10 kg child was used along with a default relative source contribution (RSC) factor of 20 %. The RSC attributed the proportion of the daily intake from all sources that is contributed, in this case, by consumption of water. Therefore, in using the default of 20 %, it is assumed that one-fifth of the total daily intake from all sources is from drinking water. The Provisional Health Advisory (PHA) guidance level therefore was set at 0.2 μg/L.

In deriving a PHA for exposure to PFOA from drinking water, USEPA Office of Water used increased maternal liver weight as the critical endpoint from a mouse developmental study (Lau et al. 2006). The derivation of this PHA is summarized in Table 15.10. A $BMDL_{10}$ value of 0.46 mg/kg/day was used as the POD, from which a HED of 0.0057 mg/kg/day was obtained after a pharmacokinetic adjustment of 81 based on the mouse: human clearance ratio. To this HED, a total uncertainty factor of 30 was applied to yield a RfD of 0.00019 mg/kg/day. Using a water consumption rate of 1 L/day based on a 10 kg child and a RSC of 20 %, the Provisional Health Advisory guidance level was set at 0.4 μg/L.

15.6.2 Drinking Water Guidance Values from States Within the United States

15.6.2.1 Maine

The Maine Department of Health and Human Services developed a health-based Maximum Exposure Guideline (MEG) for PFOA in drinking water (MEDHHS 2014). The MEG for PFOA was based on liver effects in six toxicological studies with mice and rats (Table 15.10). $BMDL_{10}$ values for various liver effects obtained from multiple gavage and dietary studies in rodents and reported by EFSA were used in the derivation. For each study, the $BMDL_{10}$ divided by a pharmacokinetic (PK) adjustment factor based on the estimated rodent (mouse or rat): human clearance ratio was used as the HED. These HED values ranged from 0.0010 to 0.0056 mg/kg/day with a geometric mean of 0.0018 mg/kg/day. This geometric mean value was used to derive the RfD of 0.000006 mg/kg/day after applying a total uncertainty factor of 300. The MEG of 0.1 μg/L was calculated from the RfD through application of a standard 70 kg adult body weight and 2 L/day water intake rate with a relative source contribution (RSC) factor of 60 % of exposure via drinking water.

It is noteworthy that the deviation from the usual default RSC of 20 % was data-driven. Maine reasoned that there were adequate background exposure data to

derive a PFOA-specific RSC value. Pursuant to this, Maine took the upper 95th percentile serum PFOA concentration level from the updated tables issued in September 2013 for most recent United States Center for Disease Control's National Health and Nutrition Examination Survey (CDC_NHANES 2009). (These updated tables were withdrawn by CDC NHANES and replaced with new updated tables in August, 2014.) This serum PFOA concentration (7.5 ng PFOA/mL serum), was considered as the upper bound serum PFOA concentration associated with background PFOA exposure of the United States general population from all sources. Maine first converted the RfD (0.006 μg/kg/day) to a "drinking water equivalent level" (DWEL), assuming that 100 % of the RfD is contributed by water. A DWEL value of 0.21 μg/L was derived based on consumption of 2 L of water containing an amount of PFOA representing the RfD for a 70 kg person. The DWEL was then converted to a corresponding serum PFOA concentration using the 100:1 serum PFOA: drinking water PFOA concentration level relationship described by Emmett et al. (2006) for a population in the mid Ohio Valley with exposure to PFOA through drinking water as a principal source. Applying this 100:1 relationship resulted in a corresponding serum PFOA concentration of 21 μg/L. The PFOA-specific RSC was then obtained by dividing the serum concentration associated with drinking water PFOA concentrations at the RfD (21 μg/L or 21 ng/mL) minus the NHANES upper 95th percentile serum PFOA from background exposure (21 ng/mL−7.5 ng/mL = 13.5 ng/mL) by the serum concentration associated with drinking water PFOA concentrations at the RfD times 100 (13.5 ng/mL/21 ng/mL 100 = 64.3 %). The resulting value of 64.3 % was rounded to 60 %. Maine is the only government authority to date that has taken such a data-driven approach to developing a RSC.

15.6.2.2 Minnesota

Perfluoroalkyls, notably PFOS, PFOA, and perfluorobutyrate (PFBA), have been found to impact the groundwater used as a supply for drinking water in several Minnesota communities (MDH 2008). Landfill leachate was thought to contribute to the PFOS and PFOA exposure via this groundwater. The Minnesota Department of Health (MDH) has derived Health Risk Limits (HRLs) for four perfluoroalkyls: PFOS (MDH 2009b); PFOA (MDH 2009a); perfluorobutanesulfonate (MDH 2011a); and, perfluorobutyrate (MDH 2011b). Derivation of HRLs for PFOS and PFOA are summarized in Tables 15.9 and 15.10, respectively, and below.

