DRAFT
TOXICOLOGICAL PROFILE FOR PERFLUOROALKYLS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

A Toxicological Profile for Perfluoroalkyls, Draft for Public Comment was released in May 2009. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch
1600 Clifton Road NE
Mailstop F-57
Atlanta, Georgia 30329-4027

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for these toxic substances described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. We plan to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov.
Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Human Health Sciences
Environmental Toxicology Branch

Regular Mailing Address:
1600 Clifton Road, N.E.
Mail Stop F-57
Atlanta, Georgia 30329-4027

Physical Mailing Address:
4770 Buford Highway
Building 106, 3rd floor, MS F-57
Chamblee, Georgia 30341

The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the National Priorities List, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Patrick N. Breysse, Ph.D., CIH
Director, National Center for Environmental Health and
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Public Health Statement: The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

Chapter 2: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

Pediatrics: Four new sections have been added to each Toxicological Profile to address child health issues:

Chapter 1	**How Can (Chemical X) Affect Children?**
Chapter 1	**How Can Families Reduce the Risk of Exposure to (Chemical X)?**
Section 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

Section 3.8	**Biomarkers of Exposure and Effect**
Section 3.11	**Methods for Reducing Toxic Effects**

ATSDR Information Center

Phone:	1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet:	http://www.atsdr.cdc.gov

The following additional material is available online at www.atsdr.cdc.gov:

Case Studies in Environmental Medicine—Case Studies are self-instructional publications designed to increase primary care provider's knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients.

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances.

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: (202) 245-0625 or 1-800-CDC-INFO (800-232-4636).

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

Clinical Resources

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.

2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.

3. Data Needs Review. The Environmental Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

A peer review panel was assembled for perfluoroalkyls. The panel consisted of the following members:

1. Edward Emmett, M.D., Professor, Center of Excellence in Environmental Toxicology, University of Pennsylvania, Philadelphia, Pennsylvania;

2. Deborah A. Cory-Slechta, Ph.D., Professor, Department of Environmental Medicine, University of Rochester School of Medicine, Rochester, New York; and

3. William L. Hayton, Ph.D., Professor Emeritus, College of Pharmacy, Ohio State University, Columbus, Ohio.

Draft for Public Comment:

1. Abby Benninghoff, Ph.D., Faculty Research Associate, Department of Environmental and Molecular Toxicology, Oregon State University, Corvallis, Oregon;

2. Edward Emmett, M.D., Professor and Deputy Director, Center of Excellence in Environmental Toxicology, University of Pennsylvania, Philadelphia, Pennsylvania;

3. Lynn R. Goldman, M.D., M.P.H., Professor of Environmental Health Science, Johns Hopkins University, Baltimore, Maryland; and

4. David A. Savitz, Ph.D., Charles W. Bluhdorn Professor of Community and Preventive Medicine, Director, Disease Prevention and Public Health Institute, Mount Sinai School of Medicine, New York, New York.

These experts collectively have knowledge of perfluoroalkyls' physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

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1. PUBLIC HEALTH STATEMENT FOR PERFLUOROALKYLS

This Public Health Statement summarizes the Division of Toxicology and Human Health Science's findings on perfluoroalkyls, tells you about them, the effects of exposure, and describes what you can do to limit that exposure.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are sites targeted for long-term federal clean-up activities. Perfluoroalkyls have not been reported at EPA NPL sites; however, it is unknown how many of the 1,699 current or former NPL sites have been evaluated for the presence of perfluoroalkyls. As more sites are evaluated, the sites at which perfluoroalkyls is found may increase. This information is important because these future sites may be sources of exposure, and exposure to perfluoroalkyls may be harmful.

If you are exposed to perfluoroalkyls, many factors determine whether you'll be harmed. These include how much you are exposed to (dose), how long you are exposed to it (duration), and how you are exposed (route of exposure). You must also consider the other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

WHAT ARE PERFLUOROALKYLS?

Perfluoroalkyls are a family of human-made chemicals that do not occur naturally in the environment. Thirteen perfluoroalkyl compounds are discussed in this profile. The names of these perfluoroalkyls are as follows: perfluorooctane sulfonic acid (PFOS), perfluorooctanoic acid (PFOA), perfluorododecanoic acid (PFDoA), perfluorodecanoic acid (PFDeA), perfluorobutyric acid (PFBA), perfluoroheptanoic acid (PFHpA), perfluorononanoic acid (PFNA), perfluoroundecanoic acid (PFUA), perfluorohexane sulfonic acid (PFHxS), perfluorobutane sulfonic acid (PFBuS), perfluorooctane sulfonamide (PFOSA), 2-(N-methyl-perfluorooctane sulfonamide) acetic acid (Me-PFOSA-AcOH), and 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid (Et-PFOSA-AcOH).

Perfluoroalkyls are unique because they repel oil, grease, and water. They have been used in surface protection products such as carpet and clothing treatments and coatings for paper and cardboard packaging. Some perfluoroalkyls have also been used in fire-fighting foams.

WHERE ARE PERFLUOROALKYLS FOUND?

Perfluoroalkyls can be released into the air, water, and soil at places where they are produced or used. Perfluoroalkyls were made in large amounts in the United States. PFOA and PFOS are the two perfluoroalkyl compounds made in the largest amounts. Companies have stopped production or have begun changing manufacturing practices to reduce releases and the amounts of these chemicals in their products. Some facilities are replacing many of the perfluoroalkyls with other substances.

Perfluoroalkyls have been found in both air and dust; surface water and groundwater; and soil and sediment. The highest levels of perfluoroalkyls in the environment are typically found near facilities that have made or used these substances. However, they have also been found at remote locations such as the Arctic and the open ocean. They may be subject to long-range transport. Perfluoroalkyls are very stable compounds and are resistant to being broken down in the environment. Perfluoroalkyls in the air are expected to settle to the ground within days to weeks. Perfluoroalkyls may be carried through soil by groundwater and flooding and become airborne during windy conditions.

HOW MIGHT I BE EXPOSED TO PERFLUOROALKYLS?

Exposure to perfluoroalkyl compounds is widespread. PFOA, PFOS, PFNA, and PFHxS were detected in 95–100% of samples of people's blood in 1999–2000 and 2003–2004. More recent monitoring data still show widespread exposure; however, the levels of these substances in people's blood appear to be declining. You may be exposed to perfluoroalkyls from the air, indoor dust, food, water, and various consumer products. Food is expected to be the primary source of exposure to perfluoroalkyls such as PFOA and PFOS for most people. Some communities near facilities where PFOA and PFOS were previously manufactured had high levels of these substances in drinking water supplies, and this is the primary route of exposure for these populations. Limited information has been located regarding pathways of human exposure to most of the other perfluoroalkyls discussed in this toxicological profile. Human breast milk may contribute to the exposure of infants to perfluoroalkyls since these substances have been detected in human breast milk. You may also be exposed to perfluoroalkyls from treated carpets and upholstery; this is especially true for children. The greatest source of exposure to PFOA and PFOS for toddlers and children is hand-to-mouth activities from treated carpets.

People who work where perfluoroalkyls are made or used are exposed to higher levels of these substances than the general population. Levels of PFOS and PFOA measured in the blood of some people who have

worked at these locations were higher than levels in people from the same communities who did not work at these locations. Workplace exposure also occurred for people with jobs that required frequent handling or use of perfluoroalkyl-treated substances, such as carpet installers. At sites where aqueous film-forming foam (AFFF) that contained perfluoroalkyl substances was used in firefighting, workers could be exposed to these substances and possibly transport them home from contaminated clothing.

HOW CAN PERFLUOROALKYLS ENTER AND LEAVE MY BODY?

Perfluoroalkyls can enter your body if you breathe air, eat food, or drink water containing them. We do not know how much will enter your body through your lungs or your digestive tract. If your skin comes into contact with dusts or aerosols of perfluoroalkyl or with liquids containing perfluoroalkyls, it is possible that a small amount may enter the body through your skin.

Once in your body, perfluoroalkyls tend to remain unchanged for long periods of time. The most commonly used perfluoroalkyls (PFOA and PFOS) stay in the body for many years. It takes approximately 4 years for the level in the body to go down by half, even if no more is taken in. It appears that, in general, the shorter the carbon-chain length, the faster the perfluoroalkyl leaves the body. Perfluoroalkyls leave the body primarily in the urine.

HOW PERFLUOROALKYLS CAN AFFECT YOUR HEALTH?

A large number of studies have examined the possible health effects of PFOA and PFOS in humans. The effect of inhalation exposure to PFOA and PFOS has been examined in workers exposed to high concentrations of these compounds. Studies have also examined a large community exposed to high levels of PFOA in the drinking water and compared this community to the general population; ingestion was the primary route of exposure for these two groups. Most human studies have looked for a relationship between levels of perfluoroalkyls in the blood and a health effect. It is difficult to interpret the results of these studies because they are not consistent; some studies have found associations, but others looking at the same health effect have not found these associations. Even though some studies have found significant associations between serum perfluoroalkyl levels and adverse health effects, it does not mean that perfluoroalkyls caused these effects. The effects may have been due to other factors that were not considered by the researchers. The available studies suggest that increases in blood cholesterol levels are associated with higher PFOA or PFOS blood levels in workers inhaling PFOA and/or PFOS as well as in people ingesting these compounds. There are data to suggest an association between serum PFOA and PFOS levels and increased uric acid levels, which may be associated with an

increased risk for high blood pressure. There is also some evidence that PFOA and PFOS exposure may cause liver damage.

Humans and rodents react differently to PFOA and PFOS, and not all of the effects observed in rats and mice may occur in humans. The liver appears to be the most sensitive target in animals ingesting perfluoroalkyls. The effects include increases in liver weight, changes in the liver cells, and changes in blood cholesterol and triglyceride levels. Studies in mice also found that the immune system is a sensitive target of PFOA and PFOS; effects include decreases in the size of the spleen and thymus and impaired immune function.

A short exposure of rats to very high levels of PFOA in the air caused irritation of the eyes and nose. Damage to the liver and weight loss were observed in rats exposed to lower levels of PFOA in the air.

Short-term application of large amounts of PFOA to the skin of animals has caused skin irritation and changes in the liver. These liver effects indicate that PFOA can be absorbed into the body through the skin and affect other parts of the body.

There is limited information on whether perfluoroalkyls can cause cancer in humans. Some increases in prostate, kidney, and testicular cancers have been found in workers or in community members living near a PFOA facility. These results should be interpreted cautiously because the effects were not consistently found and most studies did not control for other potential factors such as smoking. Feeding PFOA and PFOS to rats caused them to develop tumors. Some scientists believe that, based on the way this happens in rats and the differences between rats and humans, humans would not be expected to get cancer. Others believe that it is possible for perfluoroalkyls to cause cancer in humans, and the studies in rats should not be dismissed. More research is needed to clarify this issue. The International Agency for Research on Cancer and the Department of Health and Human Services have not yet evaluated the carcinogenicity of perfluoroalkyls. The EPA has begun an evaluation.

See Chapters 2 and 3 for more information on health effects of perfluoroalkyls.

HOW CAN PERFLUOROALKYLS AFFECT CHILDREN?

This section discusses potential health effects of perfluoroalkyls exposure in humans from when they’re first conceived to 18 years of age, and how you might protect against such effects.

No associations between serum PFOA and birth defects were observed in children of mothers living in an area with high PFOA levels in the water. Some studies of the general population and people living near a PFOA manufacturing facility have found that higher levels of serum PFOA or PFOS are associated with lower infant birth weights. However, the decrease in birth weight is small and may not affect the infant's health. A study in children exposed to high levels of PFOA in drinking water found increases in blood cholesterol, which was similar to the findings in adults.

Birth defects were seen in mice born to females that ingested relatively high amounts of PFOS during pregnancy. The blood PFOS levels associated with these effects were at least 10 times higher than the highest PFOS levels measured in workers. Oral exposure to PFOA and PFOS has resulted in early death and delayed development of mouse and rat pups, but this did not occur in animals exposed to PFBA or PFHxS. Alterations in motor activity have also been observed in mouse pups exposed to PFOA, PFOS, or PFHxS, but not PFDeA. Scientists believe that some of the effects observed in rats and mice exposed to PFOA or PFOS may not be relevant to humans.

HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PERFLUOROALKYLS?

If your doctor finds that you have been exposed to significant amounts of perfluoroalkyls, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

In the past, some perfluoroalkyls such as PFOA and PFOS were used in the manufacture of many consumer products, and low levels of these substances were detected in things such as treated carpeting, treated apparel, and paper food packaging. Companies are no longer using PFOA in the manufacture of Teflon coatings or PFOS in the manufacture of stain resistant carpet treatments; however, older products and imported materials may still contain these substances. Families may choose to use products that do not contain pre-treated stain repellent products or grease resistant food packaging. Families that have been told that their tap or well water contains high levels of perfluoroalkyls may choose to drink or cook with bottled water or to install activated carbon water filters in their drinking water system. Consuming bottled water and the use of activated carbon water filters have been shown to lead to lower PFOA levels in the blood over time by decreasing exposure to perfluoroalkyl compounds.

ARE THERE MEDICAL TESTS TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PERFLUOROALKYLS?

Perfluoroalkyl compounds can be measured in blood, but this is not a routine test that can be performed in a doctor's office. You should, however, see a physician if you believe that you have been exposed to high levels of perfluoroalkyls. Perfluoroalkyls have been measured in blood samples in 2009–2010 from a representative sample of the U.S. general population; the geometric mean serum PFOA and PFOS concentrations were 3.07 and 9.32 µg/L, respectively. Elevated serum PFOA levels were reported in Mid-Ohio Valley residents who had environmental exposure to PFOA from drinking water contaminated by a nearby industrial facility. The range of median serum PFOA levels across several communities was 12.1–224.1 ng/mL and the mean serum PFOA concentration across all of the communities was 83.6 µg/L in 2005. Higher serum perfluoroalkyl concentrations have been reported in fluorochemical product workers. Mean serum PFOA and PFOS levels for at one facility were 1,780 and 1,320 µg/L, respectively. Workers at another facility had serum PFOA levels of 1,000 µg/L.

For more information on tests to detect these substances in the body, see Chapters 3 and 7.

WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

Regulations and recommendations can be expressed as "not-to-exceed" levels; that is, levels of a toxic substance in air, water, soil, or food that do not exceed a critical value usually based on levels that affect animals; levels are then adjusted to help protect humans. Sometimes these not-to-exceed levels differ among federal organizations. Different organizations use different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or emphasize some factors over others, depending on their mission.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that issued the regulation or recommendation.

The EPA has recommended provisional drinking water health advisories of 0.4 µg/L for PFOA and 0.2 µg/L for PFOS. OSHA has not set any legal limits for perfluoroalkyl compounds in air. NIOSH has not set any recommended limits for perfluoroalkyl compounds in air.

WHERE CAN I GET MORE INFORMATION?

If you have any questions or concerns, please contact your community or state health or environmental quality department, or contact ATSDR at the address and phone number below. ATSDR can also provide publically available information regarding medical specialists with expertise and experience recognizing, evaluating, treating, and managing patients exposed to hazardous substances.

- Call the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636) or

- Write to:
  Agency for Toxic Substances and Disease Registry
  Division of Toxicology and Human Health Sciences
  1600 Clifton Road NE
  Mailstop F-57
  Atlanta, GA 30329-4027

Toxicological profiles and other information are available on ATSDR's web site: http://www.atsdr.cdc.gov.

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PERFLUOROALKYLS IN THE UNITED STATES

Perfluoroalkyls constitute a class of compounds that have been used extensively in surface coating and protectant formulations due to their unique surfactant properties. Major applications have included protectants for paper and cardboard packaging products, carpets, leather products, and textiles that enhance water, grease, and soil repellency. Perfluoroalkyls have also been used as processing aids in the manufacture of fluoropolymers such as nonstick coatings on cookware.

Perfluoroalkyls are human-made substances that do not occur naturally in the environment. The perfluoroalkyls substances discussed in this profile, especially perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), have been detected in air, water, and soil in and around fluorochemical facilities; however, these industrial releases have been declining since companies began phasing out the production and use of several perfluoroalkyls in the early 2000s. Information regarding current releases of shorter-chain perfluoroalkyls that are not included under phase-out regulations, such as perfluorobutyric acid (PFBA) and perfluorobutane sulfonic acid (PFBuS) have not been located. Production of PFBA in the United States appears to have ceased, although some is reportedly imported for commercial use. In the environment, some of the perfluoroalkyls discussed in this profile can also be formed from environmental degradation of precursor compounds that had been released during the use of consumer products containing perfluoroalkyls.

Due to their chemical structure, perfluoroalkyls are very stable in the environment and are resistant to biodegradation, photoxidation, direct photolysis, and hydrolysis. The perfluoroalkyl carboxylic acids and sulfonic acids have very low volatility due to their ionic nature. As a group, perfluoroalkyls are persistent in soil and water. Perfluoroalkyls are mobile in soil and leach into groundwater. Volatile fluorotelomer alcohols may be broken down into substances like PFOA, and atmospheric deposition can lead to contamination of soils and leaching into groundwater away from point sources. Perfluoroalkyls have been detected in environmental media and biota in many parts of the world, including oceans and the Arctic, indicating that long-range transport is possible.

PFOA and PFOS have been measured in outdoor urban air samples at concentrations up to 46 and 919 pg/m^3, respectively. Concentrations of other perfluoroalkyls measured in outdoor air are generally <1 pg/m^3. Reported concentrations of perfluoroalkyls measured in four indoor air samples were

<5 pg/m^3. PFOA, PFOS, and perfluorohexane sulfonic acid (PFHxS) have been detected in indoor dust samples at concentrations of <2.29–3,700, <4.56–5,065, and <4.56–4,305 ng/g, respectively. Reported concentrations of perfluoroalkyls measured in surface water samples are generally <50 ng/L. Concentrations of perfluoroalkyls in groundwater, drinking water, soil, and sediment can vary substantially by location, especially if there is a local point source of these substances nearby. Perfluoroalkyls have been detected in different types of foods at reported concentrations ranging from 0.05 to 10,000 ng/g fresh weight. Perfluoroalkyls have also been detected in consumer products such as treated carpeting, treated apparel, and paper food packaging. Elevated concentrations of perfluoroalkyls have been measured in air, water, soil, and sediment near industrial facilities that used or manufactured fluorochemicals.

The highest concentrations of perfluoroalkyls in animals are measured in apex predators, such as polar bears, which indicates that these substances biomagnify in food webs. The bioaccumulation potential of perfluoroalkyls is reported to increase with increasing chain length. As the chain length increases from four to eight carbons, the bioaccumulation potential increases, and then declines with further increases in chain length. In living organisms, perfluoroalkyls bind to protein albumin in blood, liver, and eggs, but do not accumulate in fat tissue. Studies in mammals demonstrate substantial differences in elimination half-times across chemical species and animal species. The elimination half-times increase with chain length, and the sulfonate compounds have longer half-times than carboxylic acid compounds with the same chain length.

Mean PFOA, PFOS, and PFHxS serum concentrations reported in various studies of the general population in the United States are 2.1–9.6, 14.7–55.8, and 1.5–3.9 ng/mL (ppb), respectively. Mean concentrations of perfluoroheptanoic acid (PFHpA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDeA), perfluoroundecanoic acid (PFUA), perfluorododecanoic acid (PFDoA), PFBuS, PFBA, perfluorooctane sulfonamide (PFOSA), 2 (N-methyl-perfluorooctane sulfonamide) acetic acid (Me-PFOSA-AcOH), and 2-(N ethyl-perfluorooctane sulfonamide) acetic acid (Et-PFOSA-AcOH) were generally <1 ng/mL in these studies.

Based on environmental measurements and theoretical models, one study has proposed that the major exposure pathways for PFOS for the general population in Europe and North America are food and water ingestion, dust ingestion, and hand-to-mouth transfer from mill-treated carpets. For PFOA, major exposure pathways were proposed to be oral exposure resulting from migration from paper packaging and wrapping into food, general food and water ingestion, inhalation from impregnated clothes, and dust

ingestion. This includes exposure to 8:2 fluorotelomer alcohol in food packaging and air, which can be broken down into PFOA. PFOS and PFOA exposure pathways are proposed to be similar for children except that exposure from hand-to-mouth transfer from treated carpets is expected to be much greater in children. Based on these exposure pathways, adult uptake doses estimated for high-exposure scenarios were approximately 30 and 47 ng/kg/day for PFOS and PFOA, respectively. PFOS and PFOA doses estimated for children under the age of 12 under high exposure scenarios were 101–219 and 65.2–128 ng/kg/day, respectively. A study evaluated potential exposure to perfluorocarboxylate homologues for different populations and also concluded that dietary intake was the primary background exposure pathway for the general population, while inhalation of indoor air was the main exposure pathway for occupationally exposed individuals with estimated intakes of >150 ng/kg/day. Ingestion of contaminated drinking water has been shown to be the major route of exposure for humans in communities located close to industrial facilities where PFOA is used.

Perfluoroalkyls have been detected in human breast milk and umbilical cord blood. The reported maximum concentrations of PFOS and PFOA measured in human breast milk samples were 0.360–0.639 and 0.210–0.490 ng/mL, respectively. Maximum concentrations of other perfluoroalkyl compounds were <0.18 ng/mL. In most umbilical cord samples, the concentrations of PFOS and PFOA were 4.9–11.0 and 1.6–3.7 ng/mL, respectively. Other perfluoroalkyls have been detected less frequently, with maximum concentrations <2.6 ng/mL.

2.2 SUMMARY OF HEALTH EFFECTS

Effects in Humans. Perfluoroalkyls are ubiquitous chemicals in the environment; they are readily absorbed following inhalation or oral exposure and are not metabolized in the body. Elimination half-times in humans of 3.8 years, 5.4 years, 8.5 years, 665 hours, and 72 hours have been estimated for PFOA, PFOS, PFHxS, PFBuS, and PFBA, respectively. Perfluoroalkyl compounds have been detected in the serum of workers, residents living near perfluoroalkyl facilities, and the general population. A large number of studies have evaluated the toxicity of perfluoroalkyls in humans by examining possible associations between serum perfluoroalkyl levels and adverse health effects. Most of the studies have focused on PFOA and/or PFOS. The human studies fall into three broad categories: occupational exposure primarily to airborne PFOA and PFOS, exposure to PFOA contaminated drinking water by residents living near a PFOA production facility, and exposure of the general population to background levels in the environment. Most of the occupational exposure studies were conducted in workers at four facilities in Minnesota, Alabama, West Virginia, and the Netherlands. Studies of the highly exposed

residents primarily come from several large scale studies (C8 Health Project, C8 Health Study) conducted in Mid-Ohio Valley residents living near the Washington Works facility in West Virginia with high levels of PFOA in the drinking water. One limitation of the C8 Health Studies is that they used blood samples collected in 2006; the facility started using PFOA in the 1950s and peak usage was in the 1990s. By 2003, there was an 87% decline in PFOA emissions, as compared to 1999 levels. General population studies primarily utilized data collected in the National Health and Nutrition Examination Surveys (NHANES) in the United States and several large-scale health studies conducted in Europe. Most of the epidemiology studies lack exposure monitoring data and there is a potential for multiple sources of exposure (inhalation and oral); however, most of the studies have used serum perfluoroalkyl levels as a biomarker of exposure. Of the three categories of subjects, workers have the highest potential exposure to perfluoroalkyls, followed by the highly-exposed residents in the Mid-Ohio Valley, and then the general population. In one study of workers at the Washington Works facility in West Virginia, the average serum PFOA level in 2001–2004 was 1,000 ng/mL; the mean PFOA level in highly-exposed residents (without occupational exposure) near this facility was 423 ng/mL in 2004–2005. By comparison, the geometric mean concentration of PFOA in the U.S. population was 3.92 ng/mL in 2005–2006. Although a large number of epidemiology studies have examined the potential of perfluoroalkyl compounds to induce adverse health effects, most of the studies were cross-sectional in design and did not establish causality. ATSDR used a weight-of-evidence approach to evaluate whether the available data supported a link between perfluoroalkyl exposure and a particular health effect. This weight-of-evidence approach takes into consideration the consistency of the findings across studies, the quality of the studies, dose-response, and plausibility. It should be noted that although the data may provide strong evidence for an association, it does not imply that the observed is biologically relevant because the magnitude of the change is within the normal limits or not indicative of an adverse health outcome. Plausibility depends primarily on experimental toxicology studies that establish a plausible biological mechanism for the observed effects.

Epidemiology studies have found statistically significant associations between serum perfluoroalkyl levels (particularly PFOA and PFOS) and a wide range of health effects. When the subjects were categorized by serum perfluoroalkyl levels, dose-response relationships were found for most of the effects. However, findings were not always consistent across studies. However, consistent findings were found for association of serum PFOA and PFOS with increases in serum lipid levels, decreases in birth weight, increases in uric acid levels, and alterations in biomarkers of liver damage. There was also equivocal evidence of carcinogenicity. Although other effects have been reported, they have not been consistently found in similar types of studies, have only been examined in a single study, or were only

found in general population studies. For a more detailed discussion of all of the effects observed in the epidemiology studies, the reader is referred to Section 3.2 of the toxicological profile.

Studies of workers, highly exposed individuals, and the general population have reported significant associations between serum perfluoroalkyl levels and serum lipid levels. However, because a number of factors can influence serum lipid levels, many of the studies adjusted for some of these potential confounders such as age, body mass index (BMI), and the use of cholesterol-lowering medication. The most consistently found alteration in serum lipid levels was increased serum total cholesterol levels. Statistically significant associations between serum PFOA levels and total cholesterol levels have been found in workers, residents of communities with high levels of PFOA in the drinking water, and the general population. Serum PFOS levels were also significantly associated with serum total cholesterol levels in workers, residents exposed to high levels of PFOA, and the general population. However, some studies of workers, highly-exposed residents, or the general population have not found associations between perfluoroalkyl exposure and total cholesterol levels. Studies in which the subjects were distributed into groups based on serum perfluoroalkyl levels typically found that subjects with the highest serum PFOA or PFOS levels had significantly higher total cholesterol levels than subjects with lowest serum PFOA or PFOS levels. A study of children and adolescents living in an area with high PFOA contamination also found an increased risk of high cholesterol levels (≥170 mg/dL). Similarly, an increased odds of high cholesterol (≥240 mg/dL) was observed in highly exposed adults with high serum PFOA and PFOS levels. Evidence of associations between serum perfluoroalkyl levels and other serum lipids is not as strong. Although increases in serum low-density lipoprotein (LDL)-cholesterol and triglyceride levels have been found in studies of workers and highly exposed individuals, a number of other studies have not found significant alterations. The relationship between perfluoroalkyl exposure and increases in serum lipid levels from longitudinal studies conducted in workers and highly exposed residents provide some evidence of an association. Serum PFOA levels were found to be a significant predictor of serum cholesterol levels in workers examined at least twice in a ≥5-year period. Similarly, a study of highly-exposed residents examined twice with approximately 4 years between examinations found that there were 3.6 and 1.7% decreases in serum LDL-cholesterol and total cholesterol levels, respectively, in subjects whose serum PFOS levels decreased by 50% between examinations. A 50% decrease in serum PFOS levels resulted in 5.0 and 3.2% decreases in LDL-cholesterol and total cholesterol. In addition, a greater change in cholesterol level per unit change in serum PFOA level was found at lower ranges of PFOA. A suggested explanation for this finding is a steep dose-response curve at low PFOA levels and a flattening out of the curve at higher PFOA levels. The mechanisms for the increased serum cholesterol in individuals with high serum PFOA and/or PFOS levels have not been

identified. Animal studies, particularly in rodents, have found alterations in serum lipid levels following oral exposure to PFOA or PFOS. However, these animal studies have found decreases in serum cholesterol levels, which is the opposite effect observed in humans. The difference may be related to differences in exposure levels; the animals were likely exposed to much higher doses of PFOA and PFOS. The differences may also be the result of different mechanisms of toxicity, or species differences in response to PFOA and PFOS.

A number of human studies have used serum liver enzymes as biomarkers of possible liver effects. In occupational exposure studies, no associations between serum liver enzymes (primarily, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and γ-glutamyl transpeptidase [GGT]) and serum PFOA or PFOS levels were consistently found. A study of residents highly exposed to PFOA found significant associations between serum PFOA and serum PFOS levels and ALT and bilirubin levels. The study also found increased risk of high ALT levels in subjects with higher PFOA and PFOS levels. Although associations were found, the magnitude of the increased serum enzymes were not great, and were probably not biologically significant. Occupational exposure studies have not found increases in deaths from liver cirrhosis or increases in the occurrence of liver disorders or cirrhosis. Studies in rats, mice, and monkeys have identified the liver as one of the most sensitive targets of toxicity; the data in humans are not as convincing. However, serum PFOA and PFOS levels were much lower than those associated with effects in animals.

Five studies have examined the possible association between serum PFOA and/or PFOS levels and uric acid levels. Based on epidemiology data, an elevated uric acid level appears to be a risk factor for hypertension and possibly renal disease. Significant associations between serum PFOA and uric acid levels were found in PFOA workers, residents highly exposed to PFOA, and adults and adolescents exposed to background levels. Increased risks of hyperuricemia were also associated with higher serum PFOA and PFOS levels in the highly exposed residents and the general population. A study of highly exposed residents found an increased prevalence of high blood pressure when subjects were categorized by age and sex. A general population study also found a significant association between serum PFOA levels and systolic blood pressure. Additionally, a study of highly exposed residents found significant associations between serum PFOA and PFOS levels and the odds of pregnancy-induced hypertension. However, another study that used predicted serum PFOA levels did not find a significant association. Two studies of highly exposed residents also found an increased risk of pre-eclampsia among women with higher serum PFOA levels. Animal studies have not examined the potential of perfluoroalkyl compounds to induce hypertension.

There is evidence to suggest that high serum PFOA or PFOS levels are associated with lower birth weights. The significant associations have come from general population studies and a study of highly exposed residents. Studies of populations with lower serum PFOA or PFOS levels have not found significant associations for birth weight. Although significant associations were found, decreases in birth weight were small and may not be biologically relevant. No studies found an increased risk of low birth weight in infants (<2,500 g) in highly exposed residents.

A number of studies have examined the carcinogenicity of PFOA and PFOS in humans. Occupational exposure studies have found significant increase in deaths from several cancer types, including prostate cancer at one facility and kidney cancer at a second facility. An increase in the risk of kidney cancer was also found in residents living near the second facility. An increased risk of testicular cancer was also found in the highly exposed residents living near the second facility. Other occupational exposure studies have not found significant increases in cancer risks. Although several studies have found significant increases in cancer risk, the results should be interpreted cautiously since most studies did not control for potential confounding variables (particularly smoking), the number of cancer cases was low, and a causal relationship between perfluoroalkyls and cancer cannot be established from these studies. Additionally, the lack of consistency across facilities may be suggestive of a causative agent other than PFOA or PFOS.

Effects in Laboratory Animals. Most of the information regarding the effects of perfluoroalkyl compounds in animals is derived from oral studies; considerably less information is available from inhalation and dermal exposure studies. PFOA and PFOS are the most studied perfluoroalkyl compounds, with considerably less data for the other compounds. The primary effects observed in laboratory animals exposed to perfluoroalkyl compounds are liver toxicity, developmental toxicity, and immune toxicity; not all of these effects have been observed or examined for all perfluoroalkyl compounds. Based on limited data, the toxicity of perfluoroalkyl compounds does not appear to be specific to the route of administration. It should be noted that, for the most part, adverse health effects in studies in animals have been associated with exposure concentrations or doses that resulted in blood levels of perfluoroalkyl compounds that were significantly higher than those reported in perfluoroalkyl workers or in the general population. It is important to note that there are profound differences in the toxicokinetics of perfluoroalkyls between humans and experimental animals. The elimination half-time of PFOA and PFOS is approximately 4 years in humans compared with days or hours in rodents. These factors, plus issues related to the mode of action of perfluoroalkyls (see below), make it somewhat

difficult at this time to determine the true relevance of some effects reported in animal studies to human health.

Many of the adverse health effects observed in laboratory animals result from the ability of these compounds (with some structural restrictions) to activate the peroxisome proliferator-activated receptor-α (PPARα), which can mediate a broad range of biological responses. Species differences in the response to PPARα agonists have been found; rats and mice are the most sensitive species and guinea pigs, nonhuman primates, and humans are less responsive. Although humans are less responsive to PPARα agonists, they do have a functional PPARα. Several explanations for these species differences have been suggested, e.g., differences in the ability of PPARα to be induced after exposure to a peroxisome proliferator, and differences in the pattern and level of tissue-specific expression of PPARα. Activation of this receptor in rodents initiates a characteristic sequence of morphological and biochemical events, principally, but not exclusively, in the liver. These events include marked hepatocellular hypertrophy due to an increase in number and size of peroxisomes, a large increase in peroxisomal fatty acid β-oxidation, an increased CYP450-mediated ω-hydroxylation of lauric acid, and alterations in lipid metabolism. There is also evidence that some developmental effects such as decreased pup survival and immune effects also result from peroxisome proliferation. Studies in PPARα-null mice provide evidence that PPARα-independent mechanisms are also involved in PFOA and PFOS toxicity, including liver toxicity. A more complete discussion of the mechanisms of PFOA and PFOS toxicity is presented in Section 3.5.2.

Inhalation Exposure

There are very limited data on the toxicity of inhaled perfluoroalkyl compounds, which consist of a few studies with PFOA dusts and one study with PFNA dusts. The available data suggest that the liver is the most sensitive target for perfluoroalkyl compounds. In male rats, absolute and relative liver weight increased and microscopic examination showed hepatocellular hypertrophy and necrosis following intermittent head-only exposure to 7.6 mg/m^3 PFOA dusts for 2 weeks. In the study with PFNA, nose-only exposure of male rats to 67 mg/m^3 (the lowest concentration tested) PFNA dusts for 4 hours induced a significant increase in liver weight; no histological evaluation was performed. Liver histopathology was also reported in rats following intermittent dermal application of 20 mg/kg PFOA to male rats for 2 weeks. In mice, application of 6.2 mg/kg, but not 2.5 mg/kg, PFOA to the skin once a day for 4 days also induced hepatomegaly.

Oral Exposure

Liver Effects. Many studies have described morphological and biochemical alterations in the liver from rodents following acute and longer-term oral exposure to PFOA. Some of the effects observed in rats include increases in liver weight, hepatocellular hypertrophy, and decreases in serum cholesterol and triglyceride levels. The observed hepatomegaly and hypertrophy is likely due to proliferation of the smooth endoplasmic reticulum and proliferation of peroxisomes, as confirmed by increased activity of biochemical markers and light and electron microscopy. It is important to note also that there appears to be different sensitivities for different end points. For example, in male rats dosed with PFOA for 14 days, absolute liver weight and fatty acid β-oxidation activity were significantly increased at 2 mg/kg/day, whereas hepatic microsomal concentration of total cytochrome P-450 was significantly increased at 20 mg/kg/day. In general, longer-term studies with PFOA have shown that the hepatic effects are reversible once dosing ceases and that recovery tends to parallel the decline in blood levels of PFOA. Studies in mice have provided similar results. However, studies in PPARα-null mice suggest that hepatomegaly may also be due to a PPARα-independent process in mice, since PFOA induced hepatomegaly to the same extent in wild-type mice and PPARα-null mice, but failed to increase acyl-CoA oxidase activity in PPARα-null mice. PFOA exposure also resulted in increases in absolute liver weight in monkeys treated with ≥3 mg/kg/day for 26 weeks, an effect that was partly associated with significant mitochondrial proliferation, but not peroxisome proliferation.

Similar to PFOA, PFOS exposure results in increases in liver weight, hepatocellular hypertrophy, and decreases in serum cholesterol and triglyceride levels in rodents. PFOS induced an increase in absolute liver weight, decreased serum cholesterol, and hepatocellular hypertrophy and lipid vacuolation in monkeys in a 26-week study. Not unexpectedly, there was no evidence of peroxisome proliferation and no increase in hepatic palmitoyl-CoA oxidase, consistent with the fact that monkeys (and humans) seem to be refractory to peroxisome proliferative responses.

Studies with other perfluoroalkyl compounds have shown that, in general, liver weight and parameters of fatty acid β-oxidation are more severely affected as the carbon length increases up to about a 10-carbon chain length. Significant peroxisome activity seems to require a carbon length >7, but increases over control levels have been reported with a four-carbon chain length. Studies have shown that the differential activity is not directly related to the carbon length *per se*, but to differential accumulation in the liver. Hydrophobicity, which increases as carbon length increases, seems to favor biliary enterohepatic recirculation, resulting in a more protracted toxicity. While perfluoroalkyl compounds

share many effects on lipid metabolism, treatment of rats with PFDeA does not result in the characteristic hypolipidemia associated with peroxisome proliferation, but instead results in the accumulation of lipids in the liver, apparently by diverting fatty acids from oxidation toward esterification in the liver. In addition, in an acute dietary study comparing the hepatic effects of PFOA and PFDeA, PFDeA was considerably more toxic to hepatocytes than PFOA, as reflected by the production of lipid droplets containing amorphous material, a sign of acute metabolic disorders.

Developmental Effects. PFOA and PFOS have induced developmental effects in rodents. Most studies with PFOA have been conducted in mice, probably because of the relatively short half-life for PFOA in female rats, which would prevent accumulation of PFOA during the dosing period. Specific effects reported include prenatal loss, reduced neonate weight and viability, neurodevelopment toxicity, and delays in mammary gland differentiation, eye opening, vaginal opening, and first estrus. These effects occurred generally in the absence of overt maternal toxicity. Some of these effects, such as reduced pup survival from birth to weaning, have been observed in mice treated with as low as 0.6 mg/kg/day PFOA on gestation days (GDs) 1–17. This dose level resulted in mean serum PFOA concentrations of 5,200 and 3,800 ng/mL in dams and pups, respectively, on postnatal day (PND) 22. A cross-fostering study in mice showed that *in utero*, lactation only, and *in utero* and lactation exposure resulted in significant decreases in postnatal growth. Alterations in spontaneous behavior were reported in 2- or 4-month-old male mice that were administered a single gavage dose of PFOA at the age of 10 days. Increases in motor activity were also observed following *in utero* exposure to PFOA. A cross-fostering study showed that the delays in mammary gland development were observed following *in utero* exposure and following lactation-only exposure; however, the results of a 2-generation study showed that the delayed development did not appear to affect lactational support. No fetal toxicity or teratogenicity was reported in offspring of rabbits exposed to up to 50 mg/kg/day PFOA on GDs 6–18, suggesting that rabbits are less susceptible than mice to the developmental effects of PFOA, although comparing administered doses is probably not very informative. There were significant increases in body weight gain in mice aged 10–40 weeks that were exposed to low levels of PFOA (0.01–0.3 mg/kg/day) on GDs 1–17. Increases in serum insulin and leptin levels were also observed, but there was no change in serum glucose or the response to a glucose challenge. A comparison of the effects of *in utero* exposure (GDs 1–17) to adult exposure (17 days at age 8 weeks) demonstrated that *in utero* exposure resulted in higher body weights, white fat weight, and brown fat weight at age 18 months.

Studies conducted with wild-type and PPARα knockout mice showed that PPARα was required for PFOA-induced postnatal lethality and that the expression of one copy of the gene was sufficient to

mediate this effect. There was no effect of strain or PPARα expression on serum PFOA levels. The mechanism of reduced postnatal viability has not been elucidated. Alterations in gene expression in both fetal liver and lung have been reported following exposure of mice to PFOA during pregnancy. In the liver, PFOA altered the expression of genes linked to fatty acid catabolism, lipid transport, ketogenesis, glucose metabolism, lipoprotein metabolism, cholesterol biosynthesis, steroid metabolism, bile acid biosynthesis, phospholipid metabolism, retinol metabolism, proteosome activation, and inflammation. In the lung, transcriptional-related changes were predominantly associated with fatty acid catabolism. Although decreased pup survival appears to be linked to PPARα expression, there are insufficient data to determine whether other developmental effects observed in rats and mice are PPARα-independent.

PFOS significantly decreased birth weight and survival in neonatal rats exposed *in utero*, and cross-fostering exposed pups with unexposed dams failed to improve survival rates. PFOS serum levels of pups at birth associated with significant decreased survival were approximately ≥70,000 ng/mL. Dosing rats late during gestation (GDs 17–20) caused significantly more lethality than dosing early (GDs 2–5). Since pups had difficulty breathing within minutes of birth and their lungs showed evidence of delayed lung maturation and other histological alterations, the possibility that this caused the early death has been suggested. Other effects include decreases in birth weight or pup body weight, delays in eye opening, cleft palate, and neurodevelopmental alterations. Alterations in spontaneous motor activity were observed in mice. A decrease in activity was observed when mice were placed in a novel environment; another study found a decrease in motor activity followed by increased activity. Evaluation of immunological parameters in 8-week-old pups from mice exposed to PFOS during gestation showed reduced natural killer (NK) cell activity, suppressed IgM response to immunization, and alterations in splenic and thymic lymphocyte subpopulations.

Similar to PFOA and PFOS, increases in fetal mortality were observed in mice exposed to PFDeA on GDs 6–15. In contrast, gestational exposure to PFBA or PFHxS did not result in alterations in pup survival or pup body weight. Decreases in spontaneous activity followed by an increase in activity were observed in mice exposed to PFHxS on PND 10; no alterations were observed in mice similarly exposed to PFDeA.

Immunological Effects. A number of studies have examined the immunotoxicity of perfluoroalkyls in rats and mice; these data suggest that mice are considerably more sensitive than rats. PFOA- and PFOS-induced immunological alterations in adult mice are characterized by thymus and spleen atrophy, alterations in thymocyte and splenocyte phenotypes, and impaired response to T-dependent antigens. The

lowest lowest-observed-adverse-effect level (LOAEL) for immune effects in mice exposed to PFOA was 3.75 mg/kg/day administered for 15 days; this dosing level resulted in a mean PFOA serum level of 75,000 ng/mL. For PFOS, several studies identified LOAELs of 0.02–0.8 mg/kg/day and one study identified a LOAEL of 0.00166 mg/kg/day for suppressed response to a T-dependent antigen. PFOA applied to the skin of mice increased serum IgE levels following a challenge with ovalbumin relative to mice treated with ovalbumin alone, which led the investigators to suggest that PFOA may increase the IgE response to environmental allergens.

Reproductive Effects. Neither PFOA nor PFOS affected fertility parameters in 2-generation reproductive studies in rats, and neither did PFHxS in a reproductive study in rats. However, PFOA delayed mammary gland differentiation in mice dosed during gestation. In general, acute- and intermediate-duration studies did not find morphological alterations in the sex organs from rats or monkeys. However, PFOA significantly increased the incidences of Leydig cell hyperplasia, vascular mineralization in the testes, and tubular hyperplasia in the ovaries in rats in 2-year dietary studies. PFOA increased serum estradiol levels in male rats by increasing the activity of aromatase (the enzyme that coverts testosterone into estradiol) in the liver. The increase in serum estradiol was thought to be responsible for a decrease in the weight of the accessory sex organ unit, a decrease in serum testosterone, and Leydig cell hyperplasia and adenoma. Serum estradiol was also found elevated in male rats treated acutely with PFDoA.

Cancer Effects. PFOA, as many other PPARα agonists, induced hepatocellular adenomas, Leydig cell adenomas, and pancreatic acinar cell adenomas in rats. However, it is uncertain whether or not this mode of action is relevant for risk assessment in humans. An extensive review of the literature concluded that although humans possess PPARα at sufficient levels to mediate the human hypolipidemic response to therapeutic fibrate drugs, there are enough qualitatively and quantitative differences between the response of the human liver to PPARα agonists and that of rats (due to differences in gene promoters, receptors activities, and receptor levels) that make the mode of action for liver tumors in animals unlikely to be operative in humans. An expert panel convened by EPA's Science Advisory Board to review this and other issues related to the toxicity of PFOA agreed that, collectively, the weight of evidence supports the hypothesis that induction of liver tumors in rats by PFOA is mediated by a PPARα agonism mode of action. A majority of the panel members also expressed the view that it is possible that PPARα agonism may not be the only mode of action for PFOA, that not all steps in the pathway of PPARα-mediated liver tumors have been demonstrated, that other hepatoproliferative lesions require clarification, and that extrapolation of the PPARα-mediated mode of action across humans of all ages is not supported. As mentioned above, increased serum estradiol due to induction of hepatic aromatase activity by PFOA was

proposed as a mode of action for PFOA-induced Leydig cell tumors in rats. A second mode of action involves inhibition of testosterone biosynthesis with consequent increases in circulating luteinizing hormone (LH), which promotes Leydig cell proliferation. A review of the data concluded that there is inadequate evidence to link PPARα and induction of Leydig cell tumors. Regarding the relevance of the second mode of action to humans, it is noted that: humans are less sensitive than rats to LH stimulation; the number of LH receptor/Leydig cells is 13-fold higher in rats than humans; an intermediate-duration study in Cynomolgus monkeys did not find treatment-related alterations in serum estradiol, estrone, estriol, or testosterone; and occupational exposure studies have not consistently reported alterations in estradiol or testosterone levels. The mechanism of PFOA-induced pancreatic acinar cell tumors has not been elucidated. The available evidence suggests that the mode of action involves stimulation of PPARα leading to reduced bile flow and/or changes in bile acid composition with subsequent increase in cholecystokinin (CCK), which stimulates pancreatic cell proliferation and tumor formation. However, a number of factors, including differences in the expression of PPARα and CCK_A receptors, in exocrine secretion regulation, and in types of pancreatic cancers between humans and rodents, suggest that PFOA probably does not represent a significant pancreatic cancer hazard for humans. EPA's expert panel agreed that the available evidence is inadequate to support a PPARα-mediated mode of action for the induction of Leydig cell tumors and pancreatic acinar cell tumors, and that at the time the review was conducted, there were insufficient data to characterize the mode of action of PFOA-induced testicular and pancreatic tumors. Under EPA's Cancer Guidelines, in the absence of sufficient data to establish a mode of action, animal tumor responses are presumed to be relevant to humans.

PFOS did not induce malignant tumors in a bioassay conducted in rats, but it increased the incidence of liver hepatocellular adenoma in rats exposed to PFOS for 2 years, and it increased the incidence of thyroid follicular cell adenoma in rats exposed for 1 year and allowed to recovery for an additional year. Liver adenomas were not observed in the rats allowed to recovery for 1 year, and thyroid tumors were not observed in the rats exposed for 2 years, consistent with a PPARα mechanism.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for perfluoroalkyls. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on

noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

The toxicity of perfluoroalkyl compounds, particularly PFOA and PFOS, has been extensively evaluated in humans and laboratory animals, and a number of issues need to be considered when deriving MRL values for these compounds. The issues include inconsistent findings in epidemiology studies; lack of clearly identified no-observed-adverse-effect levels (NOAELs) and LOAELs in the human studies; toxicokinetic differences between species, including a wide-range of half-times; species differences in the mechanisms of toxicity, particularly peroxisome proliferation; and lack of consistency between effects observed in humans and those observed in laboratory animals. There is relatively little animal or human data on the health effects of other perfluoroalkyl compounds.

Human Data. No studies are available regarding controlled exposures of volunteers to perfluoroalkyl compounds. As summarized in Section 2.2, health evaluations have been conducted of workers exposed to perfluoroalkyls, residents living near a PFOA manufacturing facility with high levels of PFOA in the drinking water, and members of the general population presumably exposed to background levels of PFOA. The epidemiology studies lack environmental monitoring data; however, most studies used serum perfluoroalkyl levels as a biomarker of exposure. A wide range of effects have been statistically associated with serum perfluoroalkyl levels; however, there is a lack of consistency of the findings across studies and across types of studies. Based on the weight of evidence, there is support for identifying several health effects in humans that appear to be related to perfluoroalkyl exposure: increases in serum lipid levels; increases in uric acid, a possible biomarker for hypertension; small decreases in birth weight; and possible changes in biomarkers of liver damage. The magnitude of the changes in birth weight and serum liver enzymes observed in the human studies are small and not likely biologically relevant.

Serum PFOA levels (Costa 2004; Costa et al. 2009; Eriksen et al. 2013; Frisbee et al. 2010; Olsen et al. 2003a; Sakr et al. 2007a, 2007b; Steenland et al. 2009b) and PFOS (Château-Degat et al. 2010; Eriksen et al. 2013; Frisbee et al. 2010; Nelson et al. 2010; Olsen et al. 1999, 2003a; Steenland et al. 2009b) were statistically associated with serum cholesterol levels in studies of workers, residents of communities with high levels of PFOA in the drinking water, and the general population. Additionally, increases in the risk of high cholesterol were observed in adults (Steenland et al. 2009b) and children and adolescents (Frisbee et al. 2010) living in an area with high serum PFOA in the drinking water. The increased risk of high cholesterol levels (≥240 mg/dL) was observed in adults with serum PFOA levels of 13.2–26.5 ng/mL and higher or serum PFOS levels of 13.3–19.5 ng/mL and higher (Steenland et al. 2009b). These data should be interpreted cautiously since associations between serum PFOA or PFOS are attenuated at higher serum perfluoroalkyl levels and a 20–30% attenuation was found when serum PFOA and PFOS levels were considered together in the same model for serum cholesterol levels (Steenland et al. 2009b).

The association between serum perfluoroalkyl levels and serum uric acid levels has not been as well investigated as serum lipids. However, the five studies examining this end point have all reported statistically significant findings. Significant associations of serum uric acid levels with serum PFOA levels were found in workers (Costa et al. 2009; Sakr et al. 2007b) and with serum PFOA and PFOS in highly exposed residents (Steenland et al. 2010b) and the general population (Geiger et al. 2013; Shankar et al. 2011b). The study of highly exposed residents also found significant increases in the risk of hyperuricemia (>6.0 mg/dL for women and >6.8 mg/dL for men) in subjects with serum PFOA levels of 11.5–20.6 ng/mL and higher or serum PFOS levels of 17.5–23.2 ng/mL and higher (Steenland et al. 2010b). In the general population study, which utilized the NHANES data set, an increased risk of hyperuricemia was observed at serum PFOA levels of 3.5–5.1 ng/mL and higher or serum PFOS levels of 11.2–17.8 ng/mL and higher (Shankar et al. 2011b). It should be noted that serum PFOA or PFOS levels accounted for <1% of the variance in serum uric acid levels (Steenland et al. 2010b).

It could be proposed that serum perfluoroalkyl levels associated with increased risks of high serum cholesterol levels or hyperuricemia be used as the basis for developing an MRL. Of the two end points, the increased risk of high cholesterol is the stronger given the well-established association between serum cholesterol levels and the risk of heart disease. However, there are a number of factors that should be considered. Although 11 studies found significant associations between serum perfluoroalkyl levels and serum cholesterol levels, several studies of workers (Olsen and Zobel 2007; Olsen et al. 2000), highly exposed residents (Emmett et al. 2006a; Wang et al. 2012), and the general population (Fisher et al. 2013) have not found statistically significant associations. The epidemiology database lacks studies in which

actual exposure concentration or doses were measured; however, most studies provided serum perfluoroalkyl levels, which is a biomarker of exposure. Exposures likely occurred via multiple routes of exposure. It is assumed that workers were primarily exposed via inhalation; however, oral exposure may have also contributed to the total perfluoroalkyl body burden. Similarly, it has been determined that drinking water was the primary source of perfluoroalkyls in residents living near a PFOA facility; it is likely that they were also exposed to airborne perfluoroalkyls. However, a study of residents living near industrial facilities where PFOA is used found little difference in serum PFOA levels between residents with minimal expected exposure to airborne PFOA (mean serum PFOA level of 418 ng/mL) and those with higher than expected exposure to airborne PFOA (mean serum PFOA level of 418 ng/mL) (Emmett et al. 2006a). It should also be noted that most, if not all, subjects were exposed to a number of perfluoroalkyl compounds. Studies of highly exposed residents and the general population have often reported significant associations for both PFOA and PFOS, and the possible interaction of the various perfluoroalkyl compounds with the health end point of concern is not known. Lastly, the mechanisms of toxicity of the observed health effects have not been established and these effects have not been reported in laboratory animals. Serum cholesterol and other lipid levels are also affected by PFOA and PFOS exposure in rats and mice; however, in rodents, exposure to perfluoroalkyls resulted in significant decreases in serum lipid levels. These uncertainties preclude the use of currently available epidemiology studies as the basis for developing an MRL for PFOA or PFOS.

Animal Data. Inspection of the animal database would suggest that there are studies, particularly by the oral route, of PFOS and PFOA in animals that established dose-response relationships that could be used for MRL derivation. However, there are uncertainties associated with derivation of MRLs for PFOA or PFOS based on animal studies, in part, because of large interspecies differences in the toxicokinetics of perfluoroalkyls for which mechanisms are not completely understood. Available information on the toxicokinetics of perfluoroalkyls in humans, nonhuman primates, and various rodent species indicate that elimination rates (and very likely elimination mechanisms and hormonal regulation of these mechanisms) vary substantially across chemical species (i.e., carbon chain length) and animal species (i.e., slower in humans compared to nonhuman primates and rodents), and show pronounced sex differences within certain species (e.g., faster elimination in female rats). As a result, extrapolation of external dose-response relationships from animals to humans would be highly uncertain. Although progress has been made in modeling toxicokinetics of PFOA and PFOS in rats and nonhuman primates (i.e., Cynomolgus monkeys), no models for humans have been developed to simulate the substantial differences in toxicokinetics of these compounds between humans and nonhuman primates or between humans and rats (Andersen et al. 2006; Tan et al. 2008). An additional uncertainty is species differences in the

mechanisms of toxicity. In rats and mice, liver and developmental toxicity are two of the more sensitive effects of oral exposure to perfluoroalkyl compounds. Available data provide strong evidence that these effects in rodents involve the activation of PPARα, and humans and nonhuman primates are less responsive to PPARα agonists than rats and mice. Studies in PPARα-null mice suggest that PPARα-independent mechanisms also play a role in the liver and developmental toxicity. A brief summary of LOAELs identified in animal studies for the most sensitive end points are summarized below.

PFOA—Inhalation Exposure. Only two relatively low-exposure inhalation studies were available for PFOA. In one study, male CD rats were exposed head-only 6 hours/day, 5 days/week for 2 weeks to ammonium perfluorooctanoate (APFO) dusts (Kennedy et al. 1986), whereas in the other study, a developmental study, pregnant Sprague-Dawley rats were exposed whole-body to APFO dusts 6 hours/day on GDs 6–15 (Staples et al. 1984). The lowest LOAEL was 7.6 mg/m^3 for exposure concentration-related increases in absolute and relative liver weight and histological alterations in the liver; no significant effects were reported at 1 mg/m^3 (Kennedy et al. 1986). Serum PFOA levels were not monitored in this study, but a toxicokinetics study in male rats exposed nose-only 6 hours/day, 5 days/week for 3 weeks reported that PFOA serum levels in a group exposed to 10 mg/m^3 had achieved a steady-state concentration of approximately 20,000 ng/mL by day 14 of the study (Hinderliter et al. 2006a). Kennedy et al. (1986) also examined several organs and tissues microscopically and reported that no significant alterations were observed. In the developmental study, an exposure concentration of 25 mg/m^3 induced a 10% decrease in newborn body weight on PND 1; this exposure concentration decreased weight gain in the dams by 37% on GDs 6–15 (Staples et al. 1984). Serum PFOA levels were not monitored in this study.

PFOA—Oral Exposure. Acute-duration oral studies are available in rats and mice and provide information on systemic, immunological, reproductive, and developmental effects. The systemic effects described were mostly alterations in liver and body weight as well as alterations in lipid metabolism. The lowest LOAEL identified for systemic effects was 1 mg/kg/day for a 35% increase in absolute liver weight in mice dosed with PFOA in the diet for 10 days (Yahia et al. 2010; Yang et al. 2001). This was accompanied by a significant increase in peroxisome proliferation, as measured by increases in acyl-CoA oxidase activity. A LOAEL of 2 mg/kg/day and a NOAEL of 0.2 mg/kg/day were identified for a significant increase in absolute and relative liver weight and increases in hepatic β-oxidation activity and serum estradiol levels in rats in a 14-day dietary study (Liu et al. 1996). The increase in serum estradiol was attributed, at least in part, to induction of hepatic aromatase activity by PFOA. Serum PFOA values were not available in the Liu et al. (1996) study. A LOAEL of 0.5 mg/kg/day was identified for reduced

postnatal litter weight in the offspring of mice exposed to PFOA on GDs 6–17 (Hu et al. 2010); a NOAEL was not identified in this study. A LOAEL of 0.58 mg/kg/day for neurodevelopmental effects was also identified in a study in which mice were administered a single gavage dose of PFOA at the age of 10 days and were tested for spontaneous behavior at the age of 2 and 4 months (Johansson et al. 2008); no NOAEL was defined in this study. Information regarding blood levels of PFOA in the treated mice was not available.

Intermediate-duration oral studies of PFOA in animals also indicate that the liver is one of the primary targets. The lowest LOAEL for liver effects was 0.5 mg/kg/day for significant increases in absolute and relative liver weight in mice in two 21-day dietary studies (Kennedy 1987; Son et al. 2008). In the Kennedy (1987) study, the NOAEL was 0.2 mg/kg/day; no NOAEL was defined in the Son et al. (2008) study. Neither one of these studies had information on concentrations of PFOA in serum. The lowest LOAEL for hepatic effects was 0.29 mg/kg/day in rats administered PFOA for 28 days (Loveless et al. 2008); decreases in serum cholesterol levels and hepatocellular hypertrophy were also observed at this dose level. The lowest LOAELs for immunological effects were 0.49 mg/kg/day for alterations in splenic lymphocyte phenotypes (Son et al. 2009) and 3.75 mg/kg/day for an impaired response to T-dependent antigens (Dewitt et al. 2008). A very low LOAEL of 0.001 mg/kg/day for developmental toxicity was reported by White et al. (2011b); at this dose level, delayed mammary gland development was observed on PNDs 22–63. However, the mammary gland effect did not result in an adverse effect on lactational support, based on normal growth and survival in F2 pups (White et al. 2011b). Other developmental effects that occurred at low concentrations include increased postnatal body weight in mice at 0.01 mg/kg/day (Hines et al. 2009), increased locomotor activity in mice at 0.3 mg/kg/day (Onishchenko et al. 2011) and reduced mouse pup survival from birth to weaning at 0.6 mg/kg/day (Abbott et al. 2007). In the Abbott et al. (2007) study, the mean serum PFOA level in the dams at weaning was 5,200 ng/mL in the 0.6 mg/kg/day group, the corresponding serum level of PFOA in the pups was 3,800 ng/mL. In a 26-week study with Cynomolgus monkeys, a LOAEL of 3 mg/kg/day (the lowest dose tested) was identified for a 36% increase in absolute liver weight, which may have been due to significant mitochondrial proliferation (Butenhoff et al. 2002). No significant hepatic peroxisomal proliferation was detected. Serum PFOA levels in the 3 mg/kg/day dose group was approximately 77,000 ng/mL.

The chronic oral animal database for PFOA is limited to dietary exposure studies in male or male and female rats (3M 1983; Biegel et al. 2001). Significant increases in relative liver weight were observed in males exposed to 13.6 mg/kg/day for 1–21 months, but were not observed after 24 months of exposure (Biegel et al. 2001); there were no increases in cell proliferation in the liver after 24 months of exposure.

The second study (3M 1983) found increases in the incidence of megalocytosis, cystoid degeneration, and portal mononuclear cell infiltration in male and female rats exposed to 15 mg/kg/day (not all effects were observed in males and females). This study also found significant increases in serum transaminase levels in male rats exposed to ≥1.5 mg/kg/day. Other non-neoplastic effects reported in these studies included pancreatic acinar cell proliferation in male rats exposed to 13.6 mg/kg/day for 15– 21 months (Biegel et al. 2001) and inflammation of the salivary glands in male rats exposed to ≥1.5 mg/kg/day (3M 1983). Treatment of male rats with 13.6 mg/kg/day PFOA increased the incidence of hepatocellular adenomas (no hepatocellular carcinomas were found) and increased the incidence of Leydig cell adenomas and the incidence of pancreatic acinar cell adenomas (Biegel et al. 2001). Dietary exposure to 15 mg/kg/day PFOA increased the incidence of fibroadenoma of the female mammary gland and of Leydig cell adenomas (3M 1983); a re-evaluation of the mammary gland pathology studies by a Pathology Working Group (Hardisty et al. 2010) did not find a significant increase in the incidence of fibroadenoma or other mammary gland benign or malignant neoplasms.

Several studies reported serum PFOA levels which were associated with adverse effects, particularly liver, immunological, and developmental effects. The serum levels and associated effects are presented in Table 2-1.

PFOS. No inhalation data were available for PFOS. Acute-duration oral studies with PFOS have described effects on body weight, liver weight, serum and liver lipid profiles, and immunological and developmental effects in rodents. Liver effects, including increases in liver weight, increases in serum enzymes (ALT and AST), and decreases in serum cholesterol levels have been observed following acute exposure; the lowest LOAEL was 1.72 mg/kg/day in rats exposed to PFOS for 7 days (Elcombe et al. 2012b). Impaired responses to T-cell mitogens and T-dependent antigens were observed in mice exposed to 5 mg/kg/day PFOS for 7 days (Zheng et al. 2009). The lowest LOAEL for developmental toxicity was 0.75 mg/kg for alterations in motor activity in 2- and 4-month-old male mice that were treated with a single gavage dose of PFOS at 10 days of age (Johansson et al. 2008). A sensitive effect was also a significant reduction in body weight gain in pregnant rabbits administered 1 mg/kg/day PFOS by gavage on GDs 6–20; food consumption was not affected during this period (Case et al. 2001). A lower dose of 0.1 mg/kg/day caused a 13% reduction in body weight gain, but the difference with controls did not achieve statistical significance.

Similar effects have been observed in rats and mice orally exposed to PFOS for an intermediate duration. Liver effects consisting of hepatocellular hypertrophy, increases in absolute and relative liver weight, and

Table 2-1. Serum PFOA Concentrations Associated With Adverse Effects In Laboratory Animals

Species	Exposure duration	Effect	Dose (mg/kg/day)	Serum concentration (ng/mL)	Reference
Hepatic effects					
Rat	8 days	Increased liver weight, decreased serum cholesterol and triglyceride levels, histological alterations	18	234,000	Elcombe et al. 2010
Rat	13 weeks	NOAEL	0.06	7,100	Perkins et al. 2004
		Histopathological alterations	0.64	41,000	
Mouse	GDs 1–17	Increased liver weight, histopathological alterations in dams	3	≈42,000	Albrecht et al. 2013
Mouse	GDs1–17	Increased liver weight in dams	1	≈25,000	Lau et al. 2006
Mouse	15 days	Increased liver weight in dams	3.75	74,913	Dewitt et al. 2008
Monkey	6 months	Increased liver weight	3	77,000	Butenhoff et al. 2002
Immunological effects					
Mouse	15 days	Immunological alterations	3.75	74,913	Dewitt et al. 2008
Reproductive effects					
Mouse	GDs1–17	Mammary gland alterations in dams	1	74.8	White et al. 2011b
Developmental effects					
Mouse	GDs 1–17 + lactation	Decreased pup weight gain and develop delays	3	29,470	Wolf et al. 2007
		Decreased pup survival	5	36,900	

GD = gestation day; NOAEL= no-observed-adverse-effect level; PFOA = perfluorooctanoic acid

decreases in serum lipid levels have been observed in rats exposed to 1.33 mg/kg/day for 14 weeks (Seacat et al. 2003) or 1.54 mg/kg/day for 28 days (Elcombe et al. 2012a). The mean serum PFOS level corresponding to this LOAEL in males was 148,000 ng/mL (Seacat et al. 2003). The lowest LOAEL for liver effects was 0.14 mg/kg/day for increased relative liver weight in rats exposed for 28 days (Curran et al. 2008; Lefebvre et al. 2008). The most sensitive immune effects in mice were decreased host resistance to a single influenza virus strain at 0.025 mg/kg/day (Guruge et al. 2009) and impaired response to T-dependent antigens at 0.00166 and 0.083 mg/kg/day (Dong et al. 2009, 2011; Peden-Adams et al. 2008). Developmental studies in rats and mice have reported decreases in postnatal survival of the pups; the lowest LOAEL was 1.6 mg/kg/day in rats (Luebker et al. 2005a, 2005b). Decreases in pup survival were observed following *in utero* and lactation exposure and *in utero* only exposure (Luebker et al. 2005a). The lowest LOAEL for any developmental effect was 0.4 mg/kg/day for decreased pup body weight (Luebker et al. 2005a). Monkeys dosed with 0.75 mg/kg/day, the highest dose tested, showed increased liver weight, decreased serum cholesterol, and hepatocellular hypertrophy and lipid vacuolation; the NOAEL was 0.15 mg/kg/day (Seacat et al. 2002). At termination of dosing, the mean PFOS serum level corresponding to the LOAEL was 171,000 ng/mL in females and 173,000 ng/mL in males.

A 2-year bioassay for PFOS also identified the liver as a main target (Butenhoff et al. 2012b; Thomford 2002b). In that study, rats were fed a diet that provided approximately 0, 0.025, 0.10, 0.25, or 1.04 mg/kg/day PFOS. A significant increase in the incidence of cystic hepatocellular degeneration was reported in males dosed with ≥0.10 mg/kg/day PFOS, and this dose level constitutes the study LOAEL; the NOAEL was 0.025 mg/kg/day. At higher dose levels, hepatotoxicity was characterized by centrilobular hypertrophy, centrilobular eosinophilic hepatocytic granules, and centrilobular hepatocytic vacuolation. No significant alterations were reported in other tissues and organs or in clinical chemistry and hematology test results.

Several studies examining the toxicity of PFOS on the liver and immune system measured serum PFOS concentrations; these data are summarized Table 2-2.

PFBA. Relatively few toxicity studies have been conducted in animals exposed to PFBA by a relevant route of exposure. Ikeda et al. (1985) reported that administration of approximately 20 mg/kg/day PFBA in the diet to male Sprague-Dawley rats for 2 weeks did not significantly affect relative liver weight, but increased catalase activity in liver homogenates by 42% and induced peroxisome proliferation, as assessed by electron microscopy. In a similar study, dietary administration of approximately

Table 2-2. Serum PFOS Concentrations Associated With Adverse Effects In Laboratory Animals

Species	Exposure duration	Effect	Dose (mg/kg/day)	Serum concentration (ng/mL)	Reference
Hepatic effects					
Rat	7 days	NOAEL	1.72	34,860	Elcombe et al. 2012a
		Decreased serum cholesterol and triglyceride levels	8.17	156,600	
Rat	7 days	Increased liver weight, decreased serum cholesterol, histopathological alterations	1.79	39,490	Elcombe et al. 2012b
Rat	28 days	Increased liver weight	0.14	1,500	Curran et al. 2008
Rat	28 days	Decreased serum cholesterol levels, histopathological alterations	1.54	94,290	Elcombe et al. 2012a
Rat	14 weeks	NOAEL	0.34	4,040	Seacat et al. 2003
		Increased liver weight, histopathological alterations	1.33	17,100	
Monkey	6 months	NOAEL	0.150	36,400	Seacat et al. 2002
		Increased liver weight	0.750	131,000	
Immunological effects					
Mouse	7 days	Suppressed response to mitogens and sRBC	5	110,460	Zheng et al. 2009
Mouse	60 days	NOAEL	0.0083	674	Dong et al. 2009
		Suppressed response to sRBC	0.083	7,132	
Mouse	60 days	NOAEL	0.0167	2,360	Dong et al. 2011
		Suppressed response to sRBC	0.0833	10,750	
Mouse	28 days	NOAEL	0.000166	17.8	Peden-Adams et al. 2008
		Suppressed response to sRBC	0.00166	91.5	
Mouse	21 days	NOAEL	0.005	189	Guruge et al. 2009
		Decreased host resistance	0.025	670	

NOAEL = no-observed-adverse-effect level; PFOS = perfluorooctane sulfonic acid; sRBC = sheep red blood cells

78 mg/kg/day PFBA to male C57BL/6 mice for 10 days induced a 63% increase in absolute liver weight (Permadi et al. 1992). The increase in liver weight was accompanied by changes in enzymes involved in drug metabolism and/or in deactivation of reactive oxygen species; however, PFBA did not have a significant effect on parameters of peroxisomal fatty acid β-oxidation (Permadi et al. 1993). Since only one dietary level was used in these studies, dose-response relationships could not be constructed. A much more recent acute-duration (5-day) gavage study in rats is also available (3M 2007a). In that study, three dose levels were tested and the highest dose used (184 mg/kg/day) had no significant effect on a wide range of end points including body and organ weights, hematology and clinical chemistry, and histopathology, and thus, constituted the study NOAEL. Data regarding serum levels of PFBA were not available in any of these studies.

The intermediate-duration oral database for PFBA consists of a developmental study in mice (Das et al. 2008), and 28- and 90-day gavage studies in rats (Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b). In the developmental study, PFBA administered to pregnant mice on GDs 1–17 did not affect newborn weight gain or viability, as usually seen with PFOA and PFOS (Das et al. 2008). The most sensitive response was a delay in eye opening in the pups at maternal doses of PFBA of 35 mg/kg/day. Both the 28- and 90-day studies identified LOAELs of 30 mg/kg/day for liver hypertrophy and alterations in the follicular epithelium of the thyroid in male rats (Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b). In addition, the 90-day study reported hematological alterations, also in male rats dosed with 30 mg/kg/day PFBA. The NOAEL for these effects was 6 mg/kg/day.

PFHxS. A limited number of studies are available for PFHxS. Administration of PFHxS from premating until PND 21 (females) resulted in increased prothrombin time at 0.3 mg/kg/day, increased liver weights and hepatocellular hypertrophy at 3 mg/kg/day, and thyroid follicular cell hyperplasia at 3 mg/kg/day (Butenhoff et al. 2009a; Hoberman and York 2003); the study did not report any reproductive or developmental effects. In another study, altered spontaneous activity and habituation were observed in adult mice administered 9.2 mg/kg/day on PND 10 (Viberg et al. 2013).

PFBuS. Limited data available on the toxicity of PFBuS in animals have identified the liver, kidneys, stomach, and hematological systems as targets of toxicity. Decreases in hemoglobin and hematocrit levels were observed in male rats administered 200 mg/kg/day PFBuS for 90 days (Lieder et al. 2009a); decreases in erythrocyte levels were observed at 600 mg/kg/day. Administration of 600 mg/kg/day for 90 days also resulted in tubular and ductal papillary epithelial hyperplasia in the kidneys and necrosis and hyperplasia/hyperkerosis in the forestomach (Lieder et al. 2009a). Increases in absolute and relative liver

weight were reported in male rats administered 900 mg/kg/day for 28 days (3M 2001). At 1,000 mg/kg/day, hepatocellular hypertrophy was observed in a 2-generation study (Lieder et al. 2009b). In general, no biologically relevant alterations in performance on functional observation battery tests or motor activity tests were observed in rats administered 900 mg/kg/day PFBuS for 28 days (3M 2001) or 600 mg/kg/day for 90 days (Lieder et al. 2009a).

PFDeA. Studies potentially useful for MRL derivation were limited to acute-duration oral studies. Most of these studies provided information on liver effects and were, in general, of limited scope. The lowest LOAEL was 2.4 mg/kg/day in rats for increased absolute liver weight, and doses of 9.5 mg/kg/day increased the number of lipid droplets containing amorphous material, indicating marked toxicity to hepatocytes; the NOAEL was 1.2 mg/kg/day (Kawashima et al. 1995). The 9.5 mg/kg/day dose also induced significant weight loss associated with significantly reduced food consumption. Reduced weight gain was also reported in pregnant mice dosed with 6.4 mg/kg/day on GDs 6–18 (Harris et al. 1989); the NOAEL was 3 mg/kg/day. The reduced maternal weight gain may have been responsible, in part, for a significant decrease in fetal weight. Other repeated dose studies tested much higher doses of PFDeA (Ikeda et al. 1985; Permadi et al. 1992, 1993). No alterations in spontaneous activity were observed in adult rats administered 10.8 mg/kg/day PFDeA on PND 10 (Johansson et al. 2008).

PFNA. Administration of 1 mg/kg/day PFNA for 14 days resulted in increases in serum glucose levels and decreases in high-density lipoprotein (HDL)-cholesterol levels in rats (Fang et al. 2012a); hepatocellular vacuolation was observed at 5 mg/kg/day (Fang et al. 2012b). An immunotoxicity study found decreases in thymus and spleen weights at 3 mg/kg/day and alterations in splenic lymphocyte phenotypes at 1 mg/kg/day, but no alteration in the response to a T-cell mitogen (Fang et al. 2008).

Derivation of MRLs. The only perfluoroalkyl compounds with sufficient data for derivation of MRLs are PFOA and PFOS. For both compounds, hepatic effects, immunological effects, and developmental effects appear to be the most sensitive end points, and rats and mice were the most sensitive species. As noted previously, perixosome proliferation via activation of PPARα is a major contributing factor to the liver effects and some of the developmental effects; the mechanisms of the immune effects are not known. Humans are less responsive to PPARα agonists than rodents; thus, derivation of MRLs based on rodent data may result in overly conservative values. Like humans, nonhuman primates are less responsive to PPARα agonists and may be a suitable model for human exposure to PFOA and PFOS. Intermediate-duration monkey studies are available for PFOA (Butenhoff et al. 2002) and PFOS (Seacat et al. 2002) and data from these studies were used to derive intermediate-duration oral MRLs. The effects

observed in monkeys exposed to PFOA or PFOS are consistent with the findings observed in more sensitive species (rats and mice). Rodent studies have also identified developmental toxicity and immune toxicity as sensitive end points; neither has been examined in monkey studies. The LOAELs for the liver and developmental effects are similar; thus, derivation of an MRL based on liver toxicity is likely to be protective of developmental effects. Immune effects have been observed at lower concentrations; however, the biological relevance of these effects is not known.

Deriving MRLs based on the PFOA or PFOS dose levels used in the monkey studies is problematic due to species differences in the toxicokinetics of the two compounds, particularly the difference in half-times. An alternative approach is to base the MRL on an internal dosimetric and assume that a serum concentration that would result in an effect in monkeys would also result in an effect in humans. This serum concentration could then be converted to an equivalent dose in humans, which is defined as the continuous ingestion dose (mg/kg/day) that would result in steady-state serum concentrations of PFOA or PFOS equal to the serum concentration (µg/mL) selected as the point of departure (POD).

The relationship between PFOA or PFOS external dosage (mg/kg/day) and steady-state serum concentration in humans can be estimated assuming a single-compartment first-order model in which elimination kinetics are adequately represented by observed serum elimination half-times for PFOA (≈1,400 days) and PFOS (≈2,000 days) in retired workers (e.g., Olsen et al. 2007a) and an assumed apparent volume of distribution (e.g., 0.2 L/kg, Butenhof et al. 2004c; Chang et al. 2012; Harada et al. 2005a) and gastrointestinal absorption fraction (e.g., 1.0; based on studies in rodents and nonhuman primates):

$$D_{SS} = \frac{C_{SS} \cdot k_e \cdot V_d}{AF} \qquad \text{Eq. (2-1)}$$

where D_{SS} is the daily external dosage (mg/kg/day), C_{SS} is the steady-state serum concentration (mg/L), k_e is the elimination rate constant (d^{-1}), V_d is the apparent volume of distribution (L/kg), and AF is the gastrointestinal absorption fraction. A more detailed description of the approach used to predict doses in humans using the serum concentrations is presented in Appendix A.

PFOA. In the Butenhoff et al. (2002) study of PFOA, groups of male Cynomolgus monkeys were administered 0, 3, 10, or 30 mg/kg/day APFO by daily capsules for 26 weeks; each group had six monkeys with the exception of the 3 mg/kg/day group, which had four monkeys. The serum levels of PFOA measured at or after week 6 are summarized in Table 2-3. During the first week of exposure,

Table 2-3. Liver Weights of Male Cynomolgus Monkeys Exposed to PFOA for 6 Months

Dose (mg/kg/day)	Serum PFOA level[a] (µg/mL)	Number of animals	Absolute liver weight (g)	Relative liver weight (%)
0	0.203±0.154[b]	4	60.2±6.9	1.5±0.1
3	77±39 (10–154)[c]	3	81.8±2.8*	1.8±0.1
10	86±33 (10–180)	4	83.2±9.7*	1.9±0.1
30/20	158±100 (20–467)	2	90.4±4.2*	2.4±0.5*

[a]Average serum PFOA levels measured every 2 weeks beginning at study week 6.
[b]Mean ± standard deviation.
[c]Range of values.
*Statistically significant when compared to controls, $p<0.01$.