In developing an HRL for PFOS, the MDH chose critical effects of decreased serum HDL cholesterol, decreased serum TT3, and increased serum TSH from the 6-month oral capsule dosing study of potassium PFOS in cynomolgus monkeys (*Macaca fascicularis*) (Seacat et al. 2002) (Table 15.9). MDH considered a number of co-critical effects, additivity endpoints, and secondary effects in their derivation. A serum PFOS concentration-based $BMDL_{10}$ of 35 mg/L (equivalent to 35 μg/mL) was used by MDH as the POD. This serum PFOS concentration was used to derive the estimated HED by assuming that the 35 μg/mL represented steady state and

calculating the estimated daily dose in humans that would be associated with that steady-state concentration. For this calculation, MDH assumed first order elimination kinetics, a non-compartmental model, an arithmetic mean human serum PFOS elimination half-life of 1,971 days, based on Olsen et al. (2007), and a human volume of distribution of 0.2 L/kg. The resulting HED was 0.0025 mg/kg/day, to which a total uncertainty factor of 30 was applied to derive an RfD of 0.00008 mg/kg/day. To obtain the HRL, MDH used a time-weighted average water consumption calculated at the 95th percentile water consumption rate over the first 27 years of life (0.049 L/kg/day). The latter time period was considered to be that representing attainment of steady state. For a 70 kg person, this represents a consumption rate of 3.4 L/day. MDH applied a RSC of 20 % to yield the HRL of 0.3 μg/L.

For drinking water exposure to PFOA, The Minnesota Department of Health (MDH) chose a critical effect of increased relative liver weight from the 6-month oral capsule dosing study of ammonium PFOA in cynomolgus monkeys (*Macaca fascicularis*) (Butenhoff et al. 2002), chosen as the critical study (Table 15.10). MDH considered a number of co-critical effects, additive endpoints, and secondary effects in their derivation. A serum PFOA concentration-based $BMDL_{10}$ of 23 mg/L (equivalent to 23 μg/mL) as derived by Butenhoff et al. (2004a) was used by MDH. This serum PFOA concentration was used to derive the estimated HED by assuming that the 23 mg/L represented steady state and calculating the estimated daily dose in humans that would be associated with that steady-state concentration. For this calculation, MDH assumed first order elimination kinetics, a non-compartmental model, an arithmetic mean human serum PFOA elimination half-life of 1,387 days, based on Olsen et al. (2007), and a human volume of distribution of 0.2 L/kg. The resulting HED was 0.0023 mg/kg/day, to which a total uncertainty factor of 30 was applied to derive an RfD of 0.000077 mg/kg/day. To obtain the HRL, MDH used a time-weighted average water consumption calculated at the 95th percentile water consumption rate over the first 19 years of life (0.053 L/kg/day), a time period in which MDH reasoned that steady state serum PFOA would be reached. For a 70 kg person, the corresponding consumption rate is 3.7 L/day. MDH then applied a RSC of 20 % to yield the HRL of 0.3 μg/L.

15.6.2.3 New Jersey

The New Jersey Department of Environmental Protection developed a health-based drinking water concentration for PFOA, which was published in 2009 (Post et al. 2009), as part of an overall evaluation of the occurrence of PFOA in New Jersey public water systems (Table 15.10). The exposure assessment and health-based water PFOA concentration were based on an observed relationship between concentrations of PFOA in drinking water and PFOA concentrations in humans exposed to drinking water containing PFOA (Emmett et al. 2006). In determining the POD for derivation of the health-based value, the 2-year dietary study of ammonium perfluorooctanoate in male and female rats (Butenhoff et al. 2012c) was chosen as the critical study. From this study, a NOAEL of 1.6 mg/kg/day for decreased body weight

in female rats was chosen as the critical effect. The estimated serum PFOA at this NOAEL was calculated from a modeled AUC taken from the USEPA draft risk assessment for PFOA (USEPA 2005), which was 44 μg·h/mL at the 1.6 mg/kg/day dose, yielding 1.8 μg/mL as an average serum concentration over a 24-h period. This serum PFOA concentration was used as the POD. Uncertainty factors of 10 for inter-individual variation and 10 for interspecies variation were applied to yield a total uncertainty of 100 and a RfD of 18 ng PFOA/mL serum. A RSC of 20 % was assumed for exposure from drinking water. Based on the observation of Emmett et al. (2006), a population exposed to PFOA in drinking water at approximately 1 μg/L (equal to 1 ng/mL) had serum PFOA concentrations of approximately 100 ng/mL. Assuming that the later observation applied to 100 % of exposure via drinking water and using this relationship, the POD of 18 ng/mL (0.018 μg/mL) would correspond to a drinking water concentration of approximately 0.18 μg/L. Applying a RSC of 20 % attributable to exposure via water consumption, New Jersey DEP derived a health-based concentration of 0.04 μg PFOA/L water.

15.6.2.4 North Carolina

In their original 2006 derivation of an Interim Maximum Allowable Concentration (IMAC) for PFOA in ground water, the North Carolina Science Advisory Board (NCSAB) derived a RfD for PFOA of 0.0003 mg/kg/day (Williams 2006), which was based on increased liver weight observed in rats from an oral (gavage) two-generation reproduction and development study that used ammonium perfluorooctanoate (APFO) as the test agent (Butenhoff et al. 2004b) (Table 15.10). The State of North Carolina found that the lowest observed adverse effect level (LOAEL) for increased liver weight was 1 mg/kg/day. Using this dose as the POD, four uncertainty factors were applied: (1) Ten for inter-individual variation; ten for interspecies variation; ten to account for the lack of a no observed adverse effect level (NOAEL) for liver weight increase; three to account for perceived deficiencies in the database. The resulting total uncertainty factor after multiplying the individual factors together was 3,000. Dividing the 1 mg/kg/day POD by the total uncertainty of 3,000 yielded a RfD of 0.0003 mg/kg/day for PFOA. On August 10, 2012, the NCSAB issued a revised IMAC for PFOA in ground water which is currently pending approval (NCSAB 2012). The derivation of this revised IMAC is summarized in Table 15.10. Using increased liver weight (with increased liver to brain weight ratio) observed in male monkeys as the critical effect (Butenhoff et al. 2002), a central estimate of BMC_{10} on serum PFOA concentration at 40 μg/mL was determined to be the basis of POD for the IMAC derivation. With PBPK (0.12 μg PFOA/kg body weight per μg PFOA/mL serum) and uncertainty factor (30) adjustments, the IMAC of 1 μg/L was proposed in North Carolina assuming a 70-kg adult with 2 L daily water consumption and a 20 % relative source contribution for exposure from drinking water.

15.6.2.5 West Virginia

The State of West Virginia was among the first jurisdictions to develop health-based guidelines for PFOA concentration in drinking water. The use of ammonium PFOA as a processing aid in the production of tetrafluoroethylene at an industrial facility in Parkerburg, West Virginia resulted in the presence of PFOA in drinking water sources in several mid Ohio River Valley communities (Emmett et al. 2006; Shin et al. 2011). The West Virginia Department of Environmental Protection released a report on the establishment of preliminary risk screening levels for PFOA in drinking water in the mid Ohio River Valley communities near a the PTFE production facility that used ammonium PFOA as a processing aid (WVDEP 2002). This report documented the results of an expert workshop of the Ammonium Perfluorooctanoate (C8) Assessment of Toxicity Team (or, CATT). The CATT was established by a consent order between E. I. DuPont de Nemours, Inc. and two West Virginia departments, the Department of Environmental Protection and the Department of Health and Human Resources. Three objectives were established for the CATT, as stated in the Executive Summary of the CATT report: "(1) determine risk-based human health protective screening levels (SLs) for this unregulated chemical in air, water, and soil; (2) provide health risk information to the public; and (3) determine an ecological health protective SL for C8 in surface water." Human health provisional risk factors for oral (RfD) and inhalation (RfC) exposures were derived by the CATT. From these RfD risk factors, health protective screening levels (SLs) were developed based on then current USEPA Region 9 standard methodology. For the oral route of exposure, an RfD of 0.004 mg/kg of body weight daily was determined, and a provisional RfC of 1 μg/m^3 of air was established. The RfD was used to derive SLs of 150 μg/L (parts per billion, or ppb) for drinking water. All water samples collected in the vicinity of this facility were below the risk screening level of 150 μg/L derived for drinking water in this process. Water samples from the 50 private wells and cisterns used for drinking water and the nine public water supplies were below 3 μg/L.