PFOA = perfluorooctanoic acid

Source: Butenhoff et al. 2002

decreases in food consumption and weight loss were exhibited by all monkeys in the 30 mg/kg/day group and dosing was suspended on day 12. On day 22, treatment was resumed at a lower dose (20 mg/kg/day). One monkey in the 30/20 mg/kg/day group was sacrificed moribund on day 29; a weight loss of 12.5% and hypoactivity were observed and were considered to be treatment-related. Dosing of three of the five remaining animals was ceased on days 43, 66, or 81 due to continued weight loss and low food consumption. One monkey in the 3 mg/kg/day group was sacrificed moribund due to weight loss, hind-limb paralysis, ataxia, and the lack of response to pain stimuli; the neurological symptoms were not consistent with effects observed in the 30/20 mg/kg/day monkeys and the cause of the effects could not be determined. Dose-related increases in absolute liver weight were observed at all dose levels; relative liver weights were significantly increased in the 30/20 mg/kg/day group. The absolute and relative liver weights are presented in Table 2-3. No other alterations in organ weights were observed. No histological alterations were observed in the liver with the exception of hepatocellular degeneration, vacuolation, and basophilia observed in the monkey in the 30/20 mg/kg/day group sacrificed on day 29. No significant alterations in serum reproductive hormone levels were observed. Free and total thyroxine (T4) levels were significantly decreased in the 10 mg/kg/day group, but there were no changes in free or total triiodothyronine (T3) levels or thyroid stimulating hormone (TSH) levels.

Using serum PFOA level as the internal dosimetric, the absolute and relative liver weight data were fit to all available continuous models in EPA's Benchmark Dose Software (BMDS, version 2.4.0). Three benchmark responses (BMRs) were considered: 1 standard deviation (SD) change from the control; 2 SD change from the control; and 10% increase in liver weight. Although a 1 SD change is the typical BMR used for continuous variable models without a biological basis to establish a cut-point for biological significance, a 2 SD BMR was also used due to the small number of animals tested. See Appendix A for a detailed discussion of the benchmark dose (BMD) modeling.

Human equivalent doses (HEDs) were calculated for each POD for alterations in absolute and relative liver weights. The HEDs were calculated using Equation 2-1, with the parameter C_{SS} (steady-state serum concentration) represented by the monkey POD, and are presented in Table 2-4. The increased absolute liver weight was selected as the critical effects because it was the more sensitive end point and was significantly increased at all three dose levels. The BMDL (lower confidence limit on the BMD) predicted with the 10% relative deviation (RD) in absolute liver weight was selected as the POD. An intermediate-duration oral MRL for PFOA was derived by dividing the HED of 1.54×10^{-3} mg/kg/day by an uncertainty factor of 90 (3 for animal to human extrapolation with a dosimetric adjustment, 10 for human variability, and 3 for uncertainties in the database, particularly the lack of developmental and

Table 2-4. Human Equivalent Doses for PFOA

	POD (µg/mL)	HED (mg/kg/day)
Absolute liver weight, $BMDL_{1SD}$; linear model	15.87	$1.57x10^{-3}$
Absolute liver weight, $BMDL_{2SD}$; linear model	31.73	$3.14x10^{-3}$
Absolute liver weight, $BMDL_{RD10\%}$; linear model	15.53	$1.54x10^{-3}$
Relative liver weight, $BMDL_{1SD}$; polynomial model	33.45	$3.31x10^{-4}$
Relative liver weight, $BMDL_{2SD}$; polynomial model	47.31	$4.68x10^{-3}$
Relative liver weight, $BMDL_{RD10\%}$; polynomial model	46.31	$4.59x10^{-3}$

BMDL = lower confidence limit on the benchmark dose; HED = human equivalent dose; PFOA = perfluorooctanoic acid; POD = point of departure; RD= relative deviation; SD = standard deviation

immunological data in monkeys). Intermediate-duration studies in rats and mice have demonstrated that the developing organism and the immune system are also sensitive targets of PFOA toxicity. The lowest LOAEL for developmental effects in mice (0.01 mg/kg/day; Hines et al. 2009) was lower than lowest LOAEL for liver effects in 21-day mouse studies (0.5 mg/kg/day; Kennedy 1987; Son et al. 2008). The lowest LOAEL for immune effects (0.49 mg/kg/day; Son et al. 2009) was similar to the lowest LOAEL for liver effects. A database uncertainty factor was used to account for the lack of studies examining the possible developmental and immune toxicity of PFOA in monkeys and to allow for a more thorough evaluation of the most sensitive target of PFOA toxicity in humans. The resulting intermediate-duration oral MRL for PFOA is $2x10^{-5}$ mg/kg/day.

PFOS. In the PFOS monkey study (Seacat et al. 2002), groups of male and female Cynomolgus monkeys were administered via capsule 0, 0.03, 0.15, or 0.75 mg/kg/day potassium PFOS for 26 weeks; there were four monkeys/sex in the 0.03 mg/kg/day group and six monkeys/sex/group in the other groups. The serum levels of PFOS measured at the end of the study are summarized in Table 2-5. Two monkeys/sex in the 0, 0.15, and 0.75 mg/kg/day were allowed to recover for 1 year. In the 0.75 mg/kg/day group, two male monkeys died or were sacrificed moribund; pulmonary necrosis was observed in one monkey and symptoms possibly related to hyperkalemia were observed in the other animal; neither effect was observed in surviving animals and it is not clear whether these were related to PFOS exposure. Decreases in body weight gain were observed in males in the 0.15 (11%) and 0.75 (13.5%) mg/kg/day groups. Significant increases in relative liver weight were observed in the male and females exposed to 0.75 mg/kg/day and absolute liver weight was significantly increased in females at 0.75 mg/kg/day; the absolute and relative liver weights are summarized in Table 2-5. Centrilobular vacuolation, hypertrophy, and mild bile stasis was observed in some monkeys in the 0.75 mg/kg/day (incidence not reported). Lipid-droplet accumulation in two of four males and two of four females and increased glycogen content was noted in the electron microscopic examination of the liver. No histological alterations were observed in the other major tissues and organs. Clinical chemistry alterations consisted of decreases in total cholesterol in the second half of the study in the 0.75 mg/kg/day group, decreases in HDL-cholesterol levels during the last month of the study in males exposed to 0.03 or 0.75 mg/kg/day and females exposed to 0.15 or 0.75 mg/kg/day, and decreases in serum bilirubin levels in 0.75 mg/kg/day males during the last half of the study. The total cholesterol levels in the 0.75 mg/kg/day group were also significantly lower than pre-treatment levels; however, HDL-cholesterol levels were only measured during the last month of the study and it is not known if the alterations reflected a treatment-related effect. Decreases in TSH levels were observed at 0.75 mg/kg/day and decreases in total T3 levels were observed in males at

Table 2-5. Liver Weights of Male and Female Cynomolgus Monkeys Exposed to PFOS for 6 Months

Nominal dose[a] (mg/kg/day)	Serum PFOS level[b] (µg/mL)	Number of animals	Absolute liver weight (g)	Relative liver weight (%)
Males				
0	0.05	3	54.9±8.1	1.6±0.2
0.03	8.6	4	62.1±5.3	1.7±0.3
0.150	43.5	4	57.3±5.5	1.8±0.1
0.75	140	2	85.3±38.4	2.7±0.3*
Females				
0	0.05	4	51.1±9.4	1.8±0.2
0.03	7.8	4	56.8±12.6	1.9±0.0
0.150	36.4	4	57.0±3.1	2.1±0.2
0.75	131	4	75.3±13.3*	2.9±0.3*

[a]KPFOS (86.9%) purity was administered; capsules for the 0.75 mg/kg/day group contained 72±35% of target dose for 0.75 mg/kg/day group and 103±25% for the 0.150 and 0.75 mg/kg/day groups).
[b]Time-weighted average of mean serum concentrations for the 6-month period; data taken from Figure 1 of the Seacat et al. (2002) paper.
*Statistically significant when compared to controls, $p<0.01$.

PFOS = perfluorooctane sulfonic acid

Source: Seacat et al. 2002

≥0.03 mg/kg/day and in females at 0.75 mg/kg/day; however, it was noted that these TSH and T3 levels were within the normal range for Rhesus monkeys.

Using serum PFOS level as the internal dosimetric, the absolute and relative liver weight data were fit to all available continuous models in EPA's BMDS (version 2.4.0). Three BMRs were considered: 1 SD change from the control; 2 SD change from the control; and 10% increase in liver weight. Although a 1 SD change is the typical BMR used for continuous variable models without a biological basis to establish a cut-point for biological significance, a 2 SD BMR was also used due to the small number of animals tested. See Appendix A for a detailed discussion of the BMD modeling.

HEDs were calculated for each potential POD for both absolute and relative liver weights. The HEDs were calculated using Equation 2-1, with the parameter C_{SS} (steady-state serum concentration) represented by the monkey POD, and are presented in Table 2-6. Because decreases in body weight were observed, increased absolute liver weight was selected as the critical effect. The HEDs calculated for the increased absolute liver weight ranged from $1.61x10^{-3}$ to $3.09x10^{-3}$ mg/kg/day; the lowest HED of $1.61x10^{-3}$ was estimated from the BMDL using a benchmark response of 10% relative deviation in absolute liver weight in the male monkeys; however, this value is lower than the empirical NOAEL identified in male monkeys ($9.07x10^{-3}$ mg/kg/day estimated from a serum concentration of 140 µg/mL) and in female monkeys ($2.52x10^{-3}$ mg/kg/day estimated from a serum concentration of 36.4 µg/mL) and was not selected as the POD for the MRL. Rather, the NOAEL identified in female monkeys was selected as the POD for the MRL. The intermediate-duration oral MRL for PFOS was derived by dividing the HED of $2.52x10^{-3}$ mg/kg/day by an uncertainty factor of 90 (3 for animal to human extrapolation with a dosimetric adjustment, 10 for human variability, and 3 for uncertainties in the database, particularly the lack of developmental and immunological data in monkeys). Intermediate-duration studies in rats and mice have demonstrated that the developing organism and the immune system are also sensitive targets of PFOS toxicity. Impaired host resistance to a virus was observed in mice exposed to 0.025 mg/kg/day (Guruge et al. 2009); this is lower than the lowest LOAEL for liver effects observed in 28-day rat studies (0.14 mg/kg/day; Curran et al. 2008; Lefebvre et al. 2008). The lowest LOAEL for developmental effects in mice (0.4 mg/kg/day; Luebker et al. 2005a) was slightly higher than the lowest LOAEL for liver effects. A database uncertainty factor was used to account for the lack of studies examining the possible developmental and immune toxicity of PFOS in monkeys which would allow for a more thorough evaluation of the most sensitive target of PFOS toxicity in humans. The resulting intermediate-duration oral MRL for PFOS is $3x10^{-5}$ mg/kg/day.

Table 2-6. Human Equivalent Doses for PFOS

	POD (µg/mL)	HED (mg/kg/day)
Absolute liver weight in males, $BMDL_{1SD}$; exponential model 2 with nonconstant variance	23.21	$1.61x10^{-3}$
Absolute liver weight in males, $BMDL_{2SD}$; exponential model 2 with nonconstant variance	44.60	$3.09x10^{-3}$
Absolute liver weight in males, $BMDL_{RD10\%}$; exponential model 2 with nonconstant variance	23.28	$1.61x10^{-3}$
Absolute liver weight in females, NOAEL	36.4	$2.52x10^{-3}$
Relative liver weight in males, $BMDL_{1SD}$; exponential model 2 with constant variance	23.11	$1.30x10^{-3}$
Relative liver weight in males, $BMDL_{2SD}$; exponential model 2 with constant variance	44.26	$2.60x10^{-3}$
Relative liver weight in males, $BMDL_{RD10\%}$; exponential model 2 with constant variance	20.87	$1.06x10^{-3}$
Relative liver weight in females, NOAEL	36.4	$2.52x10^{-3}$

BMDL = lower confidence limit on the benchmark dose; HED = human equivalent dose; NOAEL = no-observed-adverse-effect level; PFOS = perfluorooctane sulfonic acid; POD = point of departure; RD= relative deviation; SD = standard deviation

3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of perfluoroalkyls. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

This document discusses information on perfluoroalkyl compounds that have been measured in the serum collected from a representative U.S. population 12 years of age and older in the NHANES 2003–2004 (Calafat et al. 2007b). These compounds include:

Perfluoroheptanoic acid (PFHpA)
Perfluorooctanoic acid (PFOA)
Perfluorononanoic acid (PFNA)
Perfluorodecanoic acid (PFDeA)
Perfluoroundecanoic acid (PFUA)
Perfluorododecanoic acid (PFDoA)
Perfluorobutane sulfonic acid (PFBuS)
Perfluorobutyric acid (PFBA)
Perfluorohexane sulfonic acid (PFHxS)
Perfluorooctane sulfonic acid (PFOS)
Perfluorooctane sulfonamide (PFOSA)
2-(N-Methyl-perfluorooctane sulfonamide) acetic acid (Me-PFOSA-AcOH)
2-(N-Ethyl-perfluorooctane sulfonamide) acetic acid (Et-PFOSA-AcOH)

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies.

LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points (http://www.atsdr.cdc.gov/toxprofiles/index.asp). ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure.

A number of epidemiology studies have evaluated potential health effects associated with exposure to perfluoroalkyl compounds. The three primary sources of this information are occupational exposure studies, studies of a communities living near a PFOA manufacturing facility with high levels of PFOA in the drinking water, and studies of populations exposed to background levels of perfluoroalkyl compounds (referred to as general population studies). One limitation of most of the available epidemiology studies is the lack of reliable environmental monitoring data. However, most studies measured serum perfluoroalkyl levels that were used as biomarkers of exposure. Given that Section 3.2 is organized by the route of exposure, it was necessary to make some assumptions on the primary route of exposure for each population. Although workplace exposure to perfluoroalkyl compounds may occur by the

inhalation, oral, and dermal routes, the discussion of health effects in workers has been placed in Section 3.2.1, Inhalation Exposure, as this route may be more important than oral and dermal in occupational settings. The discussion of health effects in the general population and residents living near PFOA facilities with contaminated drinking water can be found in Section 3.2.2, Oral Exposure based on reports of predominant exposure via drinking water and food items, although inhalation could also occur, particularly in communities near perfluoroalkyl manufacturing facilities. One study of communities living near a perfluoroalkyl facility reported that exposure to airborne PFOA did not contribute much to the overall PFOA body burden (Emmett et al. 2006a). Results from studies in animals that indicate that the health effects of these substances are independent of the route of exposure; thus, conclusions can be drawn across exposure routes.

The majority of the epidemiology studies using serum perfluoroalkyl levels as a biomarker of exposure examined possible associations between serum perfluoroalkyl levels and a specific health outcome. In statistics, an association is any relationship between two measured quantities that renders them statistically interdependent. Although a study may find a statistical association between serum perfluoroalkyl levels and a particular health outcome, it does not necessarily indicate causality or biological significance. ATSDR examined the consistency of the finding across studies, dose-response, and plausibility of an effect in assessing whether the data provide evidence of a relationship between perfluoroalkyl compounds and a specific health outcome.

3.2.1 Inhalation Exposure

3.2.1.1 Death

Human Exposure Studies. There are no reports of human deaths from accidental or intentional acute exposure to high concentrations of PFOA or PFOS. Several studies have examined potential associations between mortality and long-term exposure in occupational settings and found no increases in deaths from all causes among PFOA (Gilliland and Mandel 1993; Leonard et al. 2008) or PFOS (Alexander et al. 2003) workers compared to U.S. rates, state rates, or rates among workers without occupational exposure to perfluoroalkyls. Cause-specific deaths are discussed in subsequent sections.

Laboratory Animal Exposure Studies—PFOA. Limited data are available regarding death in animals following inhalation exposure to perfluoroalkyl compounds. Exposure of male and female rats to 18,600 mg/m^3 ammonium perfluorooctanoate (APFO) dusts for 1 hour did not result in deaths during

exposure or during a 14-day observation period (Griffith and Long 1980). An LC_{50} of 980 mg/m^3 was reported in male CD rats exposed head-only to APFO dusts for 4 hours (Kennedy et al. 1986). The exposure concentrations ranged from 380 to 5,700 mg/m^3. Deaths occurred in all exposed groups and all deaths occurred within 48 hours of exposure. Rats dying during exposure had hyperinflated lungs. In a developmental study with APFO, whole-body exposure of 12 pregnant rats to 25 mg/m^3, 6 hours/day during gestation days (GDs) 6–15 resulted in three deaths on days 12, 13, and 17 of gestation compared with no deaths in groups exposed to ≤10 mg/m^3 (Staples et al. 1984). The cause of death was not reported.

An LC_{50} of 820 mg/m^3 was calculated for male CD rats exposed nose-only to APFO dusts for 4 hours (Kinney et al. 1989). No deaths occurred in rats (n=10) exposed to 67 mg/m^3 and one rat exposed to 590 mg/m^3 died 12 days after exposure. None of six rats exposed to 620 mg/m^3 died. Four out of six rats exposed to 910 mg/m^3 died 9–11 days after exposure, whereas all rats exposed to 1,600 mg/m^3 died 4–8 days after exposure. All rats exposed to 4,600 mg/m^3 died during exposure.

Laboratory Animal Exposure Studies—PFOS. Unpublished information summarized by the Organization for Economic Co-operation and Development (OECD) (2002) indicates that an LC_{50} of 5,200 mg/m^3 was calculated for PFOS in male and female Sprague-Dawley rats exposed to concentrations of PFOS dusts from 1,890 to 45,970 mg/m^3 for 1 hour. All rats exposed to 24,090 mg/m^3 died by day 6.

3.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category for PFOA are recorded in Table 3-1 and plotted in Figure 3-1. Data for PFNA from Kinney et al. (1989) are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects.

Human Exposure Studies. Pulmonary function tests conducted on workers potentially exposed to PFOA in a fluoropolymers production plant were within normal limits (Sakr et al. 2007b). This cross-sectional study assessed a total of 1,025 workers whose serum PFOA levels ranged from 5 to 9,550 ng/mL.

Laboratory Animal Exposure Studies—PFOA. Exposure of male and female rats to 18,600 mg/m^3 APFO dusts for 1 hour induced a red nasal discharge and dry rales (Griffith and Long 1980). Necropsy

Table 3-1 Levels of Significant Exposure to Perfluorooctanoic Acid - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (CD)	4 hr				980 M (LC50)	Kennedy et al. 1986 Ammonium perfluorooctanoate	
2	Rat (Sprague-Dawley)	Gd 6-15 6 hr/d				25 F (3/12 deaths on Gd 12, 13, and 17)	Staples et al. 1984 Ammonium perfluorooctanoate	
Systemic								
3	Rat (albino)	1 hr (NS)	Resp		18600 (red nasal discharge; dry rales)		Griffith and Long 1980 Ammonium perfluorooctanoate	
			Ocular		18600 (red material around the eyes; lacrimation)			
4	Rat (CD)	4 hr	Resp			380 M (pulmonary edema)	Kennedy et al. 1986 Ammonium perfluorooctanoate	Microscopically, the liver appeared normal.
			Gastro		380 M (stomach irritation)			
			Hepatic	380 M	810 M (liver enlargement)			
			Ocular	380 M		810 M (corneal opacity and corrosion)		
			Bd Wt			380 M (weight loss for 1-2 days after exposure)		

Table 3-1 Levels of Significant Exposure to Perfluorooctanoic Acid - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
5	Rat (CD)	2 wk 6 hr/d 5 d/wk	Resp	84 M			Kennedy et al. 1986 Ammonium perfluorooctanoate	NOAELs are for organ histopathology.
			Cardio	84 M				
			Gastro	84 M				
			Hemato	84 M				
			Musc/skel	84 M				
			Hepatic	1 M	7.6 M (increased absolute and relative liver weight; hepatocellular hypertrophy and necrosis)			
			Renal	84 M				
			Endocr	84 M				
			Dermal	84 M				
			Ocular	84 M				
			Bd Wt	7.6 M	84 M (7% body weight loss by exposure day 5)			
6	Rat (Sprague-Dawley)	Gd 6-15 6 hr/d	Hepatic	10 F	25 F (18% increase absolute liver weight)		Staples et al. 1984 Ammonium perfluorooctanoate	
			Bd Wt	1 F	10 F (12% decrease weight gain on Gd 6-15)	25 F (37% decrease weight gain on Gd 6-15)		

Table 3-1 Levels of Significant Exposure to Perfluorooctanoic Acid - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m^3)	LOAEL			Reference Chemical Form	Comments
					Less Serious (mg/m^3)		Serious (mg/m^3)		
Neurological									
7	Rat (albino)	1 hr (NS)			18600	(excessive salivation)		Griffith and Long 1980 Ammonium perfluorooctanoate	
8	Rat (CD)	2 wk 6 hr/d 5 d/wk		84 M				Kennedy et al. 1986 Ammonium perfluorooctanoate	NOAEL is for histopathology of the brain.
Reproductive									
9	Rat (CD)	2 wk 6 hr/d 5 d/wk		84 M				Kennedy et al. 1986 Ammonium perfluorooctanoate	NOAEL is for histopathology of the sex organs.
Developmental									
10	Rat (Sprague-Dawley)	Gd 6-15 6 hr/d		10	25	(10% decreased neonatal body weight on PND 1)		Staples et al. 1984 Ammonium perfluorooctanoate	

a The number corresponds to entries in Figure 3-1.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; PND = post-natal day; Resp = respiratory; wk = week(s)

Figure 3-1 Levels of Significant Exposure to Perfluorooctanoic Acid - Inhalation

Acute (≤14 days)

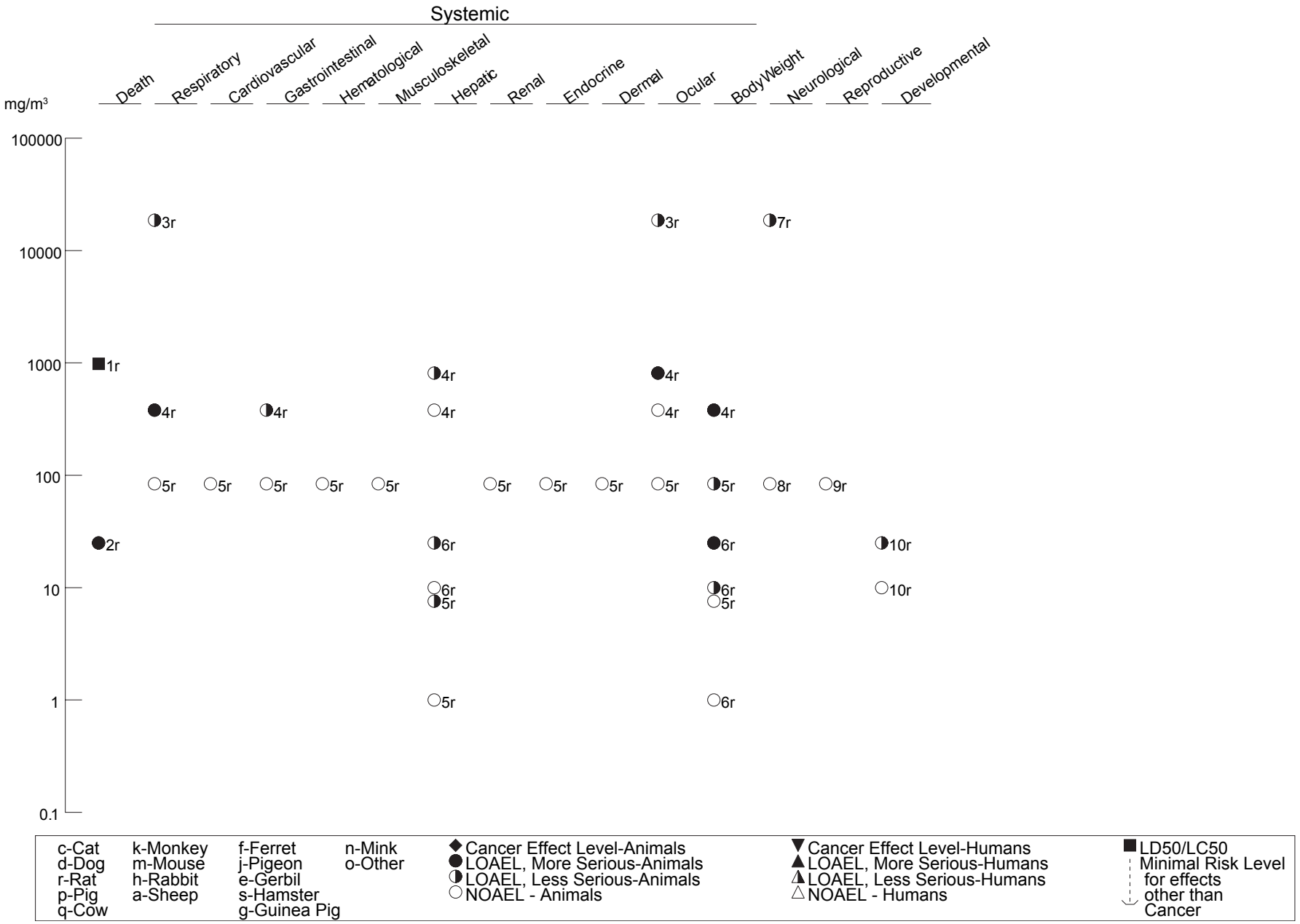


Table 3-2 Levels of Significant Exposure to Other Perfluoroalkyls - Inhalation

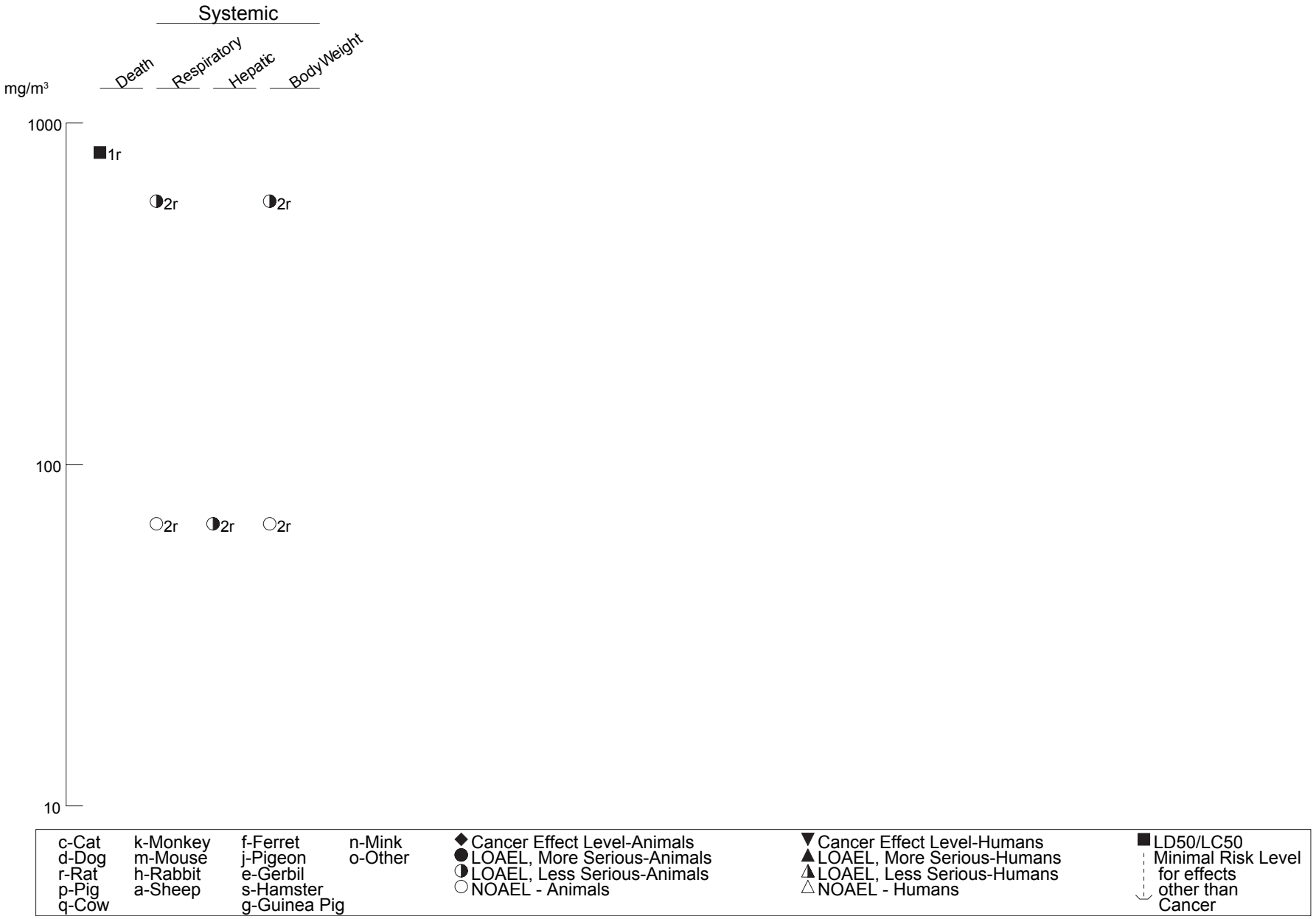
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (CD)	4 hr				820 M (14-day LC50)	Kinney et al. 1989 Perfluorononoate	Exposure was nose-only.
Systemic								
2	Rat (CD)	4 hr	Resp	67 M	590 M (lung noise; labored breathing during and after exposure)		Kinney et al. 1989 Perfluorononoate	Exposure was nose-only.
			Hepatic		67 M (28% increase in absolute liver weight 5 days after exposure)			
			Bd Wt	67 M	590 M (final body weight reduced 18% five days after exposure)			

a The number corresponds to entries in Figure 3-2.

Bd Wt = body weight; hr = hour(s); LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 3-2 Levels of Significant Exposure to Other Perfluoroalkyls - Inhalation

Acute (≤14 days)



conducted 14 days after exposure showed bilateral mottling of the lungs in 8 out of 10 rats. Head-only exposure for 4 hours to 380 mg/m^3 APFO dusts, a concentration that was lethal to some rats, produced pulmonary edema, which disappeared within 1 week of exposure (Kennedy et al. 1986). Examination of the lungs and trachea from rats exposed head-only to up to 84 mg/m^3 APFO dusts 6 hours/day, 5 days/week for 2 weeks showed no significant gross or microscopic alterations (Kennedy et al. 1986).

Male CD rats exposed nose-only to ≥590 mg/m^3 ammonium perfluorononanoate dusts for 4 hours exhibited lung noise and labored breathing during exposure and throughout a 12-day recovery period (Kinney et al. 1989).

Laboratory Animal Exposure Studies—PFOS. Unpublished data summarized by OECD (2002) indicate that exposure of rats to concentrations of PFOS between 1,890 and 45,970 mg/m^3 for 1 hour induced dry rales and other breathing disturbances.

Cardiovascular Effects.

Human Exposure Studies. The cardiotoxicity of PFOA has been examined in four cohort mortality studies of workers (Leonard 2006; Lundin et al. 2009; Sakr et al. 2009; Steenland and Woskie 2012) and a study of nonlethal cardiovascular effects in workers (Sakr et al. 2007b). Leonard (2006) conducted a cohort mortality study of DuPont employees at the Washington Works, West Virginia, polymer-manufacturing facility. The cohort (n=6,027; 80% males) was defined as all individuals who had ever worked at the plant at any time between January 1, 1948 (plant start-up) and December 31, 2002. Results from the cross-sectional study indicated that workers in all areas across the entire plant site showed some measurable level of serum PFOA ranging from 5 to 9,550 ng/mL. The standardized mortality ratios (SMRs) for cerebrovascular disease, all heart disease, and ischemic heart disease were not significantly increased, as compared to the United States and West Virginia population rates or to a population of DuPont workers residing in West Virginia and seven neighboring states. Cox proportional hazard modeling using an average exposure intensity categories and cumulative PFOA exposure categories (calculated for each member of the cohort based on categorization of jobs) for white male workers showed an increase in the ischemic heart disease mortality based on equal distribution of cases across cumulative exposure categories in one lagged analysis (the 10-year lag period). Proportional hazards calculated with 5-, 15-, or 20-year lags showed no effect, and results for a second set of models using a different set of exposure cutpoints were attenuated toward the null. Moreover, none of the hazard estimates themselves were statistically significant.

Sakr et al. (2009) extended the Leonard (2006) study by using individually measured serum PFOA levels to categorize job titles into three categories: high, medium, and low; a fourth group with minimal PFOA exposure was used as a referent. Exposure intensity was assigned using the mean serum PFOA levels of all jobs in an exposure category. Of the 4,747 male and female workers (98% male), 239 died from ischemic heart disease, 534 died of other causes, and 3,974 were alive at the end of follow-up. No statistically significant increases in the relative risk of ischemic heart disease were found; however, there was a significant trend for increasing risk from the 10-year lagged exposure categories.

A third study of workers at this facility (Steenland and Woskie 2012) extended the follow-up period through 2009 and estimated serum PFOA levels for 5,801 workers in the cohort based on job histories and serum PFOA levels collected between 1974 and 2004 from a subset of workers. No significant increases in SMRs for ischemic heart disease were found when U.S. population or DuPont regional employees were used as referent populations. Dividing the workers into quartiles or deciles based on cumulative PFOA exposure did not result in significant increases in SMRs for ischemic heart disease, as compared to DuPont regional employees, regardless of the lag period.

Lundin et al. (2009) conducted a cohort mortality study of 3,993 workers (80% male) at the 3M manufacturing facility in Cottage Grove, Minnesota. The workers were divided into three categories: definite occupational exposure to APFO, probable occupational exposure, and no or minimal occupational exposure. Exposure intensity and cumulative exposure were estimated based on job categories. No increases in the SMRs for cerebrovascular disease, all heart disease, or ischemic heart disease, as compared to mortality rates for the state of Minnesota, were found. Hazard ratio (HRs), estimated with time-dependent Cox regression models, for cerebrovascular disease were significantly increased in workers with high exposure intensity (HR 4.6, 95% confidence interval [CI] 1.3–17.0) and with exposure durations of ≥5 years (HR 2.1, 95% CI 1.0–4.6). The HRs were not significantly increased for ischemic heart disease.

No alterations in the electrocardiograms (EKG) were observed in a cross-sectional study of 1,025 workers potentially exposed to PFOA (Sakr et al. 2007b); the mean serum PFOA levels ranged from 5 to 9,550 ng/mL.

Laboratory Animal Exposure Studies—PFOA. No histopathological alterations were seen in the heart from rats exposed intermittently head-only to up to 84 mg/m^3 APFO dusts for 2 weeks (Kennedy et al. 1986).

Gastrointestinal Effects.

Human Exposure Studies. A study of 1,400 (81% males) current, retired, or former workers employed for at least 1 year at a PFOS-based fluorochemical manufacturing facility in Decatur, Alabama found no association between self-reported incidence of gastric ulcer or colon polyps and having worked in a job with either low estimated serum PFOS levels of 3,900–8,900 ng/mL) or high (estimated PFOS serum levels of 13,000–19,700 ng/mL) exposure to PFOS, as compared to workers with no direct workplace exposure (estimated serum PFOS levels of 1,100–2,900 ng/mL) (Grice et al. 2007).

Laboratory Animal Exposure Studies—PFOA. Stomach irritation was reported in male rats exposed head-only to ≥380 mg/m^3 APFO dusts for 4 hours (Kennedy et al. 1986). No histopathological alterations were seen in the stomach, small intestine, and large intestine from male rats exposed intermittently nose-only to up to 84 mg/m^3 APFO dusts for 2 weeks (Kennedy et al. 1986).

Laboratory Animal Exposure Studies—PFOS. Unpublished data summarized by OECD (2002) indicate that distension of the small intestine was observed in rats exposed to lethal concentrations of PFOS dusts (1,890–45,970 mg/m^3) for 1 hour.

Hematological Effects.

Human Exposure Studies. Hematological parameters (including hematocrit, hemoglobin, red blood cells, white blood cells, and platelets) monitored in male employees at two PFOS manufacturing plants in Decatur, Alabama and Antwerp, Belgium were not associated with serum PFOS levels (Olsen et al. 1998a, 1999); 178 workers were examined in 1995 and 149 workers were examined in 1997. Levels of PFOS measured ranged from <1,000 to 26,000 ng/mL, with a mean of 3,300 ng/mL. Subsequent studies of workers at these plants that included 97 women and 421 men reported no substantial associations between PFOA and PFOS levels and hematological parameters with the levels of these compounds measured in the study (<2 µg/mL) (Olsen et al. 2003a). The mean PFOA levels were 0.84 µg/mL in workers at the Antwerp facility and 1.78 µg/mL for workers at the Decatur facility; the mean PFOS levels were 0.80 and 1.32 µg/mL, respectively. The specific parameters monitored included percent hematocrit,

hemoglobin, red blood cells, white blood cells, and platelet count. A cross-sectional study of 1,025 workers potentially exposed to PFOA reported no alterations in complete blood count among the workers (Sakr et al. 2007b). Serum PFOA levels ranged from 5 to 9,550 ng/mL.

Laboratory Animal Exposure Studies—PFOA. No treatment-related hematological alterations were reported in male rats exposed intermittently nose-only to up to 84 mg/m^3 APFO dusts for 2 weeks (Kennedy et al. 1986). The specific parameters evaluated included erythrocyte counts, hemoglobin concentration, hematocrit, and differential leukocyte counts.

Musculoskeletal Effects. No information was located regarding musculoskeletal effects in humans following inhalation exposure to perfluoroalkyl compounds.

Laboratory Animal Exposure Studies—PFOA. The only information in animals is an examination of the sternebrae from male rats exposed head-only to up to 84 mg/m^3 APFO dusts for up to 2 weeks; results were unremarkable (Kennedy et al. 1986).

Hepatic Effects.

Human Exposure Studies. Several studies have examined the possible association between PFOA/PFOS exposure and liver diseases. No alterations in the SMR for cirrhosis of the liver were found in workers at the 3M facility in Decatur, Alabama (Alexander et al. 2003). Another study of workers at this facility found no significant alterations in the episodes of care for liver disorders or cirrhosis of the liver (Olsen et al. 2004). A third study of workers at a PFOS facility in Cottage Grove, Minnesota, did not find increases in self-reported liver disease (including cirrhosis and hepatitis) (Grice et al. 2007).

A number of occupational exposure studies have evaluated liver function (as assessed by serum liver enzymes) in workers exposed to PFOA and/or PFOS, and for the most part, no significant associations have been found. A cross-sectional study of 115 workers exposed to PFOA found no significant alterations in activities of alanine aminotransferase (ALT), asparate aminotransferase (AST) or γ-glutamyl transpeptidase (GGT) at the serum PFOA levels measured (<1,000–26,000 ng/mL, mean 3,300 ng/mL) (Gilliland and Mandel 1996). It should be noted that in obese workers only, AST and ALT activities increased with increasing PFOA, which the investigators thought had biological plausibility because obesity has been associated with elevation of transaminases through fatty infiltration.

A similar study was conducted with PFOS in male workers at plants in Decatur, Alabama and Antwerp, Belgium (Olsen et al. 1999). In 1995, the mean serum PFOS for 178 workers was 2,190 ng/mL (range 0–12,830 ng/mL); in 1997, the mean for 149 workers was 1,750 ng/mL (range 100–9930 ng/mL). For both years, 95% of the measured PFOS levels were <6,000 ng/mL. Because the employees from the two plants were dissimilar by age, body mass index (BMI), and self-reported alcohol use, the authors conducted combined analyses as well as separate analyses by plant location. There were no substantial changes in serum ALT, AST, or GGT enzymes at PFOS levels <6,000 ng/mL; a positive association with total bilirubin levels was found. No conclusions were drawn from the few workers with serum PFOS ≥6,000 ng/mL due to their small number (7 in 1995 and 5 in 1997 data). Similarly, no association of ALT, AST, or GGT and serum PFOA levels were observed in groups of workers at these facilities examined in 1993 (111 subjects), 1995 (80 subjects), and/or 1997 (74 subjects) (Olsen et al. 2000). A subsequent evaluation of workers from the same plants, but that included women and a longitudinal analysis of the workers, reported that, after adjusting for potential confounding factors, there were no substantial changes in hepatic parameters; GGT levels were significantly higher in females with PFOS levels in the fourth quartile, as compared to the first quartile, but this was not observed in males (Olsen et al. 2003a). In this study, the mean serum concentrations of PFOS and PFOA for 263 Decatur employees were 1,320 and 1,780 ng/mL, respectively. Workers at the Antwerp plant (n=255) had mean PFOA and PFOS serum values approximately 50% lower than those at the Decatur plant. A more recent assessment of 506 employees who did not take cholesterol-lowering medications at three fluorochemical production plants (Cottage Grove, Minnesota; Decatur, Alabama; Antwerp, Belgium) reported no statistically significant association between serum PFOA and ALT, AST, or total bilirubin levels for the three facilities combined, although some modest positive associations were observed between PFOA and hepatic enzymes (ALT and GGT) at one of the three facilities (Olsen and Zobel 2007). Serum PFOA levels in this study ranged from 7 to 92,030 ng/mL (arithmetic mean 2,210 ng/mL, 95% CI 1,660–2,770 ng/mL).

A study of workers (n=179) involved in the demolition of 3M perfluoroalkyl manufacturing facilities examined the effect of a change in serum PFOA levels over a mean period of 164 days on hepatic biomarkers (Olsen et al. 2012). In workers with prior exposure to PFOA who had a decrease in serum PFOA levels during the study period, there was a significant increase in ALT levels. An increase in serum PFOA levels did not significantly alter AST or total bilirubin levels. The study also found a negative association between the change in serum PFOS levels and ALT levels.

The possible association between PFOA exposure and hepatic enzymes was also examined in two studies of workers at a facility that manufactures fluoropolymers in West Virginia. Sakr et al. (2007a) examined the relationship between serum PFOA and liver enzymes in a longitudinal study of 454 workers using a linear mixed effects model. The cohort was comprised of employees who had two or more measurements of serum PFOA from 1979 until the study was conducted. The average length of employment among workers with multiple PFOA measurements was 11 years, and, on average, 10.8 years elapsed between their first and last serum PFOA measurement. The means of the first and last PFOA measurement were 1,040 and 1,160 ng/mL, respectively. After adjustment for potential confounders, PFOA was negatively associated with total bilirubin and positively with serum AST activity, but not ALT or GGT. The same groups of investigators conducted a cross-sectional study of 1,025 active workers (76% males) at the same plant with potential exposure to PFOA (Sakr et al. 2007b). Serum PFOA levels ranged from 5 to 9,550 ng/mL among the total participants. After adjustment for confounders, which included control for cholesterol-lowering medications, there was a modest but statistically significant positive association between PFOA and GGT activity. The increases in serum AST activity in the longitudinal study and serum GGT activity in the cross-sectional study were small and were not likely biologically relevant. No associations were found for bilirubin, or ALT and AST activities. A small study of Italian perfluoroalkyl workers (n=34) did not find significant associations between serum PFOA and AST or ALT activities or total bilirubin levels (Costa et al. 2009).

A health evaluation of workers exposed to PFNA is also available (Mundt et al. 2007). The cohort consisted of 630 employees at a U.S. polymer production facility using PFNA at any time between January 1, 1989 and July 1, 2003. Annual cross-sectional analyses and longitudinal analyses that accounted for multiple measurements per person were conducted over a 5-year period. After adjusting for age and BMI, some small but not clinically significant differences between groups were found. However, these observations were not consistent between men and women or over the five analysis windows. GGT, AST, ALT, and bilirubin examined in separate longitudinal models showed no significant increase or decrease by unit increase in exposure intensity score.

A number of occupational exposure studies have examined the possible associations between serum PFOA and PFOS levels and serum lipid levels in workers exposed to high levels of PFOA and/or PFOS. A small study of 35 workers at a manufacturing facility in Italy found higher total cholesterol and non-high-density lipoprotein (HDL)-cholesterol levels in the PFOA-exposed workers, as compared to levels in 94 workers who were not exposed to PFOA (Costa 2004). A second study at this facility also found significantly higher total cholesterol levels in 34 currently employed workers (mean serum PFOA level of

12,930 ng/mL), as compared to unexposed workers (Costa et al. 2009). No significant differences in HDL-cholesterol or triglyceride levels were found between the exposed and unexposed workers. A study of 506 male workers at 3M facilities in Cottage Grove, Minnesota, Decatur, Alabama, and Antwerp, Belgium (mean serum PFOA level of 2,210 ng/mL) not taking cholesterol-lowering medications did not find associations between serum PFOA levels and total cholesterol or low-density lipoprotein (LDL)-cholesterol levels; however, serum PFOA levels were positively associated with triglyceride levels and there was an increased risk of having high triglyceride levels (≥150 mg/dL) in workers with serum PFOA levels in the three highest deciles (odds ratios [ORs] of 2.7 [95% CI 1.2–6.5], 2.4 [95% CI 1.0–5.9], and 2.4 [95% CI 1.0–5.8], respectively) (Olsen and Zobel 2007). Additionally, there was a negative association between serum PFOA levels and HDL-cholesterol levels and an increased risk of low HDL cholesterol levels (≤40 mg/dL) in workers with the highest serum PFOA levels (OR 2.6, 95% CI 1.0–6.8). Sakr et al. (2007a) used medical records for 454 male and female current and former workers (74% male) at the DuPont Washington Works facility (mean serum PFOA level of 1,130 ng/mL) and found a positive association between serum PFOA and total cholesterol levels; no associations with triglycerides, LDL-cholesterol, or HDL-cholesterol were found. A larger-scale study of this facility (1,025 current workers, 76% males) (mean serum PFOA level 428 ng/mL) found significant associations between serum PFOA levels and total cholesterol, LDL-cholesterol, and very-low-density lipoprotein (VLDL)-cholesterol levels in all subjects and in a subset of subjects not taking cholesterol-lowering medication (Sakr et al. 2007b). The study did not find any association between serum PFOA and HDL-cholesterol or triglyceride levels. Workers at a PFOA production facility were examined in 1993 (111 subjects), 1995 (80 subjects), and 1997 (74 subjects) (Olsen et al. 2000). Only 17 subjects were examined at all 3 time periods; 21 subjects were examined in 1995 and 1997 and 68 subjects were examined in 1993 and 1995. The study did not adjust for the use of cholesterol-lowering medication. When workers were categorized by blood PFOA levels (0–<1,000, 1,000–<10,000, and >10,000 ng/mL), no significant differences in serum cholesterol, HDL-cholesterol, LDL-cholesterol, or triglyceride levels were found at any of the monitoring periods.

Workers at 3M facilities in Decauter, Alabama and Antwerp, Belgium were examined in 1995 and 1997 (178 male workers) (Olsen et al. 1999) and in 1995, 1997, and 2000 (421 male and 97 female workers) (Olsen et al. 2003a); neither study notes whether workers taking cholesterol-lowering medication were excluded. In workers with serum PFOS levels between 3,000 and 6,000 ng/mL, total cholesterol and LDL cholesterol levels were significantly higher compared to workers with serum PFOS levels <1,000 ng/mL (Olsen et al. 1999), but this was only found in workers examined in 1997. The latter study (Olsen et al. 2003a) found positive associations between serum PFOS levels and total cholesterol and

triglycerides among male workers. The triglyceride levels of men with PFOS levels in the fourth quartile (mean PFOS level of 2,690 ng/mL) were significantly higher than men with PFOS in the first quartile (mean PFOS of 270 ng/mL). No differences in total cholesterol or HDL-cholesterol levels were seen across PFOS quartiles.

Two studies conducted longitudinal assessments to examine the impact of changes in serum PFOA or PFOS on serum lipid levels. Olsen et al. (2012) examined 179 workers (none of the subjects reported using cholesterol-lowering medication) involved in the demolition of 3M perfluoroalkyl manufacturing facilities; serum PFOA and lipid levels were measured prior to the demolition and after demolition (mean time interval of 164 days). The mean baseline serum PFOA levels were 881 ng/mL in 14 3M workers with prior PFOA or PFOS exposure and 28.9 ng/mL in the remaining 165 workers. A decline in serum PFOA and PFOS levels were observed among the 3M workers. Among the workers with increased serum PFOA/PFOS levels (mean increase 50.9 ng/mL), there was a significant increase in HDL-cholesterol levels, but no change in total cholesterol or non HDL-cholesterol levels. No significant alterations in serum lipid levels were observed in the workers with decreased serum PFOA/PFOS levels. In workers whose baseline levels of PFOA and PFOS were <15 and <50 ng/mL, respectively, there were no significant differences between pre- and post-exposure serum lipid levels.

Longitudinal analysis was conducted using data for 174 workers with medical surveillance data in 2000 and 1997 and/or 1995 (Olsen et al. 2003a). No significant differences in serum PFOS levels were observed across the three time periods and serum PFOS level was not a significant predictor of cholesterol or triglyceride levels. In contrast, there were significant differences in serum PFOA levels between 1997 and 2000; serum PFOA levels were increased in 69 workers with only 1997 and 2000 data and decreased in 41 workers with 1995, 1997, and 2000 data. Serum PFOA was a significant predictor of cholesterol and triglyceride levels, which was primarily due to 21 workers at the Antwerp facility (mean serum level 8,400 ng/mL) whose serum PFOA levels increased and serum PFOS levels decreased over time.

Mundt et al. (2007) measured serum lipid levels in 592 workers at a polymer production facility using PFNA; blood samples were collected in 1976, 1989, 1995, 1998, and 2001. Significantly higher total cholesterol levels were observed in workers with high potential exposure to PFNA (based on job titles), as compared to the low exposure group, in 1976 and 1989; no differences were observed at other time points and no differences were found between the high-exposure and no-exposure groups. No significant alterations were observed for serum triglyceride, HDL-cholesterol, LDL-cholesterol, or VLDL-

cholesterol at any of the time points. Longitudinal analysis did not find significant differences in serum lipid levels over time.

Seven occupational studies examined the possible associations between serum PFOA levels and serum lipid levels. Five of the studies found positive associations between serum PFOA and total cholesterol levels (Costa 2004; Costa et al. 2009; Olsen et al. 2003a; Sakr et al. 2007a, 2007b); however, studies by Olsen et al. (2000) and Olsen and Zobel (2007) did not find statistically significant associations. Two studies measuring serum PFOS levels found a positive association with total cholesterol (Olsen et al. 1999, 2003a). In general, significant association were not found between serum PFOA levels and LDL-cholesterol (Olsen and Zobel 2007; Olsen et al. 2000; Sakr et al. 2007a) or triglycerides (Costa et al. 2009; Olsen et al. 2000; Sakr et al. 2007a, 2007b), although some studies did report a positive association with LDL-cholesterol (Sakr et al. 2007a) and triglycerides (Olsen and Zobel 2007; Olsen et al. 2003a). With the exception of one study that reported a negative association (Olsen and Zobel 2007), no association was found between HDL-cholesterol and serum PFOA levels (Costa et al. 2009; Olsen et al. 2000, 2003a; Sakr et al. 2007a, 2007b). One limitation of cross-sectional studies is that they do not establish causality. Longitudinal assessments provide additional insight since they can examine serum lipid levels in response to changes in serum PFOA or PFOS. Olsen et al. (2012) did not find any changes in total cholesterol in works with increasing or decreasing serum PFOA levels; the mean interval between measurements was approximately 5 months. In contrast, Olsen et al. (2003a) found that serum PFOA was a significant predictor of cholesterol and triglyceride levels in workers whose serum PFOA levels increased over a 3–5-year period. Serum PFOS levels did not predict serum lipid levels.

Laboratory Animal Exposure Studies—PFOA. Information from studies in animals is limited. Head-only exposure of male rats to 810 mg/m^3 APFO dusts for 4 hours caused liver enlargement, but microscopically, the liver tissue appeared normal (Kennedy et al. 1986). Exposure head-only of male rats to 0, 1, 7.6, or 84 mg/m^3 APFO dusts 6 hours/day, 5 days/week for 2 weeks resulted in significant increases in absolute and relative liver weight at 7.6 and 84 mg/m^3 on exposure day 10; in rats from the 84 mg/m^3 group, absolute and relative liver weight were still significantly increased 28 days after exposure ceased (Kennedy et al. 1986). The activities of serum enzymes markers of liver function were unremarkable except for alkaline phosphatase that was significantly increased in the 7.6 and 84 mg/m^3 groups immediately after exposure on day 10 and remained elevated in the 84 mg/m^3 group on day 14 of recovery. Histopathological changes were restricted to the 7.6 and 84 mg/m^3 groups and consisted of panlobular and centrilobular hepatocellular hypertrophy and necrosis. Panlobular hepatocellular hypertrophy was seen only after the 10th exposure, but was limited to the centrilobular hepatocytes 14 or

28 days after exposure terminated, and was absent 42 days follow cessation of exposure. Exposure of pregnant rats to 25 mg/m^3 APFO dusts 6 hours/day during GDs 6–15 induced an 18% increase in absolute liver weight (Staples et al. 1984); no significant effect was reported in rats exposed to ≤10 mg/m^3.

Nose-only exposure of male CD rats to 67 mg/m^3 ammonium perfluorononanoate dusts for 4 hours induced significant increases (28–37%) in absolute and relative liver weight, assessed 5 and 12 days after exposure (Kinney et al. 1989). Histopathological examinations were not conducted in this study.

Laboratory Animal Exposure Studies—PFOS. Unpublished data summarized by OECD (2002) indicate that exposure of rats to lethal concentrations (1,890–45,970 mg/m^3) of PFOS dusts for 1 hour resulted in varying discoloration of the liver.

Renal Effects.

Human Exposure Studies. In a cohort mortality study of 5801 workers at the DuPont PFOA facility in West Virginia, Steenland and Woskie (2012) found an increase in deaths from chronic renal disease (SMR 3.11, 95% CI 1.66–5.32) when compared to DuPont workers at other regional facilities. When cumulative PFOA exposure was estimated based on the worker's job history and data from a biomonitoring survey conducted from 1979 to 2004, there was a significant positive trend for nonmalignant kidney disease when the workers were divided in estimated cumulative exposure quartiles. Kidney function, assessed by levels of blood urea nitrogen (BUN) and serum creatinine, was not associated with exposure to PFOS and/or PFOA in the occupational exposure studies by Olsen et al. (1998a, 2003a), Sakr et al. (2007b), or Costa et al. (2009) or with exposure to PFNA in the study conducted by Mundt et al. (2007); these studies are briefly described in the previous section on *Hepatic Effects*.

Laboratory Animal Exposure Studies—PFOA. No gross or microscopic alterations were observed in the kidneys from male rats head-only exposed intermittently to up to 84 mg/m^3 APFO dusts for 2 weeks (Kennedy et al. 1986).

Endocrine Effects.

Human Exposure Studies. The possible association between serum PFOA and PFOS levels and hormone levels was investigated in two cross-sectional studies of male workers at a PFOA production

plant (Olsen et al. 1998a, 1998b). The studies were conducted in 1993 (n=11) and 1995 (n=80). Eleven hormones were assayed: cortisol, dehydroepiandrosterone sulfate, estradiol, follicle stimulating hormone (FSH), 17α-hydroxyprogesterone, free testosterone, total testosterone, luteinizing hormone (LH), prolactin, thyroid stimulating hormone (TSH), and sex hormone-binding globulin. Simple and stratified analysis of variance, Pearson correlation coefficients, and ordinary multivariable regressions were used to evaluate associations between serum PFOA levels and each hormone, with adjustments for potential confounding variables. For stratified analyses, workers were divided into four PFOA categories: 0–1,000, 1,000–<10,000, 10,000–<30,000, and ≥30,000 ng/mL. The results did not show significant associations between PFOA exposure and hormone levels, but workers with the highest serum PFOA levels had mean estradiol levels 10% greater than workers in other groups. The interpretation of the higher levels of estradiol was limited by the small number of workers in the high-exposure groups (four in 1994 and five in 1995) and the fact that estradiol levels were confounded by BMI. No significant associations between serum PFOS levels and hormone levels were found, with the exception of estradiol levels. However, it was found that one worker influenced the regression model; excluding this employee from the analysis resulted in a nonsignificant association between PFOS and estradiol. Limitations included the cross-sectional design of the study and the fact that the two studies could not be viewed as independent studies because 68 workers were studied in both years. In the cross-sectional study of 1,025 workers conducted by Sakr et al. (2007b) discussed previously, serum estradiol and testosterone were significantly positively associated with serum PFOA in linear regression models in men. The investigators noted that interpretation of this result was difficult because blood samples were collected at different times of the day and circadian variations were not taken into consideration. In a study by Costa et al. (2009), no significant associations between serum PFOA levels and testosterone and estradiol levels were found.

In the epidemiological assessment conducted at two perfluorooctanyl-manufacturing locations summarized above under *Hepatic Effects* (Olsen et al. 2003a), workers did not show evidence of altered thyroid function as assessed by measurements of serum levels of TSH, thyroxine (T4), free T4, triiodothyronine (T3), thyroid hormone binding ratio, and free thyroxine index. Mean concentrations of PFOS and PFOA for employees at one plant were 1.32 and 1.78 µg/mL, respectively. Mean PFOS and PFOS-serum values at the other plant were approximately 50% lower. Olsen and Zobel (2007) also found no significant associations between serum PFOA and TSH or T4 values in a study of 506 employees at three fluorochemical production facilities. Serum PFOA levels in this study ranged from 7 to 92,030 ng/mL (arithmetic mean 2,210 ng/mL). Similar results were reported in the cross-sectional study

of PFOA workers conducted by Sakr et al. (2007b). In that study, serum TSH, T4, and T3 uptake were within normal limits.

In the epidemiology study of 630 workers exposed to PFNA described above under *Hepatic Effects* (Mundt et al. 2007), there was no indication that exposure to PFNA affected thyroid function as assessed by serum levels of TSH, T4, T3 uptake, and free T4 index five times over a 25-year period. In this study, exposure was ascertained by work histories; levels of PFNA in serum were not available.

In the cohort mortality study by Leonard et al. (2008; Leonard 2006) of workers at the DuPont Washington Works facility in West Virginia exposed to APFO, a significant increase in deaths from diabetes (SMR 197, 95% CI 123–298) was found, as compared to workers at other DuPont facilities in the region. In an update of the Leonard et al. (2008) study, Steenland and Woskie (2012) also found a significant increase in diabetes deaths (SMR 1.90, 95% CI 1.35–2.61) when compared to other regional DuPont employees, but not when compared to the U.S. population. However, when the workers were categorized by estimated cumulative exposure levels, the exposure-response trend was not statistically significant. Lundin et al. (2009) also found an increase in deaths from diabetes in workers exposed to APFO at the 3M Cottage Grove facility in Minnesota, as compared to Minnesota death rates. The increase was only found in workers with probable exposure to APFO, but not with definite exposure (n=168); no deaths from diabetes were observed in the workers (n=513) with definite exposure to APFO. As noted by Steenland and Woskie (2012), diabetes mortality may not be a good surrogate for the underlying diabetes incidence data.

Laboratory Animal Exposure Studies—PFOA. Repeated intermittent head-only exposure of male rats to up to 84 mg/m^3 APFO dusts for 2 weeks did not result in significant gross or microscopic alterations in the thyroid or adrenal gland (Kennedy et al. 1986).

Dermal Effects. No studies were located regarding dermal effects in humans following inhalation exposure to perfluoroalkyl compounds.

Laboratory Animal Exposure Studies—PFOA. The only relevant information in animals is that intermittent head-only exposure of male rats to up to 84 mg/m^3 APFO dusts for 2 weeks did not result in histopathologic changes in abdominal skin (Kennedy et al. 1986).

Ocular Effects. No information was located regarding ocular effects in humans following inhalation exposure to perfluoroalkyl compounds.

Laboratory Animal Exposure Studies—PFOA. Rats exposed to 18,600 mg/m^3 APFO dusts for 1 hour exhibited a red material around the eyes and lacrimation during exposure (Griffith and Long 1980). Male rats exposed to ≥810 mg/m^3 APFO dusts for 4 hours showed corneal opacity and corrosion, which was confirmed by fluorescein staining (Kennedy et al. 1986). Examination of the eyes of male rats exposed intermittently to up to 84 mg/m^3 APFO for 2 weeks using a bright light and a slit-lamp biomicroscope on days 5 and 9 of exposure did not reveal any significant exposure-related alterations (Kennedy et al. 1986). Microscopic examination of the eyes from these rats at termination and following a recovery period of up to 42 days was unremarkable.

Body Weight Effects. No information was located regarding body weight effects in humans following inhalation exposure to perfluoroalkyl compounds.

Laboratory Animal Exposure Studies—PFOA. Male rats that survived a 4-hour exposure to 380 mg/m^3 APFO dusts lost weight for 1–2 days after a 4-hour exposure, but resumed normal weight gain thereafter (Kennedy et al. 1986). Male rats exposed intermittently to 84 mg/m^3 APFO dusts for 2 weeks lost approximately 7% of their body weight by day 5 of exposure (250 g at start of study, 237 g on day 5) (Kennedy et al. 1986), but recovered by day 16 after exposure ceased. In a developmental study, exposure of pregnant rats to 25 mg/m^3 APFO dusts during GDs 6–15 induced a 37% reduction in body weight gain relative to controls during the exposure period (Staples et al. 1984); in a pair-fed group, the reduction of weight gain during the same period was 61% relative to *ad libitum* controls.

Nose-only exposure of male CD rats to 590 mg/m^3 ammonium perfluorononanoate dusts for 4 hours resulted in 18 and 36% reductions in body weight 5 and 12 days after exposure, respectively (Kinney et al. 1989). Exposure to 67 mg/m^3 had no significant effect on body weight.

Other Effects.

Human Exposure Studies. Costa et al. (2009) reported significant higher serum uric acid levels in 34 workers at an Italian PFOA facility, as compared to 34 non-exposed workers. Sakr et al. (2007b) also noted a statistically significant association between serum PFOA levels and uric acid levels in workers in

a study of >1,000 workers at the Washington Works facility. An observed association between uric acid and hypertension has been established in humans (Palmer et al. 2013).

3.2.1.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological and lymphoreticular effects in humans following inhalation exposure to perfluoroalkyl compounds.

Laboratory Animal Exposure Studies—PFOA. Examination of the spleen and thymus of male rats exposed intermittently to up to 84 mg/m^3 APFO dusts for 2 weeks did not reveal any gross or microscopic treatment-related alterations (Kennedy et al. 1986); this study did not evaluate immune function and a NOAEL is not presented in Table 3-1 or Figure 3-1.

3.2.1.4 Neurological Effects

No information was located regarding neurological effects in humans following inhalation exposure to perfluoroalkyl compounds.

Laboratory Animal Exposure Studies—PFOA. Exposure of rats to 18,600 mg/m^3 APFO dusts for 1 hour induced excessive salivation. Intermittent, head-only exposure of male rats exposed to up to 84 mg/m^3 APFO dusts for 2 weeks did not reveal gross or microscopic alterations in the brain (Kennedy et al. 1986).

The exposure concentration of 84 mg/m^3 is presented as a NOAEL for neurological effects in Table 3-1 and Figure 3-1.

3.2.1.5 Reproductive Effects

Human Exposure Studies. The only relevant information regarding reproductive effects in humans is that regarding serum levels of sex hormones in male workers (see above under *Endocrine Effects*) in studies by Olsen et al. (1998b) and Sakr et al. 2007b). Assays for dehydroepiandrosterone sulfate, estradiol, FSH, 17α-hydroxyprogesterone, free testosterone, total testosterone, LH, prolactin, and sex hormone-binding globulin provided no evidence for associations between PFOA exposure and hormone levels, but workers with the highest serum PFOA levels had mean estradiol levels 10% greater than workers in other groups (Olsen et al. 1998b). Sakr et al. (2007b) also reported a significant association

between serum PFOA and serum estradiol levels in workers; additionally, testosterone levels were significantly associated with serum PFOA in linear regression models.

Laboratory Animal Exposure Studies—PFOA. Examination of the testes and epididymides of rats exposed intermittently head-only to up to 84 mg/m^3 APFO dusts for 2 weeks did not reveal any gross or microscopic treatment-related alterations (Kennedy et al. 1986).

The exposure concentration of 84 mg/m^3 is presented as a NOAEL for reproductive effects in Table 3-1 and Figure 3-1.

3.2.1.6 Developmental Effects

Human Exposure Studies. In the study of self-reported health conditions and exposure to PFOS, conducted by Grice et al. (2007), mentioned earlier under *Gastrointestinal Effects*, the women were asked to fill a questionnaire that assessed pregnancy outcome history including number of pregnancies, the month and year the pregnancy ended, the outcome of the pregnancy, and the weight of the live-born children, as well as tobacco use. The results of the analyses showed that birth weight of singleton births, adjusted for maternal age at birth, gravidity, and smoking status did not vary between exposure groups.

Laboratory Animal Exposure Studies—PFOA. Exposure of pregnant Sprague-Dawley rats to 25 mg/m^3 APFO on GDs 6–15 resulted in a statistically significant reduction (10.3%) in neonatal body weight on postnatal day (PND) 1, but the difference over controls was no longer significant on PND 4 (Staples et al. 1984). Exposure concentrations ≤10 mg/m^3 did not affect neonatal body weight. The incidence of malformations and variations among the exposed groups and controls was comparable.

The concentrations of 10 and 25 mg/m^3 are presented as a NOAEL and LOAEL, respectively, for developmental effects in Table 3-1 and Figure 3-1.

3.2.1.7 Cancer

Human Exposure Studies. Several studies have examined the possible association between occupational exposure to perfluoroalkyls and increased cancer risk. Gilliland and Mandel (1993) conducted a retrospective cohort mortality evaluation of 2,788 male and 749 female workers employed for at least 6 months between 1947 and 1983 at a plant that produced PFOA. Workers employed ≥1 month in the Chemical Division of the plant were categorized as exposed and those who either never worked or

worked for <1 month in the Chemical Division formed the unexposed group. The effects of latency, duration of employment, and work in the Chemical Division were examined using stratified SMR analyses. No significant increases in SMRs were observed in the male and female workers for all cancer types and for individual types of cancer as compared to U.S. and Minnesota mortality rates. However, there was a nonsignificant increase in the SMR for prostate cancer (2.03, 95% CI 0.55–4.59) in the Chemical Division group. Ten years of employment in the Chemical Division was associated with a 3.3-fold increase (95% CI 1.02–10.6) in the relative risk of prostate cancer mortality, as compared to no employment in PFOA production areas. The investigators noted that the prostate cancer findings are based on a small number of cases and could have resulted from chance or unrecognized confounding from exposure to other factors. An update of this study of workers at the 3M Company facility in Cottage Grove, Minnesota was conducted by Lundin et al. (2009). Unlike the Gilliland and Mandel (1993) study, the eligibility criterion was a minimum of 365 days of cumulative employment prior to 1997. The cohort consisted of 807 deceased workers (80% male) followed through 2002. The cohort was divided into three exposure categories of APFO exposure: definite occupational exposure (high exposure), probable occupational exposure (jobs where APFO exposure was possible, but likely lower or transient) (moderate exposure), and no or minimal occupational exposure (low exposure). No increases in deaths from all cancer types, biliary or liver cancers, pancreatic cancer, respiratory cancer, or bladder and other urinary organ cancers were found, as compared to the Minnesota general population. A nonsignificant increase in prostate cancer deaths (SMR 2.1, 95% CI 0.4–6.1) was found in the workers with definite PFOA exposure. When the cohort was divided into the three exposure categories, increased HRs for prostate cancer were found in the moderate- and high-exposure categories (HR=3.0, 95% CI 0.9–9.7 and HR=6.6, 95% CI 1.1–37.7) and in the combined moderate- and high-exposure categories (HR=3.2, 95% CI 1.0–10.3), as compared to the low-exposure category.

A study of DuPont employees (n=6,027; 81% male) who worked at the at the Washington Works, West Virginia, polymer-manufacturing facility at any time between January 1, 1948 (plant start-up) and December 31, 2002 was conducted by Leonard et al. (2008; the study was also reported in an unpublished report by Leonard 2006). Approximately one-half of the employees at the site had been assigned to APFO areas at some time in their careers. No significant increases in deaths from all cancer types were found when the workers were compared to U.S. and West Virginia population mortality rates and to workers at other DuPont facilities in the region. An increase in the number of deaths from kidney cancer relative to the DuPont regional population was observed; however, the SMR was not significantly elevated (SMR 185, 95% CI 95–323). No other elevations in specific cancer risk were found. In a follow-up study, Steenland and Woskie (2012) followed a cohort of 5801 workers through 2008. Using

blood samples collected from 1979 to 2004 from 1,308 workers participating in a health survey, serum PFOA levels over time were estimated for eight job categories/job group categories. Serum PFOA levels were estimated for each worker based on job history and the estimated serum PFOA levels for each job category/job group category. The mean cumulative exposure to PFOA was 7.8 ppm-years and the estimated average annual serum concentration was 350 ng/mL. Deaths from all cancer types were not significantly increased when compared to the U.S. population or to the DuPont regional population. A significant increase in deaths from mesothelioma was found when compared to the U.S. population (SMR 4.83, 95% CI 1.77–10.52) and the DuPont regional population (SMR 2.85, 95% CI 1.05–6.20); the investigators noted that this was likely due to asbestos exposure. Among workers with the highest exposure to PFOA, there was a significant increase in kidney cancer as compared to the DuPont regional population (SMR 2.66, 95% CI 1.15–5.24 for no lag, SMR 2.82, 95% CI 1.13–5.81 with a 10-year lag, and SMR 3.67, 95% CI 1.48–7.57 with a 20-year lag); a positive exposure-response trend was also observed for kidney cancer at all three lag times. Steenland and Woskie (2012) noted that tetrafluoroethylene, a rodent kidney carcinogen, is used in the manufacture of a variety of fluoropolymers; tetrafluoroethylene is well controlled due to its volatile and explosive properties.

Alexander et al. (2003) conducted a retrospective mortality study of a cohort of 2083 employees (83% male) at a perfluorooctanesulphonyl fluoride (PFOSF) based fluorochemical production facility in Decatur, Alabama, who had at least 1 year of cumulative employment at the facility. The geometric mean serum PFOS levels were 900 ng/mL in a randomly selected group of 126 workers in the chemical plant and 100 ng/mL in a group of 60 workers in the film plant. Biomonitoring conducted at this facility indicates that the workers also had elevated serum PFOA levels; in a 2000 survey, the mean serum PFOA level was 1,780 ng/mL (Olsen et al. 2003a). Based on job history and serum PFOS levels, workers were assigned to one of three groups: high exposure (n=982), low exposure (n=289), or no exposure (n=812). No significant increases in the SMR for all types of cancer or specific types of cancer were observed, as compared to mortality rates in the state of Alabama. There was an increased risk of death from bladder cancer for the entire cohort, 3 observed and 0.62 expected; however, the 95% CI included the null value (SMR 4.81, 95% CI 0.99–14.05). All three cases of bladder cancer occurred in workers from the high-exposure group (0.19 expected) (SMR 16.12, 95% CI 3.32–47.41) and all of them had worked in high-exposure jobs for at least 5 years. A reanalysis of workers at this facility was conducted by Alexander and Olsen (2007) and included all current, retired, and former employees (total=1,895) who had at least 365 days of cumulative exposure prior to 1998 and information from 188 deceased workers. The NIOSH Surveillance Epidemiology and End Results (SEER) referent data were used to calculate the standardized incidence ratios. Bladder cancer incidence was collected via a self-administered questionnaire; for

subjects self-reporting bladder cancer, an attempt was made to verify the diagnosis with medical records. The exposure assessment followed the method used in the previous study; workers were assigned to a high-exposure (serum PFOS 1,300–1,970 ng/mL), low-exposure (390–890 ng/mL), and no direct exposure (110–290 ng/mL) groups. Eleven cases of bladder cancer were identified from surveys (n=6) and death certificates (n=5). Only two of the six self-reported bladder cancer diagnosis were confirmed via medical records; the other four subjects declined to give consent for medical verification. The standardized incidence ratios (SIRs) were 1.28 (95% CI 0.64–2.29) for the entire cohort and 1.74 (95% CI 0.64–3.79) for those ever working in a high-exposure job. When compared with those in the lowest cumulative exposure category, the high-exposure workers had a 1.5–2.0-fold increased risk but the CIs included unity; for example, the relative risk in the workers exposed for 5–<10 years was 1.92 with a 95% CI of 0.30–12.06. Although the study did not adjust for smoking, the investigators noted that 83% of the living bladder cancer cases (five of the six subjects) reported cigarette use, as compared to 56% reported in the noncases. An additional limitation of the study is inclusion of four cases of bladder cancer that were not verified by medical records. The results of this study do not appear to confirm the findings of increased bladder cancer in the mortality study (Alexander et al. 2003).

Grice et al. (2007) also examined the potential carcinogenicity of PFOS in 1,400 workers (81% male) at the Decatur, Alabama manufacturing facility via a self-administered health questionnaire. Attempts were made to validate the self-reported diagnoses of prostate cancer, colon cancer, breast cancer, and melanoma through medical records. Exposure to PFOS was evaluated based on the job-specific exposure categories established in the Alexander et al. (2003) study. As noted previously, these workers were also likely exposed to elevated levels of PFOA. The risks of colon cancer, melanoma, and prostate cancer were not associated with any of the PFOS-exposure categories for analyses that included all self-reported or only validated cancers.

Olsen et al. (2004a) conducted a study of episodes of care in workers at the Decatur facility. An episode of care is defined as a series of events related to a particular health problem. Among the 211 long-term workers in the chemical plant, there was a nonsignificant increase in the number of episodes of care for malignant neoplasm of the prostate (risk ratio episodes of care [RRE_pC] of 8.2, 95% CI 0.8–>100), a nonsignificant increase in malignant neoplasms of the colon (RRE_pC of 12, 95% CI 0.8–>100), and a significant increase in benign colonic polyps (RRE_pC of 2.4, 95% CI 1.3–-4.5), as compared to 345 long-term workers in the film plant. No significant increases in the risk ratio episodes of care were found for liver, rectum, or respiratory tract were found.

Consistent findings regarding the association between occupational exposure to PFOA and PFOS and cancer have not been found. Among workers with longer-term exposure to higher PFOA levels, an increased risk of prostate cancer deaths was found (Gilliland and Mandel 1993; Lundin et al. 2009), but this was not found in studies of workers at a different PFOA facility (Leonard et al. 2008; Steenland and Woskie 2012). The increases in kidney cancer mortality were observed at the second facility (Leonard et al. 2008; Steenland and Woskie 2012), but not at the first facility (Gilliland and Mandel 1993; Lundin et al. 2009). For PFOS, one study reported an increase in bladder cancer (Alexander et al. 2003), but a follow-up study did not confirm this finding (Alexander and Olsen 2007). The inconsistent results across studies may be due to differences in exposures or to exposure to other compounds.

Laboratory Animal Exposure Studies. No studies were located regarding cancer in animals following inhalation exposure to perfluoroalkyl compounds.

3.2.2 Oral Exposure

Information on the health effects of perfluoroalkyl compounds come from epidemiology studies and an extensive number of oral exposure studies in laboratory animals. The epidemiology studies were grouped into two categories: studies of communities living near perfluoroalkyl manufacturing facilities and studies of the population presumably exposed to background levels of perfluoroalkyl compounds (termed general population studies). Most of the studies of communities living near perfluoroalkyl manufacturing facilities are part of the C8 Health Project and C8 Health Study. The C8 Health Project was a population study of residents living near the DuPont Washington Works facility in West Virginia and was funded by DuPont as part of a class action settlement agreement. At the time of enrollment (2005–2006), blood samples were collected from over 69,000 participants who lived, worked, or attended school in six contaminated water districts surrounding the facility for at least 12 months between 1950 and December 2004 (Frisbee et al. 2009); the six water districts were Little Hocking Water Association, Tuppers Plains Chester Water District, Village of Pomeroy, Lubeck Public Service District, Mason County Public Service District, or private water sources within these areas. The participants ranged in age from 1.5 to >100 years, with an average age of 39.1 years. Serum perfluoroalkyl levels were available for 69,030 subjects; 4,915 of the participants were <10 years old (Steenland et al. 2009a). The median PFOA level in the cohort was 28.2 ng/mL; the mean was 83.6 ng/mL and the geometric mean was 32.9 ng/mL (Steenland et al. 2009a). The highest median serum PFOA level was found in the current residents in the Little Hocking Water Association (224.1 ng/mL) and the lowest concentration among current residents was 12.1 ng/mL for the Village of Pomeroy water district. By comparison, the geometric mean for serum

PFOA in the United States in 2005–2006 was 3.92 ng/mL and the geometric mean in 2009–2010 was 3.07 ng/mL (CDC 2014).