15.6.3 United Kingdom Drinking Water Inspectorate Guidance on Water Supply Regulations for PFOA and PFOS

The UK Drinking Water Inspectorate (DWI) under the Department of Environment, Food, and Rural Affairs (DEFRA) originally issued guidance for concentrations of PFOA and PFOS in drinking water in 2007 which was then revised in 2009 to be consistent with the revised UK COT TDI for PFOA, which was lowered from 3.0 to 1.5 μg/kg/day after consideration of the EFSA TDI for PFOA, which included an additional pharmacokinetic adjustment factor (UKDWI 2009). The DWI guidance includes a multi-tiered approach consisting of four tiers with related minimum

actions to be taken. For PFOA and PFOS, Tier 1 is not associated with a water concentration; however, this tier calls for consideration of PFOA and PFOS as part of a statutory risk assessment for water companies as well as the consideration of monitoring water for PFOA and PFOS where appropriate. Tier 2 establishes a concentration of PFOA and PFOS in water, 0.3 μg/L, above which further sampling, investigation, and consultation with local health authorities is appropriate. This Tier 2 concentration for both PFOA and PFOS is based on the derived Tier 2 concentration for PFOS (see below and Table 15.9), which, in turn, is based on a RSC of 10 % of the UK COT TDI for PFOS (0.03 μg/kg) allocated to 1.0 L of drinking water consumed daily by a 10 kg child.

Tier 3 considers the wholesomeness of water and establishes a concentrations of PFOA and PFOS in water below which it is assumed that a "potential danger to human health" does not exist. For PFOA, DWI established a wholesomeness level of 5.0 μg/L or less as protective of "the whole range of consumers". This level was based on a RSC of 50 % of the TDI allocated to 0.75 L/day of water consumed by a 5 kg bottle-fed infant. In the case that PFOA concentrations in water are above 5.0 μg/L, the guidance instructs that water companies should discuss appropriate actions with local health authorities aimed at reducing exposure to PFOA via drinking water, put these exposure-reduction strategies in place as soon as practicable, an monitor PFOA in drinking water. In considering a Tier 3 level for PFOS, DWI considered how best to ascribe the source contribution for water for young children. In so doing, DWI noted that, taking worst case estimates of dietary exposure to PFOS for small adults, a Tier 3 level of 3.0 μg/L would still be protective. However, DWI noted "considerable" uncertainty in estimates of dietary intake of PFOS for small children, and that drinking water exposure to PFOS would "be appropriately restricted by establishing a value in the range zero and 2.5 μg/L". DWI further noted that, based on current toxicological expert advice, a Tier 3 water PFOS concentration of 1.0 μg/L would meet the wholesomeness requirement. The same actions would be required as for PFOA if drinking water were to exceed the 1.0 μg/L PFOS Tier 3 level.

Tier 4 requires notification by water companies of any event which has or may adversely affect the quality of water. Tier 4 also establishes a level of exceedance that would require more immediate action and notification of relevant stakeholders. For PFOA, this notification level was set to reflect allocation of the whole TDI for PFOA (0.15 μg/kg/day) to 2 L/day of drinking water consumed by a 60 kg adult (>45 μg/L). The DWI also provided water concentrations of PFOA considered to be unfit for human consumption and subject to potential prosecution. These PFOA water concentrations were noted as: 2,000 μg/L for bottle-fed babies; 3,000 μg/L for 1-year old children; 9,000 μg/L for adults. Similarly, for PFOS, in allocating all of the TDI to 2 L of drinking water per day for a 60 kg adult, the notification level is >9.0 μg/L. Concentrations of PFOS in drinking water considered unfit for human consumption and potentially subject to prosecution were noted as: 67 μg/L for bottle-fed babies; 100 μg/L for 1-year old children; 300 μg/L for adults.