Several types of general population studies examined potential associations between serum perfluoroalkyl levels and health effects. A number of investigators utilized NHANES data and others utilized data collected from other national studies such as the Danish National Birth Cohort study. The database also includes some smaller scale studies.

3.2.2.1 Death

No reports of deaths in humans exposed orally to perfluoroalkyl compounds were located in the literature.

Laboratory Animal Exposure Studies—PFOA. Oral LD_{50} values of 680 and 430 mg/kg were reported for male and female albino rats, respectively, administered single gavage doses of APFO and observed for 14 days (Griffith and Long 1980). The doses ranged from 100 to 2,150 mg/kg. One male in 100 mg/kg group died on day 7; all animals in the 2,150 mg/kg group died on day 1. Nonlethal signs observed included ptosis, piloerection, hypoactivity, decreased limb tone, ataxia, and corneal opacity. All signs were intermittent and there was no apparent dose-response relationship. In a 28-day dietary study with APFO in rats, all rats (males and females) in groups receiving approximately 1,000–1,130 mg/kg/day APFO died before the end of the first week (Griffith and Long 1980). In a similar study in mice, all mice receiving doses of approximately 180–195 mg/kg/day died before the second week of the study (Griffith and Long 1980). In this study, doses of approximately 54–58 mg/kg/day APFO were lethal to 4/5 male and 5/5 female mice before the 4^{th} week of the study.

In a 90-day gavage study, treatment of Rhesus monkeys with 100 mg/kg/day APFO by gavage resulted in the death of an unspecified number of animals (group size was 10/sex) on week 2 (Griffith and Long 1980). Doses of approximately 30 mg/kg/day were lethal to one male and two females during weeks 7–12. All animals that died in the 30 and 100 mg/kg/day groups had anorexia, emesis, black stool, pale face and gums, swollen face and eyes, hypoactivity, and prostration. Microscopic examination of tissues showed marked diffuse lipid depletion in the adrenals, slight to moderate hypocellularity of the bone marrow, moderate atrophy of the lymphoid follicles of the spleen, and moderate atrophy of the lymphoid follicles of the lymph nodes. No deaths occurred at 10 mg/kg/day. Deaths were also reported in intermediate-duration studies in Cynomolgus monkeys. One monkey exposed to 30/20 mg/kg/day PFOA (12 days of exposure to 30 mg/kg/day, 10 days with no exposure, 23 weeks of exposure to 20 mg/kg/day)

was sacrificed in moribund condition; the animal had a body weight loss of 12.5% and was notably hypoactive, and was cold to the touch (Butenhoff et al. 2002). The investigators noted that the death was likely due to the high toxicity of the 30 mg/kg/day dose. Two male monkeys exposed to 0.75 mg/kg/day PFOS died or were sacrificed due to morbidity (Seacat et al. 2002). It is unclear if these deaths were compound-related; one monkey had pulmonary necrosis with a severe acute recurrence of pulmonary inflammation and the cause of morbidity for the second monkey was likely hyperkalemia. Neither effect was observed in the surviving animals.

Laboratory Animal Exposure Studies—PFOS. Unpublished information summarized by OECD (2002) indicate that LD_{50} values of 233 and 271 mg/kg were calculated for male and female CD rats, respectively, following administration by gavage of single doses of up to 1,000 mg/kg of powdered PFOS suspended in an acetone/oil mixture and observed for 14 days. All rats (5/sex/dose group) dosed with ≥464 mg/kg PFOS died before the end of the study. The signs most frequently observed were hypoactivity, decreased limb tone, and ataxia. Gross necropsy showed stomach distension and signs of irritation of the glandular mucosa, and lung congestion. OECD (2002) also reports that a different study estimated that the acute oral LD_{50} for PFOS by gavage in water in Sherman-Wistar albino rats was >50 and <1,500 mg/kg.

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. In a 14-day study, all mice (n=10) administered approximately 54 mg/kg/day PFNA died before the study period ended; no deaths occurred at 5.3 mg/kg/day (Kennedy 1987). An LD_{50} of 120 mg/kg was estimated for PFDeA in female C57BL/6N mice administered single doses between 20 and 320 mg/kg/day PFDeA by gavage in corn oil and observed for 30 days (Harris et al. 1989). All mice (n=10) receiving 160 or 320 mg/kg were dead by 14 days; no mice died at ≤80 mg/kg PFDeA. Early death was associated with mural thrombosis in the left ventricle of the heart. Without providing any details, George and Andersen (1986) reported that the 30-day oral LD_{50} for PFDeA in male Fischer-344 rats was 57 mg/kg.

LOAEL values for death and LD_{50} values in each species and duration category are recorded in Table 3-3 and plotted in Figure 3-3.

3.2.2.2 Systemic Effects

No studies were located regarding gastrointestinal, dermal, ocular, or body weight effects in humans exposed orally to perfluoroalkyl compounds.

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Tables 3-3, 3-4, and 3-5 and plotted in Figures 3-3, 3-4, and 3-5.

Respiratory Effects.

Human Exposure Studies. Dong et al. (2013) found a significant association between the likelihood of physician diagnosed asthma and serum perfluoroalkyl levels in children aged 10–15 years with the highest quartiles for PFOS (OR 2.63, 05% CI 1.48–4.69), PFOA (OR 4.05, 05% CI 2.21–7.42), PFBuS (OR 1.90, 95% CI 1.08–3.37), PFDeA (OR 3.22, 95% CI 1.75–5.94), PFDoA (OR 1.81, 95% CI 1.03–3.23), PFHxS (OR 3.83, 95% CI 2.11–6.93), and PFNA (OR 2.56, 95% CI 1.41–4.6), as compared to the first quartile; the ORs were adjusted for sex, age, BMI, parental education, environmental tobacco smoke exposure, and month of survey. The study did not report the serum perfluoroalkyl cut-off levels for each quartiles. Significant associations were also observed for comparisons to the third quartile of PFOA (OR 2.67, 95% CI 1.49–4.79) and PFHxS (2.94, 95% CI 1.65–5.25). There were positive trends for the association of asthma severity scores and serum levels of PFOS, PFDeA, and PFDoA. Among the asthmatic children, there were dose-related trends between absolute eosinophil counts, eosinophilic cationic protein concentrations, and IgE levels and serum levels of several perfluoroalkyls. Using NHANES data, Humblet et al. (2014) found a positive association between serum PFOA levels and self-reported asthma among children aged 12–19 years. When a sensitivity analysis that incorporated NHANES survey weights so as to make the results representative of the U.S. population was conducted, the association was no longer statistically significant. No statistically significant associations were found for PFNA or PFHxS. A negative association between PFOS and asthma was found; however, it was not statistically significant.

Laboratory Animal Exposure Studies—PFOA. Dosing of male and female CD rats with up to approximately 110 mg/kg/day APFO did not induce gross or microscopic changes in the lungs (Griffith and Long 1980; Perkins et al. 2004). Dosing for 2 years with 15 mg/kg/day APFO increased the incidence of lung hemorrhage in males (3M 1983). The incidences were 10/50, 14/50, and 22/50, for groups receiving doses of 0, 1.5, and 15 mg/kg/day, respectively. Pair-wise comparison between controls and high-dose groups revealed a statistically significant difference ($p<0.05$).

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Monkey (Rhesus)	2 wk 1 x/d (G)				100 (unspecified number out of 4 died on week 2)	Griffith and Long 1980 Ammonium perfluorooctanoate	
2	Rat (albino)	once (GO)				680 M (LD50) 430 F (LD50)	Griffith and Long 1980 Ammonium perfluorooctanoate	
3	Rat (albino)	28 d ad lib (F)				1000 M (5/5 died before end of 1st week of study) 1130 F (5/5 died before end of 1st week of study)	Griffith and Long 1980 Ammonium perfluorooctanoate	
4	Mouse (CD)	28 d ad lib (F)				180 M (5/5 died before 2nd week of study) 195 F (5/5 died before 2nd week of study)	Griffith and Long 1980 Ammonium perfluorooctanoate	
Systemic								
5	Rat (CD)	14 d 1 x/d (GW)	Hepatic	1 M	10 M (46% increase in relative liver weight)		Cook et al. 1992 Ammonium perfluorooctanoate	
			Bd Wt	10 M	25 M (14% reduction in final body weight)			

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
6	Rat (Sprague-Dawley)	1 or 7 days (F)	Hepatic		18 M (incr liver weight, decr serum cholesterol, triglyceride, hepatocellular hypertrophy)		Elcombe et al. 2010 Ammonium perfluorooctanoate	
7	Rat (Wistar)	7 d ad lib (F)	Hepatic		16 M (66% increase in absolute liver weight)		Haughom and Spydevold 1992 Ammonium perfluorooctanoate	
			Bd Wt	16 M				
8	Rat (Sprague-Dawley)	14 d ad lib (F)	Hepatic		20 M (45% increase in relative liver weight)		Ikeda et al. 1985 Perfluorooctanoic acid	
9	Rat (Sprague-Dawley)	14 d 1 x/d (GW)	Hepatic	5 M	50 M (2-fold increased mean relative liver weight)		Iwai and Yamashita 2006 Ammonium perfluorooctanoate	
			Bd Wt	50 M				
10	Rat (Wistar)	1 wk ad lib (F)	Hepatic	2.4 M	4.7 M (significant increase in absolute and relative liver weight)		Kawashima et al. 1995 Perfluorooctanoic acid	
			Bd Wt	38 M				

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
11	Rat (CD)	14 d 1 x/d (G)	Hepatic	0.2 M	2 M (34% increase in absolute and relative liver weight)		Liu et al. 1996 Ammonium perfluorooctanoate	
			Bd Wt	2 M	20 M (14% lower final body weight)			
12	Rat (Sprague-Dawley)	1, 3, 7 d 1 x/d (GW)	Hepatic		50 M (2-fold increase in relative and absolute liver weight)		Pastoor et al. 1987 Ammonium perfluorooctanoate	
			Bd Wt		50 M (17% weight loss)			
13	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)	Bd Wt			100 F (33% reduced body weight gain during Gd 6-15)	Staples et al. 1984 Ammonium perfluorooctanoate	
14	Mouse (C57BL/6N)	GD 6-17 (DW)	Bd Wt	1 F			Hu et al. 2010 Ammonium perfluorooctanoate	
15	Mouse (NMRI)	PND 10 once (GO)	Bd Wt	8.7 M			Johansson et al. 2009 Perfluorooctanoic acid	
16	Mouse (CD-1)	14 d ad lib (F)	Hepatic		5.3 (123-155% increase in absolute liver weight in 14 days)		Kennedy 1987 Ammonium perfluorooctanoate	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
17	Mouse (C57BL/6N)	2-10 d ad lib (F)	Hepatic		78 M (74% increase in absolute liver weight)		Permadi et al. 1992 Perfluorooctanoic acid	
			Bd Wt			78 M (25% body weight loss after 10 days of treatment)		
18	Mouse (C57BL/6N)	2-10 d ad lib (F)	Hepatic		78 M (74% increase in absolute liver weight in 5 days)		Permadi et al. 1993 Perfluorooctanoic acid	
			Bd Wt			78 M (25% body weight loss after 5 days of treatment)		
19	Mouse (CD-1)	GD 8-17 1 x/d (GW)	Hepatic		5 F (40-120% increased relative liver weight in lactating dams on PNDs 1-10)		White et al. 2009 Ammonium perfluorooctanoate	
			Bd Wt	5 F				
20	Mouse (CD-1)	GD 7-17 GD 10-17 GD 13-17 Gd 15-17 1 x/d (GW)	Hepatic		5 F (significant increase in relative liver weight)		Wolf et al. 2007 Ammonium perfluorooctanoate	Hepatic LOAEL is for dams dosed on GD 13-17, 10-17, or 7-17. Body weight NOAEL is for dams dosed on GD 15-17.
			Bd Wt	20 F				

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
21	Mouse (C57BL/6N)	7 d ad lib (F)	Hepatic		24 M (2-fold increase in absolute liver weight)		Xie et al. 2003 Perfluorooctanoic acid	
			Bd Wt		24 M (>10% reduced final body weight)			
22	Mouse (ICR)	GD 0-17 or GD 0-18 1 x/d (GW)	Hepatic		1 F (35% increased maternal relative liver weight with hepatocellular hypertrophy)		Yahia et al. 2010 Perfluorooctanoic acid	
			Renal		1 F (35% increased maternal relative kidney weight with renal hypertrophy)			
23	Mouse (C57BL/6)	10 d ad lib (F)	Hepatic		30 M (over 90% increase in absolute and relative liver weight)		Yang et al. 2000 Perfluorooctanoic acid	
			Bd Wt		30 M (17% decrease in final body weight)			
24	Mouse (C57BL/6)	10 d ad lib (F)	Hepatic		1 M (35% increase in absolute liver weight)		Yang et al. 2001 Perfluorooctanoic acid	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
25	Mouse (C57BL/6)	7 d ad lib (F)	Hepatic		33 M (86% increase in absolute liver weight)		Yang et al. 2002b Perfluorooctanoic acid	
			Bd Wt		33 M (14% decreased mean body weight)			
Immuno/ Lymphoret								
26	Rat (Sprague-Dawley)	14 d 1 x/d (GW)		50 M			Iwai and Yamashita 2006 Ammonium perfluorooctanoate	NOAEL is for spleen weight and alterations in lymphocyte subsets.
27	Mouse (C57BL/6N)	10 days (W)		7.5 F	15 F (altered response to SRBC)		DeWitt et al. 2009 Perfluorooctanoic acid	
28	Mouse (C57BL/6)	10 d ad lib (F)			30 M (86% reduction in absolute thymus weight; 30% reduction in absolute spleen weight)		Yang et al. 2000 Perfluorooctanoic acid	
29	Mouse (C57BL/6)	10 d ad lib (F)			11.5 M (40% to 50% decrease in spleen and thymus weights)		Yang et al. 2001 Perfluorooctanoic acid	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Mouse (C57BL/6)	10 d ad lib (F)			24 M (decreased humoral response to immunization with horse red blood cells)		Yang et al. 2002a Perfluorooctanoic acid	
31	Mouse (C57BL/6)	7 d ad lib (F)			33 M (40% reduction in spleen weight and 79% reduction in thymus weight)		Yang et al. 2002b Perfluorooctanoic acid	Experiments with PPARalpha-null mice suggested PPARalpha dependent and independent immune effects.
Neurological								
32	Mouse (NMRI)	PND 10 once (GO)			8.7 M (17-142% increased CaMKII, GAP-43, synaptophysin and tau proteins in hippocampus and/or cerebral cortex on PND 11)		Johansson et al. 2009 Perfluorooctanoic acid	
Reproductive								
33	Rat (CD)	14 d 1 x/d (GW)			25 M (184% increase in serum estradiol)		Biegel et al. 1995 Ammonium perfluorooctanoate	
34	Rat (CD)	14 d 1 x/d (GW)		1 M	10 M (63% increase in serum estradiol)		Cook et al. 1992 Ammonium perfluorooctanoate	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
35	Rat (CD)	14 d 1 x/d (G)		0.2 M	2 M (2-fold increase in serum estradiol)		Liu et al. 1996 Ammonium perfluorooctanoate	
36	Mouse (CD-1)	GD 8-17 1 x/d (GW)			5 F (Immature mammary gland morphology in lactating dams on PNDs 1-10)		White et al. 2009 Ammonium perfluorooctanoate	
Developmental								
37	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		100			Staples et al. 1984 Ammonium perfluorooctanoate	NOAEL is for fetal weight and teratology.
38	Mouse (C57BL/6N)	GD 6-17 (DW)			0.5 F (decreased litter weight on PND 2)		Hu et al. 2010 Ammonium perfluorooctanoate	
39	Mouse (CD-1)	once (G)			0.58 M (altered response to nicotine injection)		Johansson et al. 2008 Ammonium perfluorooctanoate	
40	Mouse (CD-1)	GD 8-17 GD 12-17 1 x/d (GW)			5 F (altered mammary gland development in female pups; reduced pup's weight on PND 20)		White et al. 2007 Ammonium perfluorooctanoate	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
41	Mouse (CD-1)	GD 8-17 1 x/d (GW)			5 F (Delayed mammary gland development in female pups on PNDs 1-10)		White et al. 2009 Ammonium perfluorooctanoate	
42	Mouse (CD-1)	GD 7-17 GD 10-17 GD 13-17 GD 15-17 1 x/d (GW)			5 F (Delayed mammary gland development in female pups on PND 22-32 and at 18 months)		White et al. 2009 Ammonium perfluorooctanoate	
43	Mouse (CD-1)	GD 7-17, GD10-17, GD13-17, or GD 15-17 1 x/d (GW)				5 (reduced pup body weight at weaning, 43% in males and 35% in females)	Wolf et al. 2007 Ammonium perfluorooctanoate	
44	Mouse (ICR)	GD 0-17 or GD 0-18 1 x/d (GW)		1 F	5 F (9.5% reduced fetal body weight)	5 F (14% increased neonatal mortality)	Yahia et al. 2010 Perfluorooctanoic acid	
45	Rabbit (New Zealand)	GD 6-18 1 x/d (GW)		50 F			Gortner et al. 1982 Perfluorooctanoic acid	NOAEL is for standard developmental end points.

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Death								
46	Monkey (Rhesus)	90 d 1 x/d (G)				30 (1 male and 2 females died during weeks 7-12)	Griffith and Long 1980 Ammonium perfluorooctanoate	
47	Mouse (CD)	28 d ad lib (F)				54 M (4/5 died before end of 4th week) 58 F (5/5 died before 4th week of study)	Griffith and Long 1980 Ammonium perfluorooctanoate	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
48	Monkey (Cynomolgus)	26 wk 1 x/d (C)	Resp	20 M			Butenhoff et al. 2002 Ammonium perfluorooctanoate	NOAELs are for gross and microscopic alterations in organs and tissues.
			Cardio	20 M				
			Gastro	20 M				
			Hemato	20 M				
			Musc/skel	20 M				
			Hepatic		3 M[b] (36% increase in absolute liver weight)			
			Renal	20 M				
			Endocr	3 M	10 M (significant decrease in serum TT4 and FT4)			
			Dermal	20 M				
			Ocular	20 M				
			Bd Wt	10 M	20 M (body weight 12% lower than control by week 10)			

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
49	Monkey (Rhesus)	90 d 1 x/d (G)	Cardio	10			Griffith and Long 1980 Ammonium perfluorooctanoate	
			Gastro	10	30 (emesis)			
			Hemato	30				
			Hepatic	10				
			Renal	10				
			Endocr	10	30 (difuse lipid depletion in adrenals)			
			Bd Wt	10		30 (33% body weight loss by week 6)		
50	Monkey (Cynomolgus)	30 d 1x/d (C)	Hemato	20 M			Thomford 2001 Ammonium perfluorooctanoate	Endocrine NOAEL is for serum levels of thyroid hormones and TSH and histopathology of the adrenals.
			Hepatic	20 M				
			Endocr	20 M				
			Bd Wt	20 M				

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
51	Rat (CD)	1 yr ad lib (F)	Hepatic		13.6 M (increased relative liver weight)		Biegel et al. 2001 Ammonium perfluorooctanoate	Only one dose level was tested.
			Bd Wt		13.6 M (more than 10% reduced weight gain)			
52	Rat (Sprague-Dawley)	70-90 d 1 x/d (GW)	Hepatic		3 M (increased absolute and relative liver weight)		Butenhoff et al. 2004b Ammonium perfluorooctanoate	
			Renal		3 M (increased absolute and relative kidney weight)			
			Endocr	10 M	30 M (hypertrophy and/or vacuolation of zona glomerulosa of adrenal gland)			
			Bd Wt	3 M	10 M (>11% reduced body weight)			
53	Rat (Sprague-Dawley)	Daily 28 days (G)	Resp		5 M		Cui et al. 2009 Perfluorooctanoic acid	
			Hepatic		5 M (cytoplasmic vacuolization, necrosis, hypertrophy, incr liver wt)			

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
54	Rat (Sprague-Dawley)	28 days (F)	Hepatic		18 M (incr liver weight, decr serum cholesterol, triglyceride, hepatocellular hypertrophy and hyperplasia)		Elcombe et al. 2010 Ammonium perfluorooctanoate	
55	Rat (CD)	90 d ad lib (F)	Resp	110 F			Griffith and Long 1980 Ammonium perfluorooctanoate	
			Cardio	110 F				
			Gastro	110 F				
			Hemato	110 F				
			Musc/skel	110 F				
			Hepatic	1 M	3 M (hepatocyte hypertrophy; 50% increase in absolute liver weight)			
			Renal	110 F				
			Endocr	110 F				
			Dermal	110 F				
			Ocular	110 F				
			Bd Wt	30 M		100 M (33% reduction in final mean body weight)		
				110 F				

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
56	Rat (CD)	28 d ad lib (F)	Hepatic		3 M (hepatocyte hypertrophy)		Griffith and Long 1980 Ammonium perfluorooctanoate	
			Bd Wt	10 M	30 M (11% reduction in final body weight)	100 M (33% reduction in final body weight)		
57	Rat (CD)	28 days (G)	Hemato	29 M			Loveless et al. 2008 Ammonium perfluorooctanoate	
			Hepatic		0.29 M (decr serum triglyceride levels, minimal hepatocellular hypertrophy)			
			Bd Wt	0.96 M	9.6 M (10% decrease in final body weight)			
58	Rat (CD)	13 wk ad lib (F)	Resp	6.5 M			Perkins et al. 2004 Ammonium perfluorooctanoate	Respiratory NOAEL is for lung weight and histopathology.
			Hepatic	0.06 M	0.64 M (minimal to moderate hepatocellular hypertrophy)			
			Bd Wt	6.5 M				

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
59	Mouse (NS)	GD 1-17 1 x/d (GW)	Hepatic	0.6 F	1 F (increased absolute and relative liver weight of dams on pnd 22)		Abbott et al. 2007 Ammonium perfluorooctanoate	Body weight NOAEL is for changes during pregnancy.
			Bd Wt	10 F				
60	Mouse wild-type (Sv/129)	GD 1-17 1 x/d (GW)	Hepatic		3 F (28% increased liver weight, hepatocellular hypertrophy with increased peroxisomes)		Albrecht et al. 2013 Perfluorooctanoic acid	
61	Mouse (C57BL/6N)	15 d ad lib (W)	Bd Wt	7.5 F		15 F (weight loss)	Dewitt et al. 2008 Ammonium perfluorooctanoate	
62	Mouse (CD)	28 d ad lib (F)	Hepatic		5.4 M (3-fold or greater increased absolute and relative liver weight)		Griffith and Long 1980 Ammonium perfluorooctanoate	
			Bd Wt		5.4 M (final body weight 20% lower than controls)	5.8 F (final body weight 25% lower than controls)		
63	Mouse (CD-1)	21 d ad lib (F)	Hepatic	0.2	0.5 (39-41% increase in absolute liver weight in 21 days)		Kennedy 1987 Ammonium perfluorooctanoate	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
64	Mouse (CD-1)	GD 1-17 1 x/d (GW)	Hepatic		1 F (38% increase in absolute liver weight)		Lau et al. 2006 Ammonium perfluorooctanoate	
			Bd Wt	5 F		10 F (32% reduced weight gain during pregnancy)		
65	Mouse (CD)	28 days (G)	Bd Wt	0.96	0.29 (mild hepatocellular hypertrophy)	9.6 (weight loss)	Loveless et al. 2008 Ammonium perfluorooctanoate	
66	Mouse (ICR)	21 d ad lib (W)	Hepatic		0.5 M (27% increase in relative liver weight)		Son et al. 2008 Ammonium perfluorooctanoate	ALT was increased at 2.6 mg/kg/day; morphological changes occurred at 18 mg/kg/day.
			Renal	47 M				
			Bd Wt	2.6 M		18 M (significant weight loss)		
67	Mouse (C57BL/6N)	3 weeks (F)	Hepatic		5 M (hepatocellular hypertrophy and degeneration)		Tan et al. 2013 Perfluorooctanoic acid	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
68	Mouse (CD-1)	GD 1-17 1 x/d (GW)	Hepatic		3 F (significant increase in relative and absolute maternal liver weight on PND 22)		Wolf et al. 2007 Ammonium perfluorooctanoate	
			Bd Wt	5 F				
Immuno/ Lymphoret								
69	Monkey (Cynomolgus)	26 wk 1 x/d (C)		20 M			Butenhoff et al. 2002 Ammonium perfluorooctanoate	NOAEL is for gross and microscopic alterations in lymphoreticular tissues.
70	Monkey (Rhesus)	90 d 1 x/d (G)		10	30 (atrophy of lymphoid follicles in spleen and lymph nodes)		Griffith and Long 1980 Ammonium perfluorooctanoate	
71	Rat (albino)	90 d ad lib (F)		110 F			Griffith and Long 1980 Ammonium perfluorooctanoate	NOAEL is for histopathology of spleen and lymph nodes.
72	Rat (CD)	28 days (G)		29 M			Loveless et al. 2008 Ammonium perfluorooctanoate	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
73	Mouse (C57BL/6N)	15 d ad lib (W)		1.88 F	3.75 F (reduced SRBC-specific response to IgM antibody titers)		Dewitt et al. 2008 Ammonium perfluorooctanoate	
74	Mouse (CD)	28 days (G)		0.96 M	9.6 M (decr response to sheep RBC, decr number of splenocytes and thymocytes)		Loveless et al. 2008 Ammonium perfluorooctanoate	
75	Mouse (ICR)	21 days (W)			47.21 M (marked hyperplasia in spleen white pulp and thymic atrophy)		Son et al. 2009 Perfluorooctanoic acid	
					0.49 M (alterations in splenic lymphocyte phenotype)			
Neurological								
76	Monkey (Cynomolgus)	26 wk 1 x/d (C)		20 M			Butenhoff et al. 2002 Ammonium perfluorooctanoate	NOAEL is for gross and microscopic alterations in the brain and sciatic nerve.
77	Monkey (Rhesus)	90 d 1 x/d (G)		10	30 (hypoactivity and prostration)		Griffith and Long 1980 Ammonium perfluorooctanoate	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
78	Rat (Sprague-Dawley)	Daily 28 days (G)			5 M (cachexia and lethargy)		Cui et al. 2009 Perfluorooctanoic acid	
79	Rat (albino)	90 d ad lib (F)		110 F			Griffith and Long 1980 Ammonium perfluorooctanoate	NOAEL is for histopathology of central and peripheral nervous tissues.
80	Rat (CD)	13 wk ad lib (F)		6.5 M			Perkins et al. 2004 Ammonium perfluorooctanoate	NOAEL is for gross and microscopic changes in the brain.
Reproductive								
81	Monkey (Cynomolgus)	26 wk 1 x/d (C)		20 M			Butenhoff et al. 2002 Ammonium perfluorooctanoate	NOAEL is for gross and microscopic alterations in the sex organs.
82	Monkey (Rhesus)	90 d 1 x/d (G)		100			Griffith and Long 1980 Ammonium perfluorooctanoate	NOAEL is for histopahology of testes and ovaries.
83	Monkey (Cynomolgus)	30 d 1x/d (C)		20 M			Thomford 2001 Ammonium perfluorooctanoate	NOAEL is for serum estradiol, estriol and histopathology of the testes.

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
84	Rat (CD)	1 yr ad lib (F)			13.6 M (significant increase in serum estradiol at 1, 3, 6, 9, and 12 months)		Biegel et al. 2001 Ammonium perfluorooctanoate	Prolactin was decreased at all time points, but not always significantly.
85	Rat (Sprague-Dawley)	70-90 d 1 x/d (GW)		30			Butenhoff et al. 2004b Ammonium perfluorooctanoate	NOAEL is for reproductive performance of the P and F1 generations.
86	Rat (albino)	90 d ad lib (F)		100 M 110 F			Griffith and Long 1980 Ammonium perfluorooctanoate	NOAEL is for histopathology of primary sex organs.
87	Rat (CD)	13 wk ad lib (F)		6.5 M			Perkins et al. 2004 Ammonium perfluorooctanoate	NOAEL is for gross and microscopic changes in the testes and accesory sex organs.
88	Mouse (CD-1)	GD 1-17 GD 8-17 1 x/d Gd 12-17 (GW)			5 F (delayed mammary gland differentiation)		White et al. 2007 Ammonium perfluorooctanoate	
89	Mouse (CD-1)	GD 1-17 1 x/d (GW)			1 F (delayed mammary gland lactational differentiation in dams on PND 22)		White et al. 2011b Ammonium perfluorooctanoate	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
90	Mouse (CD-1)	GD 1-17 1 x/d (GW) GD 7 to PND 22 (DW)			0.001 F (delayed mammary gland lactational differentiation in dams on PND 22)		White et al. 2011b Ammonium perfluorooctanoate	Three-generation study
Developmental								
91	Rat (Sprague-Dawley)	70-90 d 1 x/d (GW)			3 M (hepatocellular hypertrophy and less commonly necrosis in F1 males)	30 (increased number of dead pups on postnatal day 6-8)	Butenhoff et al. 2004b Ammonium perfluorooctanoate	
92	Rat (Wistar)	GD 1 to PND 21 ad lib (W)			1.6 (17-18% reduced motor coordination and increased locomotor activity in pups on PND 34-36)		Cheng et al. 2013a Perfluorooctanoic acid	
93	Mouse (NS)	GD 1-17 1 x/d (GW)		0.3		0.6 (significantly reduced pups survival from birth to weaning)	Abbott et al. 2007 Ammonium perfluorooctanoate	
94	Mouse wild-type (Sv/129)	GD 1-17 1 x/d (GW)				3 (31.5% reduced pups per litter on PND 20)	Albrecht et al. 2013 Perfluorooctanoic acid	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
95	Mouse (CD-1)	GD 1-17 (GW)			5 F (decreased birth weight and postnatal body weight)		Hines et al. 2009 Ammonium perfluorooctanoate	
					0.01 F (increased postnatal body weight)			
96	Mouse (CD-1)	GD 1-17 1 x/d (GW)			3 (20% lower body weight of pups on PND 23)	5 (significantly increased full litter resorptions)	Lau et al. 2006 Ammonium perfluorooctanoate	
97	Mouse (CD-1)	Daily GD1-17 (G)			0.3 F (impaired development of mammary glands in offspring)		Macon et al. 2011 Perfluorooctanoic acid	
98	Mouse (CD-1)	Daily GD1-17 (G)			0.01 F (developmental delays in mammary gland development)		Macon et al. 2011 Perfluorooctanoic acid	
99	Mouse (C57BL/6/Bk1)	Gd 1-17 ad lib (F)			0.3 (increased locomotor activity in adult offspring)		Onishchenko et al. 2011 Perfluorooctanoic acid	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
100	Mouse (CD-1)	GD 1-17 1 x/d (GW)				5 (increased prenatal loss; 40% reduced neonatal body weight on PND 5 and 10)	White et al. 2007 Ammonium perfluorooctanoate	
101	Mouse (CD-1)	GD 1-17 1 x/d (GW)			3 F (Delayed mammary gland development in female pups on PND 22-63 and at 18 months)		White et al. 2009 Ammonium perfluorooctanoate	
102	Mouse (CD-1)	GD 1-17 1 x/d (GW)		1 F		5 F (323% increased prenatal loss, 16.7% decreased live fetuses, 24.3% decreased neonatal survival)	White et al. 2011b Ammonium perfluorooctanoate	
103	Mouse (CD-1)	GD 1-17 1 x/d (GW) GD 7 to PND 22 (DW)			0.001 F (delayed mammary gland development in female pups on PND 22-63)		White et al. 2011b Ammonium perfluorooctanoate	Three-generation study
104	Mouse (CD-1)	GD 1-17 GD1-17 + lactation 1 x/d (GW)			3 (reduced weight gain through lactation; delayed eye opening and hair growth)	5 (decreased pup survival from birth to weaning)	Wolf et al. 2007 Ammonium perfluorooctanoate	

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
105	Rat (Sprague-Dawley)	2 yr ad lib (F)	Resp	1.5 M		15 M (lung hemorrhage)	3M 1983 Perfluorooctanoic acid	
			Cardio	15				
			Gastro	15				
			Hemato	15				
			Hepatic		1.5 M (significanly increased serum transaminases)			
			Renal		15 M (significantly increased relative kidney weight at 1 year)			
			Endocr	15				
			Ocular	15				
			Bd Wt	1.5 F	15 F (10.3% lower terminal body weight)			
			Other		1.5 M (inflammation of the salivary gland)			

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
106	Rat (CD)	2 yr ad lib (F)	Hepatic		13.6 M (increased relative liver weight)		Biegel et al. 2001 Ammonium perfluorooctanoate	Only one dose level was tested.
			Bd Wt		13.6 M (more than 10% reduction in weight gain most of the study)			
			Other		13.6 M (increased incidence of acinar cell hyperplasia in pancreas)			
Immuno/ Lymphoret								
107	Rat (Sprague-Dawley)	2 yr ad lib (F)		15			3M 1983 Perfluorooctanoic acid	
Neurological								
108	Rat (Sprague-Dawley)	2 yr ad lib (F)		15			3M 1983 Perfluorooctanoic acid	
Reproductive								
109	Rat (Sprague-Dawley)	2 yr ad lib (F)		1.5 M	15 M (vascular mineralization in the testes)		3M 1983 Perfluorooctanoic acid	
					1.5 F (tubular hyperplasia in the ovaries)			

Table 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
110	Rat (CD)	2 yr ad lib (F)			13.6 M (increased incidence of Leydig cell hyperplasia; elevated serum LH at 18 months)		Biegel et al. 2001 Ammonium perfluorooctanoate	Serum estradiol was significantly increased the first year of the study.

a The number corresponds to entries in Figure 3-3.

b Used to derive an intermediate-duration oral MRL of 0.00002 mg/kg/day based on a BMDL estimated using a benchmark response of a 10% relative change in liver weight from the controls and using serum PFOA levels as an internal dose metric; a human equivalent dose (HED) of the BMDL was estimated using an empirical clearance model. The BMDL(HED) of 0.00154 mg/kg/day was divided by an uncertainty factor of 90 (3 for extrapolation from animals to humans with dosimetric adjustment, 10 for human variability, and 3 for database deficiencies).

ad lib = ad libitum; ALT = alanine aminotransferase; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; FT4 = free thyroxine; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LH = luteinizing hormone; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; PND = post-natal day; PPARalpha = peroxisome proliferator-activated receptor alpha; TT4 = total thyroxine; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 3-3 Levels of Significant Exposure to Perfluorooctanoic Acid - Oral

Acute (≤14 days)

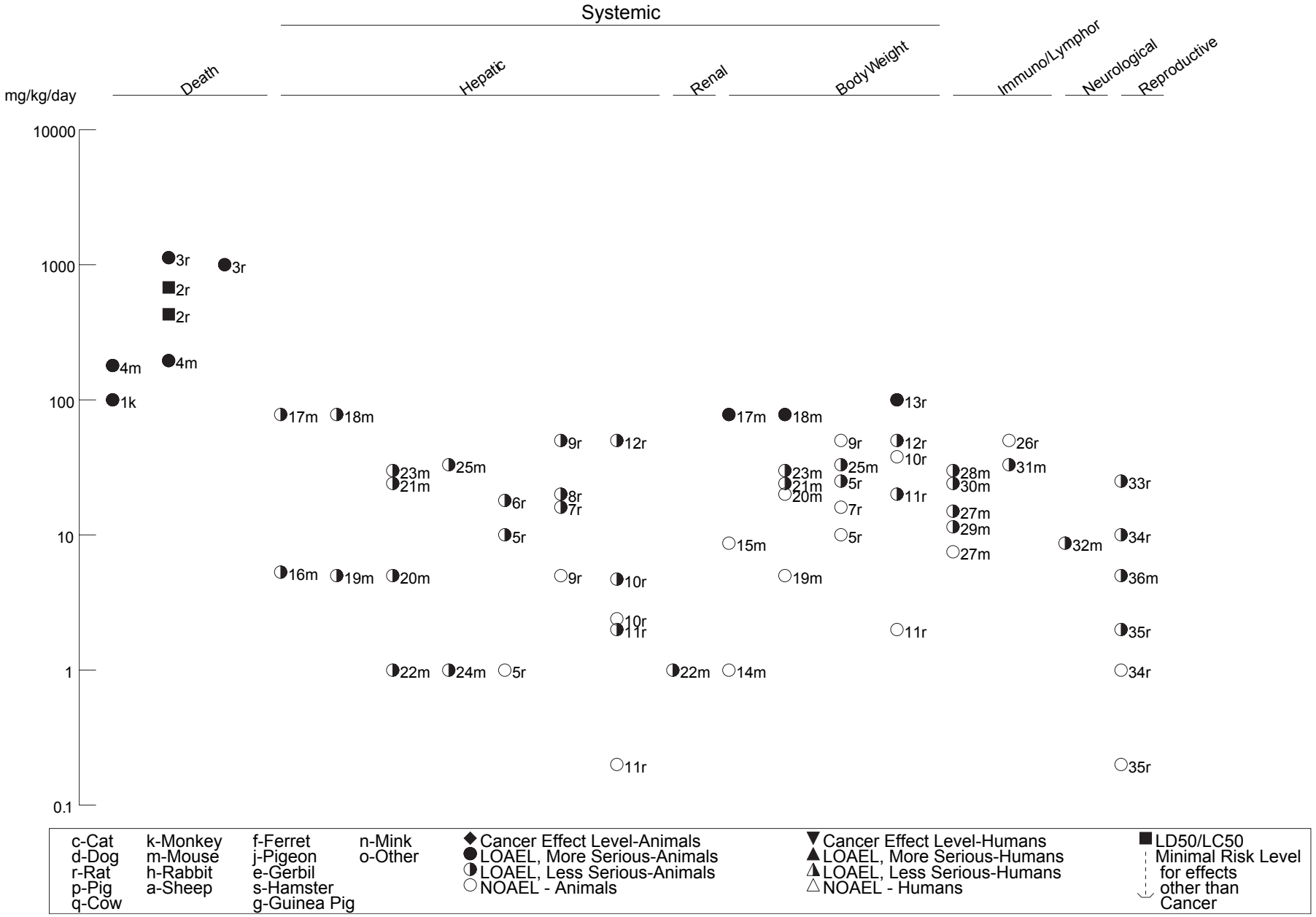


Figure 3-3 Levels of Significant Exposure to Perfluorooctanoic Acid - Oral *(Continued)*

Acute (≤14 days)

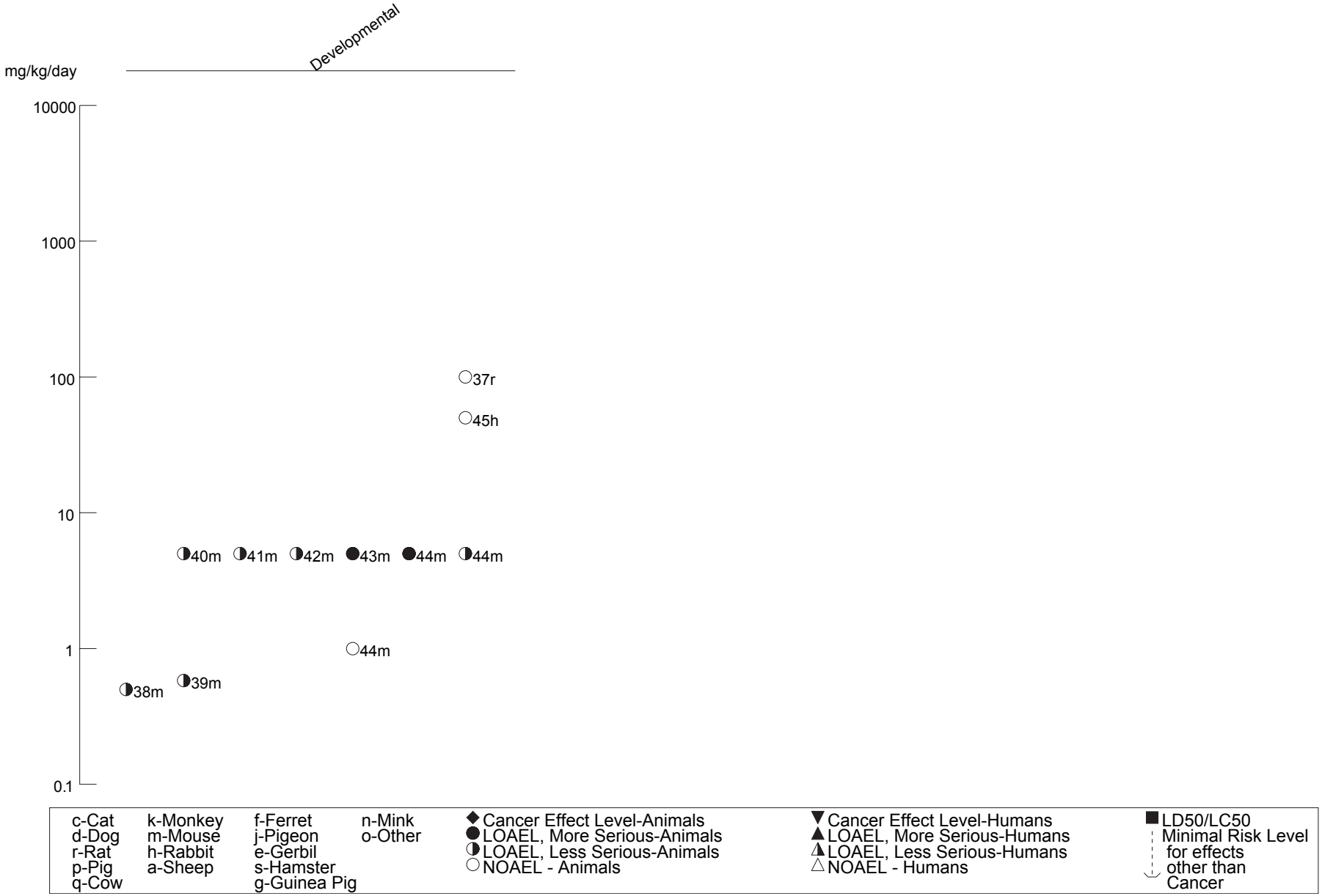


Figure 3-3 Levels of Significant Exposure to Perfluorooctanoic Acid - Oral *(Continued)*

Intermediate (15-364 days)

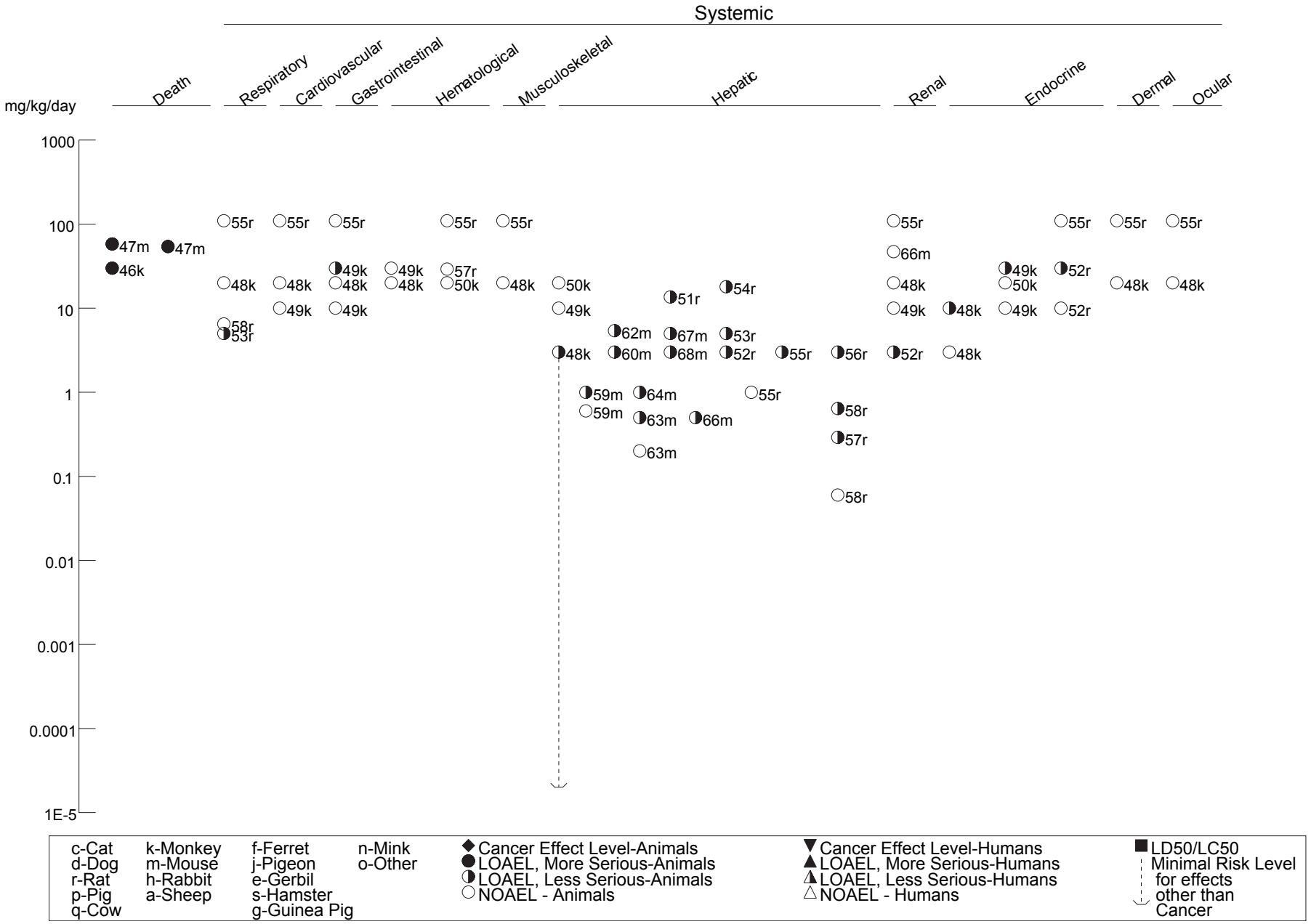


Figure 3-3 Levels of Significant Exposure to Perfluorooctanoic Acid - Oral *(Continued)*

Intermediate (15-364 days)

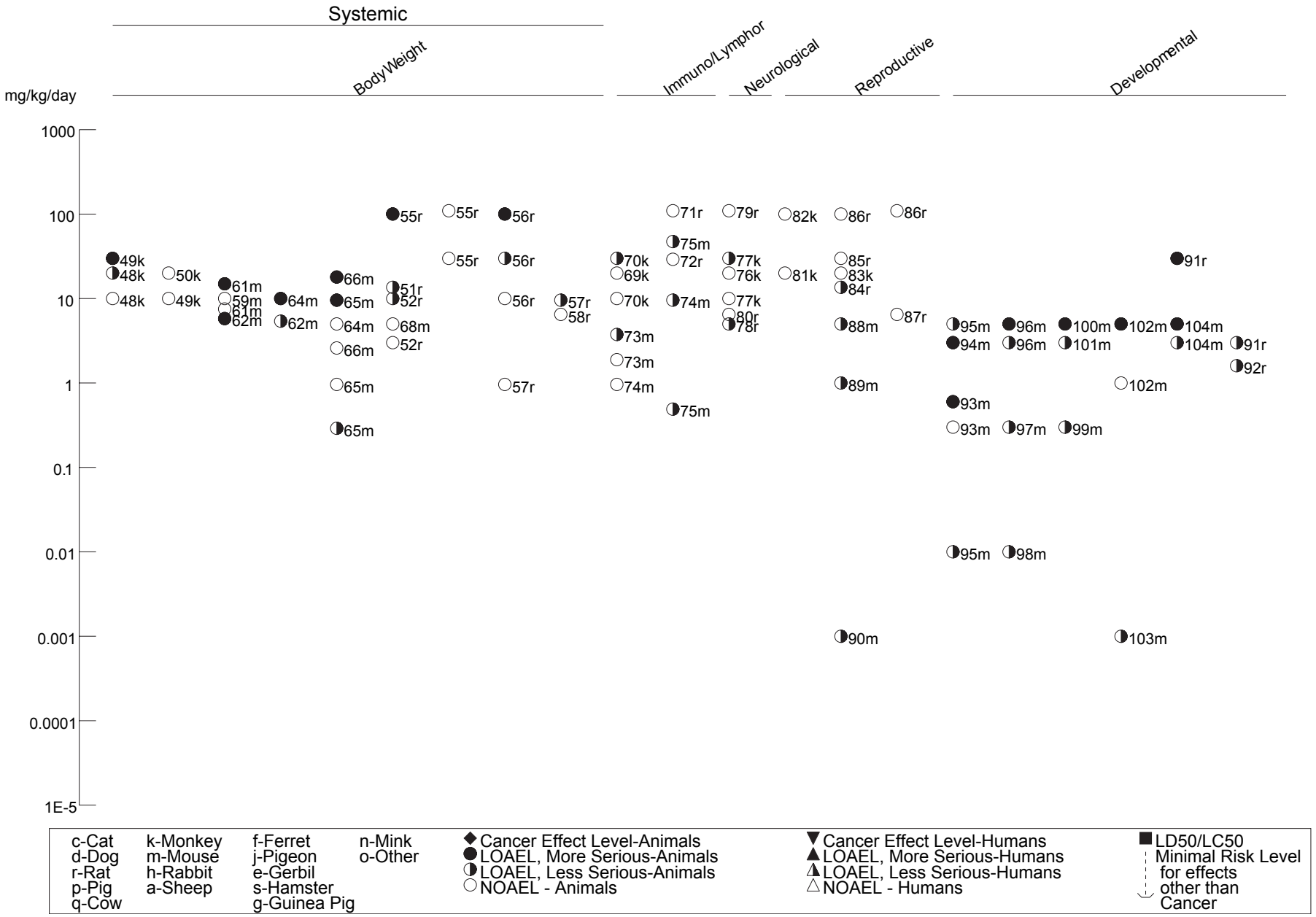


Figure 3-3 Levels of Significant Exposure to Perfluorooctanoic Acid - Oral *(Continued)*

Chronic (≥365 days)

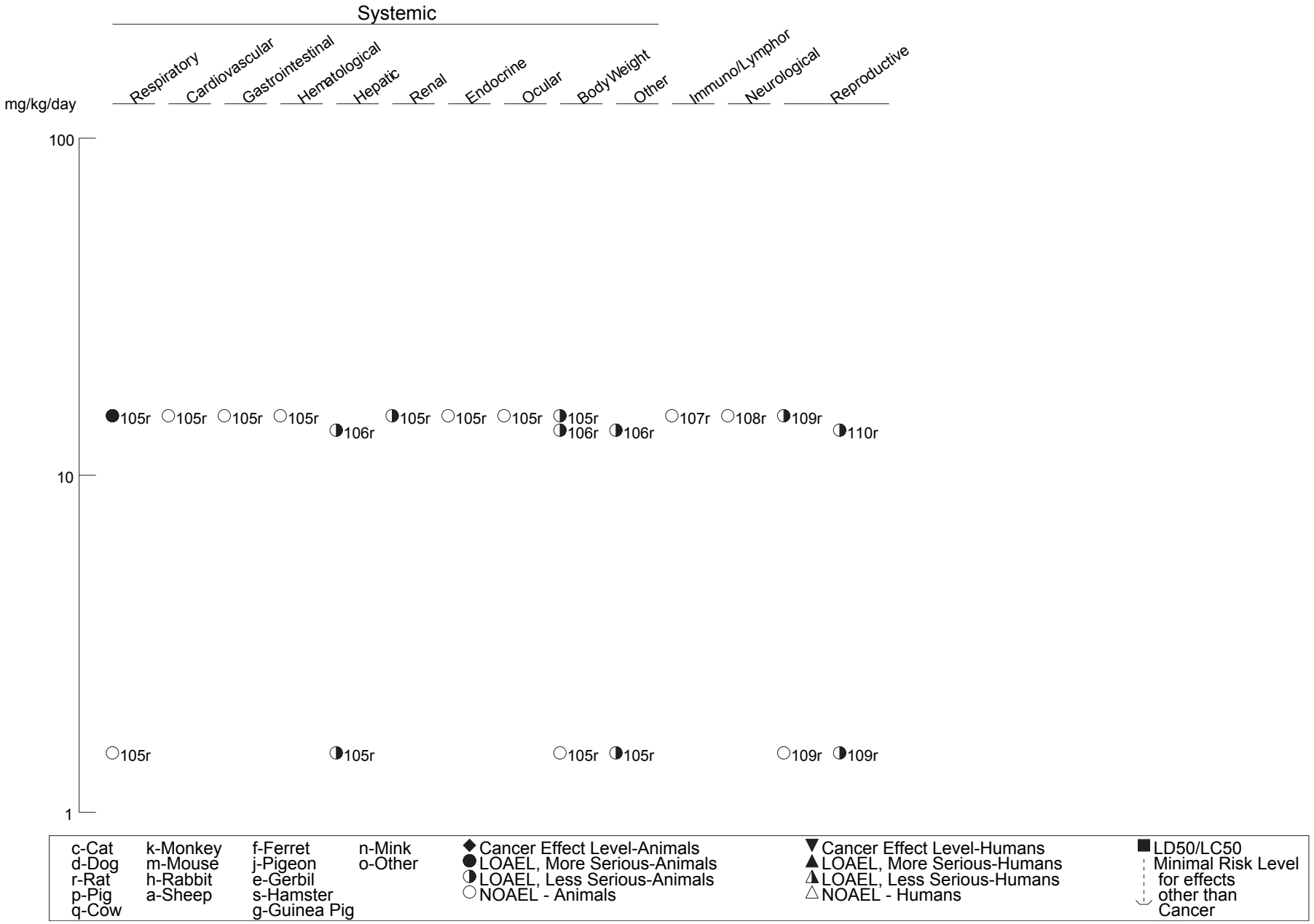


Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Rat (Sprague-Dawley)	once (GW)	Endocr		15 (transient decrease in serum TT4)		Chang et al. 2008b Potassium perfluorooctane sulfonate	
2	Rat (Sprague-Dawley)	1 day (F)	Hepatic	10.3 M			Elcombe et al. 2012a Potassium perfluorooctane sulfonate	
			Endocr	10.3 M				
3	Rat (Sprague-Dawley)	7 days (F)	Hepatic	1.72 M	8.17 M (decr serum cholesterol and triglyceride levels)		Elcombe et al. 2012a Potassium perfluorooctane sulfonate	
			Endocr	8.17 M				
4	Rat (Sprague-Dawley)	7 days (F)	Hepatic		1.79 M (hepatocellular hypertrophy, incr liver weight, decr serum cholesterol)		Elcombe et al. 2012b Potassium perfluorooctane sulfonate	
			Endocr	8.96 M				
5	Rat (Sprague-Dawley)	4 d Gd 2-5, 6-9, 10-13, 14-17, 17-20 1 x/d (GW)	Bd Wt			25 F (weight loss during treatment when treated on Gd 2-5 or 6-9)	Grasty et al. 2003 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
6	Rat (Wistar)	7 d ad lib (F)	Hepatic		15 M (40% increase in absolute liver weight)		Haughom and Spydevold 1992 Potassium perfluorooctane sulfonate	
			Bd Wt	15 M				
7	Mouse (ICR)	Gd 11-15 1 x/d (GW)	Hepatic		20 F (103% increased maternal relative liver weight)		Era et al. 2009 Potassium perfluorooctane sulfonate	
8	Mouse (CD-1)	Gd 6-18 1 x/d (GW)	Hepatic	1.5 F	3 F (21% increase in absolute liver weight)		Fuentes et al. 2006 Potassium perfluorooctane sulfonate	Endocrine NOAEL is for levels of free and total T3 and T4 in serum.
			Endocr	6 F				
			Bd Wt	6 F				
9	Mouse (CD-1)	Gd 12-18 1 x/d (GW)	Bd Wt	6 F			Fuentes et al. 2007b Potassium perfluorooctane sulfonate	
10	Mouse (NMRI)	PND 10 once (GO)	Bd Wt	11.3 M			Johansson et al. 2009 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
11	Mouse (CD-1)	14 d 1 x/d (GO)	Hepatic	1 M	5 M (~70% increased absolute liver weight)		Wan et al. 2011 Potassium perfluorooctane sulfonate	
			Bd Wt	10 M				
12	Rabbit (New Zealand)	Gd 6-20 1 x/d (GW)	Bd Wt	0.1 F		1 F (21% decreased mean maternal body weight gain on Gd 7-21; no effect on food consumption)	Case et al. 2001 Potassium perfluorooctane sulfonate	
Immuno/ Lymphoret								
13	Mouse (C57BL/6N)	7 days (G)			5 M (impaired response to T-cell mitogens; suppressed response to SRBC)		Zheng et al. 2009 Perfluorooctane sulfonic acid	
Neurological								
14	Mouse (NMRI)	PND 10 once (GO)			11.3 M (22-80% increased CaMKII, GAP-43, synaptophysin and tau proteins in hippocampus and/or cerebral cortex oN PND 11)		Johansson et al. 2009 Potassium perfluorooctane sulfonate	
Reproductive								
15	Mouse (CD-1)	14 d 1 x/d (GO)		10 M			Wan et al. 2011 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
16	Rabbit (New Zealand)	Gd 6-20 1 x/d (GW)		2.5 F		3.75 F (10 out 22 does aborted between Gd 22 and 28)	Case et al. 2001 Potassium perfluorooctane sulfonate	
Developmental								
17	Rat (Sprague-Dawley)	2 d Gd 19-20 1 x/d (GW)				25 (decreased neonatal survival)	Grasty et al. 2003 Potassium perfluorooctane sulfonate	
18	Rat (Sprague-Dawley)	4 d Gd 2-5, 6-9, 10-13, 14-17, 17-20 (GW)				25 (decreased neonatal survival)	Grasty et al. 2003 Potassium perfluorooctane sulfonate	
19	Rat (Sprague-Dawley)	Gd 19-20 1 x/d (G)				25 (increased neonatal mortality)	Grasty et al. 2005 Potassium perfluorooctane sulfonate	
20	Mouse (wild type 129S1/Svlm)	Gd 15-18 1 x/d (GW)				4.5 (31% reduced percentage of live pups per litter on PND 15)	Abbott et al. 2009 Potassium perfluorooctane sulfonate	
21	Mouse (ICR)	Gd 11-15 1 x/d (GW)			50 F (6.1% increased cleft palate and 12.7% reduced body weight in fetuses)		Era et al. 2009 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
22	Mouse (CD-1)	Gd 6-18 1 x/d (GW)		6			Fuentes et al. 2006 Potassium perfluorooctane sulfonate	NOAEL is for evaluation of standard developmental end points.
23	Mouse (CD-1)	Gd 12-18 1 x/d (GW)			6 (reduced body weight of pups on PND 4 and 8)		Fuentes et al. 2007b Potassium perfluorooctane sulfonate	
24	Mouse (CD-1)	once (G)			0.75 M (decreased motor activity)		Johansson et al. 2008 Potassium perfluorooctane sulfonate	
25	Rabbit (New Zealand)	Gd 6-20 1 x/d (GW)		1 F	2.5 F (10% decreased mean fetal body weight)	3.75 F (24% reduced fetal body weight)	Case et al. 2001 Potassium perfluorooctane sulfonate	
INTERMEDIATE EXPOSURE								
Death								
26	Rat (Sprague-Dawley)	Daily 28 days (G)				20 M (100% by day 26))	Cui et al. 2009 Perfluorooctane sulfonic acid	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
27	Monkey (Cynomolgus)	26 wk 1 x/d (C)	Resp	0.75			Seacat et al. 2002 Potassium perfluorooctane sulfonate	NOAELs are for gross and microscopic pathology of organs and tissues.
			Cardio	0.75				
			Gastro	0.75				
			Hemato	0.75				
			Musc/skel	0.75				
			Hepatic	0.15[b]	0.75	(47-55% increased absolute liver weight; 50-60% decreased serum cholesterol; hepatocellular hypertrophy and lipid vacuolation)		
			Renal	0.75				
			Endocr	0.15	0.75	(increased TSH and decreased total T3)		
			Dermal	0.75				
			Ocular	0.75				
			Bd Wt	0.15 M 0.75 F	0.75 M	(13.5% reduction in final body weight)		

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
28	Monkey (Cynomolgus)	4 wk 1 x/d (C)	Resp	2			Thomford 2002a Potassium perfluorooctane sulfonate	NOAELS are for organ histopathology.
			Hemato	2				
			Hepatic	2				
			Renal	2				
			Endocr	2				
			Ocular	2				
			Bd Wt	2				
29	Rat (Sprague-Dawley)	Daily 28 days (G)	Resp		5 M (pulmonary congestion)		Cui et al. 2009 Perfluorooctane sulfonic acid	
			Hepatic		5 M (hepatocellular hypertrophy)			

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Rat (Sprague-Dawley)	Daily 28 days (F)	Cardio	5.89			Curran et al. 2008 Potassium perfluorooctane sulfonate	
			Hemato	3.47 F	7.01 F (decreased RBC, hemoglobin, hematocrit)			
			Hepatic		0.14 F (increased relative liver weight)			
			Renal	5.89				
			Endocr	0.14	1.23 (decreased thyroxine level)			
31	Rat (Sprague-Dawley)	28 days (F)	Hepatic		1.54 M (hepatocellular hypertrophy and decreased serum cholesterol levels)		Elcombe et al. 2012a Potassium perfluorooctane sulfonate	
			Endocr	7.34 M				
32	Rat (Sprague-Dawley)	28 days (F)	Hepatic		0.14 M (increased relative liver weight)		Lefebvre et al. 2008 Perfluorooctane sulfonic acid	
			Bd Wt	1.33 M	3.21 M (12% decrease in terminal BW)			

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
33	Rat (Sprague-Dawley)	80 d 1 x/d (GW)	Bd Wt	1.6	3.2 (>10% reduction in body weight)		Luebker et al. 2005a Potassium perfluorooctane sulfonate	
34	Rat (Sprague-Dawley)	90 d 1 x/d (G)	Hepatic		0.4 F (16% reduction in serum total cholesterol on PND 5)		Luebker et al. 2005b Potassium perfluorooctane sulfonate	
			Endocr		0.4 F (46% reduction in total T4 on PND 5)			
			Bd Wt	1.6 F		2 F (22% reduction in body weight gain during premating; food consumption reduced 5.8%)		
35	Rat (Sprague-Dawley)	4 wk ad lib (F)	Hemato	1.77 F			Seacat et al. 2003 Potassium perfluorooctane sulfonate	NOAELs are for organ histopathology.
			Hepatic	1.77 F				
			Renal	1.77 F				
			Endocr	1.77 F				
			Ocular	1.77 F				
			Bd Wt	1.77 F				

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
36	Rat (Sprague-Dawley)	14 wk ad lib (F)	Hemato	0.34 M	1.33 M (45% increase in segmented neutrophils)		Seacat et al. 2003 Potassium perfluorooctane sulfonate	NOAELs are for organ histopathology.
			Hepatic	0.34 M	1.33 M (increase absolute and relative liver weight; increased serum ALT; hepatocyte hypertrophy and vacuolation)			
			Renal	1.56 F				
			Endocr	1.56 F				
			Ocular	1.56 F				
			Bd Wt	1.56 F				
37	Rat (Sprague-Dawley)	Gd 2-20 (GW)	Hepatic	1 F	5 F (27% increased liver weight)		Thibodeaux et al. 2003 Potassium perfluorooctane sulfonate	
			Endocr		1 F (reduced total and free T4 and T3)			
			Bd Wt	1 F	2 F (>10% decreased mean body weight gain)	5 F (approximately 33% reduced body weight gain)		
38	Rat (Sprague-Dawley)	91 days (W)	Endocr		0.27 M (decreased total thyroxine levels)		Yu et al. 2009a Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
39	Mouse (ICR)	Gd 1-17 1 x/d (GW)	Bd Wt		20 F (35% reduced maternal body weight)		Era et al. 2009 Potassium perfluorooctane sulfonate	
40	Mouse (B6C3F1)	Gd 1-17 1 x/d (GW)	Other	5 F			Keil et al. 2008 Potassium perfluorooctane sulfonate	
41	Mouse (CD-1)	Gd 1-17 (GW)	Hepatic	1 F	5 F (21-27% increase in absolute and relative liver weight)		Thibodeaux et al. 2003 Potassium perfluorooctane sulfonate	
			Endocr	15 F	20 F (decreased total T4 on Gd 6)			
			Bd Wt	20 F				
42	Mouse (CD-1)	21 d 1 x/d (GO)	Hepatic	1 M	5 M (~50% increased absolute liver weight)		Wan et al. 2011 Potassium perfluorooctane sulfonate	
			Bd Wt	5 M	10 M (~15% reduced body weight)			
43	Mouse (ICR)	Gd 0-17 Gd 0-18 1 x/d (GW)	Hepatic	1 F	10 F (60% increased absolute liver weight)		Yahia et al. 2008 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Immuno/ Lymphoret								
44	Monkey (Cynomolgus)	26 wk 1 x/d (C)		0.75			Seacat et al. 2002 Potassium perfluorooctane sulfonate	NOAEL is for histopathology of lymphoreticular organs.
45	Monkey (Cynomolgus)	4 wk 1 x/d (C)		2			Thomford 2002a Potassium perfluorooctane sulfonate	NOAEL is for histopathology of the spleen and thymus.
46	Rat (Sprague-Dawley)	28 days (F)		6.34 M			Lefebvre et al. 2008 Perfluorooctane sulfonic acid	
47	Rat (Sprague-Dawley)	4 wk ad lib (F)		1.77 F			Seacat et al. 2003 Potassium perfluorooctane sulfonate	NOAEL is for histopathology of spleen and mesenteric lymph nodes.
48	Rat (Sprague-Dawley)	14 wk ad lib (F)		1.56 F			Seacat et al. 2003 Potassium perfluorooctane sulfonate	NOAEL is for histopathology of the spleen and lymph nodes.
49	Mouse (C57BL/6N)	60 days (G)		0.0083 M	0.083 M (impaired response to SRBC)		Dong et al. 2009 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
50	Mouse (C57BL/6N)	60 days (G)		0.0167 M	0.0833 M (impaired response to SRBC)		Dong et al. 2011 Potassium perfluorooctane sulfonate	
51	Mouse (B6C3F1)	21 days (G)		0.005 F	0.025 F (decreased host resistance to influenza virus)		Guruge et al. 2009 Perfluorooctane sulfonic acid	
52	Mouse (B6C3F1)	28 days (G)		0.000166	0.00166 (supressed response to SRBC)		Peden-Adams et al. 2008 Potassium perfluorooctane sulfonate	
Neurological								
53	Monkey (Cynomolgus)	26 wk 1x/d (C)		0.75			Seacat et al. 2002 Potassium perfluorooctane sulfonate	NOAEL is for histopathology of the brain and spinal cord.
54	Rat (Sprague-Dawley)	Daily 28 days (G)			5 M (cachexia and lethargy)		Cui et al. 2009 Perfluorooctane sulfonic acid	
55	Rat (Wistar)	Daily 13 weeks (F)		2 M	8.5 M (tonic convulsions in response to stimuli)		Kawamoto et al. 2011 Perfluorooctane sulfonic acid	
56	Rat (Sprague-Dawley)	4 wk ad lib (F)		1.77 F			Seacat et al. 2003 Potassium perfluorooctane sulfonate	NOAEL is for histopathology of the brain.

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
57	Rat (Sprague-Dawley)	14 wk ad lib (F)		1.56 F			Seacat et al. 2003 Potassium perfluorooctane sulfonate	NOAEL is for weight and histopathology of the brain.
58	Mouse (C57BL/6)	Daily 3 months (G)		0.43	2.15 (impaired spatial learning and memory)		Long et al. 2013 Perfluorooctane sulfonic acid	
Reproductive								
59	Monkey (Cynomolgus)	26 w 1 x/d (C)		0.15	0.75 M (significant decrease in serum estradiol on day 62, 91, and 182).		Seacat et al. 2002 Potassium perfluorooctane sulfonate	Histopathology of reproductive organs was unremarkable.
60	Monkey (Cynomolgus)	4 wk 1 x/d (C)		2 M			Thomford 2002a Potassium perfluorooctane sulfonate	NOAEL is for histopathology of the testes.
61	Rat (Sprague-Dawley)	Gd 0 to PND 20 1 x/d (GW)		1 F			Butenhoff et al. 2009b Potassium perfluorooctane sulfonate	
62	Rat (Sprague-Dawley)	80 d 1 x/d (GW)		3.2			Luebker et al. 2005a Potassium perfluorooctane sulfonate	NOAEL is for mating and fertility parameters in parental generation.
63	Rat (Sprague-Dawley)	90 d 1 x/d (G)		2 F			Luebker et al. 2005b Potassium perfluorooctane sulfonate	NOAEL is for fertility.

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
64	Rat (Sprague-Dawley)	4 wk ad lib (F)		1.51 M 1.77 F			Seacat et al. 2003 Potassium perfluorooctane sulfonate	NOAEL is for histopathology of the testes and uterus.
65	Rat (Sprague-Dawley)	14 wk ad lib (F)		1.33 M 1.56 F			Seacat et al. 2003 Potassium perfluorooctane sulfonate	NOAEL is for histopathology of the testes and ovaries.
66	Mouse (CD-1)	21 d 1 x/d (GO)		5 M	10 M (~17% reduced serum testosterone, ~38% reduced epididymal sperm count)		Wan et al. 2011 Potassium perfluorooctane sulfonate	
Developmental								
67	Rat (Sprague-Dawley)	Gd 0 to PND 20 1 x/d (GW)		0.3 M	1 M (~30% increased locomotor activity and concurrent failure to habituate to test environment in male pups on PND 17)		Butenhoff et al. 2009b Potassium perfluorooctane sulfonate	
68	Rat (Sprague-Dawley)	Gd 0 to PND 20 1 x/d (GW)			1 F (2.1-fold increased fetal thyroid cell proliferation on Gd 20)		Chang et al. 2009 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
69	Rat (Sprague-Dawley)	Gd 1-21 1 x/d (GW)		0.1		2 (~5-fold increased postnatal mortality and severe lung histopathology in pups)	Chen et al. 2012b Perfluorooctane sulfonic acid	
70	Rat (Sprague-Dawley)	Gd 2-21 1 x/d (GW)			1 (reduced serum T4 in pups)	2 (approximately 60% survival at weaning vs. 80% in controls)	Lau et al. 2003 Potassium perfluorooctane sulfonate	
71	Rat (Sprague-Dawley)	90 d 1 x/d (GW)				1.6 F (increased pup mortality during PND 1-4)	Luebker et al. 2005a Potassium perfluorooctane sulfonate	Cross-foster study showed that exposure in utero alone can decrease neonatal viability.
72	Rat (Sprague-Dawley)	80 d 1 x/d (GW)			0.4 (slight but significant delayed eye opening)	1.6 (decreased pup survival to post-partum day 21)	Luebker et al. 2005a Potassium perfluorooctane sulfonate	
73	Rat (Sprague-Dawley)	90 d 1 x/d (GW)			0.4 (>10% decrease in mean pup weight per litter on PND 5)	1.6 (approximately 50% decrease mean pup survival per litter on PND 5)	Luebker et al. 2005b Potassium perfluorooctane sulfonate	
74	Rat (Sprague-Dawley)	Gd 2-20 1 x/d (GW)			10 F (increased incidences of cleft palate)		Thibodeaux et al. 2003 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
75	Rat (Sprague-Dawley)	Gd 2-21 1 x/d (GW)		0.6		2 (5-fold increased neonatal mortality on PND 1-3)	Xia et al. 2011 Perfluorooctane sulfonic acid	
76	Rat (Wistar)	Gd 1 to PND 21			3.2 F (19-36% reduced serum thyroxine levels in pups on PND 21-35 after gestation- and/or postnatal-only exposure)		Yu et al. 2009b Potassium perfluorooctane sulfonate	
77	Mouse (ICR)	Gd 1-17 1 x/d (GW)			20 F (89% increased cleft palate, 25% reduced body weight in fetuses)		Era et al. 2009 Potassium perfluorooctane sulfonate	
78	Mouse (B6C3F1)	Gd 1-17 1 x/d (GW)		0.1 M	1 M (42.5% reduced NK cell activity in male pups at 8 weeks of age)		Keil et al. 2008 Potassium perfluorooctane sulfonate	
79	Mouse (CD-1)	Gd 1-17 1 x/d (GW)			1 (delayed eye opening)	10 (approximately 50% postnatal survival at weaning vs. 90% in controls)	Lau et al. 2003 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
80	Mouse (C57BL/6/Bk1)	Gd 1-17 ad lib (F)			0.3 M (decreased locomotion, muscle strength and motor coordination in adult offspring)		Onishchenko et al. 2011 Potassium perfluorooctane sulfonate	
81	Mouse (CD-1)	Gd 1-17 1 x/d (GW)			5 (peroxisome proliferation in fetal liver)		Rosen et al. 2009 Potassium perfluorooctane sulfonate	
82	Mouse (CD-1)	Gd 1-17 (GW)		1 F	5 F (increased incidences of sternal defects)	20 F (reduced percentage of live fetuses)	Thibodeaux et al. 2003 Potassium perfluorooctane sulfonate	
83	Mouse (ICR)	Gd 0-17 1 x/d (GW)			1 F (15.8% increased sternal defects in fetuses)	20 F (decreased number of live fetuses)	Yahia et al. 2008 Potassium perfluorooctane sulfonate	
84	Mouse (ICR)	Gd 0-18 1 x/d (GW)				10 (Decreased survival at PND 4, decreased neonatal BW, intracranial blood vessel dilatation, lung atelectasis)	Yahia et al. 2008 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
85	Rat (Sprague-Dawley)	104 wk ad lib (F)	Resp	1.04			Butenhoff et al. 2012b; Thomford 2002b Potassium perfluorooctane sulfonate	
			Cardio	1.04				
			Gastro	1.04				
			Hemato	1.04				
			Musc/skel	1.04				
			Hepatic	0.25 M	0.1 M (increased incidence of cystic hepatocellular degeneration)			
			Renal	1.04				
			Endocr	1.04				
			Dermal	1.04				
			Ocular	1.04				
			Bd Wt	0.25 F	1.04 F (14% reduction in final body weight)			
Immuno/ Lymphoret								
86	Rat (Sprague-Dawley)	104 wk ad lib (F)		1.04			Butenhoff et al. 2012b; Thomford 2002b Potassium perfluorooctane sulfonate	NOAEL is for histopathology of lymphoreticular organs.
Neurological								
87	Rat (Sprague-Dawley)	104 wk ad lib (F)		1.04			Butenhoff et al. 2012b; Thomford 2002b Potassium perfluorooctane sulfonate	NOAEL is for histopathology of central and peripheral nervous tissue.

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
88	Rat (Sprague-Dawley)	104 wk ad lib (F)		1.04			Butenhoff et al. 2012b; Thomford 2002b Potassium perfluorooctane sulfonate	NOAEL is for histopathology of sex organs.

a The number corresponds to entries in Figure 3-4.

b Used to derive an intermediate-duration oral MRL of 0.00003 mg/kg/day based on a NOAEL using serum PFOS levels as an internal dose metric; a human equivalent dose (HED) of the NOAEL was estimated using an empirical clearance model. The NOAEL(HED) of 0.00252 mg/kg/day was divided by an uncertainty factor of 90 (3 for extrapolation from animals to humans with dosimetric adjustment, 10 for human variability, and 3 for database deficiencies).

ad lib = ad libitum; ALT = alanine aminotransferase; Bd Wt = body weight; BUN = blood urea nitrogen; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LOAEL = lowest-observed-adverse-effect level; M = male; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; PND = post-natal day; ppd = post-partum day; Resp = respiratory; T3 = triiodothyronine; T4 = thyroxine; TSH= thyroid-stimulating hormone; wk = week(s); x = time(s)

Figure 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral

Acute (≤14 days)

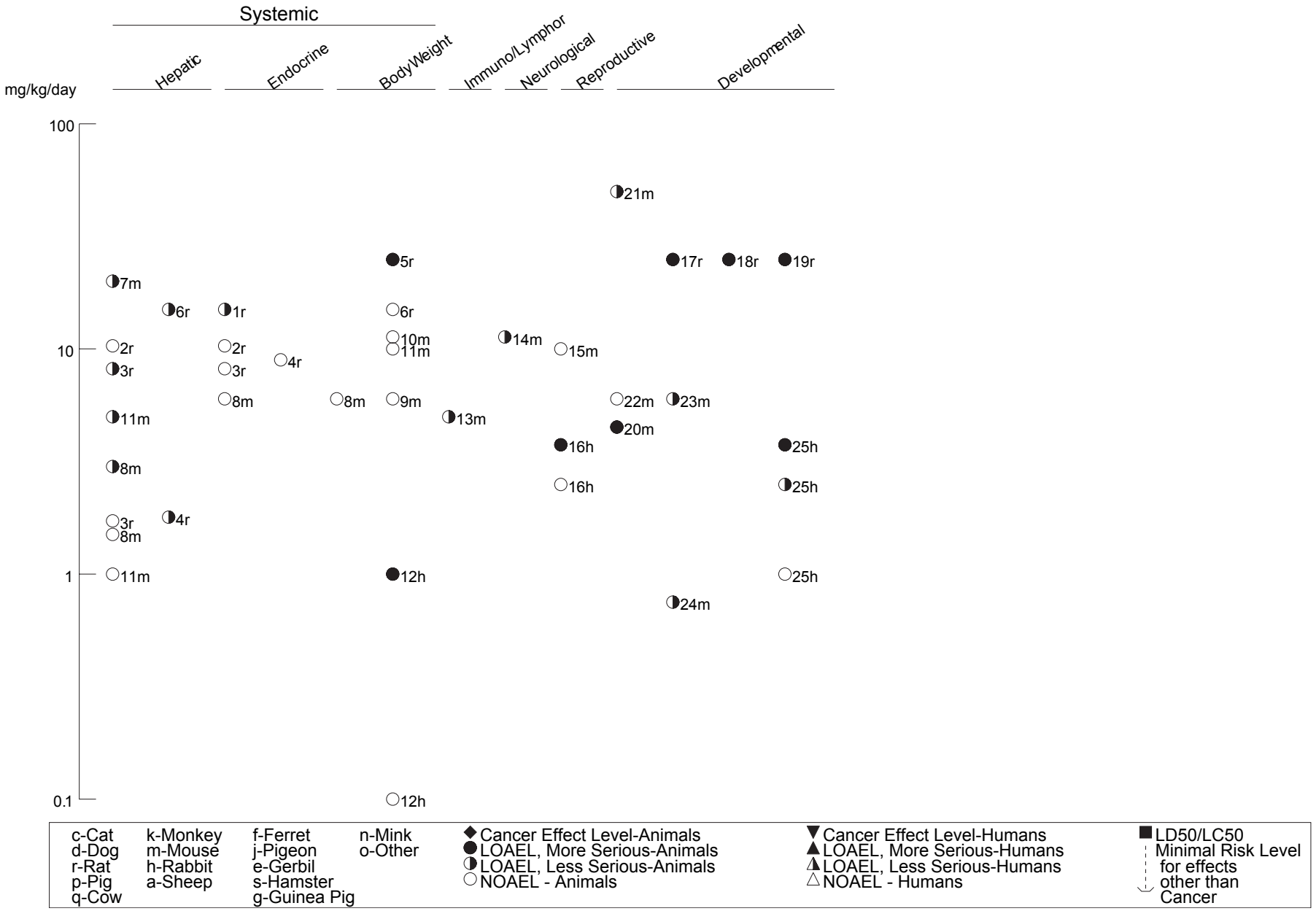


Figure 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral *(Continued)*

Intermediate (15-364 days)

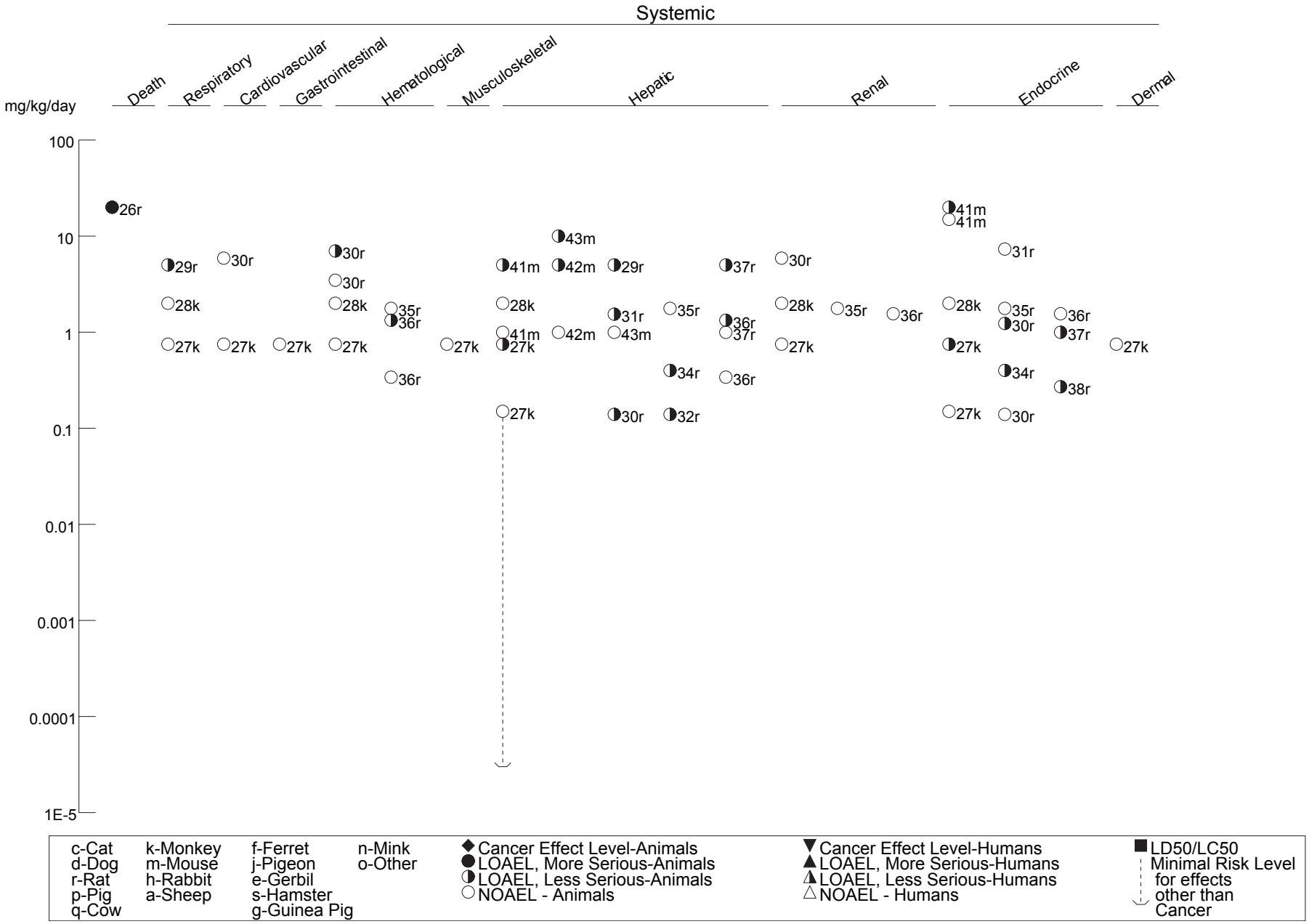


Figure 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral *(Continued)*

Intermediate (15-364 days)

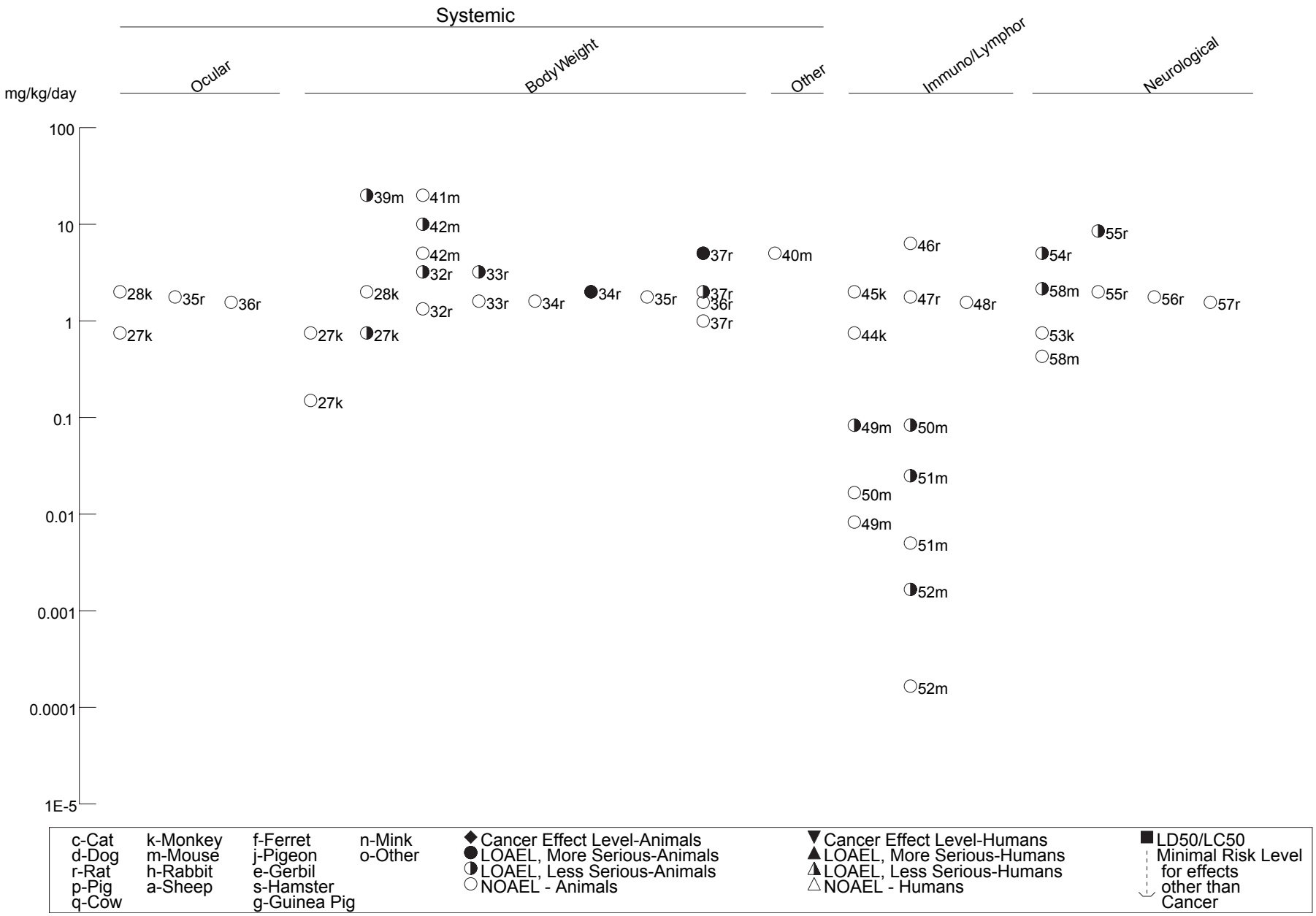


Figure 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral *(Continued)*

Intermediate (15-364 days)

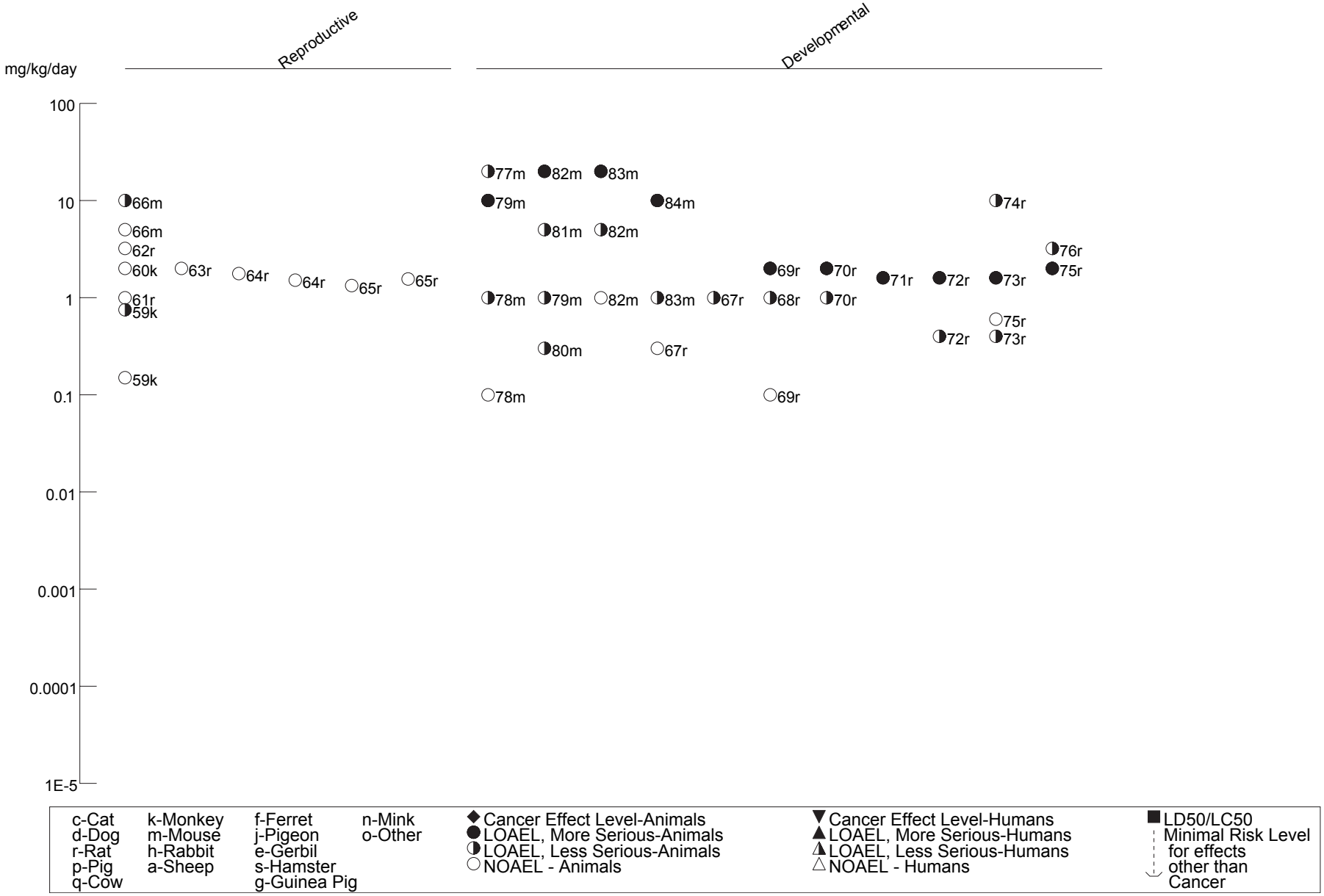


Figure 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonic Acid - Oral *(Continued)*

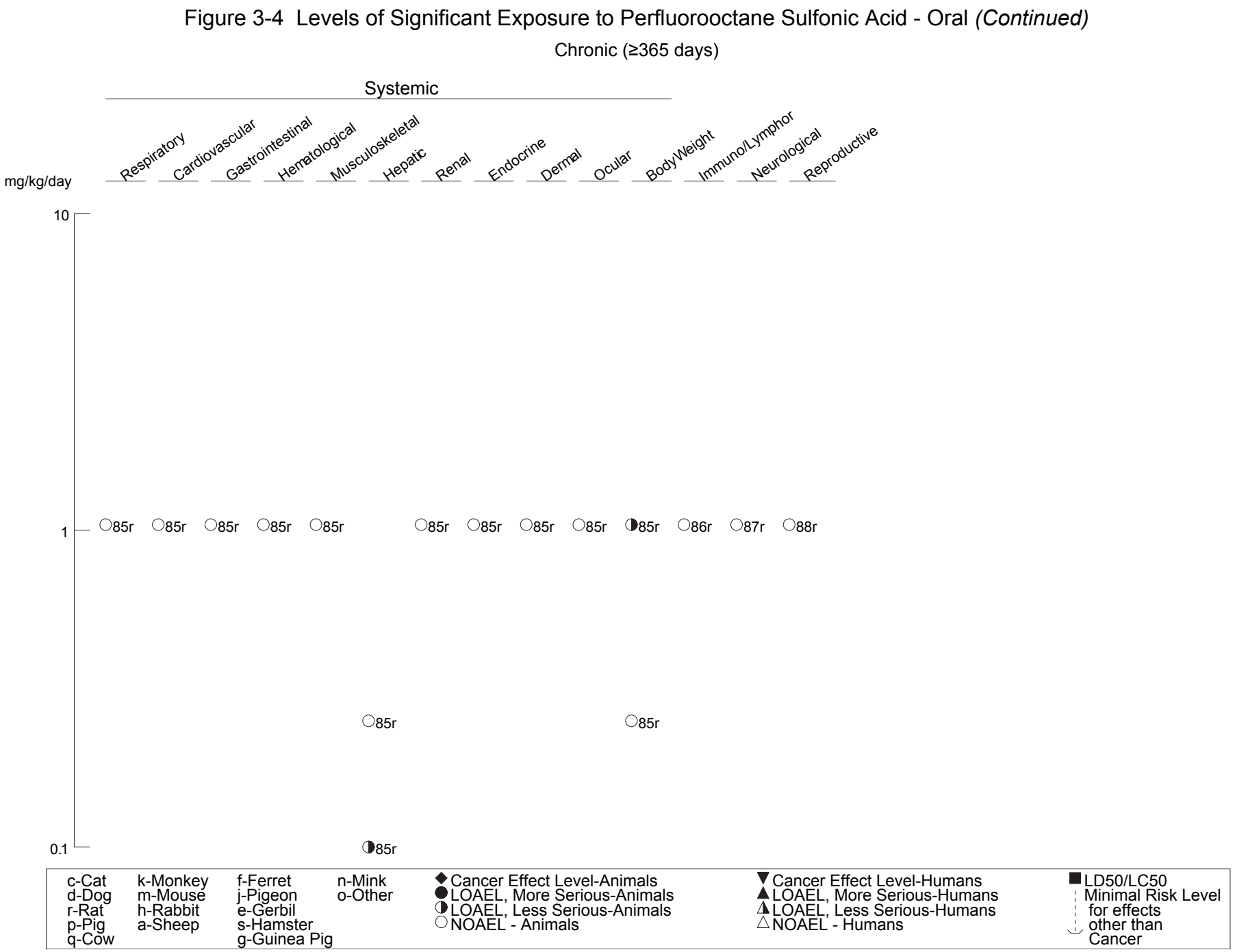


Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Mouse (C57BL/6N)	once (GO)				120 F (LD50 in 30-day observation period)	Harris et al. 1989 Perfluorodecanoic acid	
2	Mouse (CD-1)	14 d ad lib (F)				54 (all 10 mice died before day 14)	Kennedy 1987 Perfluorononanoic acid	
Systemic								
3	Rat (Sprague-Dawley)	5 d 1 x/d (GW)	Resp	184			3M 2007a Perfluorobutyric acid	
			Cardio	184				
			Gastro	184				
			Hemato	184				
			Musc/skel	184				
			Hepatic	184				
			Renal	184				
			Endocr	184				
			Bd Wt	184				
4	Rat (Sprague-Dawley)	14 days (GW)	Hepatic	0.2 M	1 M (increased serum glucose and decreased HDL levels)		Fang et al. 2012a Perfluorononanoic acid	

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
5	Rat (Sprague-Dawley)	14 days (GW)	Hepatic	1 M	5 M (hepatocellular vacuolation)		Fang et al. 2012b Perfluorononanoic acid	
6	Rat (Sprague-Dawley)	14 d ad lib (F)	Hepatic		20 M (biochemical and ultrastructural evidence of peroxisome proliferation)		Ikeda et al. 1985 Perfluorobutyric acid	
7	Rat (Wistar)	1 wk ad lib (F)	Hepatic	1.2 M	2.4 M (approximately 30% increase absolute liver weight)		Kawashima et al. 1995 Perfluorodecanoic acid	
			Bd Wt	4.7 M		9.5 M (approximately 32% weight loss)		
8	Rat (Sprague-Dawley)	once (GW)	Hepatic	5 M			Seacat and Luebker 2000 Perfluorooctane sulfonamide	Hepatic NOAEL is for absolute and relative organ weight.
			Bd Wt	5 M				
9	Rat (Sprague-Dawley)	14 d 1 x/d (GW)	Hepatic	5 M	10 M (35% increase in total serum cholesterol)		Shi et al. 2007 Perfluorododecanoic acid	
			Bd Wt	1 M		5 M (25% reduction in final body weight)		

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
10	Mouse (C57BL/6N)	once (GO)	Hepatic		40 F (69% increase in absolute liver weight in 2 days)		Brewster and Birnbaum 1989 Perfluorodecanoic acid	
11	Mouse (C57BL/6N)	Gd 6-15 1 x/d (GO)	Bd Wt	3 F	6.4 F (no weight gain on Gd 6-18)	12.8 F (weight loss during Gd 6-18)	Harris and Birnbaum 1989 Perfluorodecanoic acid	Weight gain was adjusted for weight of uterus and its contents.
12	Mouse (C57BL/6N)	once (GO)	Cardio	40 F	80 F (significant decrease in relative heart weight)		Harris et al. 1989 Perfluorodecanoic acid	
			Hepatic		20 F (85% increase in relative liver weight; hepatocellular hypertrophy)			
			Renal	80 F				
			Bd Wt	40 F	80 F (12% reduction in final body weight)			
13	Mouse (CD-1)	14 d ad lib (F)	Hepatic		0.5 (50-70% increase in absolute liver weight)		Kennedy 1987 Perfluorononanoic acid	
14	Mouse (C57BL/6N)	10 d ad lib (F)	Hepatic		78 M (63% increase in absolute liver weight)		Permadi et al. 1992 Perfluorobutyric acid	
			Bd Wt	78 M				

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
15	Mouse (C57BL/6N)	10 d ad lib (F)	Hepatic		78 M (36% increase in absolute liver weight)		Permadi et al. 1992 Perfluorodecanoic acid	
			Bd Wt			78 M (33% weight loss)		
16	Mouse (C57BL/6N)	10 d ad lib (F)	Hepatic		78 M (63% increase in absolute liver weight)		Permadi et al. 1993 Perfluorobutyric acid	
			Bd Wt	78 M				
17	Mouse (C57BL/6N)	10 d ad lib (F)	Hepatic		78 M (36% increase in absolute liver weight)		Permadi et al. 1993 Perfluorodecanoic acid	
			Bd Wt			78 M (33% weight loss)		
Immuno/ Lymphoret								
18	Rat (Sprague-Dawley)	5 d 1 x/d (GW)		184			3M 2007a Perfluorobutyric acid	NOAEL is for histopathology of the spleen and lymph nodes.
19	Mouse (BALB/c)	14 days (G)			1 M (decreases in the percentages of F4/80+ and CD49b+ cells in the spleen)		Fang et al. 2008 Perfluorononanoic acid	

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form	Comments
20	Mouse (C57BL/6N)	once (GO)		40 F	80 F	(28% decrease in relative spleen weight)	160 F	(atrophy and lymphoid depletion of thymus and spleen)	Harris et al. 1989 Perfluorodecanoic acid	
Neurological										
21	Rat (Sprague-Dawley)	5 d 1 x/d (GW)		184					3M 2007a Perfluorobutyric acid	NOAEL is for histopathology of the brain and spinal cord.
Reproductive										
22	Rat (Sprague-Dawley)	5 d 1 x/d (GW)		184					3M 2007a Perfluorobutyric acid	NOAEL is for histopathology of ovaries and testis.
23	Rat (Sprague-Dawley)	14 d 1 x/d (GW)		1 M	5 M	(decreased serum testosterone and estradiol)			Shi et al. 2007 Perfluorododecanoic acid	
Developmental										
24	Mouse (C57BL/6N)	Gd 6-15 1 x/d (GO)		0.3	1	(decrease fetal weight per litter)	12.8	(decreased live fetuses per litter)	Harris and Birnbaum 1989 Perfluorodecanoic acid	
25	Mouse (CD-1)	PND 10 once (G)		10.8 M					Johansson et al. 2008 Perfluorodecanoic acid	
26	Mouse (NMRI)	PND 10 once (GO)		6.1	9.2	(altered spontaneous behavior and habituation in adults exposed as neonates)			Viberg et al. 2013 Perfluorohexane sulfonic acid	

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
27	Rat (Sprague-Dawley)	28 d 1 x/d (GW)	Resp	900			3M 2001 Perfluorobutane sulfonic acid	NOAELs are for organ histopathology.
			Cardio	900				
			Gastro	900				
			Hemato	900				
			Musc/skel	900				
			Hepatic	300 M	900 M	(increased absolute and relative liver weight)		
			Renal	300 F	900 F	(increased absolute and relative kidney weight)		
			Endocr	900				
			Ocular	900				
			Bd Wt	900				

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
28	Rat (Sprague-Dawley)	42-56 d 1 x/d (GW)	Resp	10			Butenhoff et al. 2009a; Hoberman and York 2003 Perfluorohexane sulfonic acid	NOAELs are for organ histopathology.
			Cardio	10				
			Gastro	10				
			Hemato	10 F	0.3 M (increased prothrombin time)			
			Hepatic	1 M 10 F	3 M (increased liver weight; hypertrophy of centrilobular hepatocytes)			
			Renal	3 M 10 F	10 M (increased BUN)			
			Endocr	1 M 10 F	3 M (hypertrophy-hyperplasia of thyroid follicular cells)			
			Bd Wt	10				

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Rat (Sprague-Dawley)	28 d 1 x/d (GW)	Resp	150			Butenhoff et al. 2012a; van Otterdiijk 2007a perfluorobutyric acid	NOAELs are for organ histopathology.
			Cardio	150				
			Gastro	150				
			Hemato	150				
			Musc/skel	150				
			Hepatic	6 M	30 M (increased absolute and relative liver weight)			
			Renal	150				
			Endocr	6 M	30 M (hyperplasia/hypertrophy of follicular epithelium of the thyroid)			
			Dermal	150				
			Ocular	150				
			Bd Wt	150				

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
30	Rat (Sprague-Dawley)	90 d 1 x/d (GW)	Resp	30			Butenhoff et al. 2012a; van Otterdiijk 2007b perfluorobutyric acid	NOAELs are for lack of organ histopathology.
			Cardio	30				
			Gastro	30				
			Hemato	6	30 M (reduced erythrocyte counts, hemoglobin, and hematocrit)			
			Musc/skel	30				
			Hepatic	6 M	30 M (diffuse panlobular hepatocyte hypertrophy)			
			Renal	30				
			Endocr	6 M	30 M (hypertrophy/hyperplasia of follicular epithelium of the thyroid gland)			
			Dermal	30				
			Ocular	30				
			Bd Wt	30				

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
31	Rat (Sprague-Dawley)	90 days (G)	Resp	600			Lieder et al. 2009a perfluorobutanesulfonic acid	
			Gastro	200	600 (tubular/ductular papilla epithelial hyperplasia)			
			Hemato	60 M	200 M (decreased hemoglobin and hematocrit)			
			Musc/skel	600				
			Hepatic	600				
			Renal	200	600 (tubular/ductular papilla epithelial hyperplasia)			
			Endocr	600				
32	Rat (Sprague-Dawley)	P0: starting 70 days prior to mating; F1:starting at weaning (G)	Hepatic	100 M 1000 F	300 M (increased liver weight)		Lieder et al. 2009b Perfluorobutane sulfonic acid	
			Renal	100	300 (papillary epithelial tubular/acinar hyperplasia in P0 and F1)			
			Bd Wt	1000				

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
33	Mouse (CD-1)	18 d Gd 1-17 1 x/d (GW)	Hepatic	35 F	175 F (significant increase in absolute and relative liver weight)		Das et al. 2008 perfluorobutyric acid	
Immuno/ Lymphoret								
34	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		900			3M 2001 Perfluorobutane sulfonic acid	NOAEL is for histopathology of lymphoreticular organs. histopathology.
35	Rat (Sprague-Dawley)	42-56 d 1 x/d (GW)		10			Butenhoff et al. 2009a; Hoberman and York 2003 Perfluorohexane sulfonic acid	NOAEL is for histopathology of lymphoreticular organs.
36	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		150			Butenhoff et al. 2012a; van Otterdiijk 2007a perfluorobutyric acid	NOAEL is for histopathology of lymphoreticular organs.
37	Rat (Sprague-Dawley)	90 d 1 x/d (GW)		30			Butenhoff et al. 2012a; van Otterdiijk 2007b perfluorobutyric acid	NOAEL is for histopathology of lymphoreticular organs.
Neurological								
38	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		900			3M 2001 Perfluorobutane sulfonic acid	NOAEL is for histopathology of central and peripheral nervous tissue.
39	Rat (Sprague-Dawley)	42-56 d 1 x/d (GW)		10			Butenhoff et al. 2009a; Hoberman and York 2003 Perfluorohexane sulfonic acid	NOAEL is for a functional observation battery and motor activity.

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
40	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		30 M	150 M (delayed pupillary reflex)		Butenhoff et al. 2012a; van Otterdiijk 2007a perfluorobutyric acid	
41	Rat (Sprague-Dawley)	90 d 1 x/d (GW)		30			Butenhoff et al. 2012a; van Otterdiijk 2007b perfluorobutyric acid	NOAEL is for histopathology or nervous tissues and observation battery.
42	Rat (Sprague-Dawley)	90 days (G)		600			Lieder et al. 2009a perfluorobutanesulfonic acid	
Reproductive								
43	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		900			3M 2001 Perfluorobutane sulfonic acid	NOAEL is for histopathology of sex organs.
44	Rat (Sprague-Dawley)	42-56 d 1 x/d (GW)		10			Butenhoff et al. 2009a; Hoberman and York 2003 Perfluorohexane sulfonic acid	NOAEL is for fertility parameters and sex organs histopathology.
45	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		150			Butenhoff et al. 2012a; van Otterdiijk 2007a perfluorobutyric acid	NOAEL is for histopathology of reproductive organs.
46	Rat (Sprague-Dawley)	90 d 1 x/d (GW)		30			Butenhoff et al. 2012a; van Otterdiijk 2007b perfluorobutyric acid	NOAEL is for histopathology of reproductive organs.

Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
47	Rat (Sprague-Dawley)	P0: starting 70 days prior to mating; F1:starting at weaning (G)		1000			Lieder et al. 2009b Perfluorobutane sulfonic acid	
Developmental								
48	Rat (Sprague-Dawley)	42-56 d 1 x/d (GW)		10 F			Butenhoff et al. 2009a; Hoberman and York 2003 Perfluorohexane sulfonic acid	NOAEL is for a wide range of developmental parameters.
49	Rat (Sprague-Dawley)	P0: starting 70 days prior to mating; F1:starting at weaning (G)		1000			Lieder et al. 2009b Perfluorobutane sulfonic acid	
50	Rat (Sprague-Dawley)	28 d PND 24-72 1 x/d (GW)		1 F	3 F (40% reduced serum estradiol and 20% increased serum cholesterol in pubertal females)		Shi et al. 2009 Perfluorododecanoic acid	
51	Mouse (CD-1)	18 d Gd 1-17 1 x/d (GW)			35 (eye opening delayed approximately 1 day)		Das et al. 2008 perfluorobutyric acid	

a The number corresponds to entries in Figure 3-5.

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; Gastro = gastrointestinal; Gd = gestational day; (GW) = gavage in water; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; PFBA = perfluorobutyric acid; PFDeA = perfluorodecanoic acid; PFDoA = perfluorododecanoic acid; PFNA = perfluorononanoic acid; PFOSA = perfluorooctanatesulfonamide; wk = week(s); x = time(s)

Figure 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral

Acute (≤14 days)

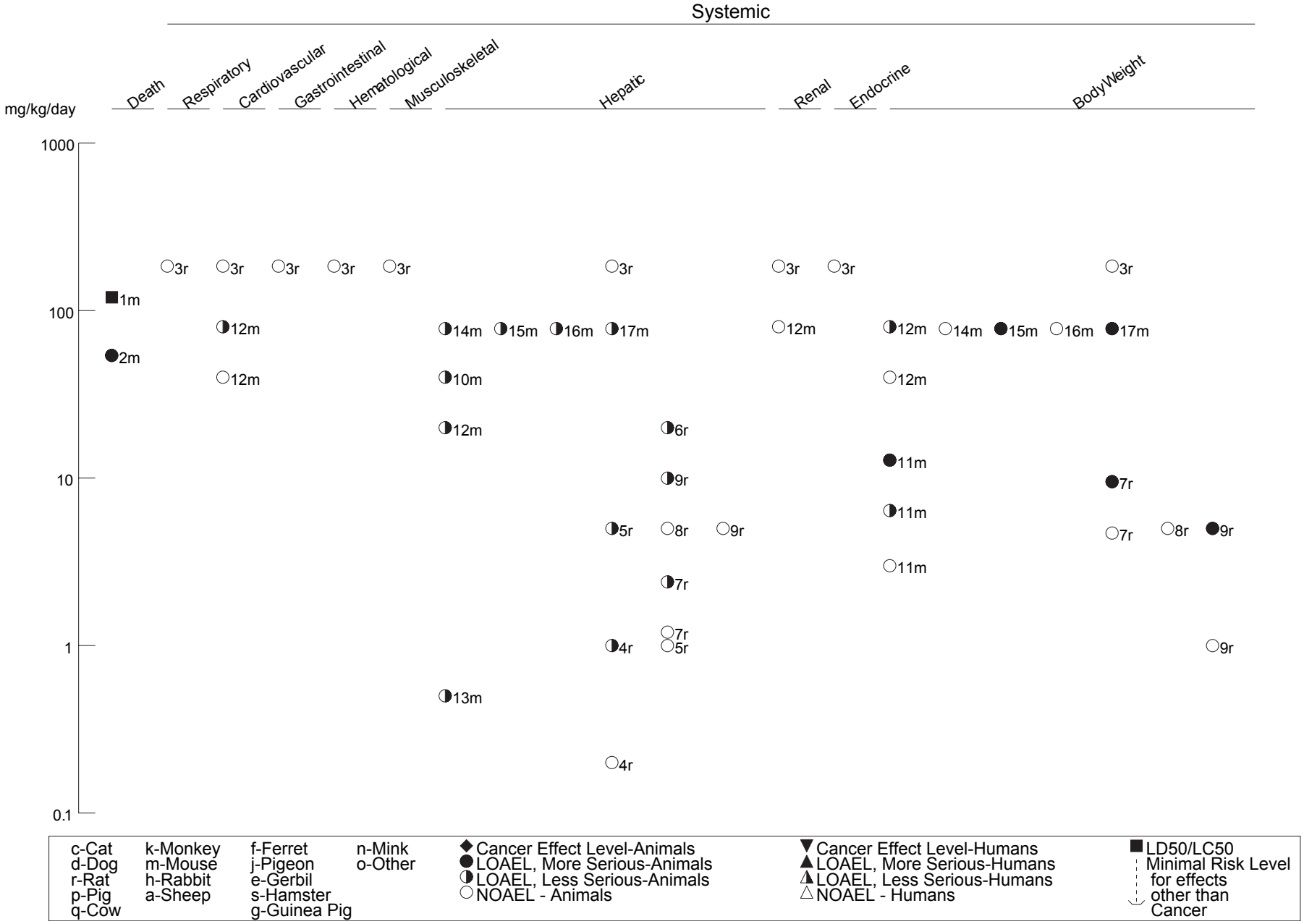


Figure 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral *(Continued)*

Acute (≤14 days)

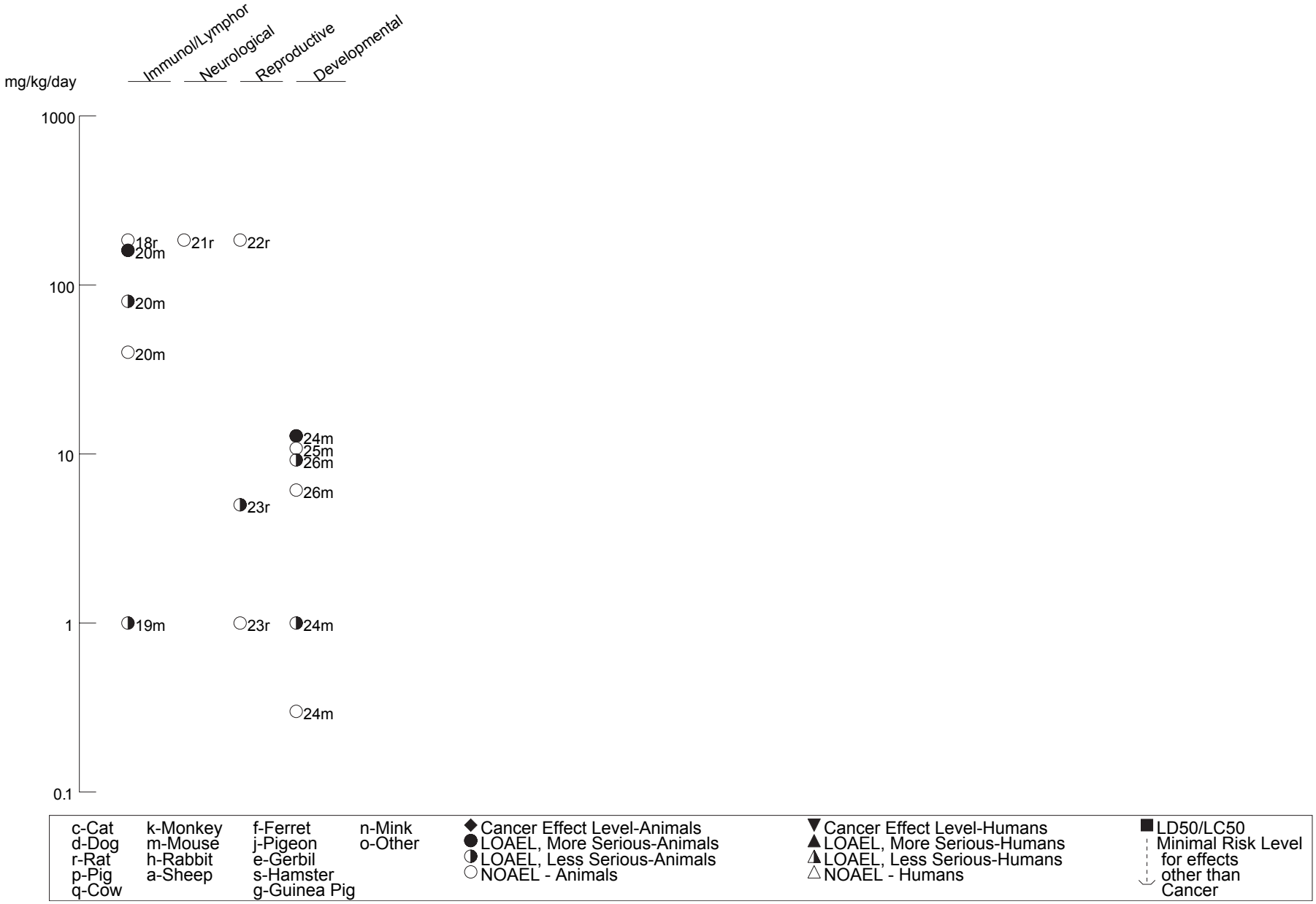


Figure 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral *(Continued)*

Intermediate (15-364 days)

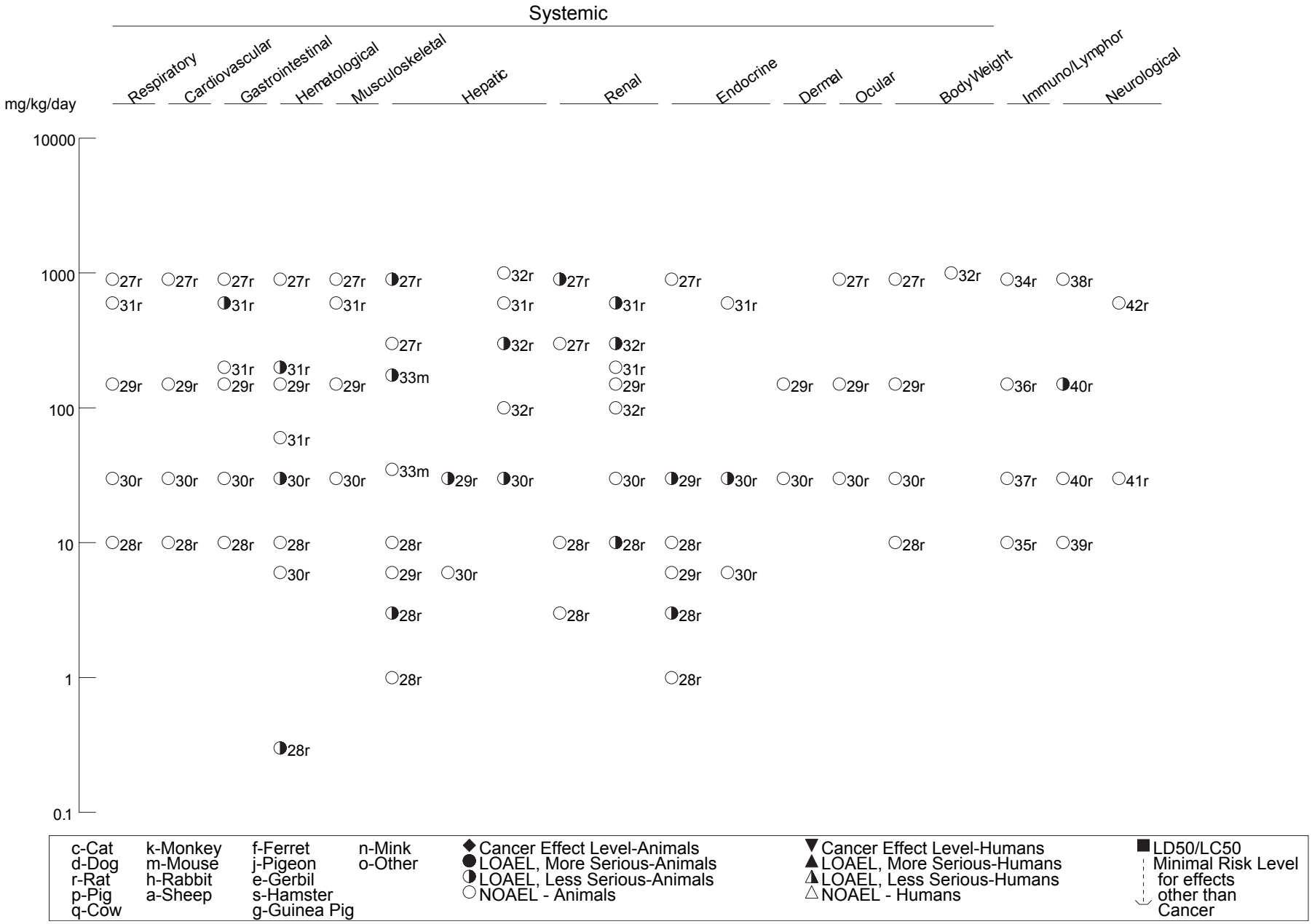
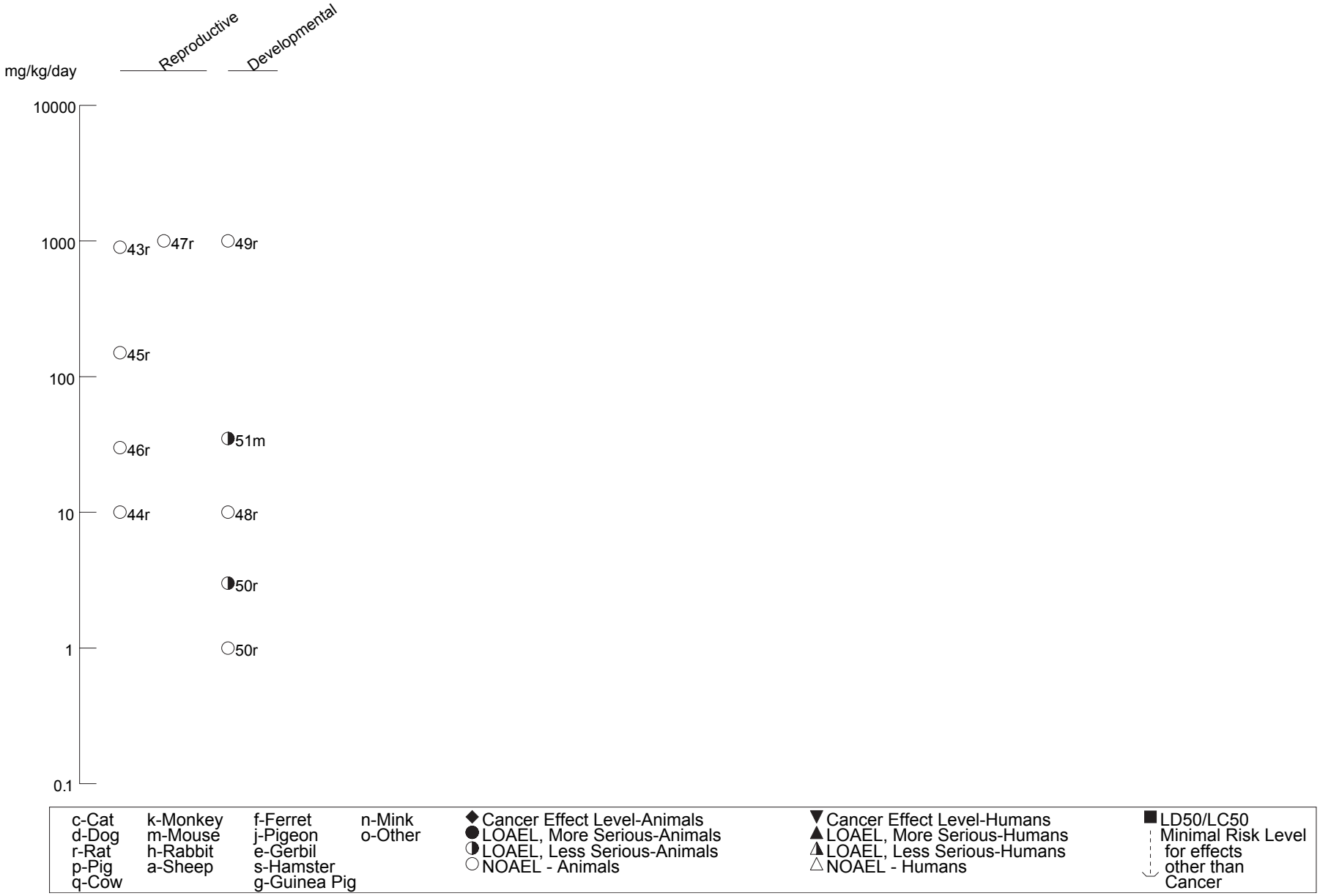


Figure 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral *(Continued)*

Intermediate (15-364 days)



In a study in monkeys administered up to 20 mg/kg/day APFO in a capsule for 26 weeks, no signs of respiratory problems were observed during the study and no gross or microscopic alterations in the lungs and trachea were observed at termination (Butenhoff et al. 2002).

Laboratory Animal Exposure Studies—PFOS. Dosing of Cynomolgus monkeys with up to 2 mg/kg/day PFOS for 4 weeks had no effect of the gross or microscopic morphology of the lungs (Thomford 2002a). Administration of doses of up to 0.75 mg/kg/day of PFOS (potassium salt) in a capsule to Cynomolgus monkeys for 26 weeks did not produce any gross or microscopic alterations in the lungs or the trachea (Seacat et al. 2002). Dosing rats with up to 1.04 mg PFOS/kg/day in the diet for 104 weeks did not induce significant gross or microscopic alterations in the lungs and trachea (Butenhoff et al. 2012b; Thomford 2002b).

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. Administration of PFBA to rats by gavage in doses of up to 184 mg/kg/day for 5 days (3M 2007a), 150 mg/kg/day for 28 days (Butenhoff et al. 2012a; van Otterdijk 2007a), or 30 mg/kg/day for 90 days (Butenhoff et al. 2012a; van Otterdijk 2007b) did not cause morphological alterations in the respiratory tract. Examination of the respiratory tract of rats exposed to up to 10 mg/kg/day PFHxS by gavage in a reproductive study (40–60 days of dosing) showed no treatment-related effects (Butenhoff et al. 2009a; Hoberman and York 2003). Administration of PFBuS at gavage doses of up to 900 mg/kg/day for 28 days or 600 mg/kg/day for 90 days had no significant effect on the gross or microscopic morphology of the lungs and trachea in rats (3M 2001; Lieder et al. 2009a); no increases in nasal lesions were observed in the 90 day study (Lieder et al. 2009a).

Cardiovascular Effects.

Human Exposure Studies. The potential of perfluoroalkyls to induce cardiovascular effects has been examined in studies of the general population (Min et al. 2012; Shankar et al. 2012) and in residents living near a PFOA facility (Anderson-Mahoney et al. 2008; Steenland et al. 2010). A study of 566 white adults in West Virginia and Ohio exposed to PFOA in contaminated drinking water from a nearby manufacturing facility calculated standardized prevalence ratios (SPRs) by comparing self-reported cardiovascular effects to expected rates from NHANES 2001–2002 (Anderson-Mahoney et al. 2008). The study did not measure serum PFOA levels in the subjects and approximately 15% of the subjects worked at the PFOA facility, which likely resulted in inhalation exposure to PFOA. Significant increases in cardiovascular problems (including myocardial infarction, stroke, and angina) were observed; the SPR

was 4.29 (95% CI 3.47–5.29). The prevalence of high blood pressure was not significantly altered; however, when the subjects were categorized by age and sex, significant increases in prevalence rates were observed in males 18–34, 35–49, 50–64, and ≥65 years old and in females 18–34, 50–64, and ≥65 years old.

Using NHANES data for 1,216 adults (≥40 years of age), Shankar et al. (2012) found significant increases in the risk of self-reported cardiovascular disease in adults with serum PFOA levels in the third (4.0–5.6 ng/mL in women and 4.4–6.1 ng/mL in men) and fourth (>5.6 ng/mL in women and >6.1 ng/mL in men) quartiles (ORs 1.77 [95% CI 1.04–3.02] and 2.01 [95% CI 1.12–3.60], respectively) and an increased risk of peripheral arterial disease in adults with PFOA levels in the fourth quartile (OR 1.78, 95% CI 1.03–3.08); cardiovascular disease was defined as physician-diagnosed coronary heart disease, heart attack, or stroke and peripheral arterial disease was defined as the ratio of <0.9 for ankle systolic blood pressure to arm systolic blood pressure. The results were similar when the subjects were categorized by sex, smoking status, and BMI, although the OR was not always statistically significant. When cardiovascular disease was divided into types of disease, significant increases in the risk of coronary heart disease and stroke were significantly higher in adults with PFOA levels in the fourth quartile. Another study using the NHANES data for 2,263 adults (>20 years of age; Min et al. 2012) found a significant positive association between serum PFOA levels and systolic blood pressure (adjusted for various factors including obesity, physical activity, smoking status, total cholesterol, and kidney function) when analyzed by linear regression and risk analysis (OR 2.62 [95% CI 2.09–3.14] when subjects with serum PFOA levels in the 80th percentile were compared to those in the 20th percentile). Categorizing subjects by serum PFOA quartiles and adjusting for serum PFOS levels also resulted in significantly elevated ORs in comparisons of the third and fourth quartiles to the first quartile. A positive association between serum PFOA and homocysteine levels, considered a marker for cardiovascular disease, was also found.

Several studies have examined the possible associations between PFOA and pregnancy-induced hypertension. Using birth record data and serum PFOA levels predicted from addresses, Savitz et al. (2012b) found no consistent associations between serum PFOA and the occurrence of pregnancy-induced hypertension in participants in the C8 Health Project. Another study of participants in the C8 Health Project that used measured serum perfluoroalkyl levels found significant increases in the ORs for pregnancy-induced hypertension in women with higher PFOA (≥6.9 ng/mL) or PFOS (≥12.1 ng/mL) levels (Darrow et al. 2013). Another study of highly exposed residents reported a weak association between serum PFOA and PFOS and pre-eclampsia in subjects whose PFOA and PFOS levels were

above the median (Stein et al. 2009); however, there was no dose-response gradient. A significant increase in the risk of pre-eclampsia was also found in subjects with PFOS levels above the 90th percentile (≥120.6 ng/mL). Savitz et al. (2012a) also found an increased risk of self-reported pre-eclampsia in C8 Health Project participants with elevated PFOA levels.

Laboratory Animal Exposure Studies—PFOA. Administration of APFO in the diet at doses up to approximately 100–110 mg/kg/day to male and female CD rats or 10 mg/kg/day by gavage to Rhesus monkeys did not cause gross or microscopic alterations in the heart and aorta (Griffith and Long 1980). Similar negative findings were reported in Cynomolgus monkeys administered up to 20 mg/kg/day APFO by capsule for 26 weeks (Butenhoff et al. 2002) and in male and female Sprague-Dawley rats that received doses of up to 15 mg/kg/day APFO for 2 years (3M 1983).

Laboratory Animal Exposure Studies—PFOS. Administration of doses of up to 0.75 mg/kg/day PFOS (potassium salt) via capsule to Cynomolgus monkeys for 26 weeks did not cause any significant gross or microscopic alterations in the heart or aorta (Seacat et al. 2002). Rats that received up to approximately 1.04 mg/kg/day of PFOS in the diet for 2 years had no significant gross or microscopic changes in the heart (Butenhoff et al. 2012b; Thomford 2002b).

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. PFBA administered to rats by gavage in doses of up to 184 mg/kg/day for 5 days, 150 mg/kg/day for 28 days, or 30 mg/kg/day for 90 days did not induce gross or microscopic alterations in the heart (3M 2007a; Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b). Dosing of rats with up to 10 mg/kg/day PFHxS by gavage for 40–60 days did not cause morphological alterations in the heart (Butenhoff et al. 2009a; Hoberman and York 2003). Similar lack of morphological alterations were reported in the heart and aorta from rats dosed with up to 900 mg/kg/day PFBuS by gavage for 28 days (3M 2001) or 600 mg/kg/day PFBuS for 90 days (Lieder et al. 2009a).

Death in female C57BL/6N mice following administration of single lethal dose of 160 or 320 mg/kg PFDeA by gavage was associated with mural thrombosis of the left ventricle of the heart (Harris et al. 1989). Doses of ≤80 mg/kg did not cause gross or microscopic alterations in the heart, assessed 30 days after dosing, but 80 mg/kg significantly decreased relative heart weight (Harris et al. 1989).

Gastrointestinal Effects.

Laboratory Animal Exposure Studies—PFOA. No significant gross or microscopic alterations of the gastrointestinal tract were observed in male and female rats exposed to approximately 100–110 mg/kg/day APFO through the diet for 90 days (Griffith and Long 1980). Similar observations were reported in male and female rats exposed to 15 mg/kg/day APFO via the diet for 2 years (3M 1983). The same investigators also reported that emesis occurred in Rhesus monkeys exposed to lethal doses (30 and 100 mg/kg/day) of APFO by gavage for 90 days (Griffith and Long 1980). In another intermediate-duration study in which Cynomolgus monkeys were exposed to up to 20 mg/kg/day APFO in a capsule for 26 weeks, no treatment-related alterations in the gastrointestinal tract were observed at termination (Butenhoff et al. 2002).

Laboratory Animal Exposure Studies—PFOS. Treatment of rats with up to approximately 1.04 mg/kg/day PFOS via the diet for 2 years did not induce morphological alterations in the gastrointestinal tract (Butenhoff et al. 2012b; Thomford 2002b).

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. Administration of PFBA to rats by gavage in doses of up to 184 mg/kg/day for 5 days, 150 mg/kg/day for 28 days, or 30 mg/kg/day for 90 days did not cause morphological alterations in the gastrointestinal tract (3M 2007a; Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b). Similar findings were reported in intermediate-duration gavage studies in rats given doses of up to 10 mg/kg/day PFHxS or 900 mg/kg/day PFBuS (3M 2001; Butenhoff et al. 2009a; Hoberman and York 2003). In contrast, necrosis of individual squamous cells and hyperplasia and hyperkeratosis were observed in the limiting ridge of the forestomach of male and female rats administered via gavage 600 mg/kg/day PFBuS (Lieder et al. 2009a); these lesions were likely due to irritation from the repeated gavage administration with PFBuS.

Hematological Effects.

Human Exposure Studies. Information on effects on hematological parameters is available from a study of 371 residents in the Little Hocking water district in southeastern Ohio where significant environmental exposure to PFOA via the water supply has been described (Emmett et al. 2006b). The cohort consisted of persons who had resided in the district for at least 2 years. The median age of the study group was 50 years, 53.4% were females, and there were 43 children under the age of 18 years. The average PFOA concentration in the water supplied by the Little Hocking Water Association over a period of 3 years

before the health evaluation was conducted was 3.5 µg/L. The population median serum PFOA was 354 ng/mL and the interquartile range was 184–571 ng/mL. Hematology parameters evaluated included hemoglobin, hematocrit, red blood cell indices, white cell count, and platelet count. No significant correlation between any of the parameters examined and serum PFOA was observed, whether the analysis included all the individuals as a group or separate analyses were done for adults or children.

Laboratory Animal Exposure Studies—PFOA. No significant hematological alterations were reported in male and female rats dosed with approximately 100–110 mg/kg/day APFO in diet for 90 days (Griffith and Long 1980). Similar results were reported in Cynomolgus monkeys treated daily with up to 20 mg/kg/day APFO in a capsule (Butenhoff et al. 2002; Thomford 2001) or in Rhesus monkeys dosed daily by gavage with up to 30 mg/kg/day (Griffith and Long 1980). In a 2-year dietary study in rats dosed with 1.5 or 15 mg/kg/day APFO, hematology tests performed at various times during the study showed changes in treated groups consisting of decreases in red blood cell counts, hemoglobin concentration and hematocrit that were not always dose-related or consistent among sexes and were within acceptable ranges for the rat (3M 1983).

Laboratory Animal Exposure Studies—PFOS. Treatment of male and female rats with approximately 1.5–1.8 mg/kg/day PFOS (potassium salt) in the diet for 4 weeks did not result in significant alterations in hematological parameters (Seacat et al. 2003). Dosing with 1.3–1.6 mg/kg/day for 14 weeks resulted in a significant increase (45%) in segmented neutrophiles (Seacat et al. 2003). The biological significance of this finding was not discussed by the investigators. In a 4-week study, administration of up to 2 mg/kg/day PFOS to Cynomolgus monkeys had no effect on hematological parameters (Thomford 2002a). In Cynomolgus monkeys dosed with 0, 0.03, 0.15, or 0.75 mg/kg/day PFOS (potassium salt) in a capsule for 26 weeks, and subjected to comprehensive hematological tests during the study, the only significant effect was a 9% decrease in hemoglobin in 0.75 mg/kg/day males at termination (Seacat et al. 2002). The investigators considered this a treatment-related effect, but not biologically significant given that the value was within the published range and there was no evidence of blood in the stools. No significant hematological effects were reported in a 2-year study in rats dosed with approximately 1.04 mg/kg/day PFOS in the diet (Butenhoff et al. 2012b; Thomford 2002b).

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. Administration of PFBA by gavage to rats in doses of up to 184 mg/kg/day for 5 days or up to 150 mg/kg/day for 28 days did not result in significant alterations in hematological parameters (3M 2007a; Butenhoff et al. 2012a; van Otterdijk 2007a). Doses of 30 mg/kg/day, but not 6 mg/kg/day, for 90 days resulted in significant reductions in red

blood cell counts, hemoglobin, and hematocrit, and an increase in red cell distribution width in male rats (Butenhoff et al. 2012a; van Otterdijk 2007b). This dose level also caused a reduction in mean corpuscular hemoglobin and reduced mean corpuscular hemoglobin concentration in male rats. The lower hemoglobin and hematocrit observed in males were still detected at the end of a 3-week recovery period. These hematological effects were considered minor and not evidence of an adverse effect on red blood cell turnover by the investigator based on lack of alterations in bone marrow or the spleen.

Treatment of male rats with doses ≥0.3 mg/kg/day PFHxS by gavage for at least 42 days significantly increased prothrombin time (Butenhoff et al. 2009a; Hoberman and York 2003). Doses ≥1 mg/kg/day significantly decreased hemoglobin concentration, whereas ≥3 mg/kg/day decreased erythrocyte count and hematocrit. Treatment of female rats with up to 10 mg/kg/day PFHxS did not significantly alter hematological parameters (Butenhoff et al. 2009a; Hoberman and York 2003). No significant hematological alterations were reported in rats dosed with up to 900 mg/kg/day PFBuS by gavage for 28 days (3M 2001). A 90-day exposure to PFBuS resulted in significant decreases in hemoglobin and hematocrit levels in males administered 200 or 600 mg/kg/day and a decrease in erythrocyte levels were observed in males administered 600 mg/kg/day; the NOAEL was 60 mg/kg/day (Lieder et al. 2009a).

Musculoskeletal Effects.

Human Exposure Studies. Two studies have examined the possible association between serum PFOA and PFOS levels and the risk of osteoarthritis; the possible mechanisms associated with these findings have not been elucidated. In a study of NHANES participants (2003–2008) aged 20–84 years (n=1,888 males and 1,921 females), the odds of self-reporting osteoarthritis were significantly higher in women with serum PFOA levels in the highest quartile (>5.88 ng/mL), as compared to women with serum PFOA levels in the first quartile (≤2.95 ng/mL) (adjusted OR 1.35, 95% CI 1.02–1.79) (Uhl et al. 2013). An elevated OR was also observed for women with serum PFOS in the fourth quartile (>20.97 ng/mL), but it was not statistically significant (adjusted OR 1.34, 95% CI 0.97–1.63). When males and females were combined, subjects with the highest PFOS levels had a significantly higher risk of osteoarthritis (adjusted OR 1.77, 95% CI 1.05–5.96). No significant associations between serum PFOA or PFOA and odds of osteoarthritis were found in males only. Innes et al. (2011) examined 49,432 male and female adult (3,731 subjects reporting physician-diagnosed osteoarthritis) participants in the C8 Health Project. After adjustment for potential confounders, the odds of a subject reporting osteoarthritis were significantly higher in subjects with serum PFOA levels in the fourth quartile (≥72.0 ng/mL) compared to subjects in the first quartile (0.25–13.5 ng/mL) (OR 1.42, 95% CI 1.26–1.59).

When segregated by age and BMI, there were stronger associations between serum PFOA levels and osteoarthritis in subjects under 55 years of age and in nonobese (BMI<30) subjects. In contrast to the serum PFOA findings, there was a lower risk of osteoarthritis in subjects with serum PFOS levels in the fourth quartile (≥29.4 ng/mL) compared to the first quartile (0.25–13.6 ng/mL) (OR 0.76, 95% CI 0.68–0.85).

Laboratory Animal Exposure Studies—PFOA. No gross or microscopic alterations were reported in the sternum from rats following dietary dosing with approximately 100–110 mg/kg/day APFO for 90 days (Griffith and Long 1980) or in the femur, sternum, and thigh skeletal muscle from Cynomolgus monkeys dosed with up to 20 mg/kg/day APFO in a capsule for 26 weeks (Butenhoff et al. 2002).

Laboratory Animal Exposure Studies—PFOS. Treatment of monkeys with up to 0.75 mg/kg/day PFOS (potassium salt) in a capsule for 26 weeks had no significant effect on the gross or microscopic appearance of the femur, sternum, or thigh skeletal muscle (Seacat et al. 2002). Similar observations were made in rats treated with up to 1.04 mg/kg/day PFOS in the diet for 2 years (Butenhoff et al. 2012b; Thomford 2002b).

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. PFBA administered to rats by gavage in doses of up to 184 mg/kg/day for 5 days did not induce morphological alterations in skeletal muscle (3M 2007a). Administration of 150 mg/kg/day PFBA for 28 days or 30 mg/kg/day for 90 days did not induce gross or microscopic alterations in bone (femur and sternum) or in skeletal muscle (Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b). Treatment of rats with up to 900 mg/kg/day PFBuS by gavage for 28 days or 90 days did not induce morphological alterations in skeletal muscle (3M 2001; Lieder et al. 2009a).

Hepatic Effects.

Human Exposure Studies. No evidence of adverse liver function (assessed via serum transaminases, alkaline phosphatase, or bilirubin) was observed among the 371 individuals with high levels of PFOA in the water supply and verified high serum PFOA levels evaluated by Emmett et al. (2006b). In 13 individuals with liver disease (information provided by the individuals), the mean serum PFOA was higher than in individuals without liver disease (527 vs. 441 ng/mL), but the difference was not statistically significant. A study of over 47,000 subjects enrolled in the C8 Health Project found a significant association between PFOA and PFOS and ALT levels and with direct bilirubin levels (direct

bilirubin levels were not significantly related to PFOA levels after adjustment for smoking status, BMI, physical activity, and insulin resistance) (Gallo et al. 2012). Additionally, the odds of having an abnormally high ALT value (≥45 IU/L in men and 34 IU/L in women) were significantly higher in subjects with serum PFOA levels in the third or higher decile and PFOS levels in the fifth or higher decile. In the fully adjusted model, there was a significant association between GGT values and serum PFOA levels; however, there was no exposure-related trend when serum PFOA levels were categorized by deciles. Lin et al. (2010) found significant trends for increasing serum ALT and GGT levels with increasing serum PFOA and PFOS levels in a general population study using the NHANES data set. Exposure-related trends were also observed for total bilirubin levels with serum PFHxS and PFNA levels. After adjusting for potential confounders, the association between serum PFOA and ALT and GGT remained statistically significant.

The possible associations between perfluoroalkyl exposure and serum lipids levels have been investigated in populations living near manufacturing facilities and in the general population. A study of 328 adults and 43 children living in a community serviced by the Little Hocking Water Authority with a median serum PFOA level of 354 ng/mL did not find a significant association between serum PFOA levels and total cholesterol levels (Emmett et al. 2006b). Similarly, Wang et al. (2012) found no associations between serum PFOA levels and total cholesterol, HDL-cholesterol, LDL-cholesterol, or triglycerides in a study of 132 adults living near a PFOA manufacturing facility in China; the mean serum PFOA level was 378.30 ng/mL. Neither study included an adjustment for the use of cholesterol-lowering medication. Three larger-scale studies of participants in the C8 Science Panel studies found significant associations between serum PFOA and PFOS levels and serum lipid levels (Fitz-Simon et al. 2013; Frisbee et al. 2010; Steenland et al. 2009b). Positive associations between serum PFOA and PFOS levels and total cholesterol and LDL-cholesterol were found in a study of over 12,000 children and adolescents; the respective mean serum PFOA and PFOS levels were 32.6 and 20.7 ng/mL in children (aged 1.0–11.9 years) and 26.3 and 19.3 ng/mL in adolescents (12.0–17.9 years) (Frisbee et al. 2010). Serum PFOA was also positively associated with triglyceride levels and serum PFOS was positively associated with HDL-cholesterol. Additionally, there was an increased risk of high cholesterol (≥170 mg/dL) in subjects with serum PFOA levels in the fourth or fifth quintiles; ORs of 1.2 (95% CI 1.1–1.4) and 1.2 (95% CI 1.1–1.4), respectively, and with serum PFOS levels in the second through fifth quintiles (ORs of 1.3 [95% CI 1.1–1.4], 1.3 [95% CI 1.2–1.5], 1.3 [95% CI 1.2–1.6], and 1.6 [95%CI 1.4–1.9], respectively). Increased odds of high LDL-cholesterol (≥110 mg/dL) were also observed for the fifth PFOA quintile (OR 1.4, 95% CI 1.2–1.7) and fourth and fifth PFOS quintiles (ORs of 1.3 (95% CI 1.1–1.6) and 1.6 (95% CI 1.3–1.9). The investigators noted that the dose-response relationship between serum PFOA

and serum lipids was nonlinear, with greater increases in lipids observed at the lower serum PFOA levels. Similar findings were reported in a study of >46,000 adults with a median serum PFOA level of 26.6 ng/mL and a median serum PFOS level of 19.6 ng/mL; the study excluded subjects who reported taking cholesterol-lowering medication (Steenland et al. 2009). Positive associations were found between serum PFOA levels and total cholesterol, LDL-cholesterol, and non-HDL cholesterol; a positive association between serum PFOA and triglycerides was also found. No significant associations between serum PFOA and PFOS levels and HDL-cholesterol levels were found. Increased risks of having high cholesterol (≥240 mg/dL) were found in subjects with serum PFOA levels in the second, third, and fourth quartiles (ORs 1.21 [95% CI 1.12–1.31], 1.33 [95% CI 1.23–1.43], and 1.38 [95% CI 1.25–1.50], respectively). Subjects with serum PFOS levels in the second, third, and fourth quartiles also has elevated risks of high cholesterol (ORs 1.14 [95% CI 1.05–1.23], 1.28 [95% CI 1.19–1.39], 1.51 [95% CI 1.40–1.64], respectively). The investigators noted that the odds of high cholesterol from the first quartile to the fifth quartile were approximately 40% for PFOA and 50% for PFOS, which may be important given that the Framingham study found that the risk of coronary heart disease was about 1.8 times higher in subjects with total cholesterol levels >240 mg/dL as compared to subjects with levels <200 mg/dL. Steenland et al. (2009b) also found a significant association between serum PFOA levels and total cholesterol levels in a study of 10,746 adults taking cholesterol-lowering medication; no consistent findings were identified for PFOS. Using both groups of subjects (taking or not taking cholesterol-lowering medication), the investigators analyzed whether taking cholesterol medication was associated with lower serum PFOA or PFOS levels, which may be indicative of reverse causality. Although serum PFOA levels were significantly lower in subjects taking cholesterol-lowering medication, the difference between the groups was low (4%); no differences in serum PFOS levels were found between the two groups.

In a longitudinal study by Fitz-Simon et al. (2013), 560 adults participating in the C8 Health Project and not taking cholesterol-lowering medication were examined twice, with an average of 4.4 years between examinations. Mean serum PFOA levels were 74.8 ng/mL at the first examination and 30.8 ng/mL at the second examination and serum PFOS levels were 18.5 and 8.2 ng/mL in the first and second examinations, respectively. In subjects whose serum PFOA levels halved between examinations, there was a 3.6% decrease in LDL-cholesterol levels and 1.7% decrease in total cholesterol levels. However, there were very small changes in LDL-cholesterol and total cholesterol levels in subjects whose serum PFOA levels decreased by >64% and there were slight increases in LDL-cholesterol and total cholesterol levels in subjects whose serum PFOA levels fell by <50%. For PFOS, halving the serum levels resulted in a 5.0% decrease in LDL-cholesterol and a 3.2% decrease in total cholesterol levels. Changes in PFOA or PFOS levels were not associated with changes in HDL-cholesterol or triglyceride levels.

General population studies were conducted in the United States, Canada, and Denmark. Using NHANES data for 860 adults not taking cholesterol-lowering medication (mean serum PFOA level of 4.6 ng/mL), there was a significant positive association between serum PFOA levels and non-HDL-cholesterol levels across PFOA quartiles; total cholesterol levels also increased with serum PFOA levels, but were not statistically associated (Nelson et al. 2010). Serum PFOS and PFNA levels (mean levels of 25.3 and 1.3 ng/mL, respectively) were also positively associated with total cholesterol and non-HDL-cholesterol levels. No associations were found for HDL-cholesterol or LDL-cholesterol levels with serum PFOA, PFOS, or PFNA levels. Serum PFHxS levels (mean level of 2.6 ng/mL) were negatively associated with a change in non-HDL-cholesterol levels across PFHxS quartiles and were not significantly associated with other serum lipid levels. No significant associations were found between HDL-cholesterol levels and serum PFOA, PFOS, PFHxS, or PFNA levels. Positive associations between serum PFOA and PFOS levels and total cholesterol levels were also found in a study of 753 Danish adults not taking cholesterol-lowering medication (mean serum PFOA and PFOS levels of 7.1 and 36.1 ng/mL, respectively) (Eriksen et al. 2013). No significant associations between serum PFOA or PFOS levels and total cholesterol, LDL-cholesterol, or non-HDL-cholesterol levels were found in 2,368 Canadian adults not taking cholesterol medication with a geometric mean serum PFOA level of 2.46 ng/mL and a PFOS level of 8.40 ng/mL (Fisher et al. 2013). The study did find positive associations between serum PFHxS levels (geometric mean level of 2.16 ng/mL) and total cholesterol, LDL-cholesterol, and non-HDL-cholesterol. Increased odds of having a high cholesterol level were also found for increasing PFHxS levels (OR 1.27, 95% CI 1.11–1.45). A study of 723 Inuit adults living in Nunavik, Canada with a high dietary exposure to n-3 polyunsaturated fatty acids found in traditional food items and not taking cholesterol lowering medication found linear trends for total cholesterol and HDL-cholesterol levels across serum PFOS quartiles (Château-Degat et al. 2010). Regression analysis showed a significant positive association between serum PFOS and HDL-cholesterol; serum PFOS level was also significantly associated with triglyceride levels, but only in females.

In summary, the available epidemiology data provide strong support for a positive association between serum PFOA and serum PFOS levels and total cholesterol and non-HDL-cholesterol, particularly LDL-cholesterol, in populations living near PFOA/PFOS facilities or the general population with mean or median serum PFOA levels >7 ng/mL and PFOS levels >20 ng/mL (Eriksen et al. 2010; Frisbee et al. 2010; Nelson et al. 2010; Steenland et al. 2009). However, in two studies of highly exposed populations (mean or median serum PFOA level >350 ng/mL), no association was found between serum PFOA and total cholesterol (Emmett et al. 2006b; Wang et al. 2012). It is not known if the conflicting result is due

to a nonlinear relationship between serum PFOA and total cholesterol levels, the low statistical power of the studies (328 and 132 adults), or the lack of adjustment for the use of cholesterol-lowering medication. Studies of the general population with lower serum PFOA levels (<5 ng/mL) or PFOS (<8 ng/mL) did not find significant alterations in serum lipid levels (Fisher et al. 2013; Nelson et al. 2010). Two studies of the C8 Health Project participants also found increased risk of high cholesterol levels in adults (Steenland et al. 2009b) or children and adolescents (Frisbee et al. 2010). The small number of studies examining possible associations between serum lipid levels and PFHxS (Fisher et al. 2013; Nelson et al. 2010) or PFNA (Nelson et al. 2010) levels preclude drawing conclusions about possible associations. Inconsistent results have been found for HDL-cholesterol. A positive association between serum PFOS and HDL-cholesterol was found in children and adolescents participating in the C8 Health Project studies (mean serum PFOS level of approximately 20 ng/mL) (Frisbee et al. 2010) and in a Canadian population with a mean serum PFOS level of 26 ng/mL (Château-Degat et al. 2010), but was not found in adult C8 participants with a mean serum PFOS level of 20 ng/mL (Steenland et al. 2009b). No studies have found associations between serum PFOA and HDL-cholesterol (Frisbee et al. 2010; Nelson et al. 2010; Steenland et al. 2009b).