15.6.4 German Drinking Water Commission

After the discovery of PFOA in drinking water at concentrations up to 0.56 μg/L in the Hochsauerland district in Germany (Skutlarek et al. 2006), the Public Health Department of Hochsauerland (Gesundheitsamt des Hochsauerlandkreises) asked the Drinking Water Commission (Trinkwasswerkommission, or TWK) of the Federal Environment Agency (Umweltbundesamt, or UBA) to determine maximum tolerable concentrations of PFOA in drinking water. This resulted in a July 13, 2006 provisional guideline issued by TWK (2006). Because PFOS was also detected in water at lower concentrations than those found for PFOA, the TWK guidance reflected the composite concentrations of both PFOA and PFOS. Four guidance values were presented. One of these was based on the 2003 UBA admissible health guidance value (Gesundheitlicher Orientierungswert, or GOW) of 0.1 μg/L for non- or low-potency genotoxic substances, which was considered applicable to lifetime exposure to combined total concentrations of PFOA and PFOS via drinking water. In addition, for less than lifetime exposure, two precautionary action values (Vorsorgemaβnahmewert, or VMW) were recommended based on UBA's action value guidance (Maβnahmewert-Empfehlung). A VMW_0 (Vorsorge-Maβnamewert für Erwachsene) of 5 μg/L is used to indicate when immediate action is required to reduce exposure to PFOA and PFOS via drinking water. For infants and pregnant women, the VMW_0 of 5 μg/L is reduced by a factor of 10 to yield an infant and pregnancy VMW_s (Vorsorge-Maβnamewert für Säuglinge) of 0.5 μg/L. In addition to these GOW and VMW values, a specific health-based value (Lietwert, or LW) for PFOA and PFOS of 0.3 μg/L was derived based on toxicological data. TDI values of 0.1 μg/kg/day for PFOA and PFOS were developed based on consideration of the NOAELs from the 2-year dietary study (Butenhoff et al. 2012c) and two-generation reproduction and development study of ammonium PFOA (Butenhoff et al. 2004b), both in rats, and the NOAEL from the 2-year dietary study in rats of potassium PFOS (Butenhoff et al. 2012b). NOAELs of 0.1 mg/kg/day and 0.025 mg/kg/day were selected for PFOA and PFOS, respectively. Total uncertainty factors of 1,000 for PFOA (10 for inter-individual, 10 for interspecies, and 10 for additional pharmacokinetic uncertainty) and 300 for PFOS (10 for inter-individual, 10 for interspecies, and 3 for additional pharmacokinetic uncertainty) were used. An RSC of 10 % was used, allocated to 2 L/day of water consumed by a 70 kg adult.

15.6.5 Conclusions Regarding Establishment of Regulatory Risk Levels for Exposure via Drinking Water

As can be seen from an inspection of Tables 15.8 and 15.9, the RfD or TDI values derived for PFOS and PFOA vary by a factor of 3–4. For PFOS (Table 15.9) the same study has been used as the critical study (Seacat et al. 2002), and the same endpoints have been considered as critical (reduced serum HDL, reduced serum Total T3, and increased serum TSH). For PFOA, increased liver weight was the

critical endpoint used in the five examples given in Table 15.10. The studies differed, with USEPA OW using the Lau et al. (2006) mouse developmental study, MDH and NCDENR using the Butenhoff et al. (2002) monkey study, Maine using multiple studies, and New Jersey DEP, which did not develop a RfD, using female data from the 2-year Sprague Dawley rat dietary study (Butenhoff et al. 2012c). When these values are used to develop safe drinking water levels, for PFOA, the μg/L values vary by a factor of 25. Again, considering that these values for PFOA are based on liver weight increase, which is not necessarily an adverse outcome, this degree of variability in the resulting safe drinking water levels raises questions about the appropriateness of the process and its potential impacts in terms of risk management.

15.7 Conclusion

In this chapter, the major human health risk assessment activities that have been undertaken for human exposure to perfluoroalkyls have been summarized. Comments have been made on several factors influencing risk assessment. It becomes apparent that the methods used to assess human health risk from exposure to perfluoroalkyls have been evolving and will likely continue to develop as new information and approaches are introduced. Perhaps the most important direction that risk assessment for perfluoroalkyls has taken has been in the use of internal dose metrics to bridge differences in pharmacokinetic elimination kinetics between species. This practice also has the benefit of integrating contributions to exposure from all sources. Although a large and robust database exists for PFOA and PFOS that covers multiple health endpoints, data are more limited for other perfluoroalkyls. Increased liver weight is a frequent and sensitive effect observed in toxicological studies with perfluoroalkyls, particularly in rodents, and data have been developed to attribute this to increased activation of the nuclear receptors PPARα and CAR/PXR. A number of the risk assessment activities discussed in this chapter considered increased liver weight as an effect appropriate for establishing a POD; however, the use of increased liver weight to represent an adverse effect in the absence of other indications of liver toxicity is not consistent with past or current guidance for the evaluation of liver weight increase as adaptive versus adverse (Hall et al. 2012). Moreover, the notable differences between the human and rodent liver response to increased activation of PPARα and CAR/PXR argue for mitigation of concern in translating liver weight increases for rodent exposure to perfluoroalkyls to humans (Corton et al. 2014; Elcombe et al. 2014; Klaunig et al. 2012). There is a need to better inform epidemiological investigations with the understanding obtained from toxicological and pharmacokinetic investigations and principals. Translating our understanding from toxicological systems into a human context will improve our collective ability to understand potential human health risk from environmental levels of exposure to perfluoroalkyls.

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