Laboratory Animal Exposure Studies—PFOA. The liver is the main target organ for perfluoroalkyl compounds in animals following short- or long-term exposures. The hepatic response to exposure to many perfluoroalkyl compounds, particularly in rodents, is initiated by the activation of the nuclear hormone receptor, PPARα, which triggers a characteristic sequence of morphological and biochemical events characterized by liver hypertrophy and alteration of a wide range of enzymes, particularly those involved in lipid metabolism. It appears that PFOA can also damage the liver via a method independent of PPARα. The most sensitive liver effect observed in rats and mice after acute oral exposure to PFOA is an increase in liver weight (Cook et al. 1992; Eldasher et al. 2013; Haughom and Spydevold 1992; Ikeda et al. 1985; Iwai and Yamashita 2006; Kawashima et al. 1995; Kennedy 1987; Liu et al. 1996; Pastoor et al. 1987; Permadi et al. 1992, 1993; Qazi et al. 2012; White et al. 2009; Wolf et al. 2007, 2008; Xie et al. 2003; Yahia et al. 2010; Yang et al. 2001, 2002b). In rats administered 50 mg/kg/day PFOA for 1, 3, or 7 days, a 10% increase in liver weight was observed after the first dose; however, the relative liver weight was not significantly different from controls (Pastoor et al. 1987). After 3 days of exposure, the relative liver weight was significantly higher (36%) than controls. Similarly in mice, exposure to 390 mg/kg/day PFOA in the diet resulted in a significant increase in liver weight after 5 days of exposure, but not after 2 days of exposure (Permadi et al. 1992). The lowest LOAELs for increased relative liver weight in rats is 4.7 mg/kg/day in a 7-day study (Kawashima et al. 1995) and 2 mg/kg/day in a 14-day study (Liu et al. 1996); these studies also identified NOAELs of 2.4 and 0.2 mg/kg/day, respectively. In mice, the lowest

LOAEL for increases in liver weight was 1 mg/kg/day PFOA administered in the diet for 10 days (Yang et al. 2001) or administered via gavage for 7 days (Eldasher et al. 2013; Wolf et al. 2008). Pastoor et al. (1987) noted that administration of 50 mg/kg/day PFOA to rats for 7 days resulted in a 2-fold increase in absolute and relative liver weight, but no significant change in total deoxyribonucleic acid (DNA), indicating that the hepatomegaly represented hypertrophy rather than hyperplasia. Few acute-duration studies included histological examinations of the liver. Centrilobular and midzonal hypertrophy was observed in mice administered via gavage 1 or 3 mg/kg/day PFOA for 7 days; panlobular hypertrophy with cytoplasmic vacuolation was observed at 10 mg/kg/day (Wolf et al. 2008). Qazi et al. (2010) reported hepatocellular hypertrophy in mice exposed to 2.5 mg/kg/day PFOA in the diet for 10 days. Elcombe et al. (2010) reported hepatocellular hypertrophy in rats exposed to 18 mg/kg/day for 7 days, but not after 1 day of exposure. A related liver effect was the finding of reduced serum cholesterol and triacylglycerol levels in rats administered 16 mg/kg/day PFOA in the diet for 7 days (Haughom and Spydevold 1992) and decreases in serum cholesterol and triglyceride levels in rats administered via gavage 18 mg/kg/day for 7 days (Elcombe et al. 2010).

Similar to the acute-duration studies, intermediate-duration exposure to PFOA resulted in increases in absolute and relative liver weights in rats (Biegel et al. 2001; Butenhoff et al. 2004; Griffith and Long 1980; Perkins et al. 2004) and mice (Abbott et al. 2007; Ahmed and Abd Ellah 2012; Albrecht et al. 2013; Griffith and Long 1980; Kennedy 1987; Lau et al. 2006; Son et al. 2008; Wolf et al. 2007). The lowest dose resulting in increases in liver weight in rats was 0.96 mg/kg/day observed following gavage administration of APFO for 28 days (Loveless et al. 2008); the lowest dose in mice is 0.5 mg/kg/day observed in two 28-day studies using APFO (Kennedy 1987; Son et al. 2008). No significant alterations in liver weight were observed in rats administered 0.29 mg/kg/day for 28 days (Loveless et al. 2008) or in mice exposed to 0.2 mg/kg/day for 21 days (Kennedy 1987). Hepatocellular hypertrophy was the predominant histopathological alteration in rats (Cui et al. 2009; Griffith and Long 1980; Loveless et al. 2008; Perkins et al. 2004) and mice (Albrecht et al. 2013; Griffith and Long 1980; Loveless et al. 2008; Tan et al. 2013); the severity of the hypertrophy was dose-related (Loveless et al. 2008). At higher doses, focal necrosis was observed (29 mg/kg/day in rats and 0.96 mg/kg/day in mice exposed for 28 days) (Loveless et al. 2008). Fatty changes were observed in rats administered 20 mg/kg/day for 28 days (Cui et al. 2009) and mice administered 9.6 mg/kg/day (Loveless et al. 2008). No significant alterations in liver weight or histopathology were observed in rats allowed to recover for 8 weeks following a 13-week exposure to 0.6–6.5 mg/kg/day (Perkins et al. 2004). Intermediate-duration exposure to PFOA also resulted in decreases in serum HDL-cholesterol levels in rats and mice administered ≥0.29 or 0.96 mg/kg/day, respectively, for 28 days (Loveless et al. 2008). Serum cholesterol levels were decreased

in rats administered 0.29 or 0.96 mg/kg/day (no changes were observed at higher doses) and in mice administered 9.6 or 29 mg/kg/day (Loveless et al. 2008). Similarly, serum triglyceride levels were decreased in rats administered 0.29–9.6 mg/kg/day and in mice administered 9.6 or 29 mg/kg/day (Loveless et al. 2008).

Chronic exposure of rats to PFOA resulted in hepatomegalocytosis, hepatocellular necrosis, and portal mononuclear cell infiltration after a 1-year exposure to 15 mg/kg/day in the diet (3M 1983). A 2-year exposure to 15 mg/kg/day resulted in hepatomegalocytosis, cystoid degeneration, and portal mononuclear cell infiltration (3M 1983). The study also found significant increases in ALT and AST levels in male rats exposed to 1.5 mg/kg/day. A second chronic exposure study found significant increases in relative liver weight in rats exposed to 13.6 mg/kg/day in the diet for 2 years; no non-neoplastic lesions were noted in the liver (Biegel et al. 2001).

Studies in monkeys suggest that longer-term exposure may also result in liver toxicity. Significant increases in absolute and relative liver weight were observed in Cynomolgus monkeys exposed to 20/30 mg/kg/day administered via capsules for 26 weeks (Butenhoff et al. 2002). A significant increase in absolute, but not relative, liver weight was also observed in monkeys administered 3 or 10 mg/kg/day. However, no histological alterations were observed in the livers at the doses tested. Similarly, no histological alterations were observed in the livers of Cynomolgus monkeys administered via capsules 2 or 20 mg/kg/day for 30 days (Thomford 2001) or Rhesus monkeys administered via gavage 3 or 10 mg/kg/day for 90 days (Griffith and Long 1980). Significant increases in serum triglyceride levels were observed in the 10 and 20/30 mg/kg/day groups; the increases were statistically significant at only some of the time points (Butenhoff et al. 2002). At 10 mg/kg/day, increases in serum triglyceride levels at 4, 10, and 14 weeks of exposure were significantly higher than pre-treatment levels. Increases in cholesterol levels were only observed in the 20/30 mg/kg/day group after 13 weeks of exposure, but not after 26 weeks. No alterations in serum cholesterol or triglyceride levels were observed in the Thomford (2001) study.

Several studies have examined PPARα null mice to assess whether PFOA-induced liver effects can also occur via a mechanism not involving peroxisome proliferation. Similar to wild-type mice, exposure to PFOA resulted in significant increases in liver weight (Abbott et al. 2007; Minata et al. 2010; Wolf et al. 2008; Yang e al. 2002b). Abbott et al. (2007) found the effect level was slightly higher in PPARα null mice than wild-type mice (3 versus 1 mg/kg/day) following exposure on GDs 1–17. Wolf et al. (2008) and Minata et al. (2010) reported the same effect level (1 or 5 mg/kg/day, respectively) in PPARα null

mice and wild-type mice administered PFOA via gavage for 7 days or 4 weeks. Wolf et al. (2008) found dose-related increases in hepatocellular cytoplasmic vacuoles at ≥1 mg/kg/day and suggested that the increase in liver weight was due to the accumulation of PFOA in the hepatocytes rather than a toxic response. Unlike the Wolf et al. (2008) study, the Minata et al. (2010) 4-week study reported hepatocellular hypertrophy and microvesicular steatosis in the PPARα null mice (no incidence data were provided and it is unclear at what dose levels these effects were found); cytoplasmic vacuolation was also reported in the hepatocytes. The study also reported cholangiopathy in both the wild-type and PPARα null mice, but noted that the effect was more intensive in the PPARα null mice. Additionally, significant decreases in serum total cholesterol levels at 5.2 and 10.2 mg/kg/day and increases at 20.7 mg/kg/day were observed in the PPARα null mice; significant decreases in total cholesterol were observed in the wild-type mice at 10.2 and 20.7 mg/kg/day doses. Serum triglyceride levels were increased in both strains at 5.2 and 10.2 mg/kg/day doses and in the PPARα null mice at 20.7 mg/kg/day (Minata et al. 2010).

Laboratory Animal Exposure Studies—PFOS. Consistent with the results for PFOA, acute-duration oral exposure of rats to PFOS resulted in increases in liver weight (Elcombe et al. 2012b; Era et al. 2009; Haugham and Spydevold 1992), hepatocellular hypertrophy (Elcombe et al. 2012b), and decreases in serum cholesterol and/or triglyceride levels (Elcombe et al. 2012a, 2012b; Haughom and Spydevold 1992). The lowest adverse effect level for increased liver weight, hypertrophy, and decreased serum cholesterol was 1.79 mg/kg/day in rats exposed to PFOS in the diet for 7 days (Elcombe et al. 2012b); however, a similar study by this group did not find significant alterations in liver weight or ALT, AST, or serum cholesterol levels after 7 days of exposure to 1.72 mg/kg/day (Elcombe et al. 2012a). Likewise in mice, increases in liver weight (Fuentes et al. 2006; Qazi et al. 2009b, 2010a; Wan et al. 2011), hepatocellular hypertrophy (Qazi et al. 2010), and decreases in serum cholesterol levels (Qazi et al. 2010) were observed following acute exposure to PFOS. The lowest LOAEL for liver weight was 3 mg/kg/day in mice administered PFOS via gavage on GDs 6–18 (Fuentes et al. 2006); no effects were observed at 1.5 mg/kg/day. The only acute-duration mouse study that included histopathological examination of the liver and measurement of serum cholesterol levels identified a LOAEL of 8.5 mg/kg/day in mice exposed to PFOS in the diet for 10 days (Qazi et al. 2010).

Intermediate-duration exposure to PFOS resulted in increases in liver weight in rats (Cui et al. 2009; Curran et al. 2008; Elcombe et al. 2012a; Seacat et al. 2003; Thibodeaux et al. 2003) and mice (Thibodeaux et al. 2003; Wan et al. 2011; Yahia et al. 2008), hepatocellular hypertrophy in rats (Cui et al. 2009; Curran et al. 2008; Elcombe et al. 2012a; Seacat et al. 2003), and decreased serum cholesterol

levels in rats (Curran et al. 2008; Elcombe et al. 2012a; Luebker et al. 2005b; Seacat et al. 2003). The intermediate-duration mouse studies were designed to assess developmental or reproductive toxicity and did not include histopathological examination of the liver. The lowest adverse effect level for liver effects in rats was 0.14 mg/kg/day for a significant increase in relative liver weight in female, but not male, rats exposed to PFOS in the diet for 28 days (Curran et al. 2008). This study also found significant decreases in serum cholesterol levels and increases in absolute and relative liver weights in males and females at 2.98 mg/kg/day and hepatocellular hypertrophy at 5.89 mg/kg/day. Seacat et al. (2003) reported increases in liver weight, hepatocellular hypertrophy, and decreased serum cholesterol levels in rats following a 14-week dietary exposure to 1.33 mg/kg/day; however, no significant alterations in liver weight or liver histopathology were observed in rats exposed to 1.77 mg/kg/day PFOS in the diet for 4 weeks (Seacat et al. 2003). In contrast, Elcombe et al. (2012a) reported increases in liver weight, hepatocellular hypertrophy, and decreased serum cholesterol in rats exposed to 1.54 mg/kg/day PFOS in the diet for 28 days.

Data on the chronic toxicity of PFOS to the liver in rodents are limited to a study in rats (Butenhoff et al. 2012b; Thomford 2002b). Hepatotoxicity characterized by centrilobular hypertrophy, centrilobular eosinophilic hepatocytic granules, and centrilobular hepatocytic vacuolation was noted in rats exposed to 0.25 and 1.04 mg/kg/day PFOS in the diet for 2 years. At ≥0.1 mg/kg/day, significant increases in the incidences of eosiniphilic clear cell altered foci and cystic hepatocellular degeneration were observed in male rats. Observations made in a group of rats exposed to 1.17 mg/kg/day PFOS for 52 weeks and allowed to continue on the control diet for an additional year showed that hepatoxicity was not a persistent response, as hepatotoxicity was generally absent at the end of the recovery period. At termination, electron microscopy showed mild to moderate smooth endoplasmic reticulum hyperplasia and minimal to mild hepatocellular hypertrophy primarily in rats dosed with 1.5 mg/kg/day PFOS, the highest dose tested.

Treatment of Cynomolgus monkeys with up to 2 mg/kg/day PFOS in a capsule for 4 weeks did not induce gross or microscopic morphological alterations in the liver and did not increase cell proliferation (Thomford 2002a). In a 26-week study in Cynomolgus monkeys, exposure to 0.75 mg/kg/day PFOS, administered via a capsule, resulted in increased absolute liver weight after 183 days of treatment (Seacat et al. 2002). Significant decreases in serum total cholesterol were also observed at 0.75 mg/kg/day after 91, 153, and 182 days of exposure. On day 182, total cholesterol decreased to 35 and 53% of predosing values in males and females, respectively. The HDL-cholesterol levels were significantly lower in males at 0.03 and 0.75 mg/kg/day on days 153 and 182 and in females at 0.15 and 0.75 mg/kg/day on days 153

and 182; the lack of pre-treatment HDL-cholesterol measurements precludes within-group comparisons. Serum bilirubin was significantly lower in males at 0.75 mg/kg/day on days 91, 153, and 182. Light microscopy of liver sections showed centrilobular vacuolation, hypertrophy, and mild bile stasis in some monkeys exposed to 0.75 mg/kg/day. Electron microscopy showed lipid-droplet accumulation in some males and females exposed to 0.75 mg/kg/day. Increased glycogen content was also noted at this dose level. No histological alterations were observed in the livers of monkeys exposed to 0.75 mg/kg/day for 26 weeks and allowed to recover for 7 months or 1 year. Similarly, serum cholesterol returned to normal 36 days post exposure and HDL-cholesterol levels returned to normal after 61 days of recovery.

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. Considerably less information exists on liver effects in animals exposed orally to perfluoroalkyl compounds other than PFOA and PFOS. Treatment of rats with up to 184 mg/kg/day PFBA by gavage for 5 days did not affect liver weight, nor did it cause gross or microscopic morphological alterations in the liver (3M 2007a). In addition, clinical chemistry tests did not indicate altered liver function. Administration of approximately 20 mg/kg/day PFBA in the diet to male rats for 2 weeks did not significantly affect relative liver weight, but the same dose of PFOA induced a 45% increase in liver weight (Ikeda et al. 1985). Dietary administration of doses of approximately 78 mg/kg/day PFBA to male mice for 10 days induced a 63% increase in absolute liver weight (Permadi et al. 1992, 1993). PFBA intermediate-duration studies have consistently found increases in liver weight and histological alterations. Dosing rats with 30 mg/kg/day PFBA by gavage for 28 days resulted in a significant increase in absolute and relative liver weight; the NOAEL was 6 mg/kg/day (Butenhoff et al. 2012a; van Otterdijk 2007a); a decrease in serum cholesterol was also observed at 30 mg/kg/day. Administration of 150 mg/kg/day induced hepatocyte hypertrophy. These liver effects were no longer detected after a 21-day recovery period. In a similar 90-day study, administration of 30 mg/kg/day resulted in increased absolute liver weight and panlobular hepatocyte hypertrophy (Butenhoff et al. 2012a; van Otterdijk 2007b); no liver effects were observed at 6 mg/kg/day. None of the liver alterations were observed after a 21-day recovery period.

Administration of single gavage doses of ≥20 mg/kg PFDeA to female mice resulted in significant and dose-related increases in relative liver weight, assessed 30 days after dosing (Harris et al. 1989). All treated mice that survived until the end of the study (30 days) showed periportal to panlobular hepatocellular hypertrophy characterized by swollen hepatocytes with abundant granular eosinophilic cytoplasm and enlarged and hyperchromatic nuclei. Also present were bile duct hyperplasia and hepatocellular necrosis. Time course studies showed significant elevations in liver weight (69%) in mice 2 days after treatment with 40 mg/kg PFDeA (Brewster and Birnbaum 1989). An increase in liver weight

was also observed in mice exposed to 78 mg/kg/day PFDeA in the diet for 10 days (Permadi et al. 1992, 1993). Kawashima et al. (1995) reported increased liver weight in rats exposed to 2.4 mg/kg/day PFDeA in the diet for 1 week; no effects were observed at 1.2 mg/kg/day. The study also compared the effects of PFDeA (1.2–9.5 mg/kg/day) and PFOA (2.4–38 mg/kg/day) on the liver. PFDeA was considerably more potent than PFOA in causing hepatomegaly, but PFDeA was only 1.5 times more potent than PFOA in inducing biochemical markers of peroxisome proliferation. Both chemicals had comparable potencies in elevating hepatic cholesterol and triacylglycerol, but only PFOA elevated hepatic phospholipids. Electron microscopy showed that both compounds increased cell size and caused peroxisome proliferation, but 9.5 mg/kg/day PFDeA increased the number of lipid droplets containing amorphous material, indicating marked toxicity to hepatocytes.

Dosing of male Sprague-Dawley rats with 10 mg/kg/day PFDoA by gavage for 14 days induced a 35% increase in total serum cholesterol; doses of 1 or 5 mg/kg/day had no significant effect (Shi et al. 2007). In a subsequent study, the same group of investigators reported that in rats dosed with 1 or 5 mg/kg/day PFDoA, there was a trend for decreased serum triglycerides but the differences with controls were not statistically significant (Zhang et al. 2008). Liver triglycerides and liver cholesterol were not affected at these dose levels. Single doses of ≥1 mg/kg/day significantly induced the expression of PPARα and PPARγ and their target genes to enhance fatty acid β-oxidation. Absolute liver weight was significantly reduced in the 5 mg/kg/day group (19%) relative to controls, but this may have been due to a marked reduction in body weight (shown in Shi et al. [2007], but not in Zhang et al. [2008]).

Acute-duration studies with PFNA showed decreases in HDL-cholesterol levels in rats administered 1 mg/kg/day for 14 days (Fang et al. 2012a) and hepatocellular vacuolation at 5 mg/kg/day (Fang et al. 2012b). A third study reported an increase in liver weight in mice exposed to 0.5 mg/kg/day PFNA in the diet for 14 days (Kennedy 1987). An intermediate-duration study with PFHxS in rats reported that gavage doses ≥3 mg/kg/day induced a significant increase in absolute and relative liver weight in males (Butenhoff et al. 2009a; Hoberman and York 2003). Light microscopy revealed minimal to moderate enlargement of centrilobular hepatocytes. Clinical chemistry tests showed a significant decrease in serum cholesterol at ≥0.3 mg/kg/day and decreased serum triglycerides at 10 mg/kg/day. None of these alterations were observed in female rats. Treatment of male rats with 900 mg/kg/day PFBuS by gavage for 28 days induced a significant increase in absolute and relative liver weight (25–30%) relative to controls, which was no longer detected following a 14-day recovery period (3M 2001). Clinical chemistry tests of liver function were unremarkable and there were no chemical-related microscopic alterations. The NOAEL for liver weight effects was 300 mg/kg/day. No alterations in liver weight,

serum chemistry parameters (ALT, AST, cholesterol), or liver morphology were observed in rats administered doses as high as 600 mg/kg/day PFBuS for 90 days (Lieder et al. 2009a). Significant increases in liver weight were observed at 300 and 1,000 mg/kg/day in a 2-generation study (Lieder et al. 2009b); the alterations were only observed in male rats. An increase in hepatocellular hypertrophy was also observed in the male P0 and F1 rats administered 1,000 mg/kg/day.

Renal Effects.

Human Exposure Studies. Using the NHANES data for the 1999–2008 cycles, Shankar et al. (2011a) found a negative association between serum PFOA or PFOS levels and estimated glomerular filtration rate in adults. The likelihood of chronic kidney disease, defined as a glomerular filtration rate of <60 mL/minute/1.73 m^2, was significantly higher in adults with the highest serum PFOA (>5.9 ng/mL, OR 1.73, 95% CI 1.04–2.88) or PFOS (>29.5 ng/mL, OR 1.82, 95% CI 1.01–3.27) levels than in adults with serum PFOA or PFOS levels in the lowest quartile after adjustment for age, sex, race/ethnicity, educational level, smoking status, alcohol consumption, BMI, blood pressure, diabetes, serum total cholesterol level, and glycohemoglobin level. The study also investigated whether the association between serum PFOA and PFOS levels and chronic kidney disease was due to reverse causality (i.e., decreased glomerular filtration leads to a decrease in perfluoroalkyl filtration) and found a stronger negative correlation between estimated glomerular filtration rate and serum PFOA and PFOS levels in subjects without chronic kidney disease; suggesting that it was not due to reverse causality.

Emmett et al. (2006a) and Watkins et al. (2013) examined biomarkers of renal function in the community living near the DuPont West Virginia facility with high levels of PFOA in the water supply. Emmett et al. (2006a) did not find significant associations between BUN or serum creatinine levels and serum PFOA levels. An examination of 9,660 children aged 1–18 years found significant negative associations between serum PFOA, PFOS, PFNA, and PFHxS levels and estimated glomerular filtration rates (Watkins et al. 2013). Unlike Shankar et al. (2011a), Watkins et al. (2013) suggested that the association between serum perfluoroalkyl levels and estimated glomerular filtration rates may be a consequence of reverse causation because no significant associations were found between estimated serum PFOA levels 3 or 10 years prior to enrollment in the study or at the time of study enrollment and estimated glomerular filtration rates; predicted serum PFOA levels were based on environmental PFOA levels, self-reported residential history, and physiologically based pharmacokinetic (PBPK) modeling.

Laboratory Animal Exposure Studies—PFOA. Significantly elevated absolute and relative kidney weight was reported in male rats dosed with ≥3 mg/kg/day PFOA by gavage in water for 70 days (Butenhoff et al. 2004b), but histological evaluation of the kidney was not conducted in this study. Rats that received much higher doses (100–110 mg/kg/day) of APFO for 90 days in the diet showed no significant morphological alterations in the kidneys, and BUN and the urinalysis were unremarkable (Griffith and Long 1980). Also, male mice dosed with up to 47 mg/kg/day APFO in the drinking water for 21 days showed no morphological alterations in the kidneys and BUN and serum creatinine levels were not significantly effected (Son et al. 2008). Treatment of Cynomolgus monkeys with daily doses of up to 20 mg/kg/day APFO in a capsule for 26 weeks (Butenhoff et al. 2002) or Rhesus monkeys dosed with up to 10 mg/kg/day by gavage for 90 days (Griffith and Long 1980) did not cause morphological alterations in the kidneys, and blood chemistries and urinalyses provided no evidence of alterations in kidney function. In a 2-year dietary study in rats, relative kidney weight from males dosed with 15 mg/kg/day APFO was significantly elevated (14%) at the 1-year interim evaluation relative to controls, but gross and microscopic appearance (at 1 year and at termination), and BUN and urinalyses (several times during the study) were not significantly affected (3M 1983).

Laboratory Animal Exposure Studies—PFOS. No significant morphological alterations or clinical evidence of impaired kidney function was reported in male and female rats dosed with up to 1.77 mg/kg/day PFOS (potassium salt) (Seacat et al. 2003) or 5.89 mg/kg/day (Curran et al. 2008) for 4 weeks. Extending the treatment to 14 weeks resulted in an increase in BUN in male (23% increase) and female rats (41% increase), but histopathology of the kidneys and urinalyses were unremarkable (Seacat et al. 2003). The NOAEL values were 0.34 and 0.4 mg/kg/day in males and females, respectively. Treatment of Cynomolgus monkeys with up to 0.75 mg/kg/day PFOS (potassium salt) in a capsule for 26 weeks did not cause morphological alterations in the kidneys, nor did it affect BUN, serum creatinine, or urinary parameters (Seacat et al. 2002). Similar results were reported in a 4-week study in monkeys dosed with up to 2 mg/kg/day PFOS (Thomford 2002a). A mild increase in BUN was reported in rats treated with approximately 0.25 or 1.04 mg/kg/day PFOS in the diet for 53 weeks in a 2-year study (Butenhoff et al. 2012b; Thomford 2002b). However, there were no significant gross or microscopic alterations in the kidneys at week 53 or at termination.

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. No alterations in renal morphology or clinical indication of impaired renal function was reported in rats treated with PFBA in doses of up to 184 mg/kg/day for 5 days (3M 2007a), 150 mg/kg/day for 28 days (Butenhoff et al. 2012a; van Otterdijk 2007a), or 30 mg/kg/day by gavage for 90 days (Butenhoff et al. 2012a; van Otterdijk 2007b).

Male rats treated by gavage with 10 mg/kg/day PFHxS for at least 42 days showed a significant increase in BUN, but there were no significant gross or microscopic alterations in the kidneys (Butenhoff et al. 2009a; Hoberman and York 2003). The NOAEL was 3 mg/kg/day. No significant effect on BUN was reported in female rats. Treatment of female rats with 900 mg/kg/day PFBuS by gavage for 28 days caused a significant increase (9–11%) in absolute and relative kidney weight, but caused no significant alterations in the microscopic appearance of the kidneys (3M 2001). The weight of the kidneys returned to control levels following a recovery period of approximately 14 days; the NOAEL for kidney weight effects was 300 mg/kg/day PFBuS. In a 90-day rat study, PFBuS did not result in alterations in kidney weights, but did result in hyperplasia of the medullary and papillary tubular and ductal epithelial cells in the inner medullary region at 600 mg/kg/day, but not at 200 mg/kg/day (Lieder et al. 2009a). Minimal to moderate papillary epithelial tubular/acinar hyperplasia was also observed in a 2-generation rat study at 1,000 mg/kg/day; the study identified a NOAEL of 300 mg/kg/day (Lieder et al. 2009b).

Administration of a single dose of up to 80 mg/kg PFDeA to female C57BL/6N mice by gavage did not induce gross of microscopic changes in the kidneys (Harris et al. 1989). However, 2 out of 10 mice that died following administration of a dose of 320 mg/kg showed mild acute necrosis of the proximal convoluted tubules.

Endocrine Effects.

Human Exposure Studies. Serum level of TSH were not correlated with PFOA levels in the health evaluation of 371 individuals whose water supply had high levels of PFOA and whose mean serum PFOA levels were significantly higher than the general U.S. population (Emmett et al. 2006b). Separate analyses of adults and children (≤18 years old) did not change the results. In addition, study individuals with thyroid disease (information provided by the individual) had lower levels of PFOA (387 ng/mL) than individuals without thyroid disease (451 ng/mL), but the difference between the two groups was not statistically significant. Similarly, Ji et al. (2012) found no significant associations between serum PFOA, PFOS, PFHpS, PFHxS, PFNA, PFUA, and PFDoA and total T4 and TSH levels in a Korean general population study. A study of 31 New York sport fishermen also did not find significant associations between serum PFOA, PFOS, PFNA, PFHxS and PFDeA levels and free T4 and TSH levels (Bloom et al. 2010). As noted by the investigators, the study did not have sufficient power to detect statistically significant associations at the observed effect sizes. In contrast to these findings for T4 and TSH, Melzer et al. (2010) found significant associations among women participating in NHANES between having serum PFOA levels in the highest quartile (mean 9.47 ng/mL) and the likelihood of ever having thyroid

disease (OR 1.62, 95% CI 1.09–2.46) or current thyroid disease and taking related medication (OR 1.86, 95% CI 1.12–3.09), as compared to women in the first quartile. No significant associations between thyroid disease and serum PFOS levels were found in women (fourth quartile mean level 0.96 ng/mL). In men, there were also increases in the odds of thyroid disease when comparing men with serum PFOA levels in the fourth quartile (mean 10.39 ng/mL) to men with levels in the first and second quartiles; however, the increase was not statistically significant. A significant increase in the odds of currently having thyroid disease and taking medication was found in men with serum PFOS levels in the fourth quartile (mean 56.45 ng/mL), as compared to men in the first and second quartiles. A study of the Inuit population in Nunavik Canada (Dallaire et al. 2009) reported that serum PFOS levels were negatively associated with serum TSH, T3, and thyroxine-binding globulin (TBG) levels in adults. Significant positive associations were found between serum PFOS levels and free T4 levels. Given that most of the subjects (≥95%) had serum TSH, T4, and T3 levels within the normal range and the relative high geometric mean serum PFOS level (18.28 ng/mL) for the subjects, the associations may not be biologically relevant. In a study of pregnant women participating in the Norwegian Mother and Child Cohort Study, a significant association was found between serum PFOS levels and TSH levels after adjustment for potential confounders; no significant associations were found for other perfluoroalkyls examined including PFOA, PFHpS, PFHxS, and PFNA (Wang et al. 2013). When the TSH levels were dichotomized (≥7.5 vs <7.5 μIU/mL), there were no significant associations; additionally, there were no associations with self-reported thyroid abnormalities. A case-control study of pregnant women undergoing a prenatal screen for trisomy 18, Down's syndrome, and open spina bifida in Canada did not significant associations between serum PFOA, PFOS, or PFHxS and a higher risk of hypothyroxinemia (Chan et al. 2011). Similarly, Inoue et al. (2004b) did not find significant associations between maternal cord PFOS levels and infant TSH and free T4 levels. Based on the results of the studies of adolescents, adults, and pregnant women, exposure to serum perfluoroalkyls does not appear to result in thyroid toxicity.

No significant associations between serum PFOA levels and type II diabetes (self-reported and validated with medical records) were found in residents living near the Washington Works facility and participating in the C8 Health Project (MacNeil et al. 2009). Additionally, there was no exposure-response relationship between serum PFOA levels and fasting serum glucose levels. Three studies utilized NHANES data to evaluate the possible association between diabetes or glucose homeostasis and serum perfluoroalkyl levels. Melzer et al. (2010) did not find a significant association between self-reported diabetes and serum PFOA or PFOS levels in adult men and women. In adolescents (12–20 years of age), no significant associations between serum PFHxS, PFOA, or PFOS and blood glucose or insulin levels,

insulin resistance status (measured via homeostasis model assessment of insulin resistance), or β-cell function were found (Lin et al. 2009). A negative association between β-cell function and serum PFNA levels was found with adjustments for age, sex, race, smoking status, alcohol intake, household income, waist circumference, C-reactive protein levels and medication use; PFNA was not significantly associated with glucose or insulin levels, or insulin resistance status. In contrast, significant positive associations were found in adults (>20 years of age) between serum PFOA and insulin levels and β-cell function and serum PFOS and insulin levels, insulin resistance status, and β-cell function (Lin et al. 2009). No significant associations were found between these markers and serum PFNA or PFHxS levels in the adults. Nelson et al. (2010) also evaluated insulin resistance and found inconsistent results. Statistically significant ($p<0.05$) negative exposure-related trend was observed for PFHxS levels and insulin resistance in adolescent females (12–19 years of age) and a positive trend was observed for PFNA in females aged 20–59 years. A study of adults living in Canada did not find significant associations between serum PFOA, PFOS, or PFHxS levels and plasma insulin or glucose levels (Fisher et al. 2013). Overall, the studies in a highly exposed population and in the general population do not suggest an association between perfluoroalkyl exposure and alterations in glucose homeostasis or increased risk of diabetes. Although some significant associations have been found, they are not consistent across studies of similar populations.

Effects on the levels of hormones related to reproductive function are discussed in Section 3.2.2.5, Reproductive Effects.

Laboratory Animal Exposure Studies—PFOA. In a 2-generation study in rats, daily treatment of the parental generation with 0, 1, 3, 10, or 30 mg/kg/day APFO by gavage in water for 70–90 days produced an increased incidence of hypertrophy and/or vacuolation of the zona glomerulosa of the adrenal gland from high-dose males (Butenhoff et al. 2004b). The respective incidences were 0/10, 0/10, 0/10, 2/10, and 7/10. This effect was also observed in F1 generation males treated with the same dose level. No explanation was apparent for this finding. In rats dosed with up to 15 mg/kg/day APFO in the diet for 2 years, there were no significant morphological alterations in the adrenals (3M 1983). A study in monkeys treated with APFO also reported effects on the adrenal glands. Griffith and Long (1980) reported diffuse lipid depletion in the adrenals from Rhesus monkeys dosed daily for 90 days with 30 mg/kg/day APFO by gavage. This dose level was lethal to some monkeys; no such effect was seen in monkeys dosed with 10 mg/kg/day.

For the most part, morphological evaluations of other endocrine glands in animals treated with PFOA have been negative. For example, male and female rats dosed via the diet with approximately 100–110 mg/kg/day APFO for 90 days showed no gross or microscopic alterations in the pituitary and thyroid glands (Griffith and Long 1980). Similar observations were reported in the pituitary, thyroid, and parathyroid glands from male and female rats dosed with up to 15 mg/kg/day APFO in the diet for 2 years (3M 1983).

Administration of up to 20 mg/kg/day PFOA in a capsule to Cynomolgus monkeys for 4 weeks did not significantly alter free T4, total thyroxine, free T3, total trioodothyronine, or TSH (Thomford 2001). Serum T4 and total T4 were significantly reduced in Cynomolgus monkeys dosed with 10 mg/kg/day APFO in a capsule for up to 6 months, but were still within the normal range (Butenhoff et al. 2002). No significant changes were seen on serum free T3, total T3, or TSH, and thyroid histology was unremarkable.

Laboratory Animal Exposure Studies—PFOS. Chang et al. (2008b) conducted a study of thyroid function in rats exposed to PFOS (potassium salt). Administration of a single dose of 15 mg/kg by gavage in water (only dose level tested) reduced serum total T4 significantly at 2, 6, and 24 hours after dosing. This effect was attributed to a PFOS-induced transient increase in tissue availability of thyroid hormones and turnover of T4 with a resulting reduction in serum total T4. Chang et al. (2008b) concluded that PFOS did not induce a classical hypothyroid state or alter the hypothalamic-pituitary-thyroid axis. In another acute-duration study, dosing of pregnant mice with 6 mg/kg/day PFOS (potassium salt) on GDs 6–18 did not affect maternal serum levels of free or total T3 or T4 (Fuentes et al. 2006).

Changes in thyroid hormones have also been reported following intermediate-duration exposure to PFOS. For example, in a 2-generation gavage study in which dosing of rats started before mating and continued through gestation, doses of ≥0.4 mg/kg/day (the lowest dose tested) caused a significant and dose-related reduction in total T4 in maternal serum on postpartum day 5 (Luebker et al. 2005b). Free T4 and TSH were not significantly affected. Exposure of pregnant rats to ≥1 mg/kg/day PFOS on GDs 2–20 induced significant reductions in total T4 and free T4 and less marked reductions in T3 during pregnancy, particularly on GD 7 (Thibodeaux et al. 2003); however, serum TSH values were not significantly altered. A similar study in pregnant mice reported a decrease in total T4 on GD 6 in mice dosed with 20 mg/kg/day PFOS on GDs 1–17 (Thibodeaux et al. 2003). No alterations in total T4 were reported in mice dosed with 15 mg/kg/day. No information was provided regarding other thyroid hormones.

Decreases in T4 levels were observed in male and female rats exposed to PFOS in the diet for 28 days (Curran et al. 2008); T3 levels were decreased in female rats exposed to 50 or 100 mg/kg/day and in male rats at 100 mg/kg/day. No histological alterations were observed in the thyroid. Another study with PFOS found no thyroid histological effects in rats exposed to 10.3 mg/kg/day for 1 day, 8.17 mg/kg/day for 7 days, or 7.34 mg/kg/day for 28 days (Elcombe et al. 2012a). Exposure of rats to ≥0.27 mg/kg/day PFOS in drinking water for 91 days resulted in decreases in total T4 levels (Yu et al. 2009a), but no changes in T3 or TSH levels (highest dose tested was 2.37 mg/kg/day). Curran et al. (2007) suggested that the apparent decreases in T4 levels, in the absence of TSH alterations and histological alterations in the thyroid may be a result of measurement error when analog assays (chemiluminometric immunoassay and radioimmunoassay) are used due to binding interference. In a study in Cynomolgus monkeys, T3 was numerically lower than controls in one female and one male monkey dosed with 2 mg/kg/day PFOS by capsule for 4 weeks (Thomford 2002a). However, it is difficult to determine whether the effect was treatment-related based on only two animals. In a 26-week study in Cynomolgus monkeys, the highest dose of PFOS tested, 0.75 mg/kg/day, induced a significant increase in serum TSH (approximately twice control value, but still within the reference range) and a decrease in total T3 at termination, but not at earlier time points; variations in other thyroid hormones, including T4, were inconsistent regarding dose and over time (Seacat et al. 2002). The clinical relevance of the lowered total T3 values was not apparent since there was no indication of a clinical hypothyroid response and thyroid histology was not altered by treatment with PFOS.

Examination of the adrenal glands from rats dosed with up to 1.77 mg/kg/day PFOS via the diet for 4 or 14 weeks did not show any significant gross or microscopic alterations (Seacat et al. 2003). No significant gross or microscopic lesions were reported in the adrenals, thyroid and parathyroid, or pituitary gland from rats dosed with up to 1.04 mg/kg/day PFOS in the diet for 2 years (Butenhoff et al. 2012b; Thomford 2002b).

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. Treatment of rats with up to 184 mg/kg/day PFBA by gavage for 5 days did not affect the gross or microscopic morphology of the adrenal, thyroid, or pituitary glands (3M 2007a). Treatment with ≥30 mg/kg/day for 28 or 90 days significantly increased the incidence of hyperplasia/hypertrophy of the follicular epithelium of the thyroid gland (Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b). These changes were not observed following a 3-week recovery period. Van Otterdijk (2007a, 2007b; Butenhoff et al. 2012a) suggested that the thyroid lesion likely reflected an increase in thyroxine producing follicular cells in response to feedback

mechanisms from the increase turnover of thyroxine by the hypertrophic hepatocytes. None of these studies measured thyroid hormones or TSH in serum.

Changes in the thyroid similar to those reported for PFBA by van Otterdijk (2007b; Butenhoff et al. 2012a) were reported in male rats treated with ≥3 mg/kg/day PFHxS for at least 42 days (Butenhoff et al. 2009a; Hoberman and York 2003). The NOAEL was 1 mg/kg/day. The investigators noted that the observed changes in rats are consistent with the known effects of inducers of microsomal enzymes where the hepatocellular hypertrophy results in a compensatory hypertrophy and hyperplasia of the thyroid due to an increase plasma turnover of thyroxine and associated stimulation of TSH. Neither thyroid hormones nor TSH were measured in the study. Treatment of rats with up to 900 mg/kg/day PFBuS by gavage for 28 days did not alter the gross or microscopic appearance of the adrenal, pituitary, or thyroid/parathyroid glands (3M 2001). Levels of thyroid hormones in serum were not available in this study.

Administration of a single dose of 80 mg/kg PFDeA to female C57BL/6N mice by gavage resulted in 2- and 4-fold increases in serum T3 and T4, respectively, relative to controls 30 days after dosing (Harris et al. 1989).

Dermal Effects.

Laboratory Animal Exposure Studies—PFOA. The only information available in animals on dermal toxicity following oral exposure is that exposure of rats to up approximately 100–110 mg/kg/day APFO via the diet for 90 days did not induce gross or microscopic alterations in the skin (Griffith and Long 1980). Similar results were reported in monkeys exposed to up to 20 mg/kg/day PFOA or 0.75 mg/kg/day PFOS for 26 weeks (Butenhoff et al. 2002; Seacat et al. 2002).

Laboratory Animal Exposure Studies—PFOS. Administration of up to approximately 1.04 mg/kg/day PFOS to rats in the diet for 2 years did not induce morphological alterations in the skin (Butenhoff et al. 2012b; Thomford 2002b).

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. There were no significant gross or microscopic alterations in the skin of rats treated with up to 150 mg/kg/day PFBA for 28 days or 30 mg/kg/day PFBA for 90 days (Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b).

Ocular Effects.

Laboratory Animal Exposure Studies—PFOA. Examination of the eyes from rats fed a diet that provided approximately 100–110 mg/kg/day APFO for 90 days did not reveal any significant gross or microscopic alterations (Griffith and Long 1980). Similar results were reported in rats that received dietary doses up to 15 mg/kg/day APFO for 2 years (3M 1983) and in monkeys dosed with up to 20 mg/kg/day APFO for 26 weeks (Butenhoff et al. 2002).

Laboratory Animal Exposure Studies—PFOS. No gross or microscopic alterations were observed in the eyes from rats exposed through the diet to up to 1.77 mg/kg/day PFOS in the diet for 4 weeks or up to 1.56 mg/kg/day for 14 weeks (Seacat et al. 2003). Similar findings were reported in monkeys dosed daily with up to 2 mg/kg/day PFOS in a capsule for 4 weeks (Thomford 2002a), or up to 0.75 mg/kg/day PFOS in a capsule for 26 weeks (Seacat et al. 2002), or in rats dosed with up to 1.04 mg/kg/day in the diet for 2 years (Butenhoff et al. 2012b; Thomford 2002b).

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. Examination of the eyes of rats treated with up to 150 mg/kg/day PFBA for 28 days or 30 mg/kg/day for 90 days did not reveal any significant alterations (Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b). Gross and microscopic examinations of the eyes of rats treated with up to 900 mg/kg/day PFBuS for 28 days were unremarkable (3M 2001).

Body Weight Effects.

Laboratory Animal Exposure Studies—PFOA. Reductions in body weight or body weight gain are typical, although not particularly sensitive, responses of rodents to exposure to perfluoroalkyl compounds. In many cases, this effect is not associated with reduced food intake, and in some cases, exposed animal have shown an increase in relative food consumption (grams of food/grams of body weight) relative to controls. For example, in acute-duration studies, rats administered 25 mg/kg/day APFO for 14 days had a mean terminal body weight 14% lower than controls (Cook et al. 1992). Administration of 50 mg/kg/day APFO for 7 days resulted in 17% weight loss, a similar decrease was observed in a pair-fed group (Pastoor et al. 1987). In mice, doses of approximately 25–30 mg/kg/day PFOA in the food for 7 days reduced terminal body weight by >10% relative to controls without a significant reduction in food intake (Xie et al. 2003; Yang et al. 2000, 2002a, 2002b). However, administration of the same dose to PPARα-null mice did not cause a reduction in weight gain, suggesting that the effect on body weight is a specific effect of peroxisome proliferators possibly due to increased fat utilization (Yang et al. 2002b). In general, body weight recovered once treatment ceased.

Intermediate-duration oral studies in rats have also reported reduced body weight gain with doses ≥10 mg/kg/day APFO (Butenhoff et al. 2004b; Griffith and Long 1980). In the former study, mean absolute food consumption was decreased, but mean relative food consumption was increased. In a 2-year bioassay, body weight gain in rats dosed with 15 mg/kg/day PFOA was reduced >10% relative to controls at the 1 year mark and at termination (Biegel et al. 2001). Similar observations have been made in mice dosed with approximately ≥18 mg/kg/day APFO for 28 days (Griffith and Long 1980) and in pregnant mice dosed during GDs 1–17 with ≥10 mg/kg/day APFO (Lau et al. 2006). A 90-day and a 26-week study in monkeys also reported significant reductions in body weight gain or weight loss associated with decreased food consumption at dose levels in the range of 20–30 mg/kg/day APFO (Butenhoff et al. 2002; Griffith and Long 1980), but a 4-week study in monkeys dosed with 20 mg/kg/day PFOA did not (Thomford 2001).

Laboratory Animal Exposure Studies—PFOS. Dietary treatment of rats with 15 mg/kg/day PFOS (only dose level tested) for 7 days did not significantly alter body weight (Haughom and Spydevold 1992). Treatment of pregnant rats with 25 mg/kg/day PFOS on GDs 2–5 or 6–9 resulted in weight loss during treatment, whereas treatment on GDs 10–13, 14–17, or 17–20 results in significant reductions in weight gain (Grasty et al. 2003). In pregnant mice, dosing with up to 6 mg/kg/day PFOS on GDs 6–18 or 12–18 did not significantly affect body weight (Fuentes et al. 2006, 2007a, 2007b). Pregnant rabbits appeared to be more sensitive as doses of 1 mg/kg/day on GDs 6–20 caused a 21% reduction in weight gain during treatment without altering food consumption (Case et al. 2001).

Reductions in body weight gain of >10% have been reported in intermediate-duration studies in rats dosed with ≥2 mg/kg/day PFOS associated with reductions in mean absolute and relative food consumption (Luebker et al. 2005a, 2005b). In a developmental toxicity study, treatment of pregnant rats with ≥2 mg/kg/day PFOS on GDs 2–20 resulted in significant reductions in body weight gain, which were associated with significant reductions in mean absolute food and water consumption (Thibodeaux et al. 2003). In a 4-week study, treatment of Cynomolgus monkeys with up to 2 mg/kg/day in a capsule did not affect body weight gain (Thomford 2002a). In a 26-week study in Cynomolgus monkeys, the highest dose of PFOS tested, 0.75 mg/kg/day, produced a 13.5% reduction in final body weight, at which time the mean concentration of PFOS in serum was 172 µg/mL (Seacat et al. 2002). In a 2-year dietary study in rats, final mean body weight of females that received doses of approximately 1.04 mg/kg/day PFOS was 14% lower than controls; this could have been due, in part, to a tendency of decreased food consumption

during weeks 28 through 104 of the study (Butenhoff et al. 2012b; Thomford 2002b). No significant effect (<10% difference with controls) was seen in females dosed with ≤0.25 mg/kg/day PFOS.

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. Information for other perfluoroalkyl compounds discussed in this document is limited. For example, dosing of male C57BL/6 mice with approximately 78 mg/kg/day PFBA via the diet for 10 days did not significantly alter body weight compared to *ad libitum* controls, but the same dose of PFOA or PFDeA caused 13 and 33% reductions in body weight, respectively (Permadi et al. 1992). Dosing with 184 mg/kg/day PFBA for 5 days also did not affect body weight (3M 2007a). Similar findings were reported in rats dosed with 150 mg/kg/day PFBA for 28 days or 30 mg/kg/day PFBA for 90 days (Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b).

Treatment of rats with up to 10 mg/kg/day PFHxS by gavage for 40–60 days did not significantly affect body weight (Butenhoff et al. 2009a; Hoberman and York 2003). Mean terminal body weights were within 10% of the body weight of a control group. Food consumption was not affected by treatment with PFHxS. Similar results were reported in rats administered up to 900 mg/kg/day PFBuS by gavage for 28 days (3M 2001).

Dosing of Sprague-Dawley rats with 5 mg/kg/day PFDoA by gavage for 14 days resulted in a 25% reduction in final body weight relative to a control group or 7% loss of body weight compared with the starting body weight (Shi et al. 2007). Body weight of female C57BL/6N mice administered a single gavage dose of 80 mg/kg PFDeA was reduced 12% relative to controls 30 days after dosing (Harris et al. 1989); no significant effect was seen at 40 mg/kg PFDeA. In a developmental study, pregnant mice dosed with 6.4 mg/kg/day PFDeA on GDs 6–15 gained 92% less weight (adjusted weight) on GDs 6–18 than controls; mice dosed with 12.8 mg/kg/day lost weight (Harris et al. 1989). Food consumption data were not provided in any of these studies.

Other Effects.

Human Exposure Studies. There is some epidemiological evidence that an elevated uric acid level is a risk factor for hypertension and renal disease (Johnson et al. 2003; Sündstrom et al. 2005). Associations between serum PFOA and/or PFOS levels and uric acid levels have been reported in a study of highly exposed residents and in the general population. Steenland et al. (2010b) measured uric acid levels in 54,951 adults (≥20 years of age) participating in the C8 Health Project as a risk factor for hypertension

and possibly other cardiovascular effects. The mean serum PFOA and PFOS concentrations were 86.4 and 23.4 ng/mL, respectively. Positive linear trends between serum uric acid levels and serum PFOA and PFOS levels were found. When the subjects were categorized by PFOA or PFOS levels, significantly increased risks of hyperuricemia (>6.0 mg/dL for women, >6.8 mg/dL for men) were observed for subjects with serum PFOA levels in the second, third, fourth, and fifth quintiles (≥11.5 ng/mL) (ORs 1.33 [95% CI 1.24–1.43], 1.11 [95% CI 1.04–1.20], 1.19 [95% CI 1.11–1.27], and 1.26 [95% CI 1.17–1.35], respectively] after adjustment for covariates including age, sex, BMI, smoking status, and alcohol consumption. Similarly, hyperuricemia were observed in subjects with PFOS levels in the third, fourth, and fifth quintiles (≥17.5 ng/mL) (ORs 1.11 [95% CI 1.04–1.20], 1.19 [95% CI 1.11–1.27], and 1.26 [95% CI 1.17–1.35], respectively).

Using the NHANES dataset for 3,883 adults (≥20 years of age), Shankar et al. (2011b) found significant associations between serum PFOA and PFOS levels and serum uric acid levels. After adjusting for multivariates (including age, smoking status, alcohol consumption, BMI, diabetes, hypertension, and total cholesterol levels), significant risks of hyperuricemia were observed in subjects with serum PFOA levels in the third and fourth quartiles (≥3.5 ng/mL in men and 4.6 ng/mL in women) (ORs 1.90 [95% CI 1.35–2.69] and 1.97 [95% CI 1.44–2.70], respectively] and with serum PFOS levels in the second and third quartiles (≥11.2 ng/mL in men and ≥17.5 ng/mL in women) (ORs 1.69 [95% CI 1.19–2.40] and 1.69 [95% CI 1.19–2.40]; the OR for the fourth quartile was 1.48 [95% CI 0.99–2.22]).

Geiger et al. (2013) also used the NHANES data set to examine the possible association between serum perfluoroalkyl levels and risk of hyperuricemia, defined as serum uric acid levels ≥6 mg/dL, in children aged 12–18 years. A significant positive association between serum PFOA and serum uric acid levels was found; the association between serum PFOS and uric acid levels was not significant after adjustments for age, sex race/ethnicity, BMI, annual household income, activity level, total cholesterol level, and serum cotinine levels. The likelihood of hyperuricemia was significantly higher in children with serum PFOA or PFOS levels in the fourth quartile (OR 1.62, 95% CI 1.10–2.37 and OR 1.65, 95% CI 1.10–2.49, respectively).

3.2.2.3 Immunological and Lymphoreticular Effects

Human Exposure Studies. The possible association between elevated serum PFOA levels and the occurrence of autoimmune diseases were examined in a cohort of 28,541 adults living or working in a community with elevated PFOA levels in the water (C8 Health Project participants) and 3,713 past and

current workers at a nearby DuPont facility (Steenland et al. 2013). A significant association between the likelihood of ulcerative colitis and serum PFOA levels was found; ORs were significantly higher for subjects with estimated annual serum PFOA levels in the three highest quartiles, as compared to the first quartile. No other significant associations between serum PFOA levels and autoimmune disease (e.g., Crohn's disease, rheumatoid arthritis, type-1 diabetes, lupus, and multiple sclerosis) were found. Another study of the C8 Health Project participants examined 411 adults who received an influenza vaccination; the geometric mean serum PFOA and PFOS concentrations were 33.74 and 8.32 ng/mL, respectively (Looker et al. 2014). A reduced antibody response to one of the three flu strain (A/H3N2) influenza vaccinations was found at higher serum PFOA concentrations; the altered response could result in an increased risk of not attaining the antibody threshold considered to offer long-term protection from this virus strain. There were no consistent alterations for the other virus strains (A/H1N1 or flu B). The study also found no associations between serum PFOA or PFOS levels and self-reported frequency of colds or flu. Grandjean and associates examined the possible association between serum antibody concentrations of tetanus and diphtheria toxoids in children living in the Faroe Islands (measured at 5 and 7 years of age) and serum perfluoroalkyl concentrations (measured at 5 years of age). Negative associations between antibody concentrations and PFOS, PFOA, PFHxS, PFNA, and PFDeA levels were found; the strongest associations were with PFOA and PFOS (Grandjean et al. 2012). Multiple regression analysis predicted that a 2-fold increase in serum PFOA levels could result in 36 and 25% decreases in tetanus and diphtheria antibody levels, respectively, at 7 years of age. Similarly, a 2-fold increase in serum PFOS could result in 24 and 28% decreases in tetanus and diphtheria antibody levels, respectively (Grandjean et al. 2012). A subsequent paper examined the dose-response relationship using benchmark dose (BMD) analysis (Grandjean and Budtz-Jørgensen 2013). Although the investigators reported BMDL values of 1.3 ng/mL for serum PFOS and 0.3 ng/mL for serum PFOA, they did not provide sufficient information regarding model fit, and although they noted that a benchmark response of 5% was used, they did not indicate that a control group was used. Similarly, Granum et al. (2013) examined possible associations between pediatric vaccine antibody levels in children 3 years of age and maternal serum PFOA, PFOS, PFNA, and PFHxS levels. Of the four vaccine antibody levels examined (rubella, measles, haemophilus influenza type b, and tetanus), the only statistically significant associations were with rubella. Negative associations were found for rubella vaccine antibody levels and maternal serum PFOA, PFOS, PFNA, and PFHxS levels. The study also examined whether there was an association between maternal perfluoroalkyl levels and the incidence of infectious disease in the children (Granum et al. 2013). Positive associations were found between serum PFOA and PFNA levels and the number of episodes of common colds in children aged 1–3 years, but when the data over the 3 years were dichotomized, there were no significant associations.

Laboratory Animal Exposure Studies—PFOA. The immunotoxicity of perfluoroalkyls has been investigated in several animal species. The available data do not suggest that PFOA is immunotoxic in rats or monkeys. Exposure of male rats to 50 mg/kg/day PFOA by gavage for 14 days did not significantly affect the absolute or relative spleen weight nor did it alter lymphocyte subsets or the numbers of T cells, natural killer (NK) cells, or helper T cells (Iwai and Yamashita 2006). Intermediate-duration studies did not find morphological alterations in lymphoreticular organs from rats dosed with approximately 110 mg/kg/day PFOS (Griffith and Long 1980) and similar results were reported in a 2-year study in rats dosed with up to 15 mg/kg/day PFOA (3M 1983). No alterations in the number of splenic or thymic lymphocytes, morphology of the spleen or thymus, or the response to sheep red blood cells were observed in rats administered 29 mg/kg/day PFOA by gavage for 28 days (Loveless et al. 2008). Dosing of Cynomolgus monkeys with up to approximately 20 mg/kg/day PFOA in a capsule for 4 or 26 weeks did not affect the gross or microscopic morphology of the spleen (Butenhoff et al. 2002; Thomford 2001). Dosing of Rhesus monkeys with 30 mg/kg/day PFOA by gavage for 90 days induced atrophy of lymphoid follicles in the spleen and lymph nodes and slight to moderate hypocellularity of the bone marrow (Griffith and Long 1980).

In contrast, immune effects have been observed in mice following acute- or intermediate-duration perfluoroalkyl exposure. In the spleen and thymus, exposure to PFOA resulted in decreases in organ weight, decreases in the number of cells, and/or atrophy (DeWitt et al. 2008; Loveless et al. 2008; Qazi et al. 2009b, 2012; Son et al. 2009; Yang et al. 2000, 2001, 2002b). Acute exposure resulted in decreases in absolute thymus weight at 11.5 mg/kg/day (Yang et al. 2001), decreases in spleen weight at 30 mg/kg/day (Qazi et al. 2012; Yang et al. 2000), and severe thymic atrophy at 30 mg/kg/day (Qazi et al. 2012; Yang et al. 2000). Exposure of mice to approximately 40 mg/kg/day PFOA for 10 days resulted in alterations in innate immunity; marked decreases in total leukocytes, lymphocytes, and neutrophils and increases in tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were observed in cells from the peritoneal cavity, bone marrow, and spleen in response to lipopolysaccharide (LPS) stimulation (Qazi et al. 2009a). A 10-day exposure to PFOA at 3.0 mg/kg/day also resulted in decreases in number of bone marrow B-lymphoid cells (Qazi et al. 2012); a decrease in bone marrow myeloid cells was also observed at 30 mg/kg/day. Examination of the B-lymphoid cell subpopulations showed decreases in pro/pre B cells, immature B cells, and early mature B cells, with the greatest reductions observed for pro/pre B cells. When mice were allowed to recover for 10 days following a 10-day exposure to 30 mg/kg/day PFOA in the diet, only a partial recovery of B-lymphoid cells was observed.

The lowest-adverse-effect levels for spleen and thymus effects identified in intermediate studies were 3.75 mg/kg/day PFOA for decreases in absolute spleen weight (DeWitt et al. 2008), 9.6 mg/kg/day for decreases in absolute and relative thymus weight, thymic depletion/atrophy, and decreased number of thymocytes and splenocytes (Loveless et al. 2008), and 29 mg/kg/day for splenic atrophy (Loveless et al. 2008). Splenic lymphocyte phenotyping demonstrated decreases in CD4+ and CD8+ lymphocytes. Several studies have demonstrated an impaired response to T-dependent antigens, such as sheep red blood cells (DeWitt et al. 2008, 2009; Loveless et al. 2008; Yang et al. 2002a); the lowest-adverse-effect level was 3.75 mg/kg/day (DeWitt et al. 2008). Tests for delayed-type hypersensitivity response in mice challenged with bovine serum albumin were negative (DeWitt et al. 2008).

A study in wild-type mice and PPARα-null mice demonstrates that PFOA-induced immunomodulation results from PPARα-dependent and -independent mechanisms (Yang et al. 2002b). A 7-day exposure to 33 mg/kg/day PFOA resulted in decreases in spleen weight, thymus weight, number of splenocytes, number of thymocytes, and CD4+ and CD8+ splenic and thymic lymphocytes in wild-type mice. However similar exposure of PPARα knockout mice did not result in alterations in spleen weight, number of splenocytes, or their phenotypes. Although decreases in thymus weight, number of thymocytes, and their phenotypes were observed in the knockout mice, the magnitudes of the changes were significantly lower in the knockout mice.

Laboratory Animal Exposure Studies—PFOS. Similar to PFOA, mice appear to be more sensitive than other species to the immunotoxicity of PFOS. Rats treated with 1.77 mg/kg/day PFOS for 4 weeks, 6.34 mg/kg/day for 28 days, 1.56 mg/kg/day for 14 weeks, or 1.04 mg/kg/day for 2 years did not show significant morphological alterations in the spleen, thymus, and mesenteric lymph nodes (Butenhoff et al. 2012b; Lefebvre et al. 2008; Seacat et al. 2003; Thomford 2002b). Similar findings were reported in Cynomolgus monkeys dosed with up to 2 mg/kg/day for 4 weeks or up to 0.75 mg/kg/day PFOS for 26 weeks (Seacat et al. 2002; Thomford 2002a).

No alterations in spleen or thymus weights were observed in mice exposed to 0.025 mg/kg/day PFOS (Guruge et al. 2009); at a higher dose (0.42 mg/kg/day), significant decreases in relative spleen and thymus weights were observed (Dong et al. 2009; Zheng et al. 2009). Decreases in splenic and thymic cellularity were also observed at ≥0.42 mg/kg/day PFOS (Dong et al. 2009; Qazi et al. 2009b, 2012; Zheng et al. 2009). Bone marrow cells (B-lymphoid and myeloid cells) were also significantly decreased in mice exposed to 30 mg/kg/day PFOS for 10 days (Qazi et al. 2012). Within the B-lympoid cell population, there were decreases in the number of pro/pre B cells and immature cells (Qazi et al. 2012). Significant

alterations in all splenic T cell CD4 and CD8 subpopulations were observed at ≥0.00331 mg/kg/day PFOS (Peden-Adams et al. 2008) and thymic lymphocyte phenotypes were altered at 0.42 mg/kg/day PFOS (Dong et al. 2009). At lower PFOS doses (0.0166–0.083 mg/kg/day), increases in NK cell activity has been observed (Dong et al. 2009; Peden-Adams et al. 2008); however, decreases in NK cell activity were observed were observed at higher doses (0.83–2.08 mg/kg/day) (Dong et al. 2009). Several studies have found an impaired response to sheep red blood cells (Dong et al. 2009, 2011; Peden-Adams et al. 2008; Zheng et al. 2009). Dong et al. (2009, 2011) identified a LOAEL of 0.083 mg/kg/day in mice exposed to PFOS for 60 days; the highest NOAEL was 0.0167 mg/kg/day. Peden-Adams et al. (2008) reported a significant suppression of the response to sheep red blood cells at 0.00166 mg/kg/day (NOAEL of 0.000166 mg/kg/day) in mice exposed for 28 days. It is unclear why the two studies found greatly different results. An impaired response to an influenza A virus challenge was also observed in mice exposed to 0.025 mg/kg/day for 21 days (Guruge et al. 2009). Qazi et al. (2009a) reported several alterations in parameters associated with the innate immune system in mice exposed to approximately 40 mg/kg/day PFOS in the diet for 10 days. These alterations included marked decreases in total leukocyte and lymphocyte levels and increases in TNF-α and IL-6 levels in the peritoneal cavity and bone marrow in response to LPS stimulation; no alterations were observed in mice exposed to a 20-fold lower dose.

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. No significant gross or microscopic alterations were reported in the spleen, thymus, or mesenteric lymph nodes from rats dosed with PFBA by gavage in doses of up to 184 mg/kg/day for 5 days, 150 mg/kg/day for 28 days, or 30 mg/kg/day for 90 days (3M 2007a; Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b). Similar findings were reported an intermediate-duration study in which rats were dosed with PFHxS in doses of up to 10 mg/kg/day (Butenhoff et al. 2009a; Hoberman and York 2003) and in rats dosed with up to 900 mg/kg/day PFBuS for 28 days (3M 2001).

A single gavage dose of 80 mg/kg PFDeA did not significantly alter relative thymus weight in female C57BL/6N mice, but it caused a 28% decrease in relative spleen weight 30 days after dosing (Harris et al. 1989). Lethal doses (160 and 320 mg/kg) induced atrophy and lymphoid depletion in both the thymus and spleen.

Administration of PFNA for 14 days resulted in decreases in thymus and spleen weight at ≥3 mg/kg/day, but no histological alterations in these tissues (Fang et al. 2008). In the spleen, there were decreased in the percentage of F4/80+ and CD49b+ cells at ≥1 mg/kg/day and decreases in CD11c+ cells at

≥3 mg/kg/day. No alterations were observed in the response of splenic T lymphocytes to ConA at 5 mg/kg/day.

Reliable NOAELs and LOAELs for immunological and lymphoreticular effects are presented in Tables 3-3, 3-4, and 3-5 and are plotted in Figures 3-3, 3-4, and 3-5.

3.2.2.4 Neurological Effects

Human Exposure Studies. Using NHANES data for adults aged 60–85 years (1999–2000 and 2003–2008 cycles), Power et al. (2013) found an inverse association between serum PFOA, PFOS, PFHxS, and PFNA levels and self-reported limitation due to difficulty remembering or periods of confusion; however, the ORs included the null value. When the subjects were categorized by diabetic status and the use of medication for the treatment of diabetes, significant inverse associations between limitations due to difficulty remembering and serum PFOS (OR 0.39, 95% CI 0.19–0.78), PFNA (OR 0.43, 95% CI 0.21–0.87), and PFHxS (0.49, 95% CI 0.29–0.84) were found. In a C8 Science Panel study of 4,462 adults aged ≥50 years conducted by Gallo et al. (2013), self-reported short-term memory loss impairment was negatively associated with serum PFOS, PFOA, and PFHxS levels. Comparisons with the referent group (subjects with serum perfluoroalkyl levels in the first quintile) were statistically significant for serum PFOS levels of ≥20.5 ng/mL (OR 0.86, 95% CI 0.78–0.96), serum PFOA levels of ≥14.1 ng/mL (OR 0.88, 95% CI 0.79–0.97), and PFHxS levels of ≥5.7 ng/mL (OR 0.89, 95% CI 0.79–0.99). Unlike the Power et al. (2013) study, the inverse association between serum perfluoroalkyls was weaker and was not statistically significant in diabetics. In sensitivity analyes, the association between serum PFOA levels and memory impairment was compared within and across water districts. Within a water district, the association between serum PFOA and memory impairment was significant, but there was no association between the geometric mean concentration of PFOA in a district and memory impairment. Several studies (Gump et al. 2011; Hoffman et al. 2010; Stein and Savitz 2011) have found significant associations between exposure to perfluoroalkyls and the likelihood of attention deficit/hyperactivity disorder (ADHD) and impulsivity in children; these studies are discussed in Section 3.2.2.6 Developmental Effects.

Laboratory Animal Exposure Studies—PFOA. A small number of studies have examined the potential toxicity of perfluoroalkyls to the nervous system in animals, but comprehensive testing has not been conducted. No overt signs of neurotoxicity or altered response to stimuli were observed in rats and mice administered up to 1,000 mg/kg PFOA via gavage and observed for 14 days (Sato et al. 2009). Exposure

of rats to up to approximately 110 mg/kg/day PFOA via the diet for 90 days did not induce gross or microscopic alterations in the brain, spinal cord, or peripheral nerves (Griffith and Long 1980). Similar results were reported in rats fed a diet that provided approximately 15 mg/kg/day PFOA for 2 years (3M 1983). Rhesus monkeys exposed to doses of PFOA that caused lethality (≥30 mg/kg/day by gavage) showed signs of hypoactivity and prostration, but examination of the brain did not reveal treatment-related alterations (Griffith and Long 1980). Treatment of Cynomolgus monkeys with doses of up to 20 mg/kg/day PFOA in a capsule did not induce morphological alterations in the brain or sciatic nerve (Butenhoff et al. 2002).

Laboratory Animal Exposure Studies—PFOS. No histological alterations were observed in the brain, spinal cord, and/or sciatic nerve of rats administered a single gavage dose of up to 500 mg/kg PFOS (Sato et al. 2009), rats treated with up to 1.6–1.8 mg/kg/day PFOS for 4 or 14 weeks (Seacat et al. 2003), rats exposed to 8.5 mg/kg/day PFOS in the diet for 13 weeks (Kawamoto et al. 2011), rats exposed to 1.04 mg/kg/day PFOS in the diet for 2 years (Butenhoff et al. 2012b; Thomford 2002b), or Cynomolgus monkeys dosed with up to 0.75 mg/kg/day PFOS for 26 weeks (Seacat et al. 2002). However, ultrasonic stimulation resulted in bursts of locomotion immediately followed by tonic convulsions in mice administered 125 mg/kg PFOS and rats administered 250 mg/kg PFOS (Sato et al. 2009); the effect was observed 1–7 days postexposure and frequently resulted in death. Similarly, tonic convulsions following ultrasonic stimulation were observed in rats exposed to 8.5 mg/kg/day PFOS in the diet for 6 weeks (Kawamoto et al. 2011); this effect was not observed at ≤2.0 mg/kg/day. Impaired spatial learning and memory, assessed using the Morris water maze test, was observed in mice administered 2.15 or 10.75 mg/kg/day PFOS, but not 0.43 mg/kg/day, for 3 months (Long et al. 2013).

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. Administration of up to 184 mg/kg/day PFBA by gavage for 5 consecutive days to rats had no significant effect on the gross or microscopic morphology of the brain and spinal cord (3M 2007a). In a 28-day gavage study, male rats dosed with 150 mg/kg/day, but not 30 mg/kg/day, showed a delay in bilateral pupillary reflex at the end of the treatment period (Butenhoff et al. 2012a; van Otterdijk 2007a). Results from other tests including hearing ability, static righting reflex, grip strength, and motor activity were comparable between groups and histological examination of the brain (including the optic nerve), spinal cord, and sciatic nerve was unremarkable. In a 90-day study, pupillary reflex tests conducted in weeks 8 and 12 showed delayed dilation under dark conditions in rats dosed with 30 mg/kg/day (2/40 in controls vs. 7/39 in high-dose rats; p=0.071 according to the Fisher Exact Test) (Butenhoff et al. 2012a; van Otterdijk 2007b). Since no abnormalities were recorded during a 3-week recovery period, and there were no histopathological

alterations in the eyes, the effect was not considered biologically significant by the investigator. Tests for hearing ability, static righting reflex, grip strength, and motor activity showed no associations with treatment with PFBA. In addition, there were no significant gross or microscopic alterations in the brain, spinal cord, or sciatic nerve.

In a reproductive study in rats dosed with PFHxS, a functional observation battery and motor activity tests were conducted in males on exposure days 36 and 39 and in females on postpartum day 17 (Butenhoff et al. 2009a; Hoberman and York 2003). The battery assessed autonomic functions, reactivity and sensitivity to stimuli, excitability, gait and sensorimotor coordination, limb grip strength, and abnormal clinical signs. No significant alterations were reported in males or females dosed with up to 10 mg/kg/day PFHxS. In a 28-day study with PFBuS in rats, neurobehavioral tests that assessed sensory reactivity to stimuli, grip strength, and motor activity were conducted on week 4 (3M 2001). The only notable effect was a significant decrease in tail flick latency to a thermal stimulus in males from all treated groups (100, 300, or 900 mg/kg/day) relative to controls. The significance of this isolated finding is difficult to ascertain. Gross and microscopic examination of the brain, spinal cord, and sciatic nerve did not show any significant alterations. A 90-day study of PFBuS in rats did not find any significant alterations in motor activity or performance on functional observation tests at doses as high as 600 mg/kg/day (Lieder et al. 2009a).

Reliable NOAELs and LOAELs for neurological effects are presented in Tables 3-3 and 3-4 and are plotted in Figures 3-3 and 3-4.

3.2.2.5 Reproductive Effects

Human Exposure Studies. Reproductive toxicity of perfluoroalkyls has been examined in several studies in the general population and in a communities living near a PFOA facility. Summaries of the available epidemiology studies are presented in Table 3-6. The possible associations between serum perfluoroalkyl levels and alterations in reproductive hormone levels in men have been examined in four general population studies. Overall, these data do not suggest that background levels of perfluoroalkyls alter reproductive hormone levels in men; some studies have found significant associations, but they are not consistent across studies and most studies have not found significant associations. A cross-sectional study of men living in Durham, North Carolina found significant positive correlations between plasma PFOA levels and free testosterone and LH levels, but not with other reproductive hormones (Raymer et al. 2012). No associations between serum PFOS levels and reproductive hormones were found. In

Table 3-6. Reproductive Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
Populations living in areas with high levels of perfluoroalkyl contamination			
25,957 women >18 years of age participating in C8 Health Project; childbearing group (n=13,458; 18–≤42 years of age), perimenopausal group (n=5,782; >42–≤51 years of age), menopausal group (n=6,717, >51–≤65 years of age)	Median serum PFOA in childbearing, perimenopausal, and menopausal groups:16.7, 23.4, and 32.5 ng/mL; 1st quintile: 0.25–11.2 ng/mL 2nd quintile: 11.3–19.8 ng/mL 3rd quintile: 19.9–36.7 ng/mL 4th quintile: 36.8–84.9 ng/mL 5th quintile: 85.0–22,412.0 ng/mL Median serum PFOS in childbearing, perimenopausal, and menopausal groups:15.0, 16.2, and 21.5 ng/mL; 1st quintile: 0.25–11.8 ng/mL 2nd quintile: 11.9–17.0 ng/mL 3rd quintile: 17.1–22.4 ng/mL 4th quintile: 22.5–30.7 ng/mL 5th quintile: 30.8–564.3 ng/mL	Increased odds of experiencing menopause increased in menopausal group in four highest PFOA quintiles (OR 1.5 [95% CI 1.1–2.1], 1.6 [1.2–2.2], 1.4 [1.1–1.9], and 1.7 [1.3–2.3]) and four highest PFOS quintiles (OR 1.5 [95% CI 1.1–2.1], 1.8 [1.3–2.5], 2.0 [1.5–2.6], and 2.1 [1.6–2.8]); in perimenopausal women in the four highest quintiles (OR 1.4 [95% CI 1.1–1.8], 1.2 [0.9–1.6], 1.4 [1.1–1.9], and 1.4 [1.1–1.8]), and in the three highest PFOS quintiles (OR 1.1 [95% CI 1.1–1.8], 1.4 [1.1–1.8], and 1.4 [1.1–1.8]). PFOS negatively associated with estradiol concentration in perimenopausal and menopausal groups; no significant association for PFOA.	Knox et al. 2011
General population			
373 women in Salt Lake City, Utah or San Francisco, California scheduled for laproscopic or laparotomy surgery	Geometric mean in women with endometriosis: serum PFOA: 2.65 ng/mL, serum PFOS: 7.20 ng/mL, serum PFNA: 0.69 ng/mL, and serum PFHxS: 0.48 ng/mL. Geometric mean in women without endometriosis: serum PFOA: 2.15 ng/mL, serum PFOS: 6.11 ng/mL, serum PFNA: 0.58 ng/mL, and serum PFHxS: 0.43 ng/mL.	Odds of endometriosis diagnosis positively associated with serum PFOA and PFNA; adjusted (age and BMI) OR 1.89 (95% CI 1.17–3.06) and 2.20 (1.02–4.75), respectively; Endometriosis associated with PFOS in unadjusted model (OR 1.55, 95% CI 1.09–2.18; adjusted OR 1.39, 95% CI 0.98–1.98). No significant association with PFHxS.	Buck Louis et al. 2012

Table 3-6. Reproductive Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
1,240 women enrolled in Danish National Birth Cohort; self-reported time to pregnancy, blood samples collected at gestation week 12	Median plasma PFOA: 5.6 ng/mL 1st quartile: LLOQ–3.91 ng/mL 2nd quartile: 3.91–5.20 ng/mL 3rd quartile: 5.21–6.96 ng/mL 4th quartile: ≥6.97 ng/mL Median plasma PFOS: 35.5 ng/mL 1st quartile: 6.4–26.0 ng/mL 2nd quartile: 26.1–-33.3 ng/mL 3rd quartile: 33.4–43.2 ng/mL 4th quartile: ≥43.3 ng/mL	Increased serum PFOA and PFOS levels in women with longer time to pregnancy, as compared to women getting pregnant within 6 months. Increased infertility (time-to-pregnancy >12 months) in women in three highest PFOS quartiles; ORs 1.70 (95% CI 1.01–2.86); 2.34 (1.40–3.89); and 1.77 (1.06–2.95), respectively. Also significant in 2nd, 3rd, and 4th PFOA quartiles; ORs 2.06 (95% CI 1.22–3.51), 1.60 (0.93–2.78), and 2.54 (1.47–4.29), respectively. Decreased fecundity (odds of successful conception) in three highest PFOS quartiles (OR 0.70 [95% CI 0.56–0.87], 0.67 [0.53–0.84], and 0.74 [0.58–0.93]) and PFOA quartiles (OR 0.71 [0.57–0.90], 0.73 [0.58–0.92], and 0.60 p0.47–0.76]).	Fei et al. 2009

Table 3-6. Reproductive Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
Same as Fei et al. 2009	Same as Fei et al. 2009	Increased infertility in two highest PFOS quartiles in nulliparous women (ORs 2.50 [95% CI 1.16–5.37] and 2.14 [1.00–4.60]). In parous women, only significant in the 2nd and 3rd quartiles and not significant overall. Increased infertility in parous women with three highest PFOA quartiles (ORs 3.39 [95% CI 1.75–6.53], 2.92 [1.44–5.93], and 2.99 [1.28–6.98]); not significant in nulliparous women. Decreased fecundity in nulligravid women in third and fourth PFOS quartiles (ORs 0.55 [95% CI 0.36–0.85] and 0.51 [0.32–0.79]) and 3rd and 4th PFOA quartiles (ORs 0.51 [95% CI 0.27–0.98] and 0.36 [0.19–0.68]).	Fei et al. 2012
105 young men (median age approximately 19 years) in Denmark; 53 men had high testosterone levels and 52 men had low testosterone levels	Median serum PFOA: 4.9 ng/mL Median serum PFOS: 24.5 ng/mL Median serum PFHxS: 6.6 ng/mL	Decreased percentage of morphologically normal sperm in the high combined PFOA and PFOS group. Decreased median number of normal spermatozoa in combined high PFOA/PFOS group. No effect on reproductive hormones or other sperm parameters.	Joensen et al. 2009

Table 3-6. Reproductive Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
247 young men (median age 19.2 years) in Denmark	Median serum PFOA: 3.02 ng/mL Median serum PFOS: 7.79 ng/mL Median serum PFHxS: 0.67 ng/mL Median serum PFHpS: 0.27 ng/mL	Negative association between PFOS and testosterone, free testosterone, free androgen index, testosterone/luteinizing hormone ratio, free testosterone/luteinizing hormone ratio, and free androgen/luteinizing hormone ratio. Negative association between PFHpS and the percentage of progressively motile sperm. No other significant associations between perfluoroalkyls and reproductive hormones or sperm parameters.	Joensen et al. 2013
588 male partners of pregnant women in Greenland (n=161, median age 30.9 years), Poland (n=122, 30.3 years), and Ukraine (n=131, 26 years)	Respective median serum PFOA in Greenland, Poland, and Ukraine groups: 4.84, 5.19, and 1.91 ng/mL Respective median serum PFOS in Greenland, Poland, and Ukraine groups: 51.65, 12.12, and 8.20 ng/mL	Positive association between serum PFOS and sperm Y:X chromosome ratios in combined group; negative association between PFOS and sperm Y:X chromosome ratios in Greenland population. Significant inter-country difference in how the Y:X chromosome ratio was affected by PFOS.	Kvist et al. 2012
256 men in Durham, North Carolina (mean age 41.6 years)	Median serum PFOS: 32.3 ng/mL Median serum PFOA: 9.2 ng/mL	Serum PFOA correlated with free testosterone and luteinizing hormone levels. No significant associations between semen parameters and PFOS or PFOA levels or between PFOS and reproductive hormone levels.	Raymer et al. 2012

Table 3-6. Reproductive Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
588 male partners of pregnant women in Greenland (n=199, median age 30.6 years), Poland (n=197, 29.6 years), and Ukraine (n=208, 25.1 years)	Respective median serum PFOA in Greenland, Poland, and Ukraine groups: 4.5, 4.8, and 1.3 ng/mL Respective median serum PFOS in Greenland, Poland, and Ukraine groups: 44.7, 18.5, and 7.6 ng/mL Respective median serum PFNA in Greenland, Poland, and Ukraine groups: 1.4, 1.2, and 1.0 ng/mL Respective median serum PFHxS in Greenland, Poland, and Ukraine groups: 2.2, 1.2, and 0.3 ng/mL	Serum PFOA levels significantly associated with sex-hormone binding globulin levels in Polish cohort; not significant after adjustment for age, BMI, caffeinated drink consumption, smoking, fever, spillage, abstinence time, genital infections, or testicular disorders. No significant associations between reproductive hormone levels and serum PFOA, PFOS, PFNA, or PFHxS levels	Specht et al. 2012
588 male partners of pregnant women in Greenland (n=196, median age 31.3 years), Poland (n=189, 29.6 years), and Ukraine (n=203, 26.2 years)	Median serum PFOA: 3.8 ng/mL Median serum PFOS: 18.4 ng/mL Median serum PFHxS: 1.1 ng/mL Median serum PFNA: 1.2 ng/mL	Proportion of normal sperm were 22 and 35% lower in second (12–27.3 ng/mL) and third (>27.3 ng/mL) PFOS tertiles, respectively, and 35% lower in third PFHxS tertile (>1.5 ng/mL) 36% higher proportion of motile sperm at the third PFOA tertile (>5.2 ng/mL) in Greenland cohort only and 19% higher in third PFOA tertile (>4.7 ng/mL) of whole cohort No other significant associations between individual perfluoroalkyls and sperm parameters	Toft et al. 2012

Table 3-6. Reproductive Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
222 Danish nulliparous couples discontinuing birth control and followed for six menstrual cycles or until clinically recognized pregnancy; mean age of women was 26.6 years	Median serum in women with no pregnancy—PFOS 35.75 ng/mL, PFOA 5.58 ng/mL, PFHxS 1.12 ng/mL, PFNA 0.45 ng/mL, PFDeA 0.10 ng/mL, Me-PFOSA-AcOH 0.45 ng/mL, Et-PFOSA-AcOH 2.12 ng/mL, PFOSA 0.10 ng/mL Median serum in women becoming pregnant—PFOS 36.29 ng/mL, PFOA 5.61 ng/mL, PFHxS 1.22 ng/mL, PFNA 0.51 ng/mL, PFDeA 0.11 ng/mL, Me-PFOSA-AcOH 0.39 ng/mL, Et-PFOSA-AcOH 1.79 ng/mL, PFOSA 0.11 ng/mL	Serum concentrations of perfluoroalkyls did not differ between women becoming pregnant and those who did not. No association between odds of not becoming pregnant within first six cycles and PFOS or PFOA levels above the median. No significant associations for time to pregnancy for PFHxS, PFNA, PFDeA, Et-PFOSA-AcOH, Me-PFOSA-AcOH, or PFOSA.	Vestergaard et al. 2012
Pregnant women enrolled in the Norwegian Mother and Child Cohort Study in 2003–2004; 416 subfecund women, 474 controls	Maternal samples collected at gestation week 17 Median PFOA: 2 and 2 ng/mL in subfecund and control groups, respectively 1st quartile: <1.66 ng/mL 2nd quartile: 1.66–2.24 ng/mL 3rd quartile: 2.25–3.02 ng/mL 4th quartile: ≥3.02 ng/mL Median PFOS: 14 and 13 ng/mL in subfecund and control groups 1st quartile: <10.34 ng/mL 2nd quartile: 10.34–13.09 ng/mL 3rd quartile: 13.10–16.60 ng/mL 4th quartile: ≥16.61 ng/mL	Increased subfecundity (>12 months time to pregnancy) in women in the highest PFOA quartiles and two highest PFOS quartiles. Nulliparous women: no significant associations with PFOA or PFOS. Parous women: increased in two highest PFOA quartiles and fourth PFOS quartile.	Whitworth et al. 2012b

BMI = body mass index; 95% CI = 95% confidence interval; Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid; Me-PFOSA-AcOH = 2-(N-methyl-perfluorooctane sulfonamide) acetic acid; OR = odds ratio; PFDeA = perfluorodecanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide

contrast, significant negative associations between PFOS and testosterone, free testosterone, and free androgen index levels were found in a study of Danish young men; no significant associations between reproductive hormone levels and serum PFOA, PFHxS, or PFHpS were found (Joensen et al. 2013). An earlier study of young Danish men with high or low testosterone levels did not find any associations between serum PFOA, PFOS, or PFHxS levels and reproductive hormone levels (Joensen et al. 2009). A study of male partners of pregnant women living in Greenland, Poland, or the Ukraine did not find significant associations between serum PFOA, PFOS, PFHxS, or PFNA levels and reproductive hormone levels (Specht et al. 2012). The study did find a significant association between serum PFOA levels and sex-hormone binding globulin levels in the Polish men, but the association was no longer significant after adjustment for potential confounds such as age, BMI, smoking, abstinence time, genital infections, or testicular disorders.

Examination of sperm parameters in the same groups of men has also resulted in conflicting results. Toft et al. (2012) reported 22 and 35% decreases in the proportion of normal sperm in male partners of pregnant women living in Greenland, Poland, and the Ukraine with the serum PFOS levels in the second (12–27.3 ng/mL) or third (≥27.3 ng/mL) tertiles, as compared to men in the first tertile. Multiple regression analysis was suggestive of a dose-response relationship ($p=0.06$) between continuous PFOS exposure and the proportion of normal sperm. Similarly, a 35% lower proportion of normal sperm was observed in men with PFHxS levels in the third tertile (>1.5 ng/mL), as compared to the first tertile. A nonsignificant decrease in the proportion of normal sperm was also observed at higher PFNA concentration and no association between the proportion of normal sperm and PFOA exposure was found. A significant increase in the proportion of motile sperm was found for men with PFOA concentrations in the third tertile (>3.8 ng/mL); this was primarily due to men living in Greenland. Joensen et al. (2009) also found decreases in the proportion of normal sperm in young men with combined PFOA and PFOS serum levels in the highest quartile, as compared to men in the first quartile. Joensen et al. (2013) studied a similar group of young men and did not find a significant association between perfluoroalkyl exposure and the proportion of morphologically normal sperm; the study only analyzed perfluoroalkyl exposure as a continuous variable and did not have a combined PFOA and PFOS group. Raymer et al. (2012) also found no significant associations between sperm parameters and PFOA or PFOS levels. Another study of the Greenland, Poland, and Ukraine cohort (Kvist et al. 2012) reported a significant positive association between serum PFOS levels and sperm Y:X chromosome ratios in the entire cohort; when the cohort was divided by country, a significant negative association between serum PFOS levels and Y:X chromosome ratio was found in the Greenland subcohort.

Buck Louis et al. (2012) examined the possible association between the occurrence of endometriosis and serum perfluoroalkyl exposure among 373 women living in Salt Lake City, Utah or San Francisco, California scheduled for laparoscopic or laparotomy surgery. Significant associations between endometriosis diagnosis and serum PFOA and PFNA levels were found; the ORs, after adjustment for age and BMI, were 1.89 (95% CI 1.17–3.06) and 2.20 (95% CI 1.02–4.75). Significant associations were also found for PFOS and PFDeA levels but only in unadjusted models. The likelihood of moderate/severe endometriosis was also significantly associated with age and BMI adjusted serum PFOS levels (OR 1.86, 95% CI 1.05–3.30) and PFOA levels (OR 2.58, 95% CI 1.18–5.64). However, when the serum perfluoroalkyl levels were adjusted for parity, the associations were no longer statistically significant.

A study of women participating in the C8 Health Project examined the possible association between serum PFOA and PFOS levels and the onset of menopause (Knox et al. 2011). Among women 52–65 years of age, there was a monotonic increase in the odds of experiencing menopause after adjusting for smoking, age, BMI, alcohol consumption, and participation in a regular exercise program in the four highest quintiles of serum PFOS levels (≤11.9 ng/mL), as compared to the first quintile. An increase in the odds of experiencing menopause was also found in women aged 43–51 years with serum PFOS levels in the third, fourth, and fifth quintiles (≥17.1 ng/mL), but it was not monotonic. No associations between menopause onset and serum PFOS levels were found in the youngest group of women (18–42 years). Similarly, PFOA levels ≥11.3 ng/mL were associated with an increased odds of experiencing menopause among the women in the two oldest groups, but not in the youngest group of women; however, the increased risk was not monotonic. Knox et al. (2011) also found that PFOS levels were negatively associated with serum estradiol levels in the two oldest groups of women; no significant associations between estradiol and serum PFOA levels were found.

Three general population studies examined the possible association between serum perfluoroalkyl levels and fertility. Serum PFOA and PFOS levels (collected during the first trimester of pregnancy) were significantly higher in women enrolled in the Danish National Birth Cohort with longer time to pregnancy, as compared to women who got pregnant in the first 6 months (Fei et al. 2009). The odds of infertility, defined as a time to pregnancy of >12 months, was also significantly higher in women with serum PFOA or PFOS levels in the second, third, or fourth quartiles (PFOA ≥3.91 ng/mL, PFOS ≥26.1 ng/mL), as compared to women in the first quartile. The fecundity ORs, which measure the odds of a successful pregnancy (odds <1 indicate a decrease in fecundity and increased time to pregnancy) were also significantly lower in women with PFOA or PFOS levels in the highest three quartiles. In a subsequent analysis of these data, Fei et al. (2012) reported an increase in the OR for infertility among

nulliparous women with PFOS levels in the third or fourth quartile, as compared to the first quartile. Among parous women, significantly elevated odds of infertility were only observed in the second and third PFOS quartile groups. For PFOA, no significant associations were found among nulliparous women, but were found for parous women in the second, third, and fourth quartiles. The fecundability odds were significantly decreased in nulliparous women with serum PFOS levels in the third and fourth quartiles and parous women with serum PFOA levels in the second, third, and fourth quartiles. Among nulligravid women, a decrease in the fecundity ORs were found in the third and fourth quartiles of PFOS (ORs 0.55 [95% CI 0.36–0.85] and 0.51 [95% CI 0.32–0.79]) and PFOA (ORs 0.51 [95% CI 0.27–0.98] and 0.36 [95% CI 0.19–0.68]). In a similar study, Whitworth et al. (2012b) found a significant increase in the odds of subfecundity (time to pregnancy >12 months) in pregnant women participating in the Norwegian Mother and Child Cohort Study with serum PFOA levels in the second, third, and fourth quartiles (≥1.66 ng/mL) or serum PFOS levels in the third or fourth quartiles (≥13.10 ng/mL). Stratifying the women based on parity resulted in no significant association in nulliparous women; increased ORs were noted in parous women with serum PFOA levels in the third and fourth quartiles and serum PFOS levels in the fourth quartile. The findings in the nulliparous women are in contrast to the Fei et al. (2012) study, which found significant associations between the odds of infertility (equivalent to the subfecundity index in the Whitworth et al. 2012b study) with serum PFOA and PFOS. The serum levels of PFOA and PFOS were much lower in the Whitworth et al. (2012b) study; 91 and 96% of the women had PFOA and PFOS serum levels, respectively, which would have fallen in the first quartile (referent group) for the Fei et al. (2009, 2012) study. Another study of Danish women (Vestergaard et al. 2012) did not find a significant association between the odds of becoming pregnant within the first six menstrual cycles after discontinuing birth control among nulliparous women with PFOA or PFOS serum concentrations above the median. Additionally, no associations were found between time to pregnancy and serum levels and serum PFHxS, PFNA, PFDeA, Et-PFOSA-AcOH, MePFOSA-AcOH, or PFOSA levels. Although the median PFOS and PFOA serum levels were similar in the Vestergaard et al. (2012) and Fei et al. (2009, 2012) studies, differences in the study design particularly the shorter follow-up period (6 versus >12 months) to evaluate time to pregnancy in the Vestergaard study and the different populations (pregnant women versus non-pregnant women) make it difficult to directly compare the study results of the Vestergaard et al. (2012) study with the Fei et al. (2009, 2012) and Whitworth et al. (2012b) studies.

Laboratory Animal Exposure Studies—PFOA. Several studies have been conducted in rats to examine whether induction of Leydig cells tumors could be due to an endocrine-related mechanism. In a 14-day gavage study in which rats were dosed with up to 50 mg/kg/day PFOA, testes weight was not significantly affected and microscopic examination did not reveal any significant alterations (Cook et al.

1992). However, the weight of the accessory sex organ unit (ventral and dorsal lateral prostate, seminal vesicles, and coagulating glands) was significantly decreased in rats dosed with 25 mg/kg/day PFOA (17% decrease) and 50 mg/kg/day PFOA (18% decrease) relative to controls and to a pair-fed group. There was also a trend for reduced serum and interstitial fluid testosterone in PFOA-treated rats; serum LH was not altered and estradiol was significantly increased (63%) at ≥10 mg/kg/day. Challenge experiments conducted with human chorionic gonadotropin, gonadotropin-releasing hormone, or naloxone suggested that the decrease in serum testosterone was due to a lesion at the level of the testes. Serum levels of progesterone and 17α-hydroxyprogesterone were not altered by 50 mg/kg/day PFOA, but androstenedione levels were reduced 2-fold. The data suggested that the decrease in serum testosterone may be due to a decrease in the conversion of 17α-hydroxyprogesterone to androstenedione, and this could be attributed to the elevated serum levels of estradiol. The decrease in weight of the accessory sex organ unit could also be attributed to the elevated estradiol serum levels. In a subsequent study from the same group of investigators, rats dosed with 25 mg/kg/day PFOA for 14 days showed a significant increase in estradiol in serum and in testicular interstitial fluid relative to controls (Biegel et al. 1995). Treatment with PFOA for 14 days significantly increased aromatase activity in the liver (aromatase converts testosterone to estradiol), but not in testes, muscle or adipose tissue, suggesting that PFOA increases serum estradiol by inducing aromatase activity in the liver. Treatment with PFOA also increased testicular interstitial fluid transforming growth factor α (TGFα). Collectively, the results were consistent with the hypothesis that increased estradiol levels ultimately produce Leydig cell hyperplasia and adenoma by acting as a mitogen or enhancing growth factor secretion. A study of the dose-response relationship for PFOA and serum estradiol reported a significant increase in serum estradiol in rats dosed with ≥2 mg/kg/day, which were well correlated with total hepatic aromatase activity (Liu et al. 1996). Significant increases in serum estradiol were also reported during the first year of treatment of male rats with 13.6 mg/kg/day PFOA in a 2-year dietary study (Biegel et al. 2001).

Significant increases in the incidence of Leydig cell hyperplasia were observed in rats exposed to 13.6 mg/kg/day PFOA in the diet for 2 years (Biegel et al. 2001). Another 2-year study found an increased incidence of vascular mineralization in the testes of rats exposed to 15 mg/kg/day PFOA in the diet; no effects were observed at 1.5 mg/kg/day (3M 1983). In female rats, increases in the incidence of tubular hyperplasia of the ovaries were observed following a 2-year exposure to 1.5 mg/kg/day (3M 1983). A peer review of the histological slides from the 3M (1983) concluded that the more current nomenclature for the tubular hyperplasia was gonadal stromal hyperplasia (Mann and Frame 2004). Additionally, the peer reviewers substantially disagreed with the incidence of lesions in the 1.5 mg/kg/day group and slightly disagreed with the incidence in the 15 mg/kg/day. Based on the incidence reported by

the peer reviewers, no statistically significant increases in the occurrence of gonadal stromal hyperplasia were observed in either group; a significant increase in grade 3 and above lesions were observed in the 15 mg/kg/day group.

In a 2-generation reproduction study in which male and female rats were dosed with up to 30 mg/kg/day PFOA by gavage in water for 70 days before mating and until sacrifice, there were no effects on estrous cycling, sperm number and quality, mating and fertility, or histopathology of the reproductive organs assessed in the parental and F1 generations (Butenhoff et al. 2004b). Intermediate-duration studies of rats and monkeys also did not find gross or microscopic alterations in the sex organs at termination; Cynomolgus monkeys were dosed with up to 20 mg/kg/day PFOA for 4 weeks or 26 weeks (Butenhoff et al. 2002; Thomford 2001), Rhesus monkeys with up to 100 mg/kg/day PFOA for 13 weeks (Griffith and Long 1980), and rats with up to approximately 100–110 mg/kg/day PFOA for 13 weeks (Griffith and Long). Serum levels of estradiol and estriol were not significantly altered in the 4-week study conducted by Thomford (2001), but estrone was reduced in monkeys dosed with 2 and 20 mg/kg/day PFOA; no possible explanation was discussed. In the 26-week study (Butenhoff et al. 2002), no treatment-related alterations were reported in serum estrone, estriol, estradiol, or testosterone, indicating that the reduced serum estrone levels in the 4-week study was transitory. In 2-year dietary studies in rats, doses of 13.6 mg/kg/day PFOA significantly increased the incidence of Leydig cell hyperplasia (Biegel et al. 2001), whereas 15 mg/kg/day increased the incidence of vascular mineralization in the testes and 1.5 mg/kg/day increased the incidence of tubular hyperplasia in the ovaries (3M 1983).

A study in pregnant mice dosed with 5 mg/kg/day PFOA (only dose level tested) reported that the mammary gland showed changes suggesting substantial delay (possibly up to 10 days) in gland differentiation on PND 20 and alterations in milk protein gene expression on PND 20 (White et al. 2007). Subsequent studies by this group support the finding of delayed mammary gland differentiation. On PND 1, the mammary glands of mice administered 5 mg/kg/day on GDs 8–17 appeared immature; the morphology was similar to that seen in late pregnancy prior to parturition and the initiation of nursing (White et al. 2009). Another study found that the normal weaning-induced mammary gland involution was compromised on PND 22 in mice exposed to 1 mg/kg/day on GDs 1–17 or 0.001 mg/kg/day administered on GD 7–PND 22 (White et al. 2011b); the investigators noted that the mammary gland structure was similar to mammary gland tissue at or near the peak of lactation (PND 10). Necrosis was observed in the placenta of mice administered via gavage 10 or 25 mg/kg/day PFOA on GDs 11–16 (Suh et al. 2011); no alterations were observed at 2 mg/kg/day.

Laboratory Animal Exposure Studies—PFOS. A significant decrease in serum testosterone levels and epididymal sperm count was observed in mice administered 10 mg/kg/day PFOS for 21 days (Wan et al. 2011). No alterations were observed in mice administered 5 mg/kg/day PFOS or in mice administered 5 or 10 mg/kg/day PFOS for 14 days. No alterations in reproductive performance (number of litters, gestation length, number of implantation sites, or potential resorptions) were observed in rats administered 1 mg/kg/day PFOS throughout gestation and lactation (Butenoff et al. 2009). Multigeneration studies with PFOS in rats did not provide indications of reproductive toxicity. Exposure of male and female rats to up to 3.2 mg/kg/day PFOS by gavage before mating and continuing during gestation did not affect mating or fertility parameters of the parental or F1 generation (Luebker et al. 2005a, 2005b). Treatment of rabbits with 3.75 mg/kg/day PFOS by gavage on GDs 6–20 resulted in 10 out of 22 does having abortions between GD 22 and 28 (Case et al. 2001). Dietary exposure of rats to 1.3–1.8 mg/kg/day PFOS for 4 or 14 weeks did not induce gross or microscopic alterations in the sex organs of males or females (Seacat et al. 2003). A similar study in Cynomolgus monkeys administered up to 0.75 mg/kg/day PFOS in a capsule also reported no significant morphological alterations in the sex organs, but serum estradiol was significantly decreased in males on days 62, 91, and 182 of the study (Seacat et al. 2002). In addition, treatment with PFOS had no significant effect on cell proliferation in the testes. Serum estradiol also was lower than in controls in one male and one female monkey dosed with 2 mg/kg/day PFOS for 4 weeks, but little can be concluded from results from just two animals (Thomford 2002a). In a 2-year dietary study in rats, administration of up to 1.04 mg/kg/day PFOS did not induce gross or microscopic alterations in the reproductive organs (Butenhoff et al. 2012b; Thomford 2002b).

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. No significant gross or microscopic alterations were reported in primary and secondary reproductive organs from rats dosed with PFBA by gavage in doses of up to 184 mg/kg/day for 5 days, 150 mg/kg/day for 28 days, or 30 mg/kg/day for 90 days (3M 2007a; Butenhoff et al. 2012a; van Otterdijk 2007a, 2007b).

Exposure to 10 mg/kg/day PFHxS did not result in alterations in reproductive organ weights or histopathology in male rats exposed for a minimum of 42 days of exposure beginning 14 days prior to cohabitation and female rats sacrificed on lactation day 21 or GD 25 (rats that did not deliver a litter) (exposure began 14 days prior to cohabitation) (Butenhoff et al. 2009a; Hoberman and York 2003). Fertility was not affected by treatment with PFHxS and there were no significant effects on sperm parameters. Also, estrous cycling was not affected by dosing with PFHxS. Administration of up to 900 mg/kg/day PFBuS to rats by gavage for 28 days did not cause any significant gross or microscopic alterations in primary or secondary sex organs from males or females (3M 2001).

Treatment of male rats with 1, 5, or 10 mg/kg/day PFDoA by gavage for 14 days induced a dose-related decrease in testes weight, which achieved statistical significance at 10 mg/kg/day (Shi et al. 2007). Measurement of serum hormone levels showed a significant decrease in LH at 10 mg/kg/day and of testosterone at 5 and 10 mg/kg/day, no significant effect on FSH levels, and a significant decrease in serum estradiol only at 5 mg/kg/day. Alterations in the ultrastructure of the testes were seen in the 5 and 10 mg/kg/day groups and consisted of the presence of large clustered lipid droplets and enlarged mitochondria in Sertoli cells, large vacuoles, and expanded mitochondria in Leydig and spermatogenic cells. Morphological features of apoptosis were seen in cells in the 10 mg/kg/day group. Assessment of mRNA expression of genes involved in cholesterol transport and steroidogenesis provided evidence of altered cholesterol transport and steroid hormone synthesis, but no effects were noted for LH receptor and aromatase mRNA expression. Considering that serum total cholesterol was unaffected at 5 mg/kg/day and increased at 10 mg/kg/day and that aromatase expression was unaffected, the decrease in testosterone synthesis probably resulted from decreased steroidogenesis gene expression.

A 2-generation study in which rats were exposed to gavage doses of potassium PFBuS as high as 1,000 mg/kg/day did not result in alterations in fertility, sperm parameters, estrus cycling, or histological alterations in reproductive tissues (Lieder et al. 2009b).

Reliable NOAELs and LOAELs for reproductive effects are presented in Tables 3-3, 3-4, and 3-5 and are plotted in Figures 3-3, 3-4, and 3-5.

3.2.2.6 Developmental Effects

Human Exposure Studies. A number of epidemiology studies have examined the potential of perfluoroalkyls to adversely affect birth outcome in the general population and in populations living in an area with high PFOA drinking water contamination; summaries of these studies are presented in Table 3-7. Many of the studies examined birth outcome, particularly birth weight; a smaller number of studies have examined growth, neurodevelopment, reproductive development, immunological end points, and endocrine end points.

Nolan et al. (2009) examined birth outcomes in women living in areas of Ohio exclusively or partially serviced by the Little Hocking Water Association (LHWA), which has been shown to have high levels of

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
Populations living in areas with high levels of perfluoroalkyl contamination			
8,764 20–40-year-old adults participating in the C8 Health Project; height and weight data self-reported	Averaged early life (first 3 years) PFOA blood levels based on environmental levels of PFOA (based lifetime residential history) and PBPK model using standard assumptions about water intake, body weight, and PFOA half-life; maternal serum levels were factored into early life estimates for years 1 and 2. Estimated serum PFOA: 1st quartile: 0 ng/mL 2nd quartile: 0.0002–8.0 ng/mL 3rd quartile: 8.1–100.0 ng/mL 4th quartile: 100.1–2,266.2 ng/mL	No significant association between early life PFOA exposure and overweight or obesity risks at age 20–40 years.	Barry et al. 2014
1,330 women participating in the C8 Health Project and giving birth between 2005 and 2010; maternal blood samples collected in 2005–2006; birth outcome data self-reported and taken from Ohio and West Virginia health departments	Median serum PFOA: 14.3 ng/mL (range:0.6–459.5 ng/mL) 1st quintile: 0–<6.9 ng/mL 2nd quintile: 6.9–<11.1 ng/mL 3rd quintile: 11.1–<18.9 ng/mL 4th quintile: 18.9–<37.2 ng/mL 5th quintile: ≥37.2 ng/mL Median serum PFOS: 13.9 ng/mL (range: LOD (0.25)–92.9 ng/mL) 1st quintile: 0–<8.6 ng/mL 2nd quintile: 8.6–<12.1 ng/mL 3rd quintile: 12.1–<15.9 ng/mL 4th quintile: 15.9–<21.4 ng/mL 5th quintile: ≥21.4 ng/mL	Increased odds of pregnancy-induced hypertension in women with PFOA levels in the 2nd, 3rd, 4th, or 5th quintiles (OR [adjusted for maternal age, educational level, smoking, parity, BMI, self-reported diabetes, time between conception and serum. measurement] of 2.39 [95% CI 1.05–5.46], 3.42 [1.50–7.82], 3.12 [1.35–7.18], and 3.16 [1.35–7.38]), as compared to the 1st quintile and PFOS levels in the 3rd and 4th quintiles (adjusted ORs 2.71 [95% CI 1.33–5.52] and 2.21 [1.07–4.54]). Nonsignificant trend for decreased birth weight among full-term infants with PFOS levels in 2nd, 3rd, and 4th quintiles. Trend statistically significant in subcohort of 783 women whose first pregnancy was conceived after sample collection. No association between birth weight and PFOA levels. No association between PFOA or PFOS levels and preterm birth, LBW, or small for gestational age.	Darrow et al. 2013

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
3,076 boys and 2,931 girls aged 8–18 years participating in the C8 Health Project and C8 Science Panel studies	Boys Median PFOA: 26 ng/mL Median PFOS: 20 ng/mL Girls Median PFOA: 20 ng/mL Median PFOS: 18 ng/mL	Significant association between PFOS levels and the age of puberty in boys (as assessed by total testosterone levels), 190-day delay in boys in the highest quartile as compared to lowest quartile. No significant association with PFOA. Significant association between PFOS and PFOA and age of puberty in girls (as assessed by self-reported menarche or estradiol levels); 139- and 130-day delay, respectively, between highest and lowest quartiles.	Lopez-Espinosa et al. 2011
1,555 singleton neonates, 11% born to mothers living in area with contaminated drinking water (LHWA), 13% living in area partially serviced by LHWA, and 76% living in area without service from LHWA; birth outcome data taken from the Ohio Department of Health	No biomonitoring was performed	Lower incidence of LBW in partial (3.8%) and exclusive (3.6%) LHWA groups as compared to the national incidence (8.1%). Lower adjusted odds of LBW (OR 0.37, 95% CI 0.16–0.86) in partial LHWA group, as compared to the no LHWA group. No significant associations between residence area and birth weights or gestational age or odds of preterm birth.	Nolan et al. 2009
1,548 singleton neonates, 11% in exclusive LWHA; 13% partial LHWA, and 76% no LHWA (see Nolan et al. 2009)	No biomonitoring was performed	No differences in the likelihood of congenital anomalies between the groups.	Nolan et al. 2010

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
8,253 singleton infants born to mothers living in an area of the Mid-Ohio Valley with known PFOA contamination from 1990 to 2004; birth outcome data taken from Ohio and West Virginia health departments	Maternal PFOA levels based on estimated environmental levels of PFOA (based on maternal address on birth certificate and assumption that mother lived at address for 6 years) and PBPK model using standard assumptions about water intake, body weight, and PFOA half-life Median estimated maternal serum PFOA: 7.7 ng/mL (range:1.0–717.6 ng/mL)	No association between estimated serum PFOA levels and stillbirths, preterm birth, small for gestational age, LBW, or birth weight.	Savitz et al. 2012b
4,547 singleton infants born to mothers living in an area of the Mid-Ohio Valley with known PFOA contamination from 1990 to 2004 and with birth records linked to the C8 Health Project; birth outcome data taken from Ohio and West Virginia health departments	Maternal PFOA blood levels based on environmental levels of PFOA (based on maternal lifetime residential history) and PBPK model using standard assumptions about water intake, body weight, and PFOA half-life; used a Bayesian time-dependent calibration that used measured serum concentrations (2005–2006) to update estimates Median maternal serum PFOA: 13.4 ng/mL (range: 3.9–921.3 ng/mL)	No association between estimated serum PFOA levels and LBW, or small for gestational age. Weak association between preterm birth (<37 weeks or <32 weeks) and PFOA levels based on continuous PFOA levels but there was no gradient across PFOA quintiles. Birth weight was associated with uncalibrated and Bayesian calibrated serum PFOA levels.	Savitz et al. 2012b
12,391 singleton infants born to mothers living in an area of the Mid-Ohio Valley with known PFOA contamination from 1990 to 2006 and with birth records linked to the C8 Health Project; birth outcome data taken from Ohio and West Virginia health departments	Maternal PFOA blood levels based on environmental levels of PFOA (based on maternal lifetime residential history) and PBPK model using standard assumptions about water intake, body weight, and PFOA half-life; used a Bayesian time-dependent calibration that used measured serum concentrations (2005–2006) to update estimates Median maternal serum PFOA: 6.0, 10.7, and 15.9 ng/mL in the 1990–1994, 1995–1999, and 2000–2005 time periods	No associations between PFOA levels and odds of miscarriage, stillbirth, preterm birth, LBW, or birth defects were found.	Savitz et al. 2012a

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
1,845 pregnancies (1,589 live births) in Mid-Ohio Valley residents that occurred within the 5 years preceding blood sample collections for the C8 Health Project; self-reported birth outcome	Median serum PFOA: 21.2 ng/mL (range: 0.25–894.4 ng/mL)	No association between PFOA levels and odds of miscarriage, pre-term birth, or LBW. No association between PFOA exposure and LBW risk, although there was a decrease in the risk in women in the 75th–90th percentile for serum PFOA. No significant association between serum PFOA and birth defects.	Stein et al. 2009
1,845 (PFOA analysis) or 5,262 (PFOS analysis) pregnancies in Mid-Ohio Valley residents that occurred within the 5 years preceding blood sample collections for the C8 Health Project; self-reported birth outcome	Median serum PFOS: 12.8 ng/mL (range: 0.25–83.4 ng/mL) <50th percentile: 0.25–<12.7 ng/mL 50th–<75th percentile:12.7–<17.7 ng/mL 75th–90th percentile:17.7–<23.2 ng/mL >90th percentile: 23.2–83.4 ng/mL	Increased odds of preterm birth in women with PFOS levels above the 90th percentile (OR 1.4, 95% CI 1.1–1.7). The increased odds of LBW with serum PFOS levels above the median (OR 1.5, 95% CI 1.1–1.9), in the 75th–90th percentile (OR 1.6, 95%CI 1.1–2.3), and above the 90th percentile (OR 1.8, 95% CI 1.2–2.8). No association between PFOS and miscarriage risk or birth defects risk.	Stein et al. 2009
10,546 non-Hispanic white children aged 5–18 years participating in the C8 Health Project	Mean serum PFOA: 66.3 ng/mL (range: 0.6–2070.6 ng/mL) Mean serum PFOS: 22.9 ng/mL (range: 0.25–202.1 ng/mL) Mean serum PFHxS: 9.3 ng/mL (range: 0.25–276.4 ng/mL) Mean serum PFNA: 1.7 ng//mL (range: 0.25–24.1 ng/mL)	Increased odds of ADHD diagnosis (as reported by child or parent) in serum PFHxS 2nd (2.9–<5.2 ng/mL), 3rd (5.2–<10.1 ng/mL), or 4th (10.1–276.4 ng/mL) quartiles (ORs 1.27 [95%CI 1.06–1.52], 1.43 [1.21–1.70], and 1.53 [1.29–1.83]); there was also a significant increase in the odds of learning problems in the 4th PFHxS quartile (OR 1.19, 95% CI 1.00–1.41). Decrease in odds of ADHD diagnosis with increasing serum PFOA levels, and PFOS and PFNA were not significantly associated with odds of ADHD diagnosis.	Stein and Savitz 2011

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
General populations			
Follow-up to Fei et al. (2007) study; infant data obtained from questionnaire completed by the mother	Maternal blood samples collected during first trimester Median serum PFOA: 5.25 ng/mL (range: 0.5–21.9 ng/mL) Median serum PFOS: 33.8 ng/mL (range: 6.4–106.7 ng/mL)	When infants were grouped by sex, associations between maternal PFOA levels and birth weight in male and female infants and association between maternal PFOS levels and birth weight in female infants. At age 5 months of age, no associations between maternal PFOA or PFOS levels and body weight or BMI. When grouped by sex, maternal PFOA levels negatively associated with body weight and BMI in male infants. At 12 months of age, negative association between maternal PFOS and body weight and BMI. When grouped by sex, maternal PFOA levels were also negatively associated with body weight and BMI in male infants.	Andersen et al. 2010
Follow-up to Fei et al. (2007) study; data regarding size obtained from the mothers of 811 children	Maternal blood samples collected during first trimester Median serum PFOA: 5.25 ng/mL (range: 0.5–21.9 ng/mL) Median serum PFOS: 33.8 ng/mL (range: 6.4–106.7 ng/mL)	At 7 years of age, no association between maternal PFOA or PFOS and child BMI or waist circumference.	Andersen et al. 2013
Cross-sectional study of 341 singleton births in Baltimore Maryland; maternal and neonatal data collected from hospital records	Cord blood serum samples Median PFOA: 1.6 ng/mL (range: 0.3–7.1 ng/mL) Median PFOS: 5 ng/mL (range: <LOD (0.2)–34.8 ng/mL)	Cord blood serum PFOA and PFOS levels were negatively associated with birth weight, ponderal index, and head circumference. No associations with neonatal length or gestation age.	Apelberg et al. 2007b

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
492 infants participating in Taiwan Birth Panel Study	Geometric cord blood levels PFOA: 1.84 ng/mL PFOS: 5.94 ng/mL PFNA: 2.36 ng/mL PFUA: 10.26 ng/mL	After adjusting for potential confounders, significant inverse associations between PFOS and gestational age, birth weight, and head circumference were found. The ORs for preterm birth (2.45, 95% CI 1.47–4.08) and small for gestational age (2.27, 1.25–4.15) were significantly elevated for PFOS; LBW was not significantly associated with cord PFOS levels after adjustment for potential confounders. A significant positive association between PFNA levels and birth length and inverse association with ponderal index were also found. No associations were found for PFNA and preterm birth, LBW, or small for gestational size. No significant associations, after adjustment for potential confounders, between PFOA and PFUA levels and gestational age, birth weight, head circumference, small for gestational age, LBW, or preterm.	Chen et al. 2012a
448 girls participating in Avon Longitudinal Study of Parents and Children in Great Britain; case-control study of girls with early menarche (<11.5 years of age, n=218) and controls (menarche ≥11.5 years, n=230)	Maternal blood samples collected at gestation week 15 Median maternal serum levels PFOA: 3.7 ng/mL PFOS: 19.8 ng/mL PFHxS: 1.6 ng/mL	No significant associations between maternal perfluoroalkyl levels and age of menarche.	Christensen et al. 2011

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
1,400 pregnant women participating in Danish National Birth Cohort study; birth outcome data obtained from National Discharge Register at the National Board of Health	Maternal blood samples collected during first trimester Mean serum PFOA: 5.6 ng/mL (range:<LLOQ (1.0)–41.5 ng/mL) Mean serum PFOS: 35.3 ng/mL (range: 6.4–106.7 ng/mL)	Maternal PFOA levels inversely associated with birth weight; birth weight significantly lower in infants of women with PFOA levels in the 2nd (3.91–5.20 ng/mL), 3rd (5.21–6.96 ng/mL), and 4th quartiles (≥6.97 ng/mL), as compared to the 1st quartile. Significant negative association between maternal PFOA and birth length and abdominal circumference. No association between maternal PFOS levels and birth weight, birth length, or head and abdominal circumference. No associations between PFOS or PFOA and gestation length, LBW, or small for gestational age.	Fei et al. 2007, 2008a
Same as Fei et al. 2007, 2008a		PFOA or PFOS were not associated with Apgar scores (assessed 5 minutes after birth) or time to achieve developmental milestones.	Fei et al. 2008b
Subgroup of the Fei et al. (2007, 2008a, 2008b) cohort consisting of 526–787 children; mothers completed questionnaires regarding behavioral and social development when the children were 7 years of age	Maternal blood samples collected during first trimester Median serum PFOA: 5.4 ng/mL (range: 0.5–21.9 ng/mL) Median serum PFOS: 34.4 ng/mL (range: 7.3–106.7 ng/mL)	Association between maternal PFOA levels in the 2nd (3.96–5.32 ng/mL) and 3rd (5.35–7.11 ng/mL) quartiles and lower odds of having a child with higher scores in total difficulties, emotional symptoms, and hyperactivity, and the prevalence of total difficulties, emotional symptoms conduct problems, and peer problems was higher in the 4th quartile (7.14–21.90), but was not statistically significant after adjustment for potential confounding variables. No associations between maternal PFOS levels and development.	Fei and Olsen 2011
83 children aged 9–11 years living in New York	Median PFOA: 3.23 ng/mL Median PFOS: 8.79 ng/mL Median PFNA: 0.72 ng/mL Median PFDeA: 0.26 ng/mL Median PFHxS: 3.67 ng/mL Median PFOSA: 0.661 ng/mL	Serum PFOS, PFNA, PFDeA, PFHxS, and PFOSA associated with poorer performance on a task requiring behavioral inhibition.	Gump et al. 2011

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
665 offspring (aged 20 years) of women participating in a birth cohort study in Denmark	Maternal blood samples collected at gestation week 30 Median serum PFOA: 3.7 ng/mL (range: 0.1–19.8 ng/mL) Median serum PFOS: 21.5 ng/mL Median serum PFOSA: 1.1 ng/mL Median serum PFNA: 0.3 ng/mL	Significant positive associations between BMI and waist circumference in female offspring and maternal serum PFOA levels; no statistically significant associations in male offspring. Biomarkers of adiposity (insulin, leptin, and leptin-adioponectin ratio) were positively associated with maternal serum PFOA levels in female offspring and adiponectin levels were negatively associated with serum PFOA levels.	Halldorsson et al. 2012
252 pregnant women in Alberta Canada undergoing prenatal screening for Down's syndrome, trisomy 18, and open spina bifida; birth outcome data obtained from medical records	Blood samples collected in early second trimester Mean serum PFOA: 2.1 ng/mL (range:<LOD (0.25)–18 ng/mL) Mean serum PFOS: 9.0 ng/mL (range: <LOD (0.25)–35 ng/mL) Mean serum PFHxS: 2.1 ng/mL (range: <LOD (0.25)–43 ng/mL)	No associations between maternal serum levels of PFOA, PFOS, or PFHxS and birth weight, small for gestational age, or preterm delivery.	Hamm et al. 2010
Children aged 12–15 years participating in NHANES 1999–2000 or 2003–2004	Median serum PFOA: 4.4 ng/mL (range: 0.4–21.7 ng/mL) Median serum PFOS: 22.6 ng/mL (range: 2.1–87.2 ng/mL) Median serum PFHxS: 2.2 ng/mL (range: ND (0.1)–64.1 ng/mL) Median serum PFNA: 0.6 ng/mL (range: ND (0.1)–5.9 ng/mL)	Significant dose-response relationship between serum PFOS levels and parent-reported ADHD after adjustment for NHANES sample cycle, age, race/ethnicity, sex, environmental tobacco smoke, and maternal smoking during pregnancy. The adjusted OR for each 1 ng/mL increase in serum PFOS was 1.03 (95% CI 1.01–1.05). The adjusted ORs were also increased for PFOA (1.12 [95% CI 1.01–1.23]) and PFHxS (1.06 [1.02–1.11]). The association between ADHD likelihood and PFNA was not statistically significant.	Hoffman et al. 2010

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
15 pregnant Japanese women	Maternal blood samples collected during gestation weeks 38–41 Range of PFOS: 4.9–7.6 ng/mL Cord blood Range of PFOS: 1.6–5.3 ng/mL	No correlation between maternal serum or cord blood serum PFOS levels and birth weight or levels of TSH and free thyroxine levels in cord blood.	Inoue et al. 2004b
44 pregnant women in South Korea; birth outcome data obtained from questionnaires	Maternal blood samples mostly collected during the third trimester Median serum PFOA: 1.46 ng/mL (range: 1.15–1.91 ng/mL) Median serum PFOS: 2.93 ng/mL (range: 2.08–4.36 ng/mL) Median serum PFHxS: 0.55 ng/mL (range: 0.46–0.85 ng/mL) Median serum PFHpS: 0.09 ng/mL (range: 0.06–0.10 ng/mL) Median serum PFNA: 0.44 ng/mL (range: 0.23–0.62 ng/mL) Median serum PFDeA: 0.31 ng/mL (range: 0.24–0.39 ng/mL) Median serum PFUA: 0.60 ng/mL (range: 0.50–0.99 ng/mL)	Maternal PFOS levels negatively correlated with fetal cord triiodothyronine concentrations. No significant associations with other perfluoroalkyls or with thyroxine levels or TSH levels. No associations between maternal or cord blood perfluoroalkyl levels and adjusted birth weights.	Kim et al. 2011
59 pregnant women in South Korea; birth outcome data obtained from medical records	Maternal blood samples collected at delivery Mean maternal serum levels PFOA: 2.73 ng/mL (range: 1.20–5.72 ng/mL) PFOS: 10.77 ng/mL (range: 2.38–35.18 ng/mL) PFHxS: 1.35 ng/mL (range: 0.53–3.67 ng/mL) Mean umbilical cord blood levels PFOA: 2.09 ng/mL (range: 0.75–5.44 ng/mL) PFOS: 3.44 ng/mL (range: 0.34–9.64 ng/mL) PFHxS: 0.67 ng/mL (range: 0.22–1.69 ng/mL)	Maternal PFOA levels significantly higher in infants whose birth weight, birth length, and ponderal index (ratio of birth weight to length) were below the median level. No significant associations between birth weight or size and maternal PFOS or PFHxS or umbilical PFOA, PFOS, or PFHxS levels. Inverse association between maternal PFOS and ponderal index (OR 0.22, 95% CI 0.05–0.90) and between umbilical PFHxS and birth weight (OR 0.26, 95% CI 0.08–0.85).	Lee et al. 2013

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
447 girls participating in Avon Longitudinal Study of Parents and Children in Great Britain; birth outcome data obtained from medical records	Maternal blood samples collected at gestation week 15 Median maternal serum levels: PFOA: 3.7 ng/mL (range: 1.0–16.4 ng/mL) PFOS: 19.6 ng/mL (range: 3.8–112.0 ng/mL) PFHxS: 1.6 ng/mL (range: 0.2–54.8 ng/mL)	Negative trend between birth weight and maternal PFOS, PFOA, and PFHxS levels. Negative trend for birth length and maternal PFOS and PFHxS levels. No significant associations were found for gestational age or ponderal index. Positive association between weight at 20 months of age (adjusted for height at 20 months and birth weight) and maternal PFOS levels.	Maisonet et al. 2012
101 pregnant women participating in the Family Study in Ontario Canada; birth outcome data obtained from medical records	Maternal blood collected at delivery Median maternal serum levels: PFOA: 1.81 ng/mL (range: 1.33–2.64 ng/mL) PFOS: 14.54 ng/mL (range: 9.19–20.22 ng/mL) PFNA: 0.69 ng/mL (range: 0.542–0.87 ng/mL) PFHxS: 1.62 ng/mL (range: 1.33–2.66 ng/mL) Median cord blood serum levels PFOA: 1.58 ng/mL (range: 1.09–2.37 ng/mL) PFOS: 6.08 ng/mL (range: 3.92–9.11 ng/mL)	No significant correlations between maternal serum perfluoroalkyl levels at delivery and birth weight. No correlations between cord blood serum PFOA or PFOS levels and birth weight.	Monroy et al. 2008
343 pregnant women in Japan; cord blood samples collected at delivery to measure total IgE levels; infant allergies and infectious disease information collected during first 18 months of age	Maternal blood samples collected after the second trimester Median serum PFOA: 1.3 ng/mL (range: ND–5.3 ng/mL) Median serum PFOS:5.2 ng/mL (range: 1.3–16.2 ng/mL)	Significant inverse association between maternal PFOA levels and cord blood IgE levels in female infants; no association in males. No association between maternal PFOA or PFOS levels and infant food allergy, eczema, wheezing, or otitis media.	Okada et al. 2012

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
169 males aged 19–21 years in Denmark whose mothers participated in pregnancy cohort study	Maternal blood samples collected during gestation week 30 Median serum PFOA: 3.8 ng/mL Median serum PFOS: 21.2 ng/mL	Negative association between maternal PFOS and sperm concentration and total sperm count; no association with PFOA. Negative association between PFOA and percentage of progressive spermatozoa. Positive trend between maternal POFA and follicle stimulating hormone and luteinizing hormone levels in men. No association with testosterone, estradiol, inhibin B, sex hormone-binding globulin or free androgen index. No associations between PFOS and semen outcome or reproductive hormone levels.	Vested et al. 2013
244 children (2 years of age) whose mothers participated in the Taiwan Birth Panel cohort study; 43% developed atopic dermatitis as evaluated via a questionnaire and a dermatologist examination of a subset of the children	Median cord blood serum levels PFOA: 1.71 ng/mL (range: 0.75–17.40 ng/mL) PFOS: 5.50 ng/mL (range: 0.11–48.36 ng/mL) PFNA: 2.30 ng/mL (range: 0.38–63.87 ng/mL) PFHxS: 0.035 ng/mL (range: 0.035–0.420 ng/mL)	No correlations between cord blood perfluoroalkyl levels and serum IgE in the children; PFOA and PFOS were correlated with cord blood IgE in males. Atopic dermatitis was significantly associated with PFOS levels at >2.775 ng/mL (5^{th} quartile); however, no longer significant when adjusted for sex, gestational age, maternal age, maternal history of atopy, duration of breast feeding, and prenatal environmental tobacco smoke.	Wang et al. 2011
428 pregnant Japanese women; infant data obtained from medical records	Blood samples collected in second trimester Median PFOA: 1.3 ng/mL (range: ND–5.3 ng/mL) Median PFOS: 5.2 ng/mL (range: 1.3–16.2 ng/mL)	Negative correlation between maternal serum PFOS and birth weight; when analyzed by sex, only significant in females. No correlation between serum PFOS and birth length, chest circumference, or head circumference. No correlations between maternal PFOA and birth weight or size (adjusted for potential confounding variables).	Washino et al. 2009

Table 3-7. Developmental Effects in Humans Exposed to Perfluoroalkyls

Design and population	Perfluoroalkyl concentrations	Significant effects	Reference
901 pregnant women enrolled in the Norwegian Mother and Child Cohort study; birth outcome data taken from Medical Birth Registry of Norway	Maternal blood samples collected around gestation week 17 Median PFOA: 2.2 ng/mL Median PFOS: 13.0 ng/mL	No association between maternal PFOS or PFOA and birth weight after adjustment for potential confounding variables. Negative association of preterm birth and maternal PFOS and PFOA levels. No association between PFOS or PFOA levels and small for gestational age or large for gestational age.	Whitworth et al. 2012a

ADHD = attention deficit/hyperactivity disorder; BMI = body mass index; 95% CI= 95% confidence interval, Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid; IgE = immunoglobin E; LBW = low birth weight, <2,500 g; LHWA = Little Hocking Water Association; LLOQ = lower limit of quantification; Me-PFOSA-AcOH = 2-(N-methyl-perfluorooctane sulfonamide) acetic acid; ND= not detected; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PBPK = physiologically based pharmacokinetic; PFDeA = perfluorodecanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide; PFUA = perfluoroundecanoic acid; TSH = thyroid stimulating hormone

PFOA, and compared the birth outcomes (taken from the Ohio Department of Health) to outcomes from women living in areas not serviced by LHWA. The incidence of low birth weight (<2,500 g) infants was significantly lower in the exclusive and partial LHWA groups, as compared to the national average, and the likelihood of low birth weight was significantly lower in the partial LHWA group, as compared to the no LHWA group; however, no association was found among the group exclusively serviced by LHWA. Additionally, no associations between residence location and mean birth weights, gestational age, or the likelihood of preterm birth were found. A later study by this group (Nolan et al. 2010) did not find significant differences in the likelihood of congenital anomalies in infants of mothers living in the partially or exclusively LHWA serviced areas, as compared to infants of mothers living in areas not serviced by LHWA. A major limitation of these studies is the lack of biomonitoring data, which would allow for a more accurate examination of possible associations between maternal PFOA exposure and birth outcome. Other studies done in residents of this area of Ohio and West Virginia (including participants in the C8 Health Project) used estimates of maternal PFOA and PFOS levels (Darrow et al. 2013; Savitz et al. 2012b; Stein et al. 2009). Stein et al. (2009) examined the self-reported outcomes of pregnancies that occurred within 5 years preceding blood sample collections for the C8 Health Project. No associations were found between serum PFOA levels in 1,845 pregnancies and the likelihood of miscarriage, preterm birth, low birth weight, or birth defects; the investigators did note that there was a decreased risk of low birth weight among infants of mothers with higher serum PFOA levels (75^{th}–90^{th} percentile), but there was no apparent dose-response relationship. Stein et al. (2009) also examined the possible association between maternal serum PFOS levels and birth outcomes from 5,262 pregnancies; the likelihood of preterm birth was significantly increased in women with PFOS levels above the 90^{th} percentile (23.2–83.4 ng/mL). The likelihood of low birth weight was increased in women with serum PFOS levels above the median (12.8 ng/mL), in the 75^{th}–90^{th} percentile (17.7–<23.2 ng/mL) and above the 90^{th} percentile (23.2–83.4 ng/mL). No association between maternal PFOS levels and the risk of miscarriage or birth defects were found. Similarly, Savitz et al. (2012b) found no association between estimated maternal serum PFOA levels and the risk of stillbirths, preterm birth, low birth weight, or birthweight in 8,253 singleton infants born to mothers living in areas of the Mid-Ohio valley with known PFOA contamination from 1990 to 2004. The maternal serum PFOA levels were estimated based on estimated environmental levels of PFOA at the mother's current address and a PBPK model using standard assumptions regarding water intake, body weight, and PFOA half-life (Shin et al. 2011); the median estimated maternal serum level was 7.7 ng/mL. Using a subset of 4,547 singleton births, the estimated maternal levels were refined to include estimated environmental levels of PFOA based on maternal lifetime residential history and adjusted using a Bayesian time-dependent calibration that incorporated measured serum concentrations (collected in 2005–2006) (Savitz et al. 2012b); the median

estimated maternal serum PFOA level was 13.4 ng/mL. Adjusting the estimated maternal serum PFOA levels resulted in a significant association between birth weight and both the uncalibrated serum PFOA levels and the Bayesian-calibrated serum PFOA levels. The adjusted serum PFOA levels were not associated with the likelihood of preterm birth, low birth weight, or small for gestational age. In the Darrow et al. (2013) study of 1,330 women participating in the C8 Health Project and giving birth between 2005 and 2010, blood samples collected in 2005–2006 were used to estimate maternal serum levels. No associations between estimated maternal serum PFOA or PFOS levels and the likelihood of preterm birth, low birth weight, or small for gestational age were found in the entire cohort or in a subcohort of 783 women whose first pregnancy occurred after blood samples were collected. In the entire cohort, there was a nonsignificant trend for decreased birth weight among full-term infants with increasing PFOS levels; this trend was statistically significant in the subcohort of nulliparous women. No association between maternal PFOA levels and birth weight was found.

Several large-scale studies of the general population have also examined the possible association between maternal blood perfluoroalkyl levels and birth outcome. In a study of 1,400 pregnant women participating in the Danish National Birth Cohort, maternal PFOA levels were inversely associated with birth weight; birth weights were significantly lower in infants of mothers with serum PFOA levels in the second (3.91–5.20 ng/mL), third (5.21–6.96 ng/mL), and fourth (≥6.97 ng/mL) quartiles, as compared to the first quartile (Fei et al. 2007). Maternal serum PFOA levels were also inversely associated with birth length and abdominal circumference (Fei et al. 2008a); however, in stratified analysis (after adjustment for potential confounding variables), only birth lengths in the infants of mothers with serum PFOA levels in the second and fourth quartile were significantly lower than in the first quartile. Grouping the infants by sex resulted in significant inverse associations between serum PFOA and birth weight in the male and female infants (Andersen et al. 2010). No significant associations between maternal serum PFOS levels and birth weight, birth length, or abdominal circumference were found (Fei et al. 2007, 2008a). However, when the infants were grouped by sex, maternal PFOS levels were inversely associated with birth weight in female infants (Andersen et al. 2010). No associations between serum PFOA or PFOS levels and gestation length, likelihood of low birth weight, or small for gestational age were found in this cohort (Fei et al. 2008a). The study also found no associations between maternal serum PFOA or PFOS levels and Apgar scores (assessed 5 minutes after birth) (Fei et al. 2008b). A study of 901 pregnant women participating in the Norwegian Mother and Child cohort study found inverse associations between maternal serum PFOA (median of 2.2 ng/mL) and PFOS (median of 13.0 ng/mL) and the likelihood of preterm birth (Whitworth et al. 2012a). No associations (after adjustment for potential confounding variables) were found between maternal serum PFOA or PFOS levels and birth weight, small for

gestational age, or large for gestational age. Significant negative trends between maternal serum PFOA, PFOS, and PFHxS levels and birth weight were found in a study of 447 female infants of mothers participating in the Avon Longitudinal Study of Parents and Children in Great Britain; birth length was also negatively associated with maternal serum PFOS and PFHxS (Maisonet et al. 2012). A negative correlation between maternal serum PFOS levels and birth weight was also observed in a study of 428 pregnant Japanese women (geometric mean PFOS level was 4.9 ng/mL); when the infants were grouped by sex, the significant association was only found in females (Washino et al. 2009). No significant association was found between birth weight and maternal serum PFOA levels (geometric mean level of 1.2 ng/mL) and no associations were found between serum PFOA or PFOS levels and birth length, chest circumference, or head circumference (Washino et al. 2009). A study of 252 pregnant women in Canada undergoing screening for Down's syndrome, trisomy 18, and open spina bifida found no association between maternal serum levels of PFOA, PFOS, or PFHxS and birth weight, small for gestational, or preterm delivery; the mean serum concentrations of PFOA, PFOS, and PFHxS were 2.1, 9.0, and 2.1 ng/mL, respectively (Hamm et al. 2010). Smaller-scale studies of pregnant women in Canada (Monroy et al. 2008), South Korea (Kim et al. 2011; Lee et al. 2013), and Japan (Inoue et al. 2004b) did not find significant associations between maternal serum PFOS levels (Inoue et al. 2004b; Kim et al. 2011; Lee et al. 2013; Monroy et al. 2008) or PFHxS (Kim et al. 2011; Lee et al. 2013) and birth weight. Kim et al. (2011) and Monroy et al. (2008) also did not find a significant association between serum PFOA and birth weight; however, Lee et al. (2013) found significantly higher maternal blood PFOA levels in infants whose birth weights were below the median level. The Lee et al. (2013) study also found significantly higher maternal PFOA levels in infants with birth length and ponderal index below the median level and an inverse association between maternal PFOS levels and ponderal index.

Cord blood serum PFOA and PFOS levels were inversely associated with birth weight, ponderal index, and head circumference in a study of 341 singleton births in Baltimore, Maryland (Apelberg et al. 2007b). Similarly, Chen et al. (2012a) found a significant inverse association between cord blood PFOS levels and birth weight, head circumference, and gestational age in a study of 492 infants whose mothers were participating in the Taiwan Birth Panel study. The likelihood of preterm birth and small for gestational age were also significantly associated with PFOS; low birth weight was not associated with cord blood PFOS levels. Cord blood PFOA, PFNA, and PFUA levels were not associated with birth weight or the likelihood of preterm birth, low birth weight, or small for gestational age; an inverse association between PFNA and ponderal index was found. Monroy et al. (2008) did not find significant correlations between cord blood PFOA or PFOS levels and birth weight in a study of 101 pregnant women in Canada. In a study of 59 women in South Korea (Lee et al. 2013), there was a significant inverse association between

cord blood PFHxS and birth weight; no associations were found between cord blood PFOA, or PFOS levels and birth weight. Kim et al. (2011) did not find any significant associations between cord blood PFOA, PFOS, PFHxS, PFHpS, PFNA, PFDeA, or PFUA levels and birth weights among infants of 44 pregnant women in South Korea.

Follow-up studies of the infants of mothers participating in the Danish National Birth Cohort study monitored growth at 5 months, 12 months, and 7 years of age. No significant associations between maternal PFOA levels and body weight or infant BMI were found at 5 or 12 months of age (Andersen et al. 2010). However, when grouped by sex, inverse associations between maternal PFOA levels and body weight and BMI were found in male infants at 5 and 12 months of age (Andersen et al. 2010). Maternal PFOS levels were inversely associated with infant body weight and BMI at 12 months, but not at 5 months; grouping by sex resulted in significant association in 12-month-old male infants. At age 7 years, there were no significant associations between maternal PFOS or PFOA levels and child BMI or waist circumference and the risk of being overweight was not significantly associated with maternal serum PFOS or PFOA levels (Andersen et al. 2013). Halldorsson et al. (2012) examined 665 offspring of women participating in a birth cohort study in Denmark and found significant positive associations between BMI and waist circumference in females and maternal serum PFOA levels (median level of 3.7 ng/mL), but no association in male offspring. Biomarkers of adiposity (insulin, leptin, and leptin-adioponectin ratio) were also positively associated with maternal serum PFOA levels in the female offspring. Maisonet et al. (2012) found a positive association between body weight at 20 months and maternal PFOS levels in a study of girls in Great Britain. A follow-up study of C8 participants found no association between early life PFOA exposure (estimated average PFOA serum concentration over the first 3 years of life) and overweight or obesity risk in men and women (Barry et al. 2014).

Neurodevelopment was also evaluated in the children of mothers in the Danish National Birth Cohort study at 6 months, 18 months, and 7 years of age. Maternal serum PFOA and PFOS levels were not associated with alterations in the time to achieve developmental milestones in 6- and 18-month-old children (Fei et al. 2008b). At 7 years of age, no significant alterations (after adjustment for potential confounders) in behavioral or social development and maternal serum PFOA and PFOS levels were found (Fei et al. 2011). Using NHANES data for serum perfluoroalkyl levels in children aged 12–15 years, Hoffman et al. (2010) found a significant dose-response relationship between serum PFOS, PFOA, and PFHxS levels and the likelihood of ADHD diagnosis; no association was found with PFNA levels. Stein and Savitz (2011) also found an increase in the likelihood of ADHD diagnosis in children aged 5–18 years participating in the C8 Health project with serum PFHxS levels in the second (2.9–<5.2 ng/mL),

third (5.2–<10.1 ng/mL) or fourth (10.1–276.4 ng/mL) quartiles; the likelihood of ADHD diagnosis was not significantly associated with serum PFOA, PFOS, or PFNA levels. The study also found an increased likelihood of learning problems in children with serum levels of PFHxS in the fourth quartile. Gump et al. (2011) evaluated the potential effect of perfluoroalkyl exposure on impulsivity, which is a defining feature of ADHD, using the differential reinforcement of low rates of responding task in 83 children aged 9–11 years living in New York and participating in another study on the effects of low-level lead exposure on cardiovascular responses to acute stress. Significant associations between serum PFOS, PFNA, PFDeA, PFHxS, and PFOSA levels and impulsivity were found; no associations were found for PFOA. Stein et al. (2013) examined 320 children aged 6–12 who lived in a PFOA-contaminated area of the Mid-Ohio Valley from the time of the mother's pregnancy until C8 Health Project enrollment. Estimated *in utero* serum PFOA concentrations or the child's serum PFOA level were not significantly associated with an adverse effect on neuropsychological tests, including IQ, reading and math skills, language, memory and learning, visual-spatial processing, and attention.

Three studies have examined the possible association between perfluoroalkyl exposure and development of the reproductive system. In a study of over 3,000 boys and 2,900 girls aged 8–18 years participating in the C8 Health Project and C8 Science Panel studies, Lopez-Espinosa et al. (2011) found inverse significant associations between serum PFOS levels and the age of puberty in boys (as assessed by total testosterone levels) and girls (as assessed by self-reported age of menarche); the differences in the age of puberty in boys and girls with serum PFOS levels in the highest quartile (geometric means of 36.0 and 35.2 ng/mL in boys and girls) compared to those in the lowest quartile (geometric means of 10.2 and 9.8 ng/mL) were 190 and 139 days, respectively. In girls, serum PFOA was also significantly inversely associated with age of puberty; the differences between the highest (geometric mean of 151.0 ng/mL) and lowest quartile (geometric mean of 7.7 ng/mL) was 130 days. The biological significance of this 4–5-month delay in sexual maturation is not known. Christensen et al. (2011) did not find any association between maternal perfluoroalkyl levels and age of menarche in 448 girls participating in the Avon Longitudinal Study of Parents and Children in Great Britain; the median maternal serum levels of PFOA, PFOS, and PFHxS were 3.7, 19.8, and 1.6 ng/mL, respectively. A third study of 169 males aged 19–21 years whose mothers participated in a pregnancy cohort study in Denmark found significant inverse associations between maternal serum PFOS levels and sperm concentration and total sperm count and between maternal serum PFOA levels and percentage of progressive spermatozoa (Vested et al. 2013). A positive trend between maternal serum PFOA levels and FSH and LH levels in men were found, but there was no association with testosterone or estradiol levels.

Okada et al. (2012) reported a significant inverse association between maternal serum PFOA levels and cord blood IgE levels in female infants, but not in male infants, in a study of 343 women in Japan. There were no associations between maternal PFOA or PFOS levels and the likelihood of infant food allergies, eczema, wheezing, or otitis media when the infants were followed for the first 18 months of age. Wang et al. (2011) also found no significant association between cord perfluoroalkyl levels and the occurrence of atopic dermatitis in a study of 242 2-year-old children whose mothers participated in the Taiwan Birth Panel cohort study. The study also found a significant correlation between cord PFOA and PFOS levels and cord blood IgE levels in males, but did not find any correlations between cord perfluoroalkyl levels and serum IgE levels in the 2 year old children.

Epidemiology studies have examined the potential developmental toxicity of perfluoroalkyls in studies of populations living in areas with high PFOA contamination and in the general population. Birth weight was the most studied end point in these studies. Although it is difficult to compare across studies due to the differences in study design and the characterization of perfluoroalkyl exposure, ranking the studies by the upper end of the blood perfluoroalkyl levels provides some suggestion of an effect on birth weight (Table 3-8). Overall, the studies suggest that higher maternal blood levels of PFOA, PFOS, and PFHxS are associated with lower birth weights. However, the magnitudes of the decreases in birth weight are small and the biological significance of the finding is not known. Although low birth weight can be associated with increased infant mortality and morbidity, the deceases in birth weight were not great enough to result in an increased risk of low birth weight infants. In general, studies of highly exposed individuals did not find an increased risk for low birth weight infants (<2500 g) associated with high maternal PFOA levels (Darrow et al. 2013; Savitz et al. 2012b; Stein et al. 2009). Two studies (Nolan et al. 2009; Stein et al. 2009) reported lower risks of low birth weight infants at the highest maternal PFOA levels. Other developmental end points have not been as widely investigated. The available data do not suggest an association between PFOA exposure and birth defect incidence (Darrow et al. 2013; Nolan et al. 2009; Savitz et al. 2012b; Stein et al. 2009) or PFOA exposure and increased risk of stillbirths or premature birth (Darrow et al. 2013; Hamm et al. 2010; Savitz et al. 2012b). The conflicting results of studies examining an association between perfluoroalkyl exposure and risk of ADHD (Grump et al. 2011; Hoffman et al. 2010; Stein and Savitz 2011) and onset of puberty (Christensen et al. 2011; Lopez-Espinosa et al. 2011) preclude a weight of evidence determination.

Table 3-8. Possible Association Between Perfluoroalkyl Exposure and Alterations on Birth Weight in Humans

Reference	Timing of blood collection	Maternal blood levels		Effect on birth weight
		Mean (ng/mL)	Range (ng/mL)	
PFOA				
Savitz et al. 2012b	Estimated	13.4 (median)	3.9–921.3	-18.55 g per 100 ng/mL increase in PFOA levels
Darrow et al. 2013	2005–2006	31.0	0.6–459.5	Nonsignificant trend, significant in women whose first pregnancy was conceived after sample collection
Nolan et al. 2009	No biomonitoring data			NS
Fei et al. 2007	First trimester	5.6	<LLOQ (1.0)–41.5	-10.63 g per 1 ng/mL increase in PFOA
Maisonet et al. 2012	Gestation week 15	3.7 (median)	1.0–16.4	Negative trend
Lee et al. 2013	Delivery	2.73	1.20–5.72	PFOA levels significantly higher in infants below the median birth weight
Hamm et al. 2010	Early 2nd trimester	2.1	<LOD (0.25)–18	NS
Washino et al. 2009	Second trimester	1.4	ND–5.3	NS
Monroy et al. 2008	Delivery	2.24	1.33–2.64	NS
Whitworth et al. 2012a	Gestation week 17	2.2 (median)	NR	NS
Kim et al. 2011	Third trimester	1.46 (median)	1.15–1.91	NS
PFOS				
Maisonet et al. 2012	Gestation week 15	19.6 (median)	3.8–112.0	Negative trend
Fei et al. 2007	First trimester	35.3	6.4–106.7	NS
Darrow et al. 2013	2005–2006	15.6	LOD (0.25)–92.9	-49 g per log unit increase in PFOS levels (nulliparous women)
Monroy et al. 2008	Delivery	16.19	9.19–20.22	NS
Whitworth et al. 2012a	Gestation week 17	13.0 (median)	NR	NS
Lee et al. 2013	Delivery	10.77	2.38–35.18	NS
Hamm et al. 2010	Early second trimester	9.0	<LOD (0.25)–35	NS
Washino et al. 2009	Second trimester	5.6	1.3–16.2	-148.8 g per 10 ng/mL increase in PFOS levels
Inoue et al. 2004b	Gestation weeks 38–41		4.9–7.6	NS
Kim et al. 2011	Third trimester	2.93 median)	2.08–4.36	NS

Table 3-8. Possible Association Between Perfluoroalkyl Exposure and Alterations on Birth Weight in Humans

Reference	Timing of blood collection	Maternal blood levels		Effect on birth weight
		Mean (ng/mL)	Range (ng/mL)	
PFHxS				
Maisonet et al. 2012	Gestation week 15	1.6 (median)	0.2–54.8	Negative trend
Monroy et al. 2008	Delivery	1.62	1.33–2.66	NS
Lee et al. 2013	Delivery	1.35	0.53–3.67	NS
Kim et al. 2011	Third trimester	0.55 (median)	0.46–0.85	NS

LLOQ = lower limit of quantification; LOD = limit of detection; NR = not reported; NS = no significant association found; PFHxS = perfluorohexane sulfonic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

A number of studies have examined the potential of perfluoroalkyls, particularly PFOA and PFOS, to induce developmental effects in laboratory animals. These studies examined birth outcome, developmental milestones, mammary gland development, neurological development, and immune development.

Laboratory Animal Exposure Studies—PFOA. *In utero* exposure to PFOA resulted in prenatal losses and decreases in pup survival. An increase in resorptions was observed in mice administered ≥5 mg/kg/day throughout gestation (Lau et al. 2006) or 2 mg/kg/day on GDs 11–16 (Suh et al. 2011). Prenatal losses were also observed in PFOA mouse studies administering ≥6 mg/kg/day (Abbott et al. 2007), 5 mg/kg/day (White et al. 2011b), or 20 mg/kg/day (Lau et al. 2006) throughout gestation; an increase in the percentage of dams with total litter loss was also observed at 5 mg/kg/day (Wolf et al. 2007). Administration of 20 mg/kg/day PFOA on GDs 7–17 or 10–17 did not result in litter loss (Wolf et al. 2007); no effect on litter size was observed as a result of administration of 5 mg/kg/day on GDs 8–17 (White et al. 2009). Gestational exposure (GDs 1–17) to PFOA also resulted in decreases in pup survival in mice exposed to ≥0.6 mg/kg/day (Abbott et al. 2007), 3 mg/kg/day (Albrecht et al. 2013), or 5 mg/kg/day (Yahia et al. 2010; White et al. 2011b, Wolf et al. 2007); 100% pup mortality was observed in the offspring of mice exposed to 10 mg/kg/day throughout gestation (Yahia et al. 2010). Decreased pup survival was also observed in mice exposed to 5 mg/kg/day PFOA on GDs 15–17 (Wolf et al. 2007). No alterations in fetuses/litter or survival were observed at 1 mg/kg/day PFOA (White et al. 2011b). Butenhoff et al. (2004b) also reported increases in pup mortality on PNDs 6–8 in the offspring of rats administered 30 mg/kg/day PFOA throughout gestation and during lactation.

Decreases in birth weight have not been consistently found in mouse studies with PFOA. No significant alterations in birth weight were observed in mice exposed to 3 mg/kg/day (Albrecht et al. 2013), 5 or 10 mg/kg/day (Lau et al. 2006), or 20 mg/kg/day (Abbott et al. 2007); decreases in birth or fetal weight were observed at 5 mg/kg/day (Hines et al. 2009; Yahia et al. 2010), 10 mg/kg/day (Suh et al. 2011), or 20 mg/kg/day (Lau et al. 2006). A decrease in mean litter weight on PNDs 2–14 was observed in mice administered ≥0.5 mg/kg/day PFOA on GDs 6–17 (Hu et al. 2010) and a decrease in pup body weight on PND 20 was observed in mice exposed to 5 mg/kg/day on GDs 8–17 or 12–17 (White et al. 2007). *In utero* exposure of mice to PFOA throughout gestation resulted in decreases in pup body weight in mice exposed to 1 mg/kg/day (Abbott et al. 2007; Hines et al. 2009), ≥3 mg/kg/day (Lau et al. 2006; Wolf et al. 2007), and 5 mg/kg/day (Yahia et al. 2010; White et al. 2007, 2011b). In a cross-fostering study, lactation only exposure (maternal dose of 5 mg/kg/day PFOA) resulted in decreased body weight in female pups on some PNDs (2, 3, 4, and 22, but not on PNDs 7, 10, 15, or 17) (Wolf et al. 2007). Hines et al. (2009)

monitored body weights from birth to 18 months of age in female mice exposed *in utero* to PFOA on GDs 1–17. At weaning, decreases in body weight were observed at 1 and 5 mg/kg/day; by 10 weeks of age, there were no differences body weight between the controls and mice exposed to ≥1 mg/kg/day. Significant increases in body weight were observed in mice exposed to 0.1 and 0.3 mg/kg/day, and by 20–29 weeks of age, the increases in body weight were observed in mice exposed to 0.01, 0.1, or 0.3 mg/kg/day. At 40 weeks of age, the increased body weight was observed in the 0.1 and 0.3 mg/kg/day groups. At termination (18 months of age), there were no differences in body weight between the controls and mice exposed to 0.01–3 mg/kg/day; a decrease in body weight was observed at 5 mg/kg/day. During the period of increased body weight in the lower-dose animals, there were no changes in serum glucose levels or the response to a glucose challenge, but there were significant increases in insulin and leptin levels at 0.01 and 0.1 mg/kg/day. Although there were no changes in the percentage of body fat to body weight measurements in mice at 42 weeks of age, at 18 months of age, significant decreases in abdominal body fat and increases in intrascapular brown fat was observed at ≥1 mg/kg/day PFOA (Hines et al. 2009).

A few studies have examined the potential of PFOA to induce malformations/variations. Lau et al. (2006) reported reductions in ossification of supraoccipital and microcardia in the offspring of mice administered 10 or 20 mg/kg/day throughout gestation; a marked decrease in neonatal survival was also observed at these doses. This study also reported enlarged fontanels in pups exposed to ≥1 mg/kg/day and tail and limb defects at ≥5 mg/kg/day; however, there was no clear dose-response for these effects. No increases in the occurrence of malformations/variations were observed in the offspring of rats administered 100 mg/kg/day on GDs 6–15 (Staples et al. 1984) or in a two-generation study at doses as high as 30 mg/kg/day (Butenhoff et al. 2004b).

Delayed eye opening was observed in the offspring of mice administered ≥1 mg/kg/day PFOA on GDs 1–17 (Abbott et al. 2007) and in mice administered 5 mg/kg/day throughout gestation (Lau et al. 2006; Wolf et al. 2007). Neither Albrecht et al. (2013) nor Lau et al. (2006) found alterations in eye opening in mice exposed to 3 mg/kg/day PFOA on GDs 1–17. Lau et al. (2006) also reported advanced preputial separation at ≥1 mg/kg/day and delayed vaginal opening at 20 mg/kg/day. The effect in the male offspring is in contrast to the Butenhoff et al. (2004b) study, which found delays in preputial separation in rats exposed to 30 mg/kg/day PFOA; a delay in vaginal patency was also observed at this dose.

A series of studies conducted by White and associates found significant delays in mammary gland development in the offspring of mice administered 1 mg/kg/day PFOA via gavage on GDs 8–17 (White et

al. 2011b) or 5 mg/kg/day PFOA on GDs 1–17, 8–17, 12–17, 10–17, 13–17, or 15–17 (White et al. 2007, 2009, 2011b). The delay was characterized as reduced ductal elongation and branching and delays in timing and density of terminal end buds and was observed at all observational periods (PNDs 10, 20, 22, and 42, and 63 and 18 months of age). Decreases in mammary epithelial growth, as assessed by developmental scoring, were observed in the offspring of mice exposed to 0.3 mg/kg/day on GDs 1–17 (Macon et al. 2011) or 0.01 mg/kg/day on GDs 10–17 (Macon et al. 2011). Albrecht et al. (2013) did not find any alterations in mammary gland development on PND 20 in mouse offspring following *in utero* exposure to PFOA on GDs 1–17. Delayed mammary gland development was also observed in offspring only exposed via lactation (maternal dose of 3 mg/kg/day PFOA on GDs 1–17); the effects were observed on PNDs 42 and 63, but not on PND 22 (White et al. 2009). In a multigeneration study conducted by White et al. (2011b), delays in mammary gland development were not consistently observed in the F2 offspring of F1 females who were exposed *in utero* to 1 or 5 mg/kg/day PFOA. However, delays in mammary gland development were observed in the F1 and F2 offspring exposed to 0.001 mg/kg/day *in utero* (GDs 7–17) and postnatally. The investigators (White et al. 2011b) noted that the delay in mammary gland development did not appear to affect lactational support based on normal survival and growth of the F2 pups.

A consistent finding in the three mouse studies evaluating the neurodevelopmental toxicity of PFOA is an increase in motor activity. In the offspring of mice exposed to 1.6 mg/kg/day throughout gestation and lactation, significant increases in open field activity was observed at PND 36 (Cheng et al. 2013a). Johansson et al. (2008) and Onishchenko et al. (2011) demonstrated a biphasic alteration in motor activity: an initial period of decreased activity followed by increased activity. Johansson et al. (2008) administered a single dose of 8.7 mg/kg/day PFOA to mice on PND 10 and monitored spontaneous activity for a 1-hour period when the mice were 2 or 4 months of age. In the first 20-minute period, there was a decrease in spontaneous activity, followed by a 20-minute period with an activity level similar to controls, and a 20-minute period with significantly increased spontaneous activity. Similarly, Onishchenko et al. (2011) reported an increase in activity in a 48-hour period in the adult offspring of mice exposed to 0.3 mg/kg/day PFOA throughout gestation; however, there was a decrease in activity during the initial 3 hours of testing. Johansson et al. (2008) also found an increased susceptibility of the cholinergic system in mice exposed to 0.58 or 8.7 mg/kg/day PFOA on PND 10. In control mice, an injection of nicotine resulted in increases in activity; mice exposed to 0.58 mg/kg/day also responded with an increase in activity, although the increase was less than that observed in the controls. In contrast, nicotine resulted in a decrease in activity in mice exposed to 8.7 mg/kg/day. Exposure to PFOA did not alter learning or memory, as evidenced by the lack of effect on maze tests (Cheng et al. 2013a; Johansson

et al. 2008). Tests of neurobehavioral development found altered motor coordination and impaired negative geotaxis reflex, but no effect on righting reflex or cliff avoidance in the offspring of mice exposed to 1.6 mg/kg/day throughout gestation and lactation (Cheng et al. 2013a).

Laboratory Animal Exposure Studies—PFOS. Increases in fetal mortality and decreases in pup survival have also been observed in rats and mice exposed to PFOS *in utero* (Abbott et al. 2009; Chen et al. 2012b; Fuentes et al. 2006; Grasty et al. 2003, 2005; Lau et al. 2003; Luebker et al. 2005a, 2005b; Thibodeaux et al. 2003; Xia et al. 2011; Yahia et al. 2008). Decreases in the number of live fetuses were observed in mice exposed to 20 mg/kg/day on GDs 1–17 (Thibodeaux et al. 2003) or 0–17 (Yahia et al. 2008); no alterations in fetal mortality were observed at 15 mg/kg/day (Thibodeaux et al. 2003). In contrast, pup survival is affected at much lower maternal doses. Significant decreases in pup survival were observed in rats at 1.6 mg/kg/day (dams were exposed for 6 weeks prior to mating and during gestation through lactation days 4 or 21) (Luebker et al. 2005a, 2005b) and in mice exposed to 4.5 mg/kg/day on GDs 19–20 (Abbott et al. 2009); no alterations in pup survival were observed in rats or mice exposed to 1 mg/kg/day (Luebker et al. 2005b; Yahia et al. 2008). A series of studies by Grasty et al. (2003) in rats that were exposed for 4 days during different gestational periods showed that the pup was more susceptible if exposure occurred later in gestation. On PND 4, pup survival was 70, 50, 60, 20, or 5% for exposures on GDs 2–5, 6–9, 10–13, 14–17, or 17–20, respectively. Grasty et al. (2003) and others (Abbott et al. 2009; Chen et al. 2012b; Lau et al. 2003) also noted that most deaths occurred within the first 4 PNDs, with the highest rates occurring on PND 1. Lau et al. (2003) and Luebker et al. (2005a) found that cross fostering did not significantly improve pup survival; deaths were observed in the *in utero* only exposure group. However, Luebker et al. (2005a) showed that rats exposed *in utero* and during lactation had the highest pup mortality, as compared to other cross-fostered groups. The mechanism involved in the early pup mortality has not been identified, but there is some indication that pulmonary deficits maybe a contributing factor. At high doses (50 mg/kg/day administered on GDs 19–20), pups demonstrated difficulty breathing within minutes of birth (Grasty et al. 2003). Histological examination of the lungs of pups exposed to 25 or 50 mg/kg/day on GDs 19–20 showed evidence of delayed lung maturation (Grasty et al. 2003, 2005), specifically, an increase in the proportion of solid lung tissue and a decrease in the proportion of small airway tissue. A comparison of the lungs of PFOS-exposed neonates to control fetuses (GD 21) showed that 17 and 50% of the lung tissue in the neonates exposed to 25 or 50 mg/kg/day, respectively, on GDs 19–20 was not histologically different from the control fetuses (Grasty et al. 2005). Administration of therapeutic agents known to enhance terminal lung maturation and accelerate surfactant production did not improve pup survival (Grasty et al. 2005). Histological damage has also been reported in pups exposed to lower PFOS levels. Lung atelectasis was observed in

pups exposed to 10 mg/kg/day on GDs 0–18 (Yahia et al. 2008). No lung effects were observed in pups exposed to 1 mg/kg/day or in fetuses exposed to 20 mg/kg/day on GDs 0–17 (Yahia et al. 2008). Alveolar hemorrhage, thickened epithelial walls of the pulmonary alveolus, focal lung consolidation, and focal infiltration of inflammation cells were observed in pups exposed to 2 mg/kg/day on GDs 0–21; no lung effects were observed at 0.1 mg/kg/day (Chen et al. 2012b).

Decreases in fetal body weight, birth weight, and pup body weight have been observed in rats, mice, and rabbits exposed to PFOS (Case et al. 2001; Chen et al. 2012b; Era et al. 2009; Fuentes et al. 2006, 2007b; Grasty et al. 2003; Lau et al. 2003; Luebker et al. 2005a, 2005b; Xia et al. 2011; Yahia et al. 2008). In rats, the lowest-adverse-effect level for decrease in fetal body weight was 10 mg/kg/day following administration on GDs 2–20 (Thibodeaux et al. 2003) and the highest no-effect level was 5 mg/kg/day, also identified in the Thibodeaux et al. (2003) study. Decreases in rat pup birth weight and body weight on PND 4 were observed in the offspring of rats exposed to 0.4 mg/kg/day for 42 days prior to mating and gestation through lactation day 4 (Luebker et al. 2005b). Mice appear to be less sensitive to the effect of PFOS on pup body weight than rats (Lau et al. 2003). Exposure of rats to 2 mg/kg/day PFOS on GDs 2–21 resulted in significant decreases in birth weight and pup body weight on PNDs 1–3; exposure to 5 mg/kg/day resulted in decreases in pup body weight through PND 19. In contrast, no alterations in birth weight or pup body weight were observed in mice exposed to doses as high as 5 mg/kg/day on GDs 1–18. Fuentes et al. (2007b) reported the lowest LOAEL of 6 mg/kg/day for decreases in pup weight in mice exposed on GDs 12–18. Decreases in fetal body weight were observed in mice exposed to 10 mg/kg/day on GDs 0–17 (Yahia et al. 2008). Fuentes et al. (2006) did not find decreases in fetal body weight following exposure to 6 mg/kg/day on GDs 6–18. In rabbits, a decrease in fetal body weight was observed following exposure to 2.5 mg/kg/day on GDs 6–20, but not at 1 mg/kg/day (Case et al. 2001). Several studies also reported delays in developmental milestones. Delays in eye opening were observed in rats exposed to 2 mg/kg/day on GDs 2–21 (Lau et al. 2003) or 0.4 mg/kg/day for 42 day prior to mating and throughout the gestation and lactation periods (Luebker et al. 2005a) and in mice exposed to 8.5 mg/kg/day on GDs 15–18 (Abbott et al. 2009). Fuentes et al. (2007b) did not find a delay in eye opening in mouse pups exposed to 6 mg/kg/day on GDs 12–18, but did find a delay in pinna detachment at this dose level. A decrease in neuromuscular development, as evidenced by a delay in tail pull reflex, climbing ability, and forelimb grip strength, was observed in mice exposed to 6 mg/kg/day on GDs 12–18 (Fuentes et al. 2007b).

Prenatal exposure to PFOS has resulted in malformations/anomalies/variations in rats, mice, and rabbits (Case et al. 2001; Era et al. 2009; Thibodeaux et al. 2003; Yahia et al. 2008). An increased incidence of

cleft palate was observed in rats exposed to 10 mg/kg/day on GDs 2–20 (Thibodeaux et al. 2003) and in mice exposed to 10 mg/kg/day on GDs 0–17 (Yahia et al. 2008), 15 mg/kg/day on GDs 1–17 (Thibodeaux et al. 2003), 20 mg/kg/day on GDs 1–17 (Era et al. 2009), and 50 mg/kg/day on GDs 11–15 (Era et al. 2009). Other skeletal and external alterations included sternal defects in rats exposed to 10 mg/kg/day on GDs 2–20 (Thibodeaux et al. 2003) and mice exposed to 1 mg/kg/day on GDs 0–17 (Yahia et al. 2008), delayed skeletal ossification in rabbits exposed to 2.5 mg/kg/day on GDs 6–20 (Case et al. 2001), wavy ribs and spina bifida occulta in mice exposed to 10 mg/kg/day on GDs 1–17 (Yahia et al. 2008) and tail abnormalities and delayed ossification of phalanges at 20 mg/kg/day (Yahia et al. 2008). Visceral abnormalities, consisting of enlarged right atrium at 10 mg/kg/day and ventricular septal defects at 20 mg/kg/day, were observed in mice exposed on GDs 1–17 (Thibodeaux et al. 2003). No malformations/anomalies/variations were found by Thibodeaux et al. (2003) in mice exposed to 1 mg/kg/day on GDs 1–17 or by Fuentes et al. (2006) in mice exposed to 6 mg/kg/day on GDs 6–18. In addition to the previously discussed histological alterations observed in the pups exposed to lethal doses, mild to severe intracranial dilatation of blood vessels were observed in fetuses exposed to 20 mg/kg/day on GDs 0–17 and in pups exposed to 10 mg/kg/day on GDs 0–18 (Yahia et al. 2008). No histological alterations were observed in the heart of rat pups exposed to 2 mg/kg/day on GDs 2–21 (Xia et al. 2011); the study also found no alterations in heart rate or blood pressure.

Neurodevelopmental studies have shown that prenatal and/or postnatal exposure to PFOS can affect motor activity, but does not appear to affect learning or memory. A significant decrease in locomotion was observed in male mice aged 5–8 weeks exposed to 0.3 mg/kg/day on GDs 1–17 when they were placed in a novel environment (Onishchenko et al. 2011). Similarly, decreases in circadian activity were noted in males and increases in the number of inactive periods were noted in males and females when they were observed over a 48-hour period. The study also found increased inactivity in an elevated plus maze test. In an open field test of 70-day old mice exposed to 6 mg/kg/day on GDs 12–18, an increase in the amount of time they spent in the center was found; no changes in vertical movement was found (Ribes et al. 2010). In 3-month-old mice exposed to 6 mg/kg/day on GDs 12–18, a decrease in the distance traveled was observed after 20–25 minutes in an open field apparatus; activity was not affected during the first 5 minutes of the test (Fuentes et al. 2007a). In a 15-minute open field test, prenatal exposure to 6 mg/kg/day PFOS on GDs 12–18 did not alter motor activity in 3-month-old mice (Fuentes et al. 2007b). In contrast, Butenhoff et al. (2009b) found a significant increase in locomotion in male rats exposed to 0.3 or 1.0 mg/kg/day PFOS throughout gestation and lactation. However, this effect was only observed in male rats on PND 17; no significant alterations were observed on PNDs 13, 21, or 61. An increase in locomotion was observed in female rats on PND 21 exposed to 1.0 mg/kg/day, but not at other time

points. To evaluate the biological relevance of the increased activity, activity was analyzed by 1-minute sequential time periods. The investigators concluded that the increased activity observed in the 0.3 mg/kg/day males at PND 17 and 1.0 mg/kg/day females at PND 21 were not treatment-related due to the lack of significant changes in total or ambulatory activity and the similarity in habituation pattern between the treated groups and controls. In the 1.0 mg/kg/day PND 17 males, the pattern of habituation differed from controls and there was an increase in ambulatory activity; this increase in locomotor activity was considered to be related to PFOS exposure. The increased activity was observed in the last three time periods. Postnatal exposure (PND 10) to 11.3 mg/kg/day resulted in an initial decrease in motor activity followed by an increase in activity in 2- and 4-month-old mice (Johansson et al. 2008). In 2-month-old mice, exposed to 0.75 mg/kg/day, there was a decrease in total activity during the first 20 minutes of testing, but not during the remaining 40 minutes of the test; no changes in activity were observed in the 4-month-old mice exposed to 0.75 mg/kg/day. Johansson et al. (2009) also found an altered response to nicotine exposure. Exposure to 11.3 mg/kg/day PFOS resulted in a decrease in motor activity in response to nicotine exposure, as compared to the increased activity observed in controls; no significant alteration was observed at 0.75 mg/kg/day. Two studies testing muscle coordination did not find alterations in the offspring of rats exposed to 3.2 mg/kg/day for 6 weeks prior to mating and throughout gestation and lactation (Luebker et al. 2005a) or mice exposed to 6 mg/kg/day on GDs 12–18 (Fuentes et al. 2007b). A decrease in muscle coordination was observed in mice exposed to 0.3 mg/kg/day on GDs 1–17 (Onishchenko et al. 2011). Prenatal exposure to PFOS did not significantly alter learning or memory in rats exposed to 2 mg/kg/day on GDs 2–21 and tested on PND 21 (Lau et al. 2003), the offspring of rats exposed 3.2 mg/kg/day for 6 weeks prior to mating and throughout gestation and lactation and tested on PNDs 21 and 70 (Luebker et al. 2005a), or mice exposed to 6 mg/kg/day on GDs 12–18 and tested at 3 months of age (Fuentes et al. 2007a).

The effect of pre- and/or postnatal exposure to PFOS on serum lipid levels, thyroid function, and immune function has also been evaluated by a small number of studies. In the offspring of rats exposed to 1.6 mg/kg/day for 6 weeks prior to mating through GD 20, a significant decrease in fetal serum cholesterol levels and increase in LDL-cholesterol levels were observed (Luebker et al. 2005b). In rats exposed through PND 4, there was a decrease in serum triglyceride levels in the pups exposed to 1 mg/kg/day (Luebker et al. 2005b). No alterations in thyroid histology or follicular morphology were observed in rats exposed to 1 mg/kg/day on GD 0–PND 20 (Chang et al. 2009), and no alterations in TSH levels were observed in the Chang et al. (2009) study or in rats exposed to 2 mg/kg/day on GDs 2–21 (Lau et al. 2003). Decreases in total and free T4 levels were observed in rats exposed to 1 mg/kg/day on GDs 2–21 (Lau et al. 2003); free T4 levels remained low through PND 35. Similarly, a cross-fostering

study found decreases in T4 levels in rats exposed to 3.2 mg/kg/day *in utero*, during lactation only, and throughout gestation and lactation (Yu et al. 2009b). Altered immune function was observed in mice exposed to PFOS on GDs 1–17 (Keil et al. 2008). At 5 mg/kg/day, an altered IgM antibody response to sheep red blood cells was observed in 8-week-old males; a decrease in CD3+ and CD4+ lymphocytes were also observed. At 1 mg/kg/kg/day, there was a decreased in NK cell activity in males; no effects were observed at 0.1 mg/kg/day.

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. Limited information is available on the developmental toxicity of other perfluoroalkyls, specifically PFDeA, PFHxS, PFBA, and PFBuS. An increase in fetal mortality was observed in mice exposed to 12.8 mg/kg/day PFDeA on GDs 6–15 (Harris and Birnbaum 1989); this dose level was also associated with a marked decrease in fetal weight/litter (50% lower than controls), 100% incidence of variations in ossification of the braincase, decreases in maternal body weight, and maternal mortality. Decreases in fetal body weight/litter were observed at ≥1 mg/kg/day. The study did not find alterations in the occurrence of cleft palate, soft tissue malformations, or skeletal malformations. In mice exposed to 10.8 mg/kg/day PFDeA on PND 10, there was no effect on spontaneous activity, habituation, performance on an elevated maze test, or the response to a nicotine injection (Johansson et al. 2008). These results differ from the Johansson et al. (2008) findings when mice were exposed to PFOA or PFOS or the findings of Viberg et al. (2013) in mice exposed to PFHxS. In the Viberg et al. (2013) study, administration of 9.2 mg/kg/day PFHxS on PND 10 resulted in a decrease in spontaneous motor activity during the first 20 minutes of the test and an increase in activity in the last 20 minutes of the test. Additionally, exposure to nicotine did not result in an increase in activity in mice exposed 9.2 mg/kg/day, which was the response to nicotine exposure in the controls and in mice exposed to 0.612 or 6.1 mg/kg/day PFHxS (Viberg et al. 2013). Another study evaluating the developmental toxicity of PFHxS did not find alterations in litter size, pup survival, or pup body weight in rats exposed to 10 mg/kg/day PFHxS for 14 days prior to mating and throughout gestation and lactation (Butenhoff et al. 2009a; Hoberman and York 2003). Exposure of mice to 350 mg/kg/day PFBA on GDs 1–17 did not affect pup survival or weight gain (Das et al. 2008). Some developmental delays were observed: eye opening at ≥35 mg/kg/day, vaginal opening at ≥175 mg/kg/day, and preputial separation at 350 mg/kg/day. No alterations in pup survival, body weight, or development were observed at doses as high as 1,000 mg/kg/day in a 2-generation rat study of potassium PFBuS (Lieder et al. 2009b).

Reliable NOAELs and LOAELs for developmental effects are presented in Tables 3-3, 3-4, and 3-5 and are plotted in Figures 3-3, 3-4, and 3-5.

3.2.2.7 Cancer

Human Exposure Studies. A number of studies have examined the potential carcinogenicity of perfluoroalkyls in communities living near a facility releasing PFOA (Barry et al. 2013; Innes et al. 2014; MDH 2007; Vieira et al. 2013) or in the general population (Bonefeld-Jorgensen et al. 2011; Eriksen et al. 2009; Hardell et al. 2014). Barry et al. (2013) examined the cancer incidence in 32,254 adults living near the DuPont Washington Works chemical plant in West Virginia and participating in the C8 Health Project and C8 Health Panel or who ever worked at the DuPont facility (11% of the cohort). Cumulative serum PFOA levels for community members were estimated based on environmental levels, residential history, drinking water source, tap water consumption, work place water consumption, and PFOA toxicokinetic properties. Serum PFOA levels in the workers were estimated based on job histories and data from a health survey that linked job titles to serum PFOA levels; these estimated serum PFOA were combined with estimated serum PFOA levels from residential exposure. Measured PFOA levels (measured in 2005–2006) were 24.2 ng/mL for community members and 112.7 ng/mL for workers. Estimated median annual PFOA serum levels were 19.4 and 174.4 ng/mL for the community and workers, respectively. Cancer incidence data were obtained from questionnaires and cancer diagnosis verified through review of medical records or from Ohio/West Virginia cancer registry. Although increases in the risk of thyroid, kidney, and testicular cancer were found, only the HRs for testicular cancer (HR=1.34, 95%CI 1.00–1.79 with no lag) was statistically significant. When serum PFOA levels were stratified, a significant positive trend across quartiles was found for testicular cancer.

In a second cancer study of Ohio and West Virginia residents living near the Washington Works DuPont facility in West Virginia, Vieira et al. (2013) examined the possible association between PFOA exposure and cancer risk. Cancer cases for 18 cancer types were identified from the Ohio Cancer Incidence Surveillance System and West Virginia Cancer Registry. The final data set included 7,869 Ohio cases and 17,238 West Virginia cases. Serum PFOA levels were estimated for the Ohio residents using estimated environmental levels, exposure assumption, and PBPK modeling. The residents were grouped by water districts with the Little Hocking district having the highest levels of PFOA (estimated serum PFOA level of 125 ng/mL) and Mason having the lowest level (5.3 ng/mL). Significant adjusted odds ratios (AORs) were found for testicular cancer in the Little Hocking district (AOR=5.1, 95% CI 1.6–15.6), kidney cancer in Tuppers Plain district (AOR=2.0, 95% CI 1.3–3.1; estimated serum PFOA level of 23.9 ng/mL), and lung cancer in Mason district (AOR=1.3, 95% CI 1.1–1.5). When analyzed based on estimated serum PFOA levels, significantly elevated AOR were found in the very high (serum PFOA levels of 110–655 ng/mL) and high (30.8–100 ng/L) annual PFOA serum level groups for kidney cancer

(AOR=2.0, 95% CI 1.0–3.9 and AOR=2.0, 95% CI 1.3–3.2, respectively), compared with cases living in unexposed areas. The AOR for testicular cancer was 2.8 (95% CI 0.8–902) in the very high PFOA group, which was based on six cases; the investigators noted there was an inverse association between testicular cancer and the lower exposure groups. Elevated AORs were also found for prostate and ovarian cancer and Non-Hodgkin's lymphoma in the very high exposure group; however, the CIs included the null value.

A third study of the communities near the Washington Works facility examined the possible association between serum PFOA and PFOS levels and the risk of colorectal cancer in over 47,000 adults (Innes et al. 2014). The mean (and range) serum PFOA and PFOS levels in this cohort were 86.6 ng/mL (<0.5–22,412 ng/mL) and 23.4 ng/mL (<0.5–759.2 ng/mL), respectively; the investigators noted that the PFOS levels were similar to those in the U.S. general population. Statistically significant inverse associations were found between the risk of colorectal cancer and serum PFOA and PFOS levels with the least likelihood of colorectal cancer in residents with PFOA and PFOS serum levels in the fourth quartile. Individuals with the highest PFOS serum level were 80% less likely to receive a diagnosis of colorectal cancer and those with the highest serum PFOA levels were 40% less likely to be diagnosed with colorectal cancer.

The Minnesota Department of Health (MDH 2007) examined cancer incidence in residents living in Washington and Dakota Counties; elevated PFOA, PFOS, and PFBA levels have been measured in municipal and private drinking water wells in these counties. As compared to statewide cancer rates, no significant increases in specific cancers were found in Washington County. In Dakota County, significant increases in liver and breast cancer rates were observed in females; no significant increases in cancer rates were found in males. The study also examined cancer incidence in eight communities in these counties: Cottage Grove, Hastings, Lake Elmo, Newport, Oakdale, South St. Paul, St Paul Park, and Woodbury. Some statistically significant increases in a specific cancer type were found; however, the results were not consistent across communities or between males and females.

Eriksen et al. (2009) examined the possible association between blood PFOA and PFOS levels in 1,240 Danish men and women with prostate (n=713), bladder (n=332), pancreatic (n=128), or liver cancer (n=67) enrolled in a prospective cohort study, but did not have cancer prior to enrollment. A group of 772 men and women without cancer also enrolled in the prospective study served as a comparison group. The respective median plasma PFOA and PFOS levels were 6.8 and 35.1 ng/mL in the cancer group and 6.9 and 35.0 ng/mL in the comparison group. No significant associations between serum PFOA or PFOS levels and the risk of prostate, bladder, pancreatic, or liver cancer were found. Although 31–38%

increases in prostate cancer was found in the second, third, and fourth serum PFOS quartiles, there was no difference between the quartiles and the 95% CI included unity.

Hardell et al. (2014) examined the possible association between prostate cancer and perfluoroalkyls among 201 cases of with186 age-matched controls living in Sweden. No significant increases in the risk of prostate cancer were associated with serum PFOA, PFOS, PFHxS, PFNA, PFDeA, or PFUA levels; similarly, there were no associations with Gleason score or prostate-specific antigen (PSA) levels. When serum perfluoroalkyl levels greater than the median were combined with heredity as a risk factor (first-degree relative with prostate cancer), significant increases in the ORs were found for PFHxS (OR 4.4, 95% CI 1.7–12), PFOS (OR 2.7, 95% CI 1.04–6.8), PFOA (OR 2.6, 95% CI 1.2–6.0), PFDeA (OR 2.6, 95% CI 1.1–6.1), and PFUA (OR 2.6, CI 1.1–5.9).

Bonefeld-Jorgensen et al. (2011) examined 31 breast cancer cases among Inuit women in Greenland to evaluate a possible association with blood PFOA and PFOS levels; the comparison group consisted of 115 matched controls. Blood levels of PFOS and PFOA was significantly higher in the cancer group, as compared to the comparison group. The median levels of PFOS and PFOA were 45.6 and 2.5 ng/mL in cancer group and 31.1 and 1.6 ng/mL in the comparison group. A significant increase in the likelihood of breast cancer (OR 1.03, 95% CI 1.001–1.07) was only found for PFOS. The study also looked for possible associations between breast cancer and other persistent pollutants. No significant difference in polychlorinated biphenyls (PCBs), organochlorine pesticides, selenium, cadmium, mercury, or lead blood levels were found between the two groups; when the PCB levels were divided into quartiles, the fourth quartile blood PCB levels were significantly higher in the cancer group than in the comparison group. Zinc levels were significantly higher in the cases.

Laboratory Animal Exposure Studies—PFOA. Two studies have examined the carcinogenic potential of PFOA in rats. In the first one, male and female Sprague-Dawley rats were fed a diet that provided 0, 1.5, or 15 mg/kg/day PFOA for 2 years (3M 1983). Gross and microscopic evaluation of tissues and organs was done at the 1-year mark (control and 15 mg/kg/day groups only) and at termination. Treatment with PFOA did not affect survival. Terminal body weight was reduced 4.5% in males and 10.3% in females; food consumption was not significantly affected. Significant neoplastic lesions consisted of fibroadenoma of the mammary gland (females, 22, 42, 48% incidence in control, low-, and high-dose groups, respectively) and Leydig cell adenoma (males, 0, 4, 14%); in both cases, the incidence in the high-dose groups was significantly different than in controls. High incidence of pituitary adenoma occurred among all groups, including controls. The incidence of hepatocellular carcinoma was not

significantly increased (males, 6, 2, 10%; females, 0, 0, 2%). The investigators noted that the incidence of fibroadenoma in the mammary gland in the high dose group was similar to the incidence found in untreated aging rats and the incidence of Leydig cell adenoma was similar to the spontaneous incidence of this tumor in aged rats. The mammary gland pathology slides from the 3M (1983) study were re-examined in 2005 by a Pathology Working Group (PWG) using current diagnostic criteria (Hardisty et al. 2010). The incidence of fibroadenoma found by the PWG was 36, 44, and 46% in the control, low-dose, and high-dose groups, respectively; there were no statistically significant differences between the groups (Hardisty et al. 2010). Additionally, there were no significant differences in the incidence of adenocarcinoma, total benign neoplasms, or total malignant neoplasms between the groups. In the second study, male Sprague-Dawley rats were fed a diet that provided 0 or 13.6 mg/kg/day PFOA for 2 years (Biegel et al. 2001). Survival in treated rats and pair-fed rats was increased relative to controls. Treatment with PFOA increased the incidence of hepatocellular adenomas (13 vs. 3 or 1% in *ad libitum* controls or controls pair-fed), but there were no hepatocellular carcinomas in the treated group. PFOA also increased the incidence of Leydig cell adenomas (11 vs. 0 or 3% in *ad libitum* controls and pair-fed controls). In addition, PFOA increased the incidence of pancreatic acinar cell adenomas (9 vs. 0 and 1% in the control groups); a pancreatic carcinoma was observed in one treated rat. Hepatic peroxisome proliferation was increased significantly at all interim evaluation time points (1, 3, 6, 9, 12, 15, 18, and 21 months), but there was no increase in cell proliferation. In Leydig cells, neither peroxisome proliferation nor cell proliferation were increased.

PFOA was a positive modulator of hepatocarcinogenesis in male Wistar rats in a biphasic (initiation with diethylnitrosamine followed by oral treatment with PFOA) or triphasic (initiation with DEN followed by dosing with 2-acetylaminofluorene and then PFOA) promotion protocol (Abdellatif et al. 1991, 2004). PFOA induced a marked increase in acylCoA oxidase activity and only a slight increase in catalase activity (Abdellatif et al. 2004). Since PFOA did not significantly increase 8-hydroxydeoxyguanosine (a marker of oxidative DNA damage *in vivo*) in isolated liver DNA, it appeared that PFOA did not require extensive DNA damage for its promoting activity (Abdellatif et al. 2004). PFOA was also found to act as a promoter in male Wistar rats in an initiation-selection-promotion protocol (Nilsson et al. 1991).

Laboratory Animal Exposure Studies—PFOS. A 2-year bioassay for PFOS in Sprague-Dawley rats was conducted (Butenhoff et al. 2012b; unpublished study by Thomford 2002b); male and female rats were administered approximately 0, 0.025, 0.10, 0.25, or 1.04 mg/kg/day PFOS in the diet. An additional group was treated with 1.17 mg/kg/day for 52 weeks and kept on a control diet during the second year of the study (recovery group). PFOS induced a significant positive trend of hepatocellular adenoma in

males, which was associated with a significant increase in the high-dose group over controls (7/60 vs. 0/60). No hepatocellular adenomas were seen in the recovery group (0/40). High-dose males from the recovery group showed a significant increase in thyroid follicular cell adenoma relative to controls (9/39 vs. 3/60). No significant increase in this type of tumor was observed in the high-dose males dosed with PFOS for 2 years. In females, there was a significant positive trend for incidences of hepatocellular adenoma, which was associated with a significant increase in the high-dose group relative to controls (5/60 vs. 0/60). In females, there were also significant negative trends for mammary adenoma and fibroadenoma carcinoma combined.

3.2.3 Dermal Exposure

3.2.3.1 Death

No reports of death in humans following dermal exposure to perfluoroalkyl compounds were identified in the literature.

Laboratory Animal Exposure Studies—PFOA. The dermal LD_{50} values for APFO were 7,000 mg/kg in male CD rats and >7,500 mg/kg in female rats (Kennedy 1985). The protocol consisted of application of PFOA (as an aqueous paste) to a clipped area of the skin, which immediately was covered with gauze pads and wrapped with rubber sheeting around the trunk. The contact period was 24 hours, at which time the application site was washed with water and the rats were observed for clinical signs for 14 days. Using the same protocol, the dermal LD_{50} in male rabbits was 4,300 mg/kg (Kennedy 1985). Rabbits treated with 1,500 mg/kg showed skin irritation with formation of a large crusty area at the application site. No deaths occurred at 1,500 mg/kg. Rabbits treated with 3,000 mg/kg were lethargic and a single death occurred 7 days after treatment. At 5,000 mg/kg, deaths occurred in 3–4 days. These rabbits also showed nasal discharge, pallor, diarrhea, weakness, severe weight loss, and severe skin irritation along with areas of necrosis.

The LD_{50} values for rats and rabbits are presented in Table 3-9.

3.2.3.2 Systemic Effects

No information was located regarding systemic effects in humans following dermal exposure to perfluoroalkyl compounds.

Table 3-9 Levels of Significant Exposure to Perfluorooctanoic Acid - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference Chemical Form	Comments
ACUTE EXPOSURE									
Death									
Rat (CD)	once					7000 M mg/kg	(14 day LD50)	Kennedy 1985 Ammonium perfluorooctanoate	LD50 in females was greater than 7500 mg/kg.
Rabbit (New Zealand)	once					4300 M mg/kg	(14 day LD50)	Kennedy 1985 Ammonium perfluorooctanoate	
Systemic									
Rat (CD)	once	Dermal	3000 B mg/kg	5000 B mg/kg	(mild skin irritation)			Kennedy 1985 Ammonium perfluorooctanoate	
		Bd Wt				3000 B mg/kg	(transient weight loss)		

Table 3-9 Levels of Significant Exposure to Perfluorooctanoic Acid - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
Rat (CD)	2 wk 6 hr/d 5 d/wk	Resp	2000 M mg/kg					Kennedy 1985 Ammonium perfluorooctanoate	
		Cardio	2000 M mg/kg						
		Gastro	2000 M mg/kg						
		Hemato	2000 M mg/kg						
		Hepatic		20 M mg/kg	(foci of coagulative necrosis)				
		Renal	2000 M mg/kg						
		Endocr	2000 M mg/kg						
		Dermal	20 M mg/kg	200 M mg/kg	(skin irritation)	2000 M mg/kg	(acute necrotizing dermatitis)		
		Ocular	2000 M mg/kg						
		Bd Wt	20 M mg/kg			200 M mg/kg	(14% weight loss)		

Table 3-9 Levels of Significant Exposure to Perfluorooctanoic Acid - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Mouse (BALB/c)	4 d 1 x/d	Hepatic	2.5 F mg/kg	6.25 F mg/kg	(52% increase in absolute liver weight)	Fairley et al. 2007 Perfluorooctanoic acid	
		Bd Wt	50 F mg/kg				
Rabbit (albino)	once (NS)	Ocular		100 mg	(moderate eye irritation)	Griffith and Long 1980 Ammonium perfluorooctanoate	
Rabbit (albino)	24 hr (NS)	Dermal	500 mg			Griffith and Long 1980 Ammonium perfluorooctanoate	
Immuno/ Lymphoret							
Rat (CD)	2 wk 6 hr/d 5 d/wk		2000 M mg/kg			Kennedy 1985 Ammonium perfluorooctanoate	NOAEL is for histopathology of the spleen, thymus, and lymph nodes.
Mouse (BALB/c)	4 d 1 x/d		12.5 F mg/kg	18.8 F mg/kg	(increased serum IgE following ovalbumin challenge)	Fairley et al. 2007 Perfluorooctanoic acid	
Neurological							
Rat (CD)	2 wk 6 hr/d 5 d/wk		2000 M mg/kg			Kennedy 1985 Ammonium perfluorooctanoate	NOAEL is for histopathology of the brain.

Table 3-9 Levels of Significant Exposure to Perfluorooctanoic Acid - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Reproductive							
Rat (CD)	2 wk 6 hr/d 5 d/wk		2000 M mg/kg			Kennedy 1985 Ammonium perfluorooctanoate	NOAEL is for histopathology of the testes.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); IgE = immunoglobulin E; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-9.

Respiratory Effects.

Laboratory Animal Exposure Studies—PFOA. No gross or microscopic alterations in the lung and trachea from male CD rats following application of up to 2,000 mg/kg/day APFO as an aqueous paste to an area of the shaven back (approximately 15% of the total body surface) 6 hours/day, 5 days/week for 2 weeks (Kennedy 1985).

Cardiovascular Effects.

Laboratory Animal Exposure Studies—PFOA. No morphological alterations were seen in the heart from male rats in the APFO study conducted by Kennedy (1985).

Gastrointestinal Effects.

Laboratory Animal Exposure Studies—PFOA. Intermittent application of up to 2,000 mg/kg/day APFO to the skin of male rats for up to 2 weeks did not result in gross or microscopic alterations in the gastrointestinal tract (Kennedy 1985).

Hematological Effects.

Laboratory Animal Exposure Studies—PFOA. Hematology tests (erythrocyte count, hemoglobin concentration, hematocrit, total and differential leukocyte count, and red cell indices) conducted in blood from rats following intermittent dermal exposure to up to 2,000 mg/kg/day APFO for 2 weeks showed inconsistent alterations or changes of unlikely biological significance (Kennedy 1985).

Musculoskeletal Effects. No information was located regarding musculoskeletal effects in animals following dermal exposure to perfluoroalkyl compounds.

Hepatic Effects.

Laboratory Animal Exposure Studies—PFOA. Intermittent application of 20, 200, or 2,000 mg/kg APFO to the skin of rats for 2 weeks resulted in the presence of one or more foci of coagulative necrosis in the livers from all treated groups (Kennedy 1985). The Kupffer cells within the foci of hepatocellular necrosis contained large vesicular nuclei and were markedly increased in number. At 2,000 mg/kg/day, these changes were seen in three out of five rats killed on the 10th day of exposure, in three out of five rats killed on recovery day 14 and in one out of five rats killed on recovery day 42. This lesion occurred in two out of five rats from the 20 mg/kg/day dose group killed on day 10 of exposure. Serum ALT activity appeared elevated at termination of exposure in a dose-related manner, but without achieving statistical significance. A similar trend was seen for AST activity, but achieving statistical significance in the high-dose group. The blood concentration of organofluorine on the 10th day of exposure was 10.2, 52.4, 79.2, and 117.8 µg/mL in the control, low-, mid-, and high-dose groups, respectively. A study in mice reported that application of 6.25 mg/kg/day PFOA on the dorsal surface of each ear for 4 days resulted in a 52% increase in absolute liver weight (Fairley et al. 2007); no significant effect occurred after application of 2.5 mg/kg/day.

Renal Effects.

Laboratory Animal Exposure Studies—PFOA. No gross or microscopic alterations were seen in the kidneys from rats that received applications of up to 2,000 mg/kg/day APFO to the shaven skin for 2 weeks in the Kennedy (1985) study.

Endocrine Effects.

Laboratory Animal Exposure Studies—PFOA. The only relevant information is that no morphological alterations were observed in the thyroid of rats following dermal application of up to 2,000 mg/kg/day APFO for 2 weeks in the Kennedy (1985) study.

Dermal Effects.

Laboratory Animal Exposure Studies—PFOA. Application of as single dose of 5,000 mg/kg of an aqueous paste of APFO to a clipped area of the skin of rats, and left in place covered for 24 hours produced mild skin irritation (Kennedy 1985); no irritation was apparent with a dose of 3,000 mg/kg. In

the 2-week study, acute necrotizing dermatitis was seen in two out of five high-dose rats after the 10th treatment; doses of 200 mg/kg/day produced skin irritation. Application of 500 mg/kg (only dose tested) APFO to the intact or abraded skin of young rabbits and left covered for 24 hours was non-irritating, as scored according to the Draize procedure immediately after removal of the cover and 48 hours later (Griffith and Long 1980).

Ocular Effects.

Laboratory Animal Exposure Studies—PFOA. Examination of the eyes of rats following the 9th dermal treatment in the Kennedy (1985) study of APFO did not reveal any significant gross alteration. Microscopic examination of the eyes also did not reveal treatment-related changes.

In a study in rabbits, 0.1 g APFO was instilled once in the conjunctival sac of the right eye and examinations were conducted after 1, 24, 48, and 72 hours and 5 and 7 days after the application (Griffith and Long 1980). APFO produced moderate irritation of the eye characterized by iridal and conjunctival effects. The effects were most pronounced 1 hour after instillation. The irritation was persistent, but by day 7, it had subsided. In a different experiment in which 0.1 g APFO was instilled for 5 or 30 seconds before washing with 200 mL of water, there was limited conjunctival irritation, but the effects were immediate and persistent.

Body Weight Effects.

Laboratory Animal Exposure Studies—PFOA. Transient weight loss was reported in rats applied 3,000 mg/kg APFO to the shaven skin for 24 hours (Kennedy 1985). In the 2-week study, rats in the 200 and 2,000 mg/kg/day groups lost weight during the treatment period (14 and 24%, respectively, on test day 10), but body weights were comparable to control after 42 days of recovery. No changes in body weight were reported in mice applied daily for 4 days up to 50 mg/kg/day PFOA on the dorsal surface of the ears (Fairley et al. 2007).

3.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans following dermal exposure to perfluoroalkyl compounds.

Laboratory Animal Exposure Studies—PFOA. Application of ≥18.8 mg/kg/day PFOA to the dorsal surface of the ears of mice and subsequently injected with ovalbumin resulted in a significant increase in serum total IgE compared to mice exposed only to ovalbumin (Fairley et al. 2007). Ovalbumin-specific airway hyperreactivity also increased in mice coexposed to ovalbumin and 25 mg/kg PFOA relative to mice exposed to ovalbumin alone. The investigators suggested that PFOA exposure may increase the IgE response to environmental allergens.

In the 2-week study conducted by Kennedy (1985), treatment of rats with dermal doses of up to 2,000 mg/kg/day PFOA did not induce gross or microscopic alterations in the spleen, thymus, or lymph nodes.

Data from Fairley et al. (2007) and Kennedy (1985) are presented in Table 3-9.

3.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans following dermal exposure to perfluoroalkyl compounds.

Laboratory Animal Exposure Studies—PFOA. No gross or microscopic alterations were reported in the brain from rats exposed to APFO in the Kennedy (1985) study.

3.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following dermal exposure to perfluoroalkyl compounds.

Laboratory Animal Exposure Studies—PFOA. No gross or microscopic alterations were reported in the testes from rats in the Kennedy (1985) study. The dose level of 2,000 mg/kg/day APFO is presented as a NOAEL for reproductive effects in Table 3-9.

3.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals following dermal exposure to perfluoroalkyl compounds.

3.2.3.7 Cancer

No studies were located regarding cancer effect effects in humans or animals following dermal exposure to perfluoroalkyl compounds.

3.2.4 Other Routes of Exposure

Laboratory Animal Exposure Studies—Other Perfluoroalkyls. Considerable information on the toxicity of PFDeA has been gathered from studies that administered the chemical to experimental animals by intraperitoneal injection. Some of this information is summarized below. For the most part, these studies have demonstrated that the liver is the primary target for PFDeA toxicity and that PFDeA has a higher toxic potency than PFOA.

In male Fischer-344 rats, the intraperitoneal LD_{50} for PFDeA for a 30-day observation period was 41 mg/kg (43 mg/kg in females), compared with 189 mg/kg for PFOA (George and Andersen 1986; Olson and Andersen 1983). While PFOA injection produced no mortality after 5 days, significant lethality in the second and third weeks occurred with PFDeA. These investigators also studied the effect of a single 50 mg/kg intraperitoneal dose on various parameters in rats sacrificed at 2, 4, 8, and 16 days after treatment. Body weight and food consumption decreased significantly; in the 16-day observation period, mean body weight decreased from 207 to 109 g. In a pair-fed group, body weight did not decrease as much as in the PFDeA-treated rats, and dehydration was ruled out as significant cause for the lost weight. In rats treated with PFOA, there was only a transient decrease in food consumption and body weight decreased in the first day and then paralleled controls. Similar differences between the effects of PFOA and PFDeA were reported by Goecke et al. (1992). Treatment with PFDeA increased liver weight, but had little effect on the testes, kidneys, adrenals, and heart compared to the pair-fed controls up to observation day 8. On day 16, the weight of the testes, adrenals, and heart was significantly decreased relative to pair-fed controls. PFDeA caused marked, prolonged alteration in liver lipids, which differed from changes caused by PFOA. Liver from PFDeA-treated rats showed relative increases in palmitate and oleate and relative decreases stearate, arachidonate, and docosahexaenoate; maximal effects were observed by day 8. In a subsequent study, rats were administered a single intraperitoneal dose of 50 mg/kg PFDeA and were monitored for up to 30 days after dosing, tissues were processed for histological examination (George and Andersen 1986). Significant changes were found in the thymus (thymic atrophy), testes (atrophy and degeneration of seminiferous tubules), stomach (inflammation, hyperkeratosis, edema), bone marrow (hypocellularity), kidney (fatty changes in proximal tubular epithelium), and liver (swelling of liver cells with some necrosis). The changes in the thymus, testes, and

liver were still seen 30 days after dosing. Hematology and clinical chemistry tests did not show significant alterations except for a decrease in serum protein levels. Analysis of liver samples showed no significant effects on phospholipid or total lipid levels, but free cholesterol levels were lower and cholesterol esters were higher on days 8 and 16 in PFDeA-treated rats than in controls. A general shift in the ratio of saturated to unsaturated fatty acids was observed.

The effects of PFDeA on heart function also have been studied. Langley and Pilcher (1985) reported that administration of a single injection of 75 mg/kg significantly decreased heart rate in male Wistar rats 4–8 days after dosing relative to pair-fed control group. This effect was attributed, at least partly, to alterations in circulating thyroid hormones (see below). Pilcher and Langley (1986) studied the effects of PFDeA on the isolated perfused heart from male Wistar rats 6–8 days following a single intraperitoneal injection of 75 mg/kg PFDeA. Specifically, the investigators measured heart rate and right ventricular pressure in response to sympathetic nerve stimulation or infusion of norepinephrine. Treatment with PFDeA reduced both responses to the same extent, indicating that the effects may have been mediated by an action of the myocardium rather than on the releases of norepinephrine in response to stimulation of the sympathetic nerves. β-Receptor binding studies conducted 8 days after dosing showed that maximum binding capacity was reduced without significant changes in receptor affinity. A follow-up study from the same group of investigators reported that injection of PFDeA reduced the apparent number of β-receptor binding sites, which could have been due to alteration in the lipid composition of different myocardial membranes. The reduced number of β-receptors was reflected in a reduced ability of norepinephrine to activate adenylate cyclase (Pilcher et al. 1987).

The effects of PFDeA on the thyroid gland have also been studied. Administration of a single intraperitoneal dose of 80 mg/kg, but not 40 mg/kg, PFDeA to male Sprague-Dawley rats resulted in a significant reduction in thyroid gland weight 7 days after dosing relative to *ad libitum* controls (Van Rafelghem et al. 1987a). Pair-fed controls also exhibited a significant reduction in body weight, but not as marked as the treated rats, suggesting that the hypophagia only partially accounted for the reduction in thyroid gland weight. Thyroid gland histology did not reveal significant alterations due to treatment with PFDeA or to hypophagia. Treatment with PFDeA caused a significant reduction in plasma T4 level even at the lowest dose tested, 20 mg/kg, relative to *ad libitum* or pair-fed controls. Plasma T3 levels were not significantly affected by PFDeA and neither was T3 uptake, suggesting that PFDeA treatment did not induce marked alterations in the levels of thyroid-binding proteins in the plasma. PFDeA induced a slight decrease in basal metabolic rate (8% at 80 mg/kg) and did not significantly affect thermogenesis or body core temperatures. The results suggested that the overt toxicity of PFDeA is not

due to effects on functional thyroid status. Similar findings regarding T4 were reported by Gutshall et al. (1988). These investigators also showed that supplementation with T4 reversed the hypophagia, but not the decrease in T4 concentration, suggesting that PFDeA reduces circulating T4 independent of its hypophagic effect. Somewhat divergent results regarding plasma T3 levels and body temperature were reported by Langley and Pilcher (1985). These investigators reported that a single intraperitoneal injection of 75 mg/kg PFDeA reduced T3 levels and body temperature in male Wistar rats during a 3–8-day period following dosing. Van Rafelghem et al. (1987a) speculated that the difference in rat age and strain could have contributed to the difference in results. Subsequent studies by Gutshall et al. (1989) suggested that the reduction in T4 and T3 levels induced by PFDeA in rats result from reduced responsiveness of the pituitary and/or displacement of the hormones from plasma protein binding sites.

A study of the comparative toxicity of PFDeA in rats, mice, hamsters, and guinea pigs was conducted by Van Rafelghem et al. (1987b). Male animals were injected once with PFDeA and were observed for up to 28 days after dosing. The study showed that, with some variation, the toxic potency of PFDeA was essentially the same in the four species studied. A severe body weight reduction was apparent in the four species studied. While rats stopped eating for 5–6 days 6 days after dosing, hamsters continued to consume food at a reduced level. PFDeA caused marked hepatomegaly in rats, mice, and hamsters and a moderate swelling in guinea pigs. Microscopic examination of the liver showed similar alterations in the species studied consisting of a panlobular swelling of the parenchymal cells. PFDeA induced thymic atrophy in hamsters, mice, and guinea pigs. PFDeA also induced seminiferous tubular degeneration in the testes from rats, but not mice; the lesion in hamsters and guinea pigs was less severe than in rats. Ultrastructurally, the liver from all species showed disruption of the rough endoplasmic reticulum, rounding and swelling of the mitochondria, and mild to extensive proliferation of peroxisomes. The latter response was greatest in mice and almost absent in guinea pigs. Accumulation of lipid droplets in liver cells was more pronounced in treated hamsters and guinea pigs then in rats and mice.

3.3 GENOTOXICITY

No studies of genotoxicity in humans exposed to perfluoroalkyl compounds were located.

Administration of a single intraperitoneal injection of 100 mg/kg PFOA to male Fischer-344 rats resulted in a significant increase in the levels of 8-hydroxydeoxyguanosine (a marker of oxidative DNA damage) in liver DNA, but not in kidney DNA; the same dose of PFBA had no effect on liver or kidney DNA (Takagi et al. 1991). Oral administration of approximately 20 mg/kg/day PFOA or 10 mg/kg/day PFDeA

in the diet for 2 weeks to male Fischer-344 rats induced hepatomegaly and also increased the levels of 8-hydroxydeoxyguanosine in liver DNA but not in kidney DNA (Takagi et al. 1991). These findings led the authors to conclude that induction of peroxisome proliferation also leads to organ specific oxidative DNA damage. Unpublished studies summarized by Kennedy et al. (2004) did not find increases in the occurrence of polychromatic erythrocytes in the bone marrow of mice orally exposed to PFOA. PFOS induced micronuclei frequency and decreased the ratio of polychromatic erythrocytes to normochromatic erythrocytes in bone marrow of rats following oral exposure to 0.6–2.5 mg/kg for 30 days (Celik et al. 2013).

In vitro studies provide evidence that PFOA and PFOS are not mutagenic at non-cytotoxic concentrations. Kennedy et al. (2004) summarized the results of various unpublished mutagenicity studies with PFOA. Negative results were found in Ames tests of point mutations using *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538), *Saccharomyces cerevisiae*, and *Escherichia coli* (WP2uvrA strain) with or without metabolic activation. In mammalian cells, PFOA was negative for forward mutations using Chinese hamster ovary cells, for chromosomal aberrations in Chinese hamster ovary cells and human lymphocytes, and for cell transformation in C3H 10T1/2 cells. Similarly, two *in vivo* assays found no alterations in the occurrence of micronuclei in mice. PFOA also was not mutagenic in *S. typhimurium* TA1535/pSK1002 (*hisG46, rfa, uvrB*) with or without metabolic activation using the *umu* test (Oda et al. 2007) or in *S. typhimurium* TA98, TA100, TA102, and TA104 strains with or without metabolic activation using an Ames assay (Fernández Freire et al. 2012).

Incubation of human hepatoma HepG2 cells with 50–400 μM PFOA caused DNA strand breaks and 100–400 μM increased the incidence of micronuclei, in a dose-related manner in both cases (Yao and Zhong 2005). These effects were accompanied by a significant increase in reactive oxygen species (ROS), which the investigators suggested caused the DNA damage. Bjork and Wallace (2009) measured mRNA expression for DNA damage inducible *Ddit3* to assess DNA damage in primary rat and human hepatocyte cultures and in HepG2/C3a hepatoma cells. Significant increases in mRNA transcription for *Ddit3* were found in primary rat hepatocytes at 100 μM PFOA and in primary human hepatocytes and HepG2/C3a hepatoma cells at 200 μM PFOA. Although both studies provide evidence of DNA damage, the tested concentrations were very high as compared to what could be expected to occur in the environment.
A significant increase in mutation frequencies was observed in hamster-human hybrid cells exposed to 200 μM PFOA for 1–16 days; a 79% decrease in cell viability was also observed at this concentration (Zhao et al. 2011). Concurrent treatment with a ROS inhibitor significantly decreased the mutagenic potential, indicating that ROS may play an important role in mediating the genotoxic effects of PFOA.

PFOA induced DNA damage in *Paramecium caudatum* following exposure to 100 µM for 12 and 24 hours (Kawamoto et al. 2010). Intracellular ROS was significantly increased and DNA damage was not reversed by the application of glutathione, a ROS-inhibitor, indicating that intracellular ROS may not be the cause of PFOA-induced DNA damage. PFOS did not induce DNA damage in this study. In contrast, no increases in DNA damage or micronuclei formation were found in human hepatoma HepG2 cells following a 24-hour exposure to PFOA concentrations as high as 800 µM (Florentin et al. 2011); cytotoxicity was observed at ≥200 µM. Eriksen et al. (2010) also found no evidence of DNA damage in HepG2 cells incubated with 100 or 400 µM PFOA for 24 hours.

OECD (2002) summarized unpublished mutagenicity studies conducted with PFOS. PFOS was negative in all assays that tested. It did not induce reverse mutations in *S. typhimurium* or in *Escherichia coli* with or without metabolic activation. A study published after this review also found that PFOS was not mutagenic in *S. typhimurium* TA1535/pSK1002 (*hisG46, rfa, uvrB*) with or without metabolic activation using the *umu* test (Oda et al. 2007). As summarized by OECD (2002), PFOS did not induce chromosomal aberrations in human lymphocytes with or without metabolic activation and did not induce unscheduled DNA synthesis in primary cultures of rat hepatocytes. In addition, PFOS did not induce micronuclei in the bone marrow of CD-1 mice in an *in vivo* assay. PFOS did not result in DNA damage in Syrian hamster embryo (SHE) cells at concentrations up to 50 µg/mL, but did induce cell transformation at non-cytotoxic concentrations (0.2 and 2 µg/mL) following 5 and 24 hours of exposure (Jacquet et al. 2012). Similarly, PFOS did not induce DNA damage or micronuclei formation in human hepatoma HepG2 cells following a 24-hour exposure to PFOA concentrations as high as 600 µM; cytotoxicity was observed at ≥300 µM (Florentin et al. 2011). Another study of with HepG2 cells did not find evidence of DNA damage at concentrations of 100 and 400 µM PFOS (Eriksen et al. 2010).

Limited *in vitro* data on the genotoxicity of other perfluoroalkyls were located. No DNA damage was found in HepG2 cells incubated with 100 or 400 µM PFHxS or PFBuS for 24 hours (Eriksen et al. 2010). A “modest” increase in DNA damage was observed at 400 µM PFNA, a cytotoxic concentration (Eriksen et al. 2010).

3.4 TOXICOKINETICS

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Studies of the absorption of perfluoroalkyls in humans following inhalation exposure were not located; elevated serum concentrations of perfluoroalkyls in workers in fluorochemical production industry have been reported (see Table 6-14) and provide evidence that perfluoroalkyls are absorbed through the respiratory tract. Occupational exposures in these workers are likely to have included inhalation of aerosols of perfluoroalkyls complexed with airborne dusts. Higher serum levels in workers compared to the general population (see Table 6-12) probably reflects a predominant contribution from inhaled perfluoroalkyls.

Studies conducted in rodents provide direct evidence for absorption of inhaled perfluoroalkyls. PFOA was detected in plasma of rats within 30 minutes of initiating nose-only exposures to aerosols (mass median aerodynamic diameter [MMAD]=1.9–2.1 μm) of 1–25 mg ammonium PFOA/m^3. Plasma concentrations increased during the 6-hour exposure, with the highest concentrations observed in male rats at 9 hours (3 hours after cessation of exposure) and at 7 hours (1 hour after cessation of exposure) in females (Hinderliter et al. 2006a). Assuming an elimination $t_{1/2}$ of absorbed PFOA of approximately 160 hours in male rats, a peak plasma concentration at 9 hours would correspond to an absorption $t_{1/2}$ of approximately 1.3 hours (see Section 3.4.1.2, Equations 3-1 and 3-2). The earlier time of highest plasma concentration observed in female rats appears to be associated with faster elimination of absorbed PFOA in female rats, compared to male rats (see Section 3.4.2.1).

Nose-only exposure of male rats to dusts of ammonium perfluorononanoate induced significant increases in absolute and relative liver weight, assessed 5 and 12 days after exposure, providing indirect evidence of absorption of this compound through the respiratory airways (Kinney et al. 1989).

3.4.1.2 Oral Exposure

Studies of absorption of perfluoroalkyls through the gastrointestinal tract in humans are not available. A study of the general population of Europe and North America estimated that the greatest portion of the chronic exposure to PFOS and PFOA results from the intake of contaminated food, including drinking water (Trudel et al. 2008). Direct evidence of oral absorption of perfluoroalkyl compounds was provided in studies that found significant associations between environmental levels (e.g., drinking water) and

perfluoroalkyl concentrations in human serum (Emmett et al. 2006a; Hoffman et al. 2011; Hölzer et al. 2008; Seals et al. 2011; Wilhelm et al. 2008) and by reductions in serum levels after exposures from water were eliminated or reduced (Bartell et al. 2010; Emmett et al. 2009).

Animal data provide quantitative estimates of the fractional absorption of orally administered PFOA, PFOS, PFBA, and PFHxS, with estimates ranging from >50% for PFHxS to >95% for PFOA and PFBA. Greater than 95% of an oral dose of ammonium [^{14}C]PFOA was absorbed in rats that received a single gavage doses ranging from 0.1 to 25 mg/kg (Kemper 2003). A comparison of ^{14}C disposition in rats, mice, hamsters, and rabbits, following an oral dose of 10 mg ammonium [^{14}C]PFOA/kg showed that similar fractions of the dose were absorbed (Hundley et al. 2006). The estimated absorbed fractions (i.e., ^{14}C in tissues, urine, and exhaled air measured 120–168 hours after the dose) in males were: 89% in rats, 82% in mice, 92% in hamsters, and 88% in rabbits. Corresponding values for females were: 76% in rats, 61%, in mice, 75% in hamsters, and 88% in rabbits. These estimates exclude ^{14}C excreted in feces, which may have been absorbed and secreted in bile before excretion (see Section 3.4.4.2). Fasting appears to increase absorption of PFOA. Plasma PFOA concentrations in rats, 24 hours following a gavage dose of 10 mg ammonium PFOA/kg, were 2–3 times higher when administered to fasted rats, compared to fed rats (Hinderliter et al. 2006b). The estimated absorption fractions of ingested ammonium [^{14}C]PFOA or potassium [^{14}C]PFOS (administered as a 4.2 mg/kg oral dose) were >93 and >95% in rats, respectively (Johnson and Ober 1979, 1999a). Based on combined urinary excretion and retention in the carcass (excluding the gastrointestinal tract and its contents), the estimated oral absorption fraction of [^{14}C]PFOS (administered as a single 4.2 mg/kg dose of potassium [^{14}C]PFOS) in male rats was >95% (Chang et al. 2012). The estimated absorption fraction of PFBA (administered as 30 mg/kg oral dose of PFBA) was >95% in rats (Chang et al. 2008a). Cumulative excretion of PFBA 96 hours after an oral dose (administered as 10, 30, or 100 mg/kg ammonium PFBA) was approximately 35% in urine and 4–11% in feces in male mice; and 65–69% in urine, and 5–7% in feces in female mice (Chang et al. 2008a). Based on comparison of the area under the curve (AUC) for oral and intravenous administration, the estimated oral absorption fraction for potassium [^{14}C]PFHxS (administered as a single 10 mg/kg dose) in female rats was 50%; however, the study authors state that this estimate may not be reliable due to the short (24 hours) observation period (Sundström et al. 2012).

Studies examining the rate of absorption of PFOA, PFBA, and PFBuS show rapid absorption from the gastrointestinal tract, with values for absorption $t_{1/2}$ of <2 hours. For PFOA, the highest observed concentrations of ^{14}C in plasma occurred in male rats at approximately 10 hours (range 7.5–15 hours) following single oral doses ranging from 0.1 to 25 mg ammonium PFOA/kg (Kemper 2003). The

elimination $t_{1/2}$ of ^{14}C in plasma, estimated in these same animals was approximately 170 hours (range 138–202 hours), corresponding to an elimination rate constant (k_e) of 0.0044 $hour^{-1}$ (range 0.004–0.005). The corresponding absorption $t_{1/2}$ of approximately 1.5 hours (k_a=0.45 $hour^{-1}$) can be calculated from these observations (Equations 3-1 and 3-2):

$$t_{\max} = \ln\frac{k_a}{k_e} \cdot \frac{1}{(k_a - k_e)} \qquad \text{Eq. (3-1)}$$

$$t_{1/2} = \frac{\ln(2)}{k_e} \qquad \text{Eq. (3-2)}$$

Absorption rate of PFOA appears to be greater in female rats compared to male rats (t_{max} = time of maximum concentration of ^{14}C; k_e = elimination rate constant). The time to peak concentrations of ^{14}C in plasma occurred at approximately 1.1 hour (range 0.6–1.5 hours) in female rats and 10 hours (range 7–15 hours) in male rats following single oral doses ranging from 0.1 to 25 mg/kg mg ammonium PFOA/kg (Kemper 2003). The elimination $t_{1/2}$ of ^{14}C in plasma estimated in these same animals varied with dose and ranged from 3.2 hours at the lowest dose (k_e=0.23 $hour^{-1}$) to 16.2 hours at the highest dose (k_e=0.059 $hour^{-1}$). The estimated absorption half-time from the observations made at all doses (0.1, 1, 5, and 25 mg/kg), based on Equations 3-1 and 3-2, was approximately 0.25 hours (range 0.12–0.38 hours). The absorption $t_{1/2}$ of PFBA in male and female rats following administration of a single oral dose (30 mg/kg ammonium PFBA) was 0.23 hours (3.04 $hour^{-1}$) in males and 0.17 hours (4.15 $hour^{-1}$) in females (Chang et al. 2008a). In male and female mice administered 10–30 mg/kg ammonium PFBA, the absorption $t_{1/2}$ was <1 hour, although the absorption rate may be dose-dependent in males, with higher absorption $t_{1/2}$ at doses >30 mg/kg (Chang et al. 2008a). Similar results for were reported by Olsen et al. (2009) based on estimated compartmental pharmacokinetic parameters for PFBuS in serum of male and female rats following a single intravenous or gavage dose of 30 mg potassium PFBuS. Plasma concentration-time profiles were fit to a two-compartment elimination model. The absorption $t_{1/2}$ can be approximated from these data using Equation 3-1, with the elimination rate constant represented by the fast-phase elimination rate constant estimated for either the oral or intravenous dose. Using the oral or intravenous parameters yield similar values for the absorption $t_{1/2}$ (0.12–0.16 hours). The estimated t_{max} following the gavage dose was 0.42 hours in males and 0.33 hours in females. The fast-phase elimination rate constant following the gavage dose was 0.892 $hours^{-1}$ ($t_{1/2}$=0.79 hours) in males and 1.308 $hours^{-1}$ ($t_{1/2}$=0.53 hours) in females. The corresponding values for absorption $t_{1/2}$ are 0.14 hours (k_a=5.0 $hours^{-1}$) in males and 0.12 hours (k_a=5.8 $hours^{-1}$) in females. Using the fast-phase elimination rate constants estimated following intravenous administration (male: 1.143 $hours^{-1}$; female: 1.956 $hours^{-1}$) yields values for the absorption $t_{1/2}$ of 0.16 hours in males (k_a=4.30 $hours^{-1}$) and females (k_a=4.45 $hours^{-1}$).

3.4.1.3 Dermal Exposure

Dermal exposures of rats to ammonium PFOA has been shown to produce systemic (e.g., liver, immunotoxicity) toxicity in animals (see Section 3.3.3). Estimates of the amount or rates of dermal absorption in humans or animals have not been reported. PFOA was detected serum of mice following dermal application of PFOA dissolved in acetone (Franko et al. 2012). Dermal absorption of PFOS was assessed following application of single doses of potassium PFOS (doses up to 0.30 mg/kg) and the diethanolamine salt of PFOS (doses up to 20 µg/kg) to clipped, intact skin of rabbits (Johnson 1995a, 1995b). Analysis of the liver 28 days after application showed no increase in content of total organic fluoride compared to controls, indicating that dermal absorption was not detectable at low dose levels using this methodology. Dermal penetration of PFOA has been studied in preparations of isolated rat, mouse, and human epidermis (Fasano et al. 2005; Franko et al. 2012). These studies indicate that the rat and mouse skin may be more permeable to PFOA than human skin. Approximately 24% of a dermal dose of PFOA (0.5 mg in 1% acetone) was absorbed across isolated full thickness human skin in 24 hours and 45% of the dose was retained in skin (Franko et al. 2012). Permeability was sensitive to pH and was higher when the skin was buffered at pH 2.5 ($5.5x10^{-2}$ cm/hour) compared to pH 5.5 ($4.4x10^{-5}$ cm/hour), well above the pKa for the terminal carboxylic acid of PFOA (Franko et al. 2012). This suggests that permeability of the unionized acid is greater than that of the dissociated anion. Lower permeability of ionized PFOA is also suggested by relatively low permeability of the ammonium salt of PFOA in isolated preparations of rat and human skin. Following application of the ammonium salt of PFOA to isolated human or rat epidermis (150 µL/cm^2 of a 20% aqueous solution of ammonium PFOA; approximately 30 mg ammonium PFOA/cm^2), approximately 0.048% of the dose was absorbed across human epidermis and 1.44% was absorbed across rat epidermis. When applied to isolated rat epidermis at the same dose, 1.44% of the applied dose was absorbed in 40 hours. The estimated dermal penetration coefficient was $9.49x10^{-7}$ cm/hour in the isolated human epidermis and $3.25x10^{-5}$ cm/hour in the isolated rat epidermis.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

Studies of the tissue distribution of perfluoroalkyls in humans or animals following inhalation exposure were not located. Serum concentrations of perfluoroalkyls in workers in fluorochemical production industry have been reported (see Table 6-14). Occupational exposures in these workers are likely to have included inhalation of aerosols of perfluoroalkyls.

3.4.2.2 Oral Exposure

Distribution in Blood. In a study of perfluoroalkyl workers, serum:plasma ratios for PFHxS, PFOS, and PFOA were 1:1 and this ratio was independent of the concentrations measured (Ehresman et al. 2007). The ratio of whole blood:plasma (or serum) were approximately one-half, which corresponded to volume displacement by red blood cells, suggesting that these perfluoroalkyls do not enter cellular components of blood. In studies conducted in animals, most of the PFOA in blood is in the plasma fraction. In rats, 24 or 48 hours following an oral dose of 11.4 mg ammonium [^{14}C]PFOA/kg, the red blood cell:plasma PFOA concentration ratio ranged from 0.2 to 0.3, suggesting that there was no selective retention of PFOA by red blood cells (Johnson and Ober 1999a). Blood:plasma (or serum) ratios of approximately 0.5 have also been observed in rats following intravenous injection of PFOA (Kudo et al. 2007).

Perfluoroalkyls in plasma bind to serum albumin. The dissociation constant for binding of PFOA to serum albumin is approximately 0.4 mM (0.38 mM, ±0.04 SD for human serum albumin; 0.36 nM, ±0.08 SD for rat serum albumin) and involves 6–9 binding sites (Han et al. 2003). Given a dissociation constant of 0.4 mM and an albumin concentration of approximately 0.6 mM, >90% of PFOA in serum would be expected to be bound to albumin when the serum concentration of PFOA is <1 mM (<440 mg/L). This is consistent with observations of the bound fraction of perfluoroalkyls in plasma of rats that received a gavage dose of 25 mg PFOA/kg (Han et al. 2003, 2005; Ylinen and Auriola 1990), and in human, rat, and monkey plasma incubated *in vitro* with perfluoroalkyls (e.g., PFHxA, PFOA, PFOS, PFNA, PFDeA; Ohmori et al. 2003; Kerstner-Wood et al. 2003). PFBuS was found to bind only to albumin, whereas PFOS, PFOA, and PFHxS were found to have the potential to bind to other human serum binding proteins, including plasma gamma-globulin, alpha-globulin, alpha-2-macroglobulin, transferrin, and beta-lipoproteins (Kerstner-Wood et al. 2003).

Distribution to Extravascular Tissues. Absorbed perfluoroalkyls distribute from plasma to soft tissues, with the highest extravascular concentrations achieved in liver. An analysis of samples from human cadavers attempted to quantify PFOA, PFOS, PFOSA, and PFHxA concentrations in serum and liver (Olsen et al. 2003c). The route of exposure was unknown. Mean serum PFOS concentrations were 17.7 ng/mL (95% CI 13.0–22.5, range <6.9 [limit of quantification]–57 ng/mL, n=24) and were not different in males (18.2 ng/mL, n=13) and females (17.2 ng/mL, n=11). Mean liver concentration was18.8 ng/g (95% CI 14.1–23.5; range <7.3–53.8 ng/g, n=30). The mean liver:serum concentration ratio was 1.3 (95%CI 0.9–1.7, n=23) and was not different in males (1.3, n=13) and females (1.3, n=10). Most liver and serum concentrations for PFOA, PFOSA, and PFHxA were below the limit of quantification;

these limits were <17.9–<35.9 ng/mL for PFOA, <7.5–<19.6 ng/g for PFOSA, and <3.4–<18.5 ng/mL for PFHxA.

Studies conducted in nonhuman primates and rodents have provided additional information on the distribution of absorbed perfluoroalkyls to extravascular tissues. Distribution, as assessed from tissue perfluoroalkyl concentrations and tissue:serum ratios, exhibits profound species and sex differences as well as dose-dependencies (e.g., tissue levels that change disproportionately with dose). These differences have been attributed, in part, to species and sex differences in elimination kinetics of absorbed perfluoroalkyls and dose-dependence of elimination kinetics (see Section 3.4.4). In general, a consistent finding across species is that the liver receives a relatively high fraction of the absorbed dose and may also experience relatively high tissue concentrations compared with other tissues, with blood (i.e., plasma) and kidney also showing relatively high concentrations. The most extensive investigations of tissue distribution have been conducted in rodents.

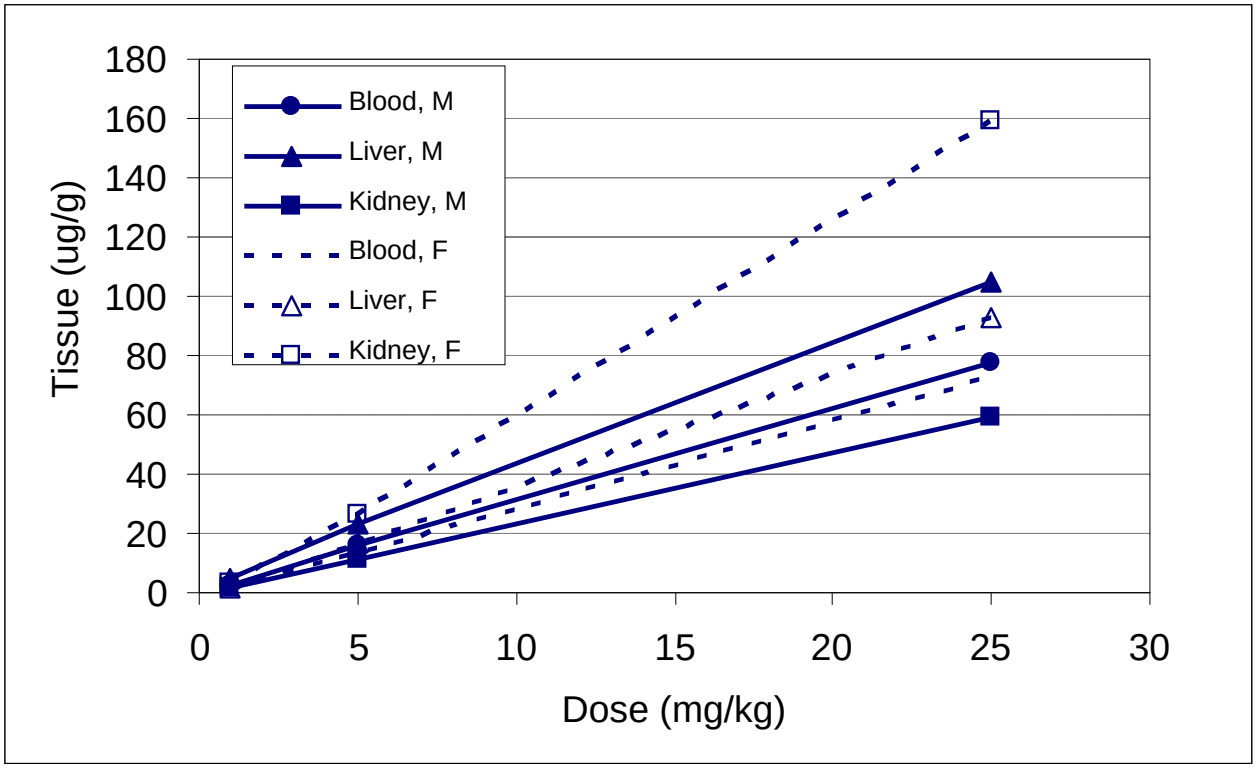
Bogdanska et al. (2011) examined distribution of ^{35}S following dietary exposure to adult male C57/BL6 mice to low (environmentally relevant; 0.031 mg//kg/day) and high (experimentally relevant; 23 mg/kg/day) doses of [^{35}S]PFOS for 1–5 days. For both low and high doses after 1, 3, and 5 days of exposure, ^{35}S was distributed to the following tissues: blood, liver, lung, kidney, skin, whole bone, pancreas, spleen, thymus, heart, testes, epididymal fat, fat pads, brain, and muscle; ^{35}S was also detected in tissues throughout the gastrointestinal tract. Similar tissue:blood ratios were observed in both dose groups. In low-dose animals after 5 days of treatment, the highest tissue concentrations (excluding the gastrointestinal tract) were liver (tissue:blood=5.8), followed by lung (tissue:blood=1.4), whole bone, including marrow (tissue:blood=1.1), blood, and kidney (tissue:blood=0.94). In high-dose animals, the highest tissue concentrations were liver (tissue:blood=3.6), followed by lung (tissue:blood=1.6), blood, kidney (tissue:blood=0.81), and whole bone, including marrow (tissue:blood=0.72). A similar pattern of distribution was observed following intravenous administration of [^{14}C]potassium PFOS (4.2 mg/kg) to male rats (Johnson and Ober 1980). For both dose groups, the tissue:blood ratios for all other tissues were <1. In male and female CD-1 mice administered a single oral dose (4.2 mg/kg) of [^{14}C]PFOS, the highest concentrations of ^{14}C was observed in the liver, followed by serum, and then kidney, with similar tissue levels observed in males and females (Chang et al. 2012). In male and female rats fed diets containing 0, 2, 20, 50, or 100 mg/kg [^{13}C]sodium PFOS (equivalent to 0, 0.14, 1.33, 3.21, and 6.34 and 0, 0.15, 1.43, 3.73, and 7.58 mg/kg/day in males and females, respectively) for 28 days, PFOS levels were highest in liver, followed by spleen, heart, and serum. Liver:serum ratios for the 2, 20, 50, and 100 mg/kg/day diets were approximately 52, 42, 41, and 35, respectively, in males and 30, 47, 20, and 23,

respectively, in females (Curran et al. 2008). Except for rats fed diets containing 20 mg/kg, the liver:serum ratio in males was higher than in females. No additional data were reported to determine if PFOS distribution differed between male and female rats.

Kemper (2003) determined the distribution of ^{14}C in male and female rats at the approximate time of maximum plasma concentration in both sexes, following single gavage doses of [^{14}C]PFOA (as ammonium PFOA, 0.1–25 mg/kg). This design allows a more direct comparison of patterns of tissue distribution in male and female rats at similar plasma concentrations, even though the elimination kinetics in the female rat are substantially faster than in male rats. The highest concentrations of ^{14}C were observed in blood, liver, and kidney (Figure 3-6). Liver, blood, and kidney accounted for approximately 22, 22, and 2% of the administered dose of 1 mg/kg in male rats; and 6, 7, and, 3% in female rats (the sex difference reflected more rapid excretory elimination in females). Although blood, liver, and kidney concentrations appeared to increase proportionately with increasing dose in male rats; in female rats, a disproportionately higher concentration in kidney was observed following the 25 mg/kg dose (Figure 3-6). Concentrations in other tissues ranged from 0.1 to 0.25 of that in liver or kidney; concentrations in bone and fat were <0.1 of that in liver or kidney. Profound sex difference and dose-dependencies in tissue concentrations of PFOA were also observed in rats that received oral doses of PFOA for 28 days at doses of 3, 10, or 30 mg PFOA/kg/day (Ylinen et al. 1990; Figure 3-7). Mean serum, kidney, or liver concentrations did not increase proportionally with dose, in either sex. Kidney concentrations exhibited a disproportionate increase as the dose increased from 3 to 10 mg/kg/day, with little further increase at the 30 mg/kg/day dose. Sex differences in tissue distribution of PFOA in rats are not explained by sex differences in bioavailability since the differences persist in animals that received parenteral doses of PFOA (Johnson and Ober 1999b; Vanden Heuvel et al. 1991b, 1991c). The differences have been attributed to more rapid elimination of PFOA in female rats, compared to male rats (see Section 3.4.2).

A comparison of PFOA disposition in rats, mice, hamsters, and rabbits, showed pronounced species and sex differences (Hundley et al. 2006; Table 3-10). In this study, rats, mice, hamsters, or rabbits received an oral dose of 10 mg ammonium [^{14}C]PFOA/kg and tissue ^{14}C in tissues was measured at 120 or 168 hours (rabbits) hours post-dosing. In male rats, the highest concentrations of ^{14}C occurred in blood, liver and kidney, and all tissues combined accounted for approximately 60% of the dose. However, in female rats, concentrations of ^{14}C in all tissues were below limits of quantification. In mice, liver concentrations were similar in males and females, and liver showed the highest concentrations; ^{14}C levels in all tissues combined were lower in females compared to males. The opposite pattern was evident in

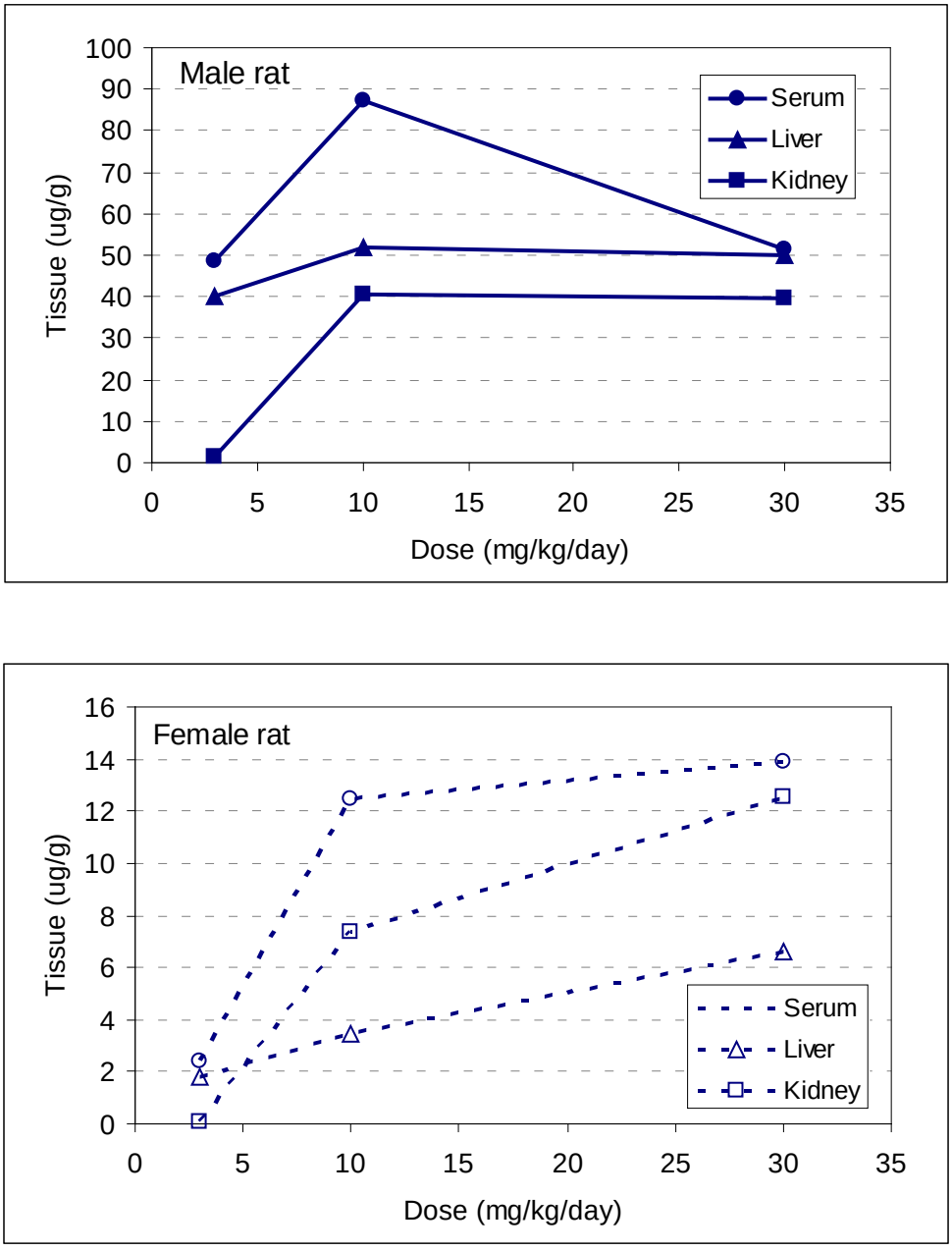
Figure 3-6. Tissue Concentrations of ^{14}C in Male and Female Rats Following a Single Gavage Dose of [^{14}C]PFOA at 1, 5, or 25 mg/kg*



*Tissue levels are measured at time of maximum concentration in each tissue.

Source: Kemper 2003

Figure 3-7. Tissue Concentrations of ^{14}C in Male (Upper Panel) and Female (Lower Panel) Rats Following Oral Doses of PFOA for 28 Days at Doses of 3, 10, or 30 mg/kg/day



Source: Ylinen et al. 1990

Table 3-10. Tissue Distribution and Excretion of ^{14}C-Radioactivity From Both Sexes of Rats, Mice, Hamsters, and Rabbits Dosed with ^{14}C-Labeled APFO[a]

µg Equivalent per g (mL) wet weight[b]								
	Rat		Mouse		Hamster		Rabbit	
Sample	Male	Female	Male	Female	Male	Female	Male	Female
Blood	23.5	<0.1	13.8	10.1	0.1	8.8	<0.1	0.1
Liver	40.0	<0.1	43.2	45.3	0.3	7.3	0.1	1.5
Kidneys	24.0	<0.1	2.9[c]	2.2[c]	0.2	7.1	0.1	0.4
Lungs	8.7	<0.1	1.4[c]	1.3[c]	<0.1	3.8	<0.1	0.1
Heart	6.4	<0.1	1.2[c]	0.6[c]	<0.1	2.9	<0.1	<0.1
Skin	4.8	<0.01	3.5	0.2	<0.1	3.4	<0.1	<0.1
Testes	3.2	–	0.9[c]	–	<0.1	–	<0.1	–
Muscle	1.9	<0.1	1.1	0.5	<0.1	0.9	<0.1	<0.1
Fat	1.7	<0.1	1.6	1.3	<0.1	1.5	<0.1	<0.1
Brain	0.6	<0.1	0.2[c]	0.8[c]	<0.1	0.3	<0.1	<0.1
Percent of dose								
Tissues	59.6	0.6	73.6	50.0	0.7	26.5	<0.1	0.3
Urine	25.6	73.9	3.4	6.7	90.3	45.3	76.8	87.9
Feces	9.2	27.8	8.3	5.4	8.2	9.3	4.2	4.6
Expiration	3.6	1.5	5.2	4.4	1.3	2.9	No data	No data
Cage wash	0.6	0.8	4.9	4.9	0.6	2.1	0.5	4.8
Percent recovered	98.5	104.6	95.4	71.4	101.1	86.1	81.6	97.6

[a]The rabbits were sacrificed 168 hours after dosing; all other animals were sacrificed 120 hours after dosing.
[b]The µg equivalent calculations were based on the specific activity of ^{14}C-labeled APFO, which was 1.1×10^6 DPM/mg. The µg equivalent per g wet weight could not accurately be determined below 0.1 µg/g.
[c]Represents the µg equivalents for the entire organ.

APFO = ammonium perfluorooctanoate

Source: Hundley et al. 2006

hamsters and rabbits, with males having lower tissue levels than females; although, in common with rats and mice, blood, liver and kidney had the highest concentrations. Male rats that received a single oral dose of 5 mg PFOSA/kg had liver PFOSA concentrations that were 3–5 times higher than serum concentrations 1 day post-dosing (Seacat and Luebker 2000).

Sex differences in elimination that give rise to sex differences in tissue levels following oral exposure to perfluoroalkyls in rats are not evident in studies conducted with nonhuman primates. Rhesus monkeys that received 3 or 10 mg ammonium PFOA/kg/day for 90 days had liver concentrations of 48 µg/g (one male) or 50 µg/g (one female) at the low dose and 45 µg/g (one male) and 72 µg/g (one female) at the higher dose, with corresponding serum concentrations of 3 and 7 µg/mL, and 9 and 10 µg/mL, respectively (Griffith and Long 1980). Although limited to only one animal per sex, these results suggest that liver levels did not increase proportionately with increasing dose. A similar observation was made in a study of male Cynomolgus monkeys (Butenhoff et al. 2004c). In male monkeys that received daily oral doses of 3 or 10 mg ammonium PFOA kg/day for 27 weeks, liver PFOA concentrations ranged from 11 to 18 µg/g at the low dose and from 6 to 22 µg/g at the higher dose. Mean serum concentrations measured after 6 weeks of exposure (which may have represented steady-state concentrations) were 77,000 ng/mL in the low-dose group and 86,000 ng/mL in the higher dose group. In this same study, an analysis of serum PFOA kinetics following an intravenous dose of PFOA revealed similar elimination kinetics in males and females (Butenhoff et al. 2004c; see Section 3.4.2). In Cynomolgus monkeys that received daily oral doses of PFOS (0, 0.03, 0.15, or 0.75 mg PFOS/kg/day) for 26 weeks, liver concentrations of PFOS and serum concentration were similar in males and females (liver:serum ratios ranged from 1 to 2) and increased in approximate proportion to the administered dose (Seacat et al. 2002).

Subcellular Distribution. The subcellular distribution of perfluoroalkyls has been examined in rats (Han et al. 2004, 2005; Kudo et al. 2007; Vanden Heuvel et al. 1992b). Two hours following an oral dose of 25 mg ammonium [^{14}C]PFOA/kg, sex differences were noted in the subcellular distribution of ^{14}C in liver; females had approximately 50% of total ^{14}C in the cytosolic fraction compared to 26% in males (Han et al. 2005). The distributions to other cell fractions were: nuclear/cell debris fraction, 30% females, 40% males; lysosomes, 12% females, 14% males; mitochondria, 8% females, 16% males; ribosomes, <3% males and females. In kidney, 80 and 70% of the ^{14}C was associated with the cytosolic fraction in males and females, respectively, 16–22% in the nuclear/cell debris fraction, and the remainder in lysosome/mitochondria/ribosome fractions. In liver, approximately 55% of cytosolic ^{14}C was bound to proteins (>6,000 Da) in both males and females, whereas in kidney, 42% of the cytosolic fraction was bound to protein in males and 17% in females. The subcellular distribution of PFOA is dose-dependent.

In rats, 2 hours following an intravenous dose of 0.041 mg [^{14}C]PFOA/kg, approximately 5% ^{14}C in the liver was associated with the cytosolic fraction, whereas approximately 45% was in the cytosolic fraction following a dose of 16.6 mg/kg (Kudo et al. 2007). A small component of tissue-associated PFOA and PFDeA appears to be bond covalently to protein. Following an intraperitoneal dose of 9.4 µmol/kg [^{14}C]PFDeA or [^{14}C]PFOA (4.2 mg/kg), approximately 0.1–0.5% of liver ^{14}C was bound covalently (i.e., was not removed by repeated extraction with a methanol/ether and ethyl acetate; Vanden Heuvel et al. 1992b). Covalent binding was detected when cytosolic or microsomal fractions of rat liver were incubated *in vitro* with [^{14}C]PFDeA (Vanden Heuvel et al. 1992b).

PFOA binds to rat kidney and urine α2µ-globulin; dissociation constants were estimated to approximately 1.5 and >2 mM (for a single binding site) for the proteins isolated from rat kidney of urine. These values suggest relatively low affinity for the protein, compared to other ligands that are known to induce hyaline droplet nephropathy (10^{-4}–10^{-7} M; Han et al. 2004)

Maternal-fetal Transfer. Perfluoroalkyls can be transferred to the fetus during pregnancy (Fei et al. 2007; Fromme et al. 2010; Gutzkow et al. 2012; Hanssen et al. 2013; Inoue et al. 2004b; Kim et al. 2011; 2013; Lee et al. 2013; Lien et al. 2013; Liu et al. 2011; Midasch et al. 2007; Monroy et al. 2008; Needham et al. 2011; Ode et al. 2013; Porpora et al. 2013). Studies that measured perfluoroalkyls in maternal and fetal cord blood of matched mother-infant pairs found relatively strong correlations (r>0.8) between maternal and fetal serum (or plasma); however, fetal/maternal serum ratios vary depending on the structure of the perfluoroalkyl (Table 3-11). Longer fluoroalkyl chain length and a terminal sulfonate group are associated with lower fetal/maternal ratios (Gutzkow et al. 2012; Hanssen et al. 2013; Kim et al. 2011; Liu et al. 2011; Needham et al. 2011). PFOS was detected in amniotic fluid obtained from amnocentisis (Jensen et al. 2012). The median concentration in amniotic fluid samples from 300 pregnancies (from the Danish amniotic fluid sample back) was 1.1 ng/mL.

Studies in rats and mice provide further support for maternal-fetal transfer of perfluoroalkyls. Following gavage administration of 0.1–10 mg/kg/day PFOS to rats during gestation, PFOS was distributed to fetal serum, liver, and brain, with fetal concentrations increasing with maternal dose (Chang et al. 2009; Lau et al. 2003; Luebker et al. 2005a, 2005b; Thibodeaux et al. 2003). Levels in fetal serum and liver generally were similar and higher than in brain. Studies did not report on concentrations of PFOS in other fetal tissues. Paired fetal-maternal levels of PFOS were examined in rats following exposure (gavage) to potassium PFOS at doses of 0.1, 0.4, 1.6, or 3.2 mg/kg/day on GDs 0–20 (Leubker et al. 2005b). On GD 21, fetal:maternal serum ratios were 2.1, 1.7, 1.6, and 1.1 at doses of 0.1, 0.4, 1.6, and 3.2 mg/kg/day,

Table 3-11. Serum (or Plasma) Concentrations in Matched Humans Maternal-Infant Pairs

Study	Perfluoro-alkyl	Perfluoroalkyl chain length	N	Maternal (ng/mL)	Cord (ng/mL)	Ratio	r
Fromme et al. 2010	PFHxS	6	53	0.60	0.30	0.50	0.89
	PFOA	7	53	2.60	1.70	0.65	0.94
	PFOS	8	53	3.50	1.10	0.31	0.89
	PFNA	8	53	0.60	<0.4	ND	ND
Gützkow et al. 2012	PFHxS	6	123	0.34	0.23	0.68	0.70
	PFOA	7	123	1.25	1.03	0.82	0.82
	PFOS	8	123	5.37	1.78	0.33	0.74
	PFNA	8	123	0.40	0.16	0.40	0.64
	PFDeA	9	123	0.10	0.04	ND	ND
	PFUA	10	123	0.19	0.06	0.32	0.67
	PFTrDA	12	123	0.06	0.07	ND	NA
Hanssen et al. 2013	PFHxS	6	7	0.26	0.17	0.65	ND
	PFOA	7	7	1.50	1.26	0.84	ND
	PFOS	8	7	10.70	3.93	0.37	ND
	PFNA	8	7	0.89	0.50	0.56	ND
	PFOSA	8	7	0.41	0.45	1.10	ND
	PFUA	10	7	0.33	0.16	0.48	ND
Inoue et al. 2004b	PFOA	7	15	8.90	2.90	0.32	0.94
Kim et al. 2011	PFHxS	6	20	0.89	0.58	0.65	ND
	PFOA	7	20	1.60	1.10	0.69	ND
	PFOS	8	20	5.60	2.00	0.36	ND
	PFNA	8	20	0.79	0.37	0.47	ND
	PFDeA	9	20	0.36	0.01	0.03	ND
	PFUA	10	20	1.60	0.46	0.29	ND
Lee et al. 2013	PFHS	6	70	1.35	0.67	0.57	ND
	PFOA	7	70	2.73	2.09	0.84	ND
	PFOS	8	70	10.77	3.44	0.35	ND
Liu et al. 2011	PFHxS	6	50	0.08	0.06	0.79	0.59
	PFOA	7	50	1.66	1.50	0.91	0.91
	PFOS	8	50	3.18	1.69	0.53	0.75
	PFNA	8	50	0.55	0.33	0.61	0.82
	PFDeA	9	50	0.58	0.24	0.41	0.82
	PFUA	10	50	0.56	0.30	0.53	0.70
	PFDoA	11	50	0.08	ND	ND	ND
	PFTrDA	12	50	0.08	0.14	1.87	0.66
Midasch et al. 2007	PFOA	7	11	2.70	3.40	1.30	0.42
	PFOS	8	11	12.10	7.20	0.60	0.72

Table 3-11. Serum (or Plasma) Concentrations in Matched Humans Maternal-Infant Pairs

Study	Perfluoro-alkyl	Perfluoroalkyl chain length	N	Maternal (ng/mL)	Cord (ng/mL)	Ratio	r
Monroy et al. 2008	PFHxS	6	101	4.05	5.05	1.25	ND
	PFOA	7	101	2.24	1.94	0.87	0.94
	PFOS	8	101	16.19	7.19	0.44	0.91
	PFNA	8	101	0.80	0.94	1.18	ND
Needham et al. 2011	PFHxS	6	12	12.30	9.10	0.74	0.05
	PFOA	7	12	4.20	3.10	0.72	0.91
	PFOS	8	12	19.70	6.60	0.34	0.82
	PFNA	8	12	0.76	0.37	0.50	0.84
	PFDeA	9	12	0.34	0.10	0.29	0.91
Ode et al. 2013	PFOA	7	263	2.30	2.80	1.30	0.74
	PFOS	8	263	17.00	7.40	0.45	0.76
	PFNA	8	263	0.31	0.26	0.93	0.51
Porpora et al. 2013	PFOA	7	38	2.90	1.60	0.55	0.70
	PFOS	8	38	3.20	1.40	0.44	0.72

ND = no data (detected but below limit of quantification); PFDeA = perfluorodecanoic acid;
PFDoA = perfluorododecanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid;
PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide;
PFTrDA = perfluorotridecanoic acid; PFUA = perfluoroundecanoic acid;

respectively; results suggest that fetal:maternal serum ratios varied inversely with dose. Fetal:maternal liver ratios (0.37–0.44) were similar across the dose range. In mice administered a single gavage dose of 12.5 mg/kg [^{35}S]PFOS on GD 16, fetal organ:maternal blood ratios of ^{35}S on GD 18 were 2.8 for kidneys, 2.6 for liver, 2.3 for blood, 2.1 for lungs, and 1.2 for brain (Borg et al. 2010).

Maternal-fetal transfer of PFOA has also been studied in rats and mice (Das et al. 2008; Hinderliter et al. 2005). PFOA concentrations in amniotic fluid, placenta, and fetus (measured on days 10, 15, or 21 of gestation) increased with increasing maternal oral dose (3, 10, or 10 mg/kg/day, administered daily beginning on GD4) (Hinderliter et al. 2005). Fetal plasma concentrations of PFOA measured on GD 21 were approximately 40% of maternal plasma concentration. Following gavage administration of 0.01, 1, or 5 mg/kg ammonium PFOA on GD 17, PFOA was detected in amniotic fluid and pup serum, with dose-dependent increases (Fenton et al. 2009). On PND 1, pup serum PFOA concentrations were approximately 1.7–2.0-fold greater than levels in maternal serum.

Following administration of ammonium PFBA (35, 175, or 350 mg/kg) to pregnant mice on GDs 0–17, fetal serum and liver levels of PFBA were determined on PND 1 (Das et al. 2008). The fetal:maternal serum ratio of PFBA was approximately 0.15 and did not vary with maternal dose. Fetal liver:serum ratios were 0.44, 0.75, and 0.78 at maternal doses of 35, 175, and 350 mg/kg, respectively. PFHxS was detected in fetal blood and liver of neonates following exposure of dams to potassium PFHxS (0.3, 1, 3, and 10 mg/kg) throughout gestation (Butenhoff et al. 2009a); concentrations in serum and liver increased with dose.

Maternal-infant Transfer. Perfluoroalkyls can be transferred to nursing infants (Barbarossa et al. 2013; Fromme et al. 2010; Kärrman et al. 2007; Kim et al. 2011; Kuklenyik et al. 2004; Liu et al. 2011; Tao et al. 2008a, 2008b). Studies that measured perfluoroalkyls in maternal serum (or plasma) and breast milk in matched mother-infant pairs found highly variable correlations (Table 3-12). Relatively high correlations have been reported for PFOA (Kärrman et al. 2007; Liu et al. 2011). Transfer to breast milk appears to be a significant route of elimination of perfluoroalkyls during breastfeeding. Comparisons of serum concentrations of women who did or did not breastfeed their infants showed that breastfeeding significantly decreases maternal serum concentrations of PFOA, PFOS, PFHxS, and PFNA (Bjermo et al. 2013; Brantsaeter et al. 2013; Mondal et al. 2012, 2014; von Ehrenstein et al. 2009). The decrease was estimated to be 2–3% decrease per month of breastfeeding (Brantsaeter et al. 2013; Mondal et al. 2012, 2014). Concentrations of perfluoroalkyls in breast milk also decrease with breastfeeding duration (Tao et

Table 3-12. Matched Serum (or Plasma) and Breast Milk Concentrations in Humans

Study	Perfluoroalkyl	Perfluoroalkyl chain length	N	Serum (ng/mL)	Milk (ng/mL)	Ratio	r
Karrman et al. 2007a	PFHxS	6	12	4.7	0.085	0.020	ND
	PFOA	7	12	3.8	0.49	0.120	0.88
	PFOS	8	12	20.7	0.20	0.010	0.83
	PFOSA	8	12	0.24	0.013	0.070	ND
	PFNA	8	12	0.80	0.017	0.010	ND
Kim et al. 2011	PFHxS	6	20	0.89	0.007	0.008	NS
	PFOA	7	20	1.60	0.041	0.026	NS
	PFOS	8	20	5.60	0.061	0.011	0.60
	PFNA	8	20	0.79	<0.0088	ND	ND
	PFDeA	9	20	0.36	<0.018	ND	ND
	PFUA	10	20	1.60	<0.024	ND	ND
Liu et al. 2011	PFHxS	6	50	0.08	ND	ND	ND
	PFOA	7	50	1.66	0.181	0.109	0.77
	PFOS	8	50	3.18	0.056	0.018	0.57
	PFNA	8	50	0.55	0.026	0.048	0.62
	PFDeA	9	50	0.58	0.02	0.034	0.54
	PFUA	10	50	0.56	0.026	0.046	0.44
	PFDoA	11	50	0.08	ND	ND	ND
	PFTrDA	12	50	0.08	ND	ND	ND

ND = no data (detected but below limit of quantification); NS = not significantly correlated; PFDeA = perfluorodecanoic acid; PFDoA = perfluorododecanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide; PFTrDA = perfluorotridecanoic acid; PFUA = perfluoroundecanoic acid;

al. 2008b; Thomsen et al. 2010). Numerous perfluoroalkyl compounds (including PFOS, PFOA, PFHxS, PFNA, PFDeA, PFDoDA, PFUA, and PFOSA) have been detected in breast milk samples in women in China, Korea, Japan, Malaysia, Cambodia, India, Vietnam, Indonesia, Philippines, and Sweden (Fujii et al. 2012; Karrman et al. 2007; Kim et al. 2011; Liu et al. 2010, 2011; So et al. 2006b; Tao et al. 2008a). The mean concentrations for perfluoroalkyls in breast milk collected from 45 women in Massachusetts were 0.131 ng/mL (range of <0.032.0–617 ng/mL) for PFOS, 0.043.8 ng/mL (<0.0301–0.161 ng/mL) for PFOA, and 0.0145 ng/mL (<0.0120–0.0638 ng/mL) for PFHxs (Tao et al. 2008b). PFHpA, PFDeA, PFUA, PFDoA, and PFBuS were also detected in the breast milk; however, ≤4 samples had levels that exceeded the limit of quantitation. Serum concentrations in breastfed infants can be higher than maternal levels (Fromme et al. 2010; Post et al. 2012).

Studies conducted in rats and mice provide further support for maternal-infant transfer of perfluoroalkyls through breast milk (Fenton et al. 2009; Hinderliter et al. 2005; Lau et al. 2003; Luebker et al. 2005a; Yu et al. 2009b). PFOA concentrations in breast milk of nursing rats increased with increasing maternal oral dose (3, 10, or 10 mg/kg/day, administered daily beginning on GD 4). Milk concentrations of PFOA measured on postpartum days 3, 7, 14, or 21 in rats were approximately 0.1 of maternal plasma concentration. In dams exposed to 0.1, 1, or 5 mg/kg PFOA by gavage on GD 17, a dose-dependent increase in PFOA concentrations in breast milk was observed on PND 2, with breast milk:serum ratios of approximately 0.15, 0.38, and 0.25 at 0.1, 1, and 5 mg/kg doses, respectively, and milk/serum concentration ratios for PFOA ranged from 0.15 to 0.56 (Fenton et al. 2009). Following lactational exposure of control rat pups to PFOS in breast milk of dams treated with dietary PFOS (3.2 mg/kg diet; approximately equivalent to 0.33 mg/kg/day), pup serum and liver increased throughout the 35-day lactation period (Yu et al. 2009b). At PND 35, the pup liver:serum PFOS ratios were 2.55 and 2.43 in male and female pups, respectively. Results of a cross-foster study show that pups are exposed to PFOS through breast milk (Luebker et al. 2005a). Postnatal toxicity observed in cross-fostered pups that nursed from exposed dams provides additional evidence of maternal-infant transfer of PFOS in rats and mice (see Section 3.2.2.6).

3.4.2.3 Dermal Exposure

Studies of the distribution of perfluoroalkyls in humans or animals following dermal exposure were not located.

3.4.3 Metabolism

3.4.3.1 Inhalation Exposure

Studies of metabolism of inhaled perfluoroalkyls in humans or animals were not located.

3.4.3.2 Oral Exposure

Studies conducted in rodents and nonhuman primates have not found quantitatively significant metabolism of perfluoroalkyls PFOA, PFOS, or PFDeA (Goecke et al. 1992; Vanden Heuvel et al. 1991b, 1991c; Ylinen and Auriola 1990). PFOA was not metabolized when incubated with microsomal fractions of human or rat intestine, kidney, or liver homogenates (Kemper and Nabb 2005). Results of these studies suggest that perfluoroalkyls are not metabolized and do not undergo chemical reactions in the body.

3.4.3.3 Dermal Exposure

Studies of metabolism of perfluoroalkyls in humans or animals following dermal exposures were not located.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Studies of the elimination of inhaled perfluoroalkyls in humans were not located. Studies conducted in animals indicate that elimination of absorbed perfluoroalkyls will be similar for various routes of absorption (e.g., oral, intravenous, intraperitoneal; see Section 3.4.4.2). The pronounced sex difference in elimination rates in rats (faster elimination in females) was observed in rats following 30-minute nose-only exposures to aerosols (MMAD=1.9–2.1 μm) of 1–25 mg ammonium PFOA/m^3 (Hinderliter et al. 2006a). Plasma PFOA concentrations were not detectable 12 hours after exposure of female rats, and were approximately 90% of peak plasma concentrations 24 hours after the exposure in male rats. The slower elimination of PFOA in male rats resulted in steady-state plasma concentrations within 3 weeks of repeated exposures (6 hours/day, 5 days/week) in male rats, whereas in female rats, daily periodic oscillations of plasma concentrations from peak to below detection occurred on each day of exposure. Steady-state plasma concentrations in male rats were approximately 10 times that of daily peak concentrations in female rats.

3.4.4.2 Oral Exposure

Absorbed perfluoroalkyls are excreted in urine in humans. Estimates of renal clearance of PFOA and PFOS from serum in humans ranged from 0.8 to 3.3 mL/day for PFOA (serum concentration range: 5–16 ng/mL) and 0.1–1.5 mL/day for PFOS (serum concentration range 9–49 ng/mL). These clearance values were <0.001% of glomerular filtration rate (Harada et al. 2005a). Assuming that 99% of the serum PFOA and PFOS was bound to albumin (see Section 3.4.2), <0.1% of filtered perfluoroalkyls were excreted in urine, suggesting extensive reabsorption of filtered PFOA and PFOS in the renal tubule. Renal clearance was not different in males and females. Mean renal clearance for PFOA was 2.12 mL/day (±0.80 SD, n=5) in males and 1.15 (±0.33 SD, n=5) in five females (mean age 22 and 23 years, respectively). Mean renal clearance for PFOS was 0.66 mL/day (±0.48 SD, n=5) in males and 0.91 (±0.56 SD, n=5) for females. Absorbed PFOA and PFOS are also secreted into bile in humans, but the biliary pathway is not a major excretory pathway because PFOA and PFOS are reabsorbed after biliary secretion. Estimates of total body clearance, serum-to-urine clearance, and serum-to-bile clearance of PFOA and PFOS in humans are presented in Table 3-13 (Harada et al. 2007). Biliary clearances of PFOA and PFOS were 1.06 and 2.98 mL/kg body weight/day, respectively, and greatly exceeded total body clearance (0.150 and 0.106 mL/kg/day) and urinary clearance (0.030 and 0.015 mL/kg/day). Based on these estimates, approximately 89% of the PFOA secreted into bile and 97% of secreted PFOS was estimated to have been reabsorbed from the gastrointestinal tract.

Studies conducted in nonhuman primates and rodents provide further evidence that urine is the major route of excretion of perfluoroalkyls, accounting for >93% of absorbed PFOA and PFOS (Benskin et al. 2009; Butenhoff et al. 2004c; Chang et al. 2008a, 2012; Chengelis et al. 2009; Hanhijarvi et al. 1982, 1987; Hundley et al. 2006; Johnson and Ober 1979, 1980, 1999a, 1999b; Kemper 2003; Kudo et al. 2001; Olsen et al. 2009; Sundström et al. 2012; Vanden Heuvel et al. 1991b, 1991c). Studies conducted in rats have shown that PFDeA, PFNA, PFOA and PFHxA are secreted in bile and undergo extensive reabsorption from the gastrointestinal tract (Kudo et al. 2001; Vanden Heuvel et al. 1991b, 1991c). PFOS, PFHxS and PFBuS, are excreted in feces following intravenous dosing of rats, suggesting that these perfluoroalkyls may also be secreted into bile (Chang et al. 2012; Johnson et al. 1984; Olsen et al. 2009; Sundström et al. 2012). Renal clearances of PFOA from plasma in rats were approximately 0.032 mL/minute/kg body weight in male rats and 0.73 mL/minute/kg in female rats; plasma concentrations of PFOA during these measurements ranged from approximately 0.8 to 80 µg/mL (Kudo et al. 2002). In the latter study, approximately >95% of plasma PFOA was bound to high molecular weight protein and glomerular filtration rate (GFR) was approximately 10 mL/minute/kg; therefore,

Table 3-13. Excretory Clearance of PFOA and PFOS in Humans

Parameter	Units	PFOA	PFOS
Serum $t_{1/2}$[a]	day	1,387	1,971
Total clearance[b]	mL/kg/day	0.150	0.106
Urinary clearance[c]	mL/kg/day	0.030	0.150
Biliary clearance[d]	mL/kg/day	1.06	2.98
Reabsorbed from bile[e]	%	89	97

[a]Estimates from Olsen et al. (2005).
[b]$\ln(t_{1/2})$xVd, where Vd is the volume of distribution (300 mL/kg).
[c]Estimates from Harada et al. (2005a).
[d]Estimates form Harada et al. (2007).
[e]1-(Total-Urinary)/Biliary.

PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Source: Harada et al. (2007)

urinary excretion of PFOA was approximately 6% of the rate of glomerular filtration of PFOA in males and 146% in females. These estimates indicate that net renal tubular reabsorption of filtered PFOA occurred in male rats, whereas net renal tubular secretion of PFOA occurred in female rats (i.e., clearance of free PFOA in plasma >GFR). The pronounced sex difference in renal clearance of PFOA has been attributed to modulation of renal excretory transport of PFOA by testosterone and estradiol (Kudo et al. 2002; Vanden Heuvel et al. 1992a; see Section 3.5.1).

Rates of elimination of perfluoroalkyls vary substantially across chemical species and animal species, and show sex differences and age-dependencies within certain species. Table 3-14 summarizes estimates of the elimination half-times ($t_{1/2}$) for perfluoroalkyls in humans and experimental animals. In compiling the estimates presented in Table 3-14, preference was given to the terminal $t_{1/2}$ when multiple $t_{1/2}$ values were reported. The significance of the terminal $t_{1/2}$ is that it determines the time required for complete elimination of the perfluoroalkyl as well as the exposure duration required to achieve a steady state. Most of the $t_{1/2}$ values in Table 3-14 were estimated from analyses of data on declining serum concentrations of perfluoroalkyls after a single dose or following cessation of a period of repeated dosing. Estimates of the terminal $t_{1/2}$ based on serum concentrations can vary with the length of the observation period following the last dose, and with the modeling approach used to estimate the $t_{1/2}$. Longer observation times are required to estimate the slowest phases of elimination. As a result, estimates of $t_{1/2}$ based on observation periods of 1–2 days can be much shorter than estimates for the same perfluoroalkyl based on observation periods of several weeks. Direct comparisons of $t_{1/2}$ values should be made with consideration of whether or not the observation periods were comparable. Differences in estimation methodology can also contribute to differences in $t_{1/2}$ values. Values reported in Table 3-14 are based on fitting data to single or multi-compartment models, or noncompartmental modeling of the data. While the terminal $t_{1/2}$ provides a metric for comparing times required for complete elimination and steady state, it does not always provide a measure of how rapidly the perfluoroalkyl is cleared from the body. A more useful metric for this is the systemic clearance (Cl_S), typically estimated from the absorbed dose (AD) and the area under the serum concentration curve (AUC_S):

$$Cl_S = \frac{AD}{AUC_S} \qquad \text{Eq. (3-3)}$$

Equation 3-3 will provide an accurate estimate of systemic clearance following an oral dose if the oral dose is completely absorbed. Accurate estimation of AUC_S also depends on fitness of the underlying

Table 3-14. Summary Elimination Half-times for Perfluoroalkyls Estimated in Humans and Experimental Animals

Species, age, and sex	Route	Dose	Exposure duration[a]	Elimination half-time[b]	Reference
PFOA—Human					
Human (n=26), adult, M (24) F (2)	NA	NA	NA	3.8 years (95% CI: 3.1–4.4, GM: 3.5)	Olsen et al. 2007a
Human (n=5), 22±0.9, M	NA	NA	NA	2.3 years	Harada et al. 2005a
Human (n=5), 68±5, M	NA	NA	NA	2.6 years	Harada et al. 2005a
Human (n=5), 23±3, F	NA	NA	NA	3.5 years	Harada et al. 2005a
Human (n=5), 69±5, F	NA	NA	NA	2.9 years	Harada et al. 2005a
Human (n=200) 54±15, M,F	Oral	NA	NA	2.3 years (95% CI: 2.1–2.4)	Bartell et al. 2010
Human (n=643) Adults, M,F	Oral	NA	NA	2.9 years (<4 years) (95% CI: 2.3–3.8) 10.1 years (>4 years)	Seals et al. 2011
Human (n=1029) Adults, M,F	Oral	NA	NA	8.5 years (<9 years) (95% CI: 7.1–10.1)	Seals et al. 2011
Humans (n=17)m Adluts, M,F	Oral	NA	NA	5.1 years (SD: 1.7, GM 4.8)	Costa et al. 2009
PFOS—Human					
Human (n=26), adult, M (24) F (2)	NA	NA	NA	5.4 years (95% CI: 3.9–6.9, GM: 4.8)	Olsen et al. 2007a
Human (n=5), 22±0.9, M	NA	NA	NA	4.9 years	Harada et al. 2005a
Human (n=5), 68±5, M	NA	NA	NA	7.4 years	Harada et al. 2005a
Human (n=5), 23±3, F	NA	NA	NA	4.5 years	Harada et al. 2005a
Human (n=5), 69±5, F	NA	NA	NA	4.6 years	Harada et al. 2005a
PFHxS—Human					
Human (n=26), adult, M (24) F (2)	NA	NA	NA	8.5 years (95% CI: 6.4–10.6, GM:7.3)	Olsen et al. 2007a
PFBA—Human					
Human (n=3), adult, M	NA	NA	NA	81 hours (SD 41)	Chang et al. 2008b
Human (n=9), adult, M (7) F (2)	NA	NA	NA	72 hours (SD 38)	Chang et al. 2008b

Table 3-14. Summary Elimination Half-times for Perfluoroalkyls Estimated in Humans and Experimental Animals

Species, age, and sex	Route	Dose	Exposure duration[a]	Elimination half-time[b]	Reference
PFBuS—Human				665 hours (SD 266)	Olsen et al. 2009
Human (n=6), adult M(5) F(1)					
PFOA—Nonhuman primate					
Cynomolgus monkey, adult, M	Oral	10 mg/kg/day	6 months	20.1 days	Butenhoff et al. 2004c
Cynomolgus monkey, adult, M	IV	10 mg/kg	1 day	20.9 days (SD 12.5)	Butenhoff et al. 2004c
Cynomolgus monkey, adult, F	IV	10 mg/kg	1 day	32.6 days (SD 8.0)	Butenhoff et al. 2004c
PFOS—Nonhuman primate					
Cynomolgus monkey, adult, M	Oral	0.15 mg/kg/day	6 months	170 days	Seacat et al. 2002
Cynomolgus monkey, adult, M	Oral	0.75 mg/kg/day	6 months	170 days	Seacat et al. 2002
Cynomolgus monkey, adult, F	Oral	0.15 mg/kg/day	6 months	170 days	Seacat et al. 2002
Cynomolgus monkey, adult, F	Oral	0.75 mg/kg/day	6 months	170 days	Seacat et al. 2002
Cynomolgus monkey, adult, M	IV	2 mg/kg	1 day	132 days (SE 7)	Chang et al. 2012
Cynomolgus monkey, adult, F	IV	2 mg/kg	1 day	110 days (SE 15)	Chang et al. 2012
PFHxA—Nonhuman primate					
Cynomolgus monkey, adult, M	IV	10 mg/kg	1 day	5.3 days (SD 2.5)	Chengelis et al. 2009
Cynomolgus monkey, adult, F	IV	10 mg/kg	1 day	2.4 days (SD 1.7)	Chengelis et al. 2009
PFHxS—Nonhuman primate					
Cynomolgus monkey, adult, M	IV	10 mg/kg	1 day	141 days (SE 30.)	Sundström et al. 2012
Cynomolgus monkey, adult, F	IV	10 mg/kg	1 day	87 days (SE 27)	Sundström et al. 2012
PFBA—Nonhuman primate					
Cynomolgus monkey, adult, M	IV	10 mg/kg	1 day	40.3 hours (SD 2.4)	Chang et al. 2008b
Cynomolgus monkey, adult, F	IV	10 mg/kg	1 day	41.0 hours (SD 4.7)	Chang et al. 2008b
PFBuS—Nonhuman primate					
Cynomolgus monkey, adult, M	IV	10 mg/kg	1 day	15.0 hours (SD 9.8)	Chengelis et al. 2009
Cynomolgus monkey, adult, F	IV	10 mg/kg	1 day	8.0 hours (SD 2.0)	Chengelis et al. 2009

Table 3-14. Summary Elimination Half-times for Perfluoroalkyls Estimated in Humans and Experimental Animals

Species, age, and sex	Route	Dose	Exposure duration[a]	Elimination half-time[b]	Reference
Cynomolgus monkey, adult, M	IV	10 mg/kg	1 day	95.2 hours (SE 27.1)	Olsen et al. 2009
Cynomolgus monkey, adult, F	IV	10 mg/kg	1 day	83.2 hours (SE 41.9)	Olsen et al. 2009
PFOA—Rat					
Rat (CR), adult, M	Oral	11.4 mg/kg	1 day	115 hours	Johnson and Ober 1980
Rat (Sprague-Dawley), adult, M	Oral	0.1 mg/kg	1 day	202 hours (SD 38)	Kemper 2003
Rat (Sprague-Dawley), adult, M	Oral	1 mg/kg	1 day	138 hours (SD 32)	Kemper 2003
Rat (Sprague-Dawley), adult, M	Oral	5 mg/kg	1 day	174 hours (SD 29)	Kemper 2003
Rat (Sprague-Dawley), adult, M	Oral	25 mg/kg	1 day	157 hours (SD 38)	Kemper 2003
Rat (Sprague-Dawley), adult, M	IV	1 mg/kg	1 day	185 hours (SD 19)	Kemper 2003
Rat (Sprague-Dawley), adult, M	Oral	0,4 mg/kg	1 day	322 hours (SD 38)	Benskin et al. 2009
Rat (Sprague-Dawley), adult, M	Oral	0.022 mg/kg/day	12 weeks	218 hours (95%CL 127–792)	DeSliva et al. 2009
Rat (Wistar), adult, M	IV	21.5 mg/kg	1 day	136 hours (SD 24)	Kudo et al. 2002
Rat (Wistar), adult, M	IV	20.1 mg/kg	1 day	135 hours (SD 29)	Ohmori et al. 2003
Rat (Sprague-Dawley), adult, M	IP	3.9 mg/kg	1 day	216 hours (SE 30.9)	Vanden Heuvel et al. 1991c
Rat (Wistar), adult, M	IP	50 mg/kg	1 day	105 hours	Ylinen et al. 1990
Rat (Sprague-Dawley), (SD), adult, F	Oral	0.1 mg/kg	1 day	3.2 hours (SD 0.9)	Kemper 2003
Rat (Sprague-Dawley), adult, F	Oral	1 mg/kg	1 day	3.5 hours (SD 1.1)	Kemper 2003
Rat (Sprague-Dawley), adult, F	Oral	5 mg/kg	1 day	4.6 hours (SD 0.6)	Kemper 2003
Rat (Sprague-Dawley), adult, F	Oral	25 mg/kg	1 day	16.2 hours (SD 9.9)	Kemper 2003
Rat (Sprague-Dawley), adult, F	IV	1 mg/kg	1 day	2.8 hours (SD 0.5)	Kemper 2003
Rat (Wistar), adult, F	IV	21.5 mg/kg	1 day	1.9 hours (SD 0.7)	Kudo et al. 2002
Rat (Wistar), adult, F	IV	20.1 mg/kg	1 day	1.9 hours (SD 0.7)	Ohmori et al. 2003
Rat (Sprague-Dawley), adult, F	IP	3.9 mg/kg	1 day	2.9 hours (SE 0.2)	Vanden Heuvel et al. 1991c
Rat (Wistar), adult, F	IP	50 mg/kg	1 day	24 hours	Ylinen et al. 1990

Table 3-14. Summary Elimination Half-times for Perfluoroalkyls Estimated in Humans and Experimental Animals

Species, age, and sex	Route	Dose	Exposure duration[a]	Elimination half-time[b]	Reference
PFOS—Rat					
Rat (Sprague-Dawley), adult, M	Oral	4.2 mg/kg	1 day	179 hours	Johnson and Ober 1979
Rat (Sprague-Dawley), adult, M	Oral	0.27 mg/kg	1 day	809 hours	Benskin et al. 2009
Rat (Sprague-Dawley), adult, M	Oral	0.023 mg/kg/day	12 weeks	1,968 hours (95%CL 1.584–2.568)	DeSliva et al. 2009
Rat (Sprague-Dawley), adult, M	Oral	2 mg/kg	1 day	1,495 hours (SE 50)	Chang et al. 2012
Rat (Sprague-Dawley), adult, M	Oral	15 mg/kg	1 day	1,707 hours (SE 270)	Chang et al. 2012
Rat (Sprague-Dawley), adult, F	Oral	0.023 mg/kg/day	12 weeks	1,992 hours (95% CL 1,752–2,280)	DeSliva et al. 2009
Rat (Sprague-Dawley), adult, F	Oral	2 mg/kg	1 day	919 hours (SE 56)	Chang et al. 2012
Rat (Sprague-Dawley), adult, F	Oral	15 mg/kg	1 day	989 hours (SE 48)	Chang et al. 2012
PFOSA—Rat					
Rat (Sprague-Dawley), adult, M	Oral	5.0 mg/kg	1 day	125 hours	Seacat and Luebker 2000
PFDeA—Rat					
Rat (Sprague-Dawley), adult, M	IP	4.8 mg/kg	1 day	1,008 hours	Vanden Heuvel et al. 1991b
Rat (Wistar), adult, M	IV	25 mg/kg	1 day	958 hours (SD 207)	Ohmori et al. 2003
Rat (Wistar), adult, F	IV	25 mg/kg	1 day	1,406 hours (SD 140)	Ohmori et al. 2003
Rat (Sprague-Dawley), adult, F	IP	4.8 mg/kg	1 day	552 hours	Vanden Heuvel et al. 1991b
PFNA—Rat					
Rat (Sprague-Dawley), adult, M	Oral	0.2 mg/kg	1 day	974 hours	Benskin et al. 2009
Rat (Sprague-Dawley), adult, M	Oral	0.029 mg/kg/day	12 weeks	1,128 hours (95% CL 935–1,416)	DeSilva et al. 2009
Rat (Wistar), adult, M	IV	22.6 mg/kg	1 day	710 hours (SD 55)	Ohmori et al. 2003
Rat (Wistar), adult, F	IV	22.6 mg/kg	1 day	58.6 hours (SD 9.8)	Ohmori et al. 2003
PFHpA—Rat					
Rat (Wistar), adult, M	IV	17.7 mg/kg	1 day	2.4 hours (SD 1.2)	Ohmori et al. 2003
Rat (Wistar), adult, F	IV	17.7 mg/kg	1 day	1.2 hours (SD 0.2)	Ohmori et al. 2003

Table 3-14. Summary Elimination Half-times for Perfluoroalkyls Estimated in Humans and Experimental Animals

Species, age, and sex	Route	Dose	Exposure duration[a]	Elimination half-time[b]	Reference
PFHxA—Rat					
Rat (Sprague-Dawley), adult, M	IV	10 mg/kg	1 day	1.0 hour	Chengelis et al. 2009
Rat (Sprague-Dawley), adult, M	Oral	50 mg/kg	1 day	2.2 hours	Chengelis et al. 2009
Rat (Sprague-Dawley), adult, M	Oral	150 mg/kg	1 day	2.4 hours	Chengelis et al. 2009
Rat (Sprague-Dawley), adult, M	Oral	300 mg/kg	1 day	2.5 hours	Chengelis et al. 2009
Rat (Sprague-Dawley), adult, F	IV	10 mg/kg	1 day	0.42 hour	Chengelis et al. 2009
Rat (Sprague-Dawley), adult, F	Oral	50 mg/kg	1 day	2.6 hours	Chengelis et al. 2009
Rat (Sprague-Dawley), adult, F	Oral	150 mg/kg	1 day	2.2 hours	Chengelis et al. 2009
Rat (Sprague-Dawley), adult, F	Oral	300 mg/kg	1 day	2.1 hours	Chengelis et al. 2009
PFHxS—Rat					
Rat (Sprague-Dawley), adult, M	Oral	0.030 mg/kg	1 day	382 hours	Benskin et al. 2009
Rat (Sprague-Dawley), adult, M	IV	10 mg/kg	1 day	688 hour s(SE 14.4)	Sundström et al. 2012
Rat (Sprague-Dawley), adult, F	IV	10 mg/kg	1 day	39 hour s(SE 1.9)	Sundström et al. 2012
PFBA—Rat					
Rat (Sprague-Dawley), adult, M	Oral	30 mg/kg	1 day	9.22 hours (SE 0.75)	Chang et al. 2008b
Rat (Sprague-Dawley), adult, M	IV	30 mg/kg	1 day	6.38 hours (SE 0.53)	Chang et al. 2008b
Rat (Sprague-Dawley), adult, F	Oral	30 mg/kg	1 day	1.76 hours (SE 0.26)	Chang et al. 2008b
Rat (Sprague-Dawley), adult, F	IV	30 mg/kg	1 day	1.03 hours (SE 0.03)	Chang et al. 2008b
PFBuS—Rat					
Rat (Sprague-Dawley), adult, M	IV	10 mg/kg	1 day	2.1 hours	Chengelis et al. 2009
Rat (Sprague-Dawley), Rat (SD), adult, M	IV	30 mg/kg	1 day	4.51 hours (SE 2,22)	Olsen et al. 2009
Rat (Sprague-Dawley), adult, M	Oral	30 mg/kg	1 day	4.68 hours (SE 0.07)	Olsen et al. 2009
Rat (Sprague-Dawley), adult, F	IV	10 mg/kg	1 day	0.64 hours	Chengelis et al. 2009

Table 3-14. Summary Elimination Half-times for Perfluoroalkyls Estimated in Humans and Experimental Animals

Species, age, and sex	Route	Dose	Exposure duration[a]	Elimination half-time[b]	Reference
Rat (Sprague-Dawley), adult, F	IV	30 mg/kg	1 day	3.96 hours (SE 0.21)	Olsen et al. 2009
Rat (Sprague-Dawley), adult, F	Oral	30 mg/kg	1 day	7.42 hours (SE 0.79)	Olsen et al. 2009
PFOS—Mouse					
Mouse (CD), adult, M	Oral	1 mg/kg	1 day	1,027 hours	Chang et al. 2012
Mouse (CD), adult, M	Oral	20 mg/kg	1 day	874 hours	Chang et al. 2012
Mouse (CD), adult, F	Oral	1 mg/kg	1 day	907 hours	Chang et al. 2012
Mouse (CD), adult, F	Oral	20 mg/kg	1 day	731 hours	Chang et al. 2012
PFHxS—Mouse					
Mouse (CD), adult, M	Oral	1 mg/kg	1 day	732 hours	Sundström et al. 2012
Mouse (CD), adult, M	Oral	20 mg/kg	1 day	671 hours	Sundström et al. 2012
Mouse (CD), adult, F	Oral	1 mg/kg	1 day	597 hours	Sundström et al. 2012
Mouse (CD), adult, F	Oral	20 mg/kg	1 day	643 hours	Sundström et al. 2012
PFBA—Mouse					
Mouse (CD1), adult, M	Oral	10 mg/kg	1 day	13.34 hours (SE 4.55)	Chang et al. 2008b
Mouse (CD1), adult, M	Oral	30 mg/kg	1 day	16.3 hours (SE 7.2)	Chang et al. 2008b
Mouse (CD1), adult, M	Oral	100 mg/kg	1 day	5.22 hours (SE 2.27)	Chang et al. 2008b
Mouse (CD1), adult, F	Oral	10 mg/kg	1 day	2.87 hours (SE 0.30)	Chang et al. 2008b
Mouse (CD1), adult, F	Oral	30 mg/kg	1 day	3.08 hours (SE 0.26)	Chang et al. 2008b
Mouse (CD1), adult, F	Oral	100 mg/kg	1 day	2.79 hours (SE 0.3)	Chang et al. 2008b

[a]Exposure durations of 1 day indicate that the a single dose was administered.
[b]Reported half-times are arithmetic mean for the terminal elimination phase if multiple elimination phases were observed.

CI = confidence interval; CL = confidence limit; F = female; GM = geometric mean; IP = intraperitoneal; IV = intravenous; M = male; NA = not applicable; PFBA = perfluorobutyric acid; PFDeA = perfluorodecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide; SD = standard deviation; SE = standard error

Model used to predict serum concentrations. Estimates of systemic clearance based on pharmacokinetics analyses of serum data from animal studies are presented in Table 3-15.

Elimination of Perfluoroalkyls in Humans. Elimination $t_{1/2}$ values for PFOA, PFOS, PFHxS, PFBA, and PFBuS have been estimated in humans (Bartell et al. 2010; Costa et al. 2009; Chang et al. 2008a; Harada et al. 2005a; Olsen et al. 2007a, 2009; Seals et al. 2011). Estimates in humans are based on measurements of the decline in serum perfluoroalkyl concentrations following cessation or an abrupt decrease in exposure; or measurements of renal plasma clearance from serum in a general population sample from Japan (Harada et al. 2005a). The latter clearance estimates were converted to $t_{1/2}$ values, for display in Table 3-14 as follows (Equations 3-4 and 3-5):

$$k_e = \frac{Cl}{V} \qquad \text{Eq. (3-4)}$$

$$t_{1/2} = \frac{\ln(2)}{k_e} \qquad \text{Eq. (3-5)}$$

where k_e is the elimination rate constant (e.g., day^{-1}), Cl is the renal plasma clearance (e.g., mL plasma/day/kg), and V is the plasma volume (L/kg), which is assumed to be 4.3% of body weight (ICRP 1981). In general, these studies show that longer chain length is associated with slower elimination rates. For example, the elimination $t_{1/2}$ for PFBA was estimated to be 70–80 hours (Chang et al. 2008a), whereas the $t_{1/2}$ values for PFHxS, PFOS, and PFOA range from 2 to 10 years (Bartell et al. 2010; Harada et al. 2005a; Olsen et al. 2007a; Seals et al. 2011). Longer $t_{1/2}$ values for PFOA have been reported with longer monitoring follow-up times, which allow the detection of slower elimination phases of multiphasic elimination kinetics (Seals et al. 2011). Analytical methods typically used to measure serum perfluoroalkyls do not discriminate between linear and branched isomers and, as a result, these studies estimate elimination rates for the isomer mixture. Studies conducted in rats have shown that linear isomers tend to be eliminated more slowly than branched isomers (Benskin et al. 2009; De Silva et al. 2009).

Estimated elimination $t_{1/2}$ values for PFOA and PFOS in humans are not appreciably different in males and females (Harada et al. 2005a; Olsen et al. (2007a). The Olsen et al. (2007a) study provided estimates of $t_{1/2}$ values of 3.3 years (1,221 and 1,223 days) in two females; the group mean (22 males, 2 females) was 3.8 years (95% CI 3.1–4.4; geometric mean: 3.5 years, 95% CI 3.0–4.1). Serum concentrations of PFOA in these subjects (n=5) ranged from 17 to 5,100 ng/mL. Estimates of $t_{1/2}$ values were similar, 2.3–3.5 years, in the Harada et al. (2005a) study, in subjects whose serum PFOA concentrations ranged from 3 to 21 ng/mL.

Table 3-15. Summary Systemic Clearance for Perfluoroalkyls Estimated in Experimental Animals

Species, age, and sex	Route	Dose (mg/kg)	Exposure duration	Systemic clearance (mL/day/kg)[a]	Reference
PFOA—Nonhuman primate					
Cynomolgus monkey, adult, M	IV	10	1 day	12.4 (SD 7.4)	Butenhoff et al. 2004c
Cynomolgus monkey, adult, F	IV	10	1 day	5.3 (SD 3.3)	Butenhoff et al. 2004c
PFOS—Nonhuman primate					
Cynomolgus monkey, adult, M	IV	2	1 day	1.10 (SE 0.06)	Chang et al. 2012
Cynomolgus monkey, adult, F	IV	2	1 day	1.65 (SE 0.04)	Chang et al. 2012
PFHxA—Nonhuman primate					
Cynomolgus monkey, adult, M	IV	10	1 day	569	Chengelis et al. 2009
Cynomolgus monkey, adult, F	IV	10	1 day	535	Chengelis et al. 2009
PFHxS—Nonhuman primate					
Cynomolgus monkey, adult, M	IV	10	1 day	1.3 (SE 0.1)	Sundström et al. 2012
Cynomolgus monkey, adult, F	IV	10	1 day	1.9 (SE 0.4)	Sundström et al. 2012
PFBA—Nonhuman primate					
Cynomolgus monkey, adult, M	IV	10	1 day	2,371 (SE 293)	Chang et al. 2008a
Cynomolgus monkey, adult, F	IV	10	1 day	1,075 (SE 91)	Chang et al. 2008a
PFBuS—Nonhuman primate					
Cynomolgus monkey, adult, M	IV	10	1 day	159	Chengelis et al. 2009
Cynomolgus monkey, adult, F	IV	10	1 day	238	Chengelis et al. 2009
Cynomolgus monkey, adult, M	IV	10	1 day	12,264 (SE 3384)	Olsen et al. 2009
Cynomolgus monkey, adult, F	IV	10	1 day	8,832 (SE 2880)	Olsen et al. 2009
PFOA—Rat					
Rat (Sprague-Dawley), adult, M	Oral	0.1	1 day	23.1 (SD 5.8)	Kemper 2003
Rat (Sprague-Dawley), adult, M	Oral	1	1 day	20.9 (SD 3.8)	Kemper 2003

Table 3-15. Summary Systemic Clearance for Perfluoroalkyls Estimated in Experimental Animals

Species, age, and sex	Route	Dose (mg/kg)	Exposure duration	Systemic clearance (mL/day/kg)[a]	Reference
Rat (Sprague-Dawley), adult, M	Oral	5	1 day	20.4 (SD 5.0)	Kemper 2003
Rat (Sprague-Dawley), adult, M	Oral	25	1 day	27.1 (SD 7.4)	Kemper 2003
Rat (Sprague-Dawley), adult, M	IV	1	1 day	21.5 (SD 2.0)	Kemper 2003
Rat (Sprague-Dawley), adult, F	Oral	0.1	1 day	778 (SD 144)	Kemper 2003
Rat (Sprague-Dawley), adult, F	Oral	1	1 day	655 (SD 173)	Kemper 2003
Rat (Sprague-Dawley), adult, F	Oral	5	1 day	1,164 (SD 118)	Kemper 2003
Rat (Sprague-Dawley), adult, F	Oral	25	1 day	842 (SD 166)	Kemper 2003
Rat (Sprague-Dawley), adult, F	IV	1	1 day	816 (SD 221)	Kemper 2003
Rat (Wistar), adult, M	IV	21.5	1 day	50.4 (SD 14.4)	Kudo et al. 2002
Rat (Wistar), adult, F	IV	21.5	1 day	2,233 (SD 805)	Kudo et al. 2002
Rat (Wistar), adult, M	IV	20.1	1 day	135 (SD 29)	Ohmori et al. 2003
Rat (Wistar), adult, F	IV	20.1	1 day	2,233 (SD 805)	Ohmori et al. 2003
PFOS—Rat					
Rat (Sprague-Dawley), adult, M	Oral	2	1 day	11.3 (SE 0.56)	Chang et al. 2012
Rat (Sprague-Dawley), adult, M	Oral	15	1 day	4.9 (SE 0.52)	Chang et al. 2012
Rat (Sprague-Dawley), adult, F	Oral	2	1 day	22.2 (SE 0.28)	Chang et al. 2012
Rat (Sprague-Dawley), adult, F	Oral	15	1 day	5.4 (SE 20)	Chang et al. 2012
PFDeA—Rat					
Rat (Wistar), adult, M	IV	25	1 day	207 (SD 0.054)	Ohmori et al. 2003
Rat (Wistar), adult, F	IV	25	1 day	140 (SD 0.008)	Ohmori et al. 2003
PFNA—Rat					
Rat (Wistar), adult, M	IV	22.6	1 day	6.9 (SD 0.6)	Ohmori et al. 2003
Rat (Wistar), adult, F	IV	22.6	1 day	106 (SD 31)	Ohmori et al. 2003
PFHpA—Rat					
Rat (Wistar), adult, M	IV	17.7	1 day	1,604 (SD 558)	Ohmori et al. 2003
Rat (Wistar), adult, F	IV	17.7	1 day	3,071 (SD 781)	Ohmori et al. 2003

Table 3-15. Summary Systemic Clearance for Perfluoroalkyls Estimated in Experimental Animals

Species, age, and sex	Route	Dose (mg/kg)	Exposure duration	Systemic clearance (mL/day/kg)[a]	Reference
PFHxA---Rat					
Rat (Sprague-Dawley), adult, M	IV	10	1 day	2,784	Chengelis et al. 2009
Rat (Sprague-Dawley), adult, F	IV	10	1 day	18,600	Chengelis et al. 2009
PFHxS---Rat					
Rat (Sprague-Dawley), adult, M	IV	10	1 day	6.7 (SE 0.06)	Sundström et al. 2012
Rat (Sprague-Dawley), adult, F	IV	10	1 day	53.4 (SE 4.38)	Sundström et al. 2012
PFBA—Rat					
Rat (Sprague-Dawley), adult, M	IV	30	1 day	851 (SE 61)	Chang et al. 2008a
Rat (Sprague-Dawley), adult, F	IV	30	1 day	2,949 (SE 59)	Chang et al. 2008a
Rat (Sprague-Dawley), adult, M	Oral	30	1 day	494 (SE 29)	Chang et al. 2008a
Rat (Sprague-Dawley), adult, F	Oral	30	1 day	1,527 (SE 145)	Chang et al. 2008a
PFBuS---Rat					
Rat (Sprague-Dawley), adult, M	IV	10	1 day	946	Chengelis et al. 2009
Rat (Sprague-Dawley), adult, F	IV	10	1 day	7,464	Chengelis et al. 2009
Rat (Sprague-Dawley), adult, M	IV	30	1 day	2,856 (SE 816)	Olsen et al. 2009
Rat (Sprague-Dawley), adult, F	IV	30	1 day	11,265 (SE 960)	Olsen et al. 2009
PFOS---Mouse					
Mouse (CD), adult, M	Oral	1	1 day	4.7	Chang et al. 2012
Mouse (CD), adult, M	Oral	20	1 day	4.7	Chang et al. 2012
Mouse (CD), adult, F	Oral	1	1 day	5.0	Chang et al. 2012
Mouse (CD), adult, F	Oral	20	1 day	6.0	Chang et al. 2012
PFHxS---Mouse					
Mouse (CD), adult, M	Oral	1	1 day	2.9	Sundström et al. 2012
Mouse (CD), adult, M	Oral	20	1 day	4.8	Sundström et al. 2012
Mouse (CD), adult, F	Oral	1	1 day	2.7	Sundström et al. 2012
Mouse (CD), adult, F	Oral	20	1 day	3.8	Sundström et al. 2012

Table 3-15. Summary Systemic Clearance for Perfluoroalkyls Estimated in Experimental Animals

Species, age, and sex	Route	Dose (mg/kg)	Exposure duration	Systemic clearance (mL/day/kg)[a]	Reference
PFBA—Mouse					
Mouse (CD1), adult, M	Oral	10	1 day	280 (SE 72)	Chang et al. 2008b
Mouse (CD1), adult, M	Oral	30	1 day	296 (SE 640)	Chang et al. 2008b
Mouse (CD1), adult, M	Oral	100	1 day	784 (SE 112)	Chang et al. 2008b
Mouse (CD1), adult, F	Oral	10	1 day	564 (SE 24)	Chang et al. 2008b
Mouse (CD1), adult, F	Oral	30	1 day	696 (SE 32)	Chang et al. 2008b
Mouse (CD1), adult, F	Oral	100	1 day	1,336 (SE 64)	Chang et al. 2008b

[a]As reported in units of mL/day/kg or converted from mL/hour (x24), mL/hour (x24/body weight) or mL/minute (x60x24).

CI = confidence interval; F = female; IV = intravenous; M = male; PFBA = perfluorobutyric acid; PFBuS = perfluorobutane sulfonic acid; PFDeA = perfluorodecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxA = perfluorohexanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; SD = standard deviation; SE = standard error

Estimated values for $t_{1/2}$ were similar in males (2.3, 2.6 years) and females (3.5, 2.9 years). Declines in serum PFOA concentrations were observed in populations following initiation of activated carbon filtration of public water supplies that had been contaminated with PFOA (Bartell et al. 2010). The estimated mean serum $t_{1/2}$ f or a group of 200 adults followed for 1 year after filtration was initiated was 2.3 years (95% CI 2.1–2.4). Elimination rates were not different in males and females. Serum PFOA concentration ranged from 16 to 1,200 ng/mL. A larger follow-up study measured serum PFOA concentrations in two populations of former residents (n=1,672) of the same water districts (Seals et al. 2011). In one population (n=643), the serum $t_{1/2}$ increased with increasing elapsed time since leaving the water district. The $t_{1/2}$ was 2.9 years (95% CI 2.3–3.8) for elapsed time of <4 years and 10.1 for elapsed time of >4 years. In a second population whose elapsed time since residence was <9 years, the $t_{1/2}$ was 8.5 years (95% CI 7.1–10.1). Elimination rates (based on the annual percent decrease in serum concentrations) were faster in males (27%) compared to females (18%) for the first 4 years post-exposure; however, no difference was evident between sexes when elapsed time from exposure was >4 years.

Analysis of kinetics of serum PFOS concentrations in retired U.S. fluorochemical production workers (24 males, 2 females) yielded a mean estimate 5.4 years (95% CI 3.9–6.9; geometric mean: 4.8 years, 95% CI 4.0–5.8) for the serum elimination $t_{1/2}$ in subjects whose serum PFOS concentrations ranged from 37 to 3,490 ng/mL (Olsen et al. 2007a). Estimates for the two females in the same study were 4.9 and 6.8 years. Estimates based on renal clearance of PFOS from serum in subjects from the general population of Japan ranged from 2.9 to 7.4 years; these subjects had serum PFOS concentrations that ranged from 4 to 49 ng/mL (Harada et al. 2005a). Estimates in males (7.4, 2.9 years) were similar to females (4.5, 4.6 years). This same study measured serum PFHxS concentrations in retired U.S. fluorochemical production workers (24 males, 2 females) yielded a mean estimate of 8.5 years (95% CI 6.4–10.6; geometric mean: 7.3 years, 95% CI 5.8–9.2) for the serum elimination $t_{1/2}$ in subjects whose serum PFHxS concentrations ranged from 10 to 1,295 ng/mL (Olsen et al. 2007a). Estimates for the two females in the same study were 12.2 and 13.3 years.

Elimination rate of PFBA was estimated in fluorochemical workers who may have been exposed to various PFBA precursors (Chang et al. 2008a). In three male workers, the estimated mean $t_{1/2}$ based on serum PFBA kinetics was 81 hours (±41 standard deviation). In a larger study of nine workers (seven males, two females), the mean $t_{1/2}$ was 72 hours (±38 standard deviation). Estimates for the two female subjects were 56 and 118 hours. The combined mean value for the 12 estimates was 75 hours (±38 standard deviation). Olsen et al. (2009) estimated serum $t_{1/2}$ in six fluorochemical workers. The mean $t_{1/2}$ was 27.4 days (±11.1 standard deviation). The group included a single female whose $t_{1/2}$ was

45.7 days. Based on these observations, PFBA and PFBuS are eliminated substantially faster in humans than perfluoroalkyls having longer carbon chain lengths (e.g., PFHxS, PFOA, PFOS).

Elimination of Perfluoroalkyls in Non-human Primates. Elimination $t_{1/2}$ values and systemic clearances for PFOA, PFOS, PFHxA, PFHxS, PFBA, and PFBuS have been estimated in Cynomolgus monkeys (Butenoff et al. 2004c; Chang et al. 2012; Chengelis et al. 2009; Olsen et al. 2009; Seacat et al. 2002; Sundström et al. 2012). Estimated terminal $t_{1/2}$ values were 20–30 days for PFOA, 100–170 days for PFOS, 90–140 days for PFHxS, 40 days for PFBA and 8–95 hours for PFBuS. Elimination of perfluoroalkyls in monkeys is multiphasic and, as a result, estimates of the terminal $t_{1/2}$ can vary with the duration of the observation period and assumptions made in modeling elimination kinetics (Chang et al. 2012; Chengelis et al. 2009; Olsen et al. 2009; Sundström et al. 2012). For example, the $t_{1/2}$ for PFBuS was 8 and 15 hours in female and male monkeys, respectively, when monkeys were monitored for 48 hours following a single intravenous dose (Chengelis et al. 2009), whereas the $t_{1/2}$ was 95 and 83 hours in male and female monkeys, respectively, when the monitoring period was extended to 14 days and a three-compartment model was used to estimate the terminal $t_{1/2}$ (Olsen et al. 2009). Studies in monkeys confirm general trends observed in humans that perfluoroalkyl sulfonates are more slowly eliminated than perfluoroalkyl carboxylates and that elimination of longer-chain perfluoroalkyls occurs more slowly than short-chain perfluoroalkyls. Systemic clearances were lower for PFOS, PFHxS, and PFBuS compared to the corresponding carboxylates, PFOA, PFHxA, and PFBA (Table 3-15). Systemic clearances were similar in male and female monkeys (Table 3-15).

Elimination of Perfluoroalkyls in Rats. Elimination $t_{1/2}$ values and systemic clearances for PFOA, PFOS, PFOSA, PFDeA, PFNA, PFHpA, PFHxA, PFHxS, PFBA, and PFBuS have been estimated in rats (Benskin et al. 2009; Chang et al. 2008b, 2012; Chengelis et al. 2009; DeSilva et al. 2009; Johnson and Ober 1979; Kemper 2003; Kudo et al. 2002; Ohmori et al. 2003; Olsen et al. 2009; Ohmori et al. 2003; Seacat and Luebker 2000; Sundström et al. 2012; Vanden Heuvel et al. 1991b, 1991c; Ylinen et al. 1990). Consistent with observations made in humans and Cynomolgus monkeys, perfluoroalkyl sulfonates are more slowly eliminated than perfluoroalkyl carboxylates and short-chain perfluoroalkyls (e.g., PFNA, PFOA, PFOS, PFHxA, PFHxS) are eliminated faster in rats than long-chain perfluoroalkyls (e.g., PFBA, PFBuS; Tables 3-14 and 3-15). Linear PFOA isomers tend to be eliminated more slowly than branched isomers (Benskin et al. 2009; DeSilva et al. 2009).

Elimination of perfluoroalkyls exhibits pronounced sex differences in rats, with faster elimination in females than in males (Benskin et al. 2009; Chang et al. 2008b; Chengelis et al. 2009; Kemper et al. 2003;

Kudo et al. 2002; Ohmori et al. 2003; Sundström et al. 2012; Vanden Heuvel et al. 1991c; Ylinen et al. 1990). Estimates of systemic clearance for PFOA in male rats ranged from 20 to 50 mL/day/kg, whereas estimates for female rats ranged from 600 to 2,200 mL/day/kg (Kemper et al. 2003; Kudo et al. 2002; Ohmori et al. 2003). Systemic clearances of PFOA, PFOS, PFNA, PFHxA, PFHxS, PFBA, and PFBuS are also higher in female rats compared to male rats (Table 3-15).

Pronounced dose dependence appears in the $t_{1/2}$ estimates for PFOA in female rats. With increasing dose, plasma elimination kinetics in female rats converts from monophasic to biphasic. Following an oral dose of PFOA of 0.1, 1, 5, or 25 mg/kg, the terminal $t_{1/2}$ values in female rats were 3.2, 3.5, 4.6, or 16.2 hours, respectively; no apparent dose dependence was observed in male rats over the same dose range (Kemper 2003). Dose-dependent elimination of PFOA has been attributed to a capacity-limited renal tubular secretion of PFOA in female rats (see Section 3.5.1). The divergence in elimination kinetics between male and female rats appears to be age-dependent, with faster elimination becoming evident in female rats after 30 days of age, consistent with the timing of sexual maturation and involvement of sex hormones in the modulation of the renal excretion of PFOA in rats (Hinderliter et al. 2006b).

Elimination of Perfluoroalkyls in Mice. Elimination $t_{1/2}$ values and systemic clearances for PFOS, PFHxS, and PFBA have been estimated in mice (Chang et al. 2008a, 2012; Sundström et al. 2012). Consistent with studies conducted in rats and monkeys, PFBA is eliminated more rapidly in mice than PFOS and PFHxS. Systemic clearances ranged from 5 to 6 mL/day/kg for PFOS (Chang et al. 2012), from 3 to 5 mL/day/kg for PFHxS (Sundström et al. 2012), and from 300 to 1,300 mL/day/kg for PFBA (Chang et al. 2008a). Sex differences in elimination in mice were observed for PFBA but not PFOS or PFHxS. Systemic clearances of PFBA in female mice were approximately 2 times that of males (Chang et al. 2008a). Sex differences in PFOA elimination, for which profound differences are evident in rats, have not been evaluated in mice. Systemic clearance of PFBA in male and female mice appeared to be dependent on dose. Systemic clearance following a single oral dose of 100 mg PFBA/kg was approximately 2 times higher than the systemic clearance following a dose of 10 or 30 mg PFBA/kg. Possible explanations for the apparent dependence of clearance on dose are dose-dependent bioavailability or that the one-compartment model used to estimate elimination rates and serum AUC did not adequately fit the serum kinetics observed at the higher dose (Chang et al. 2008a). The latter could occur if renal tubular reabsorption of PFBA or plasma protein binding of PFBA is saturable in mice.

Elimination of Perfluoroalkyls in Other Species. Sex differences in elimination of PFOA have also been observed in hamsters; unlike the rat, male hamsters excreted absorbed PFOA more rapidly than female

hamsters. Following a single gavage dose of 10 mg/kg as ammonium [^{14}C]PFOA, cumulative excretion of ^{14}C in urine at 24 hours post-dosing was 96.4% of the dose in female rats and 8.7% in male rats; 24.6% in female hamsters and 84.5% in male hamsters; 4.1% in male and female mice; and 90.5 and 80.2% in female and male rabbits, respectively (Hundley et al. 2006).

3.4.4.3 Dermal Exposure

Studies on excretion of perfluoroalkyls following dermal exposure of humans or animals were not located. Routes and rates of excretion of perfluoroalkyls absorbed through the skin are expected to be the same as that following absorption from other routes (see Section 3.4.4.2).

3.4.4.4 Other Routes of Exposure

Selected studies in which elimination rates (i.e., half-times) of perfluoroalkyls have been determined are summarized in Table 3-14. In general, elimination $t_{1/2}$ values are similar following intravenous, intraperitoneal, oral exposures, suggesting that route of absorption has no substantial effect of rates of elimination of absorbed perfluoroalkyls (Butenhoff et al. 2004c; Chang et al. 2008a; Kemper 2003; Kudo et al. 2002; Ohmori et al. 2003; Vanden Heuvel et al. 1991b; Ylinen et al. 1990).

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 1994; Andersen et al. 1987). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from

route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

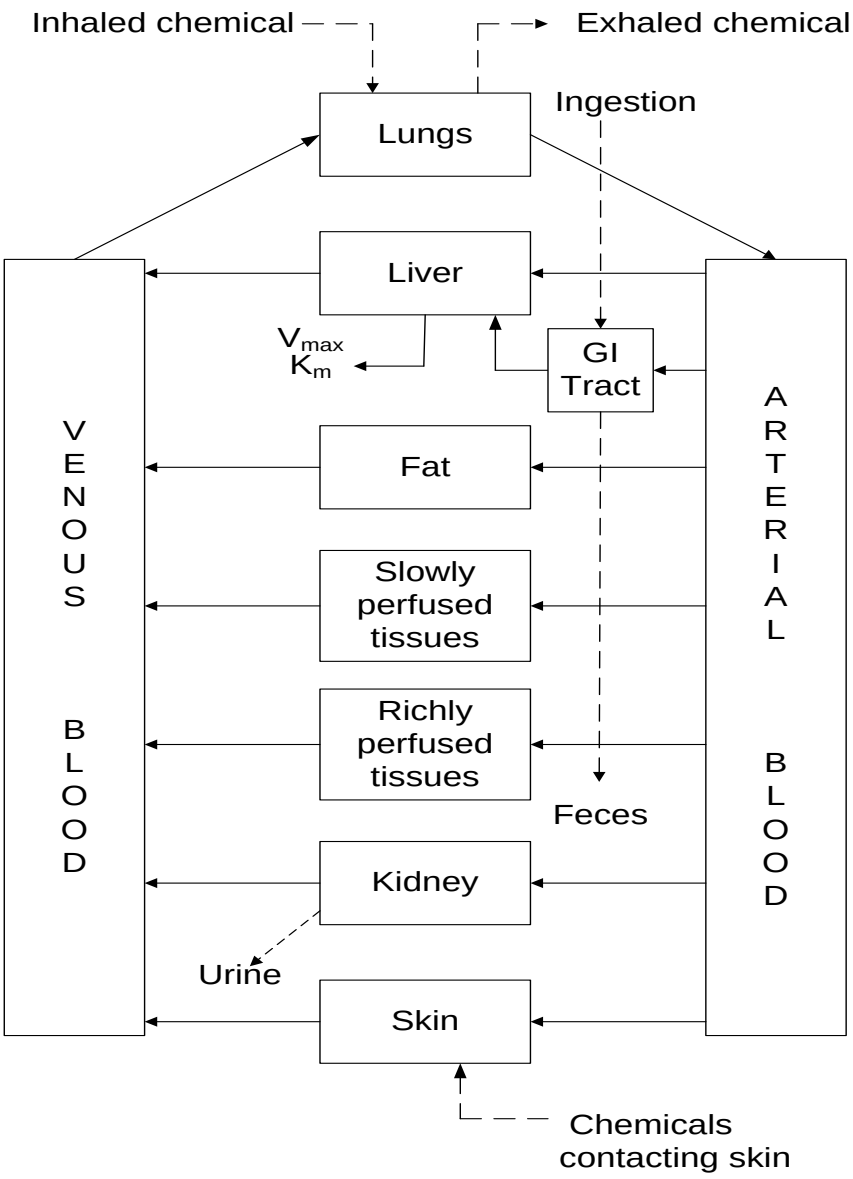
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-8 shows a conceptualized representation of a PBPK model.

If PBPK models for perfluoroalkyls exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

Figure 3-8. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Source: adapted from Krishnan and Andersen 1994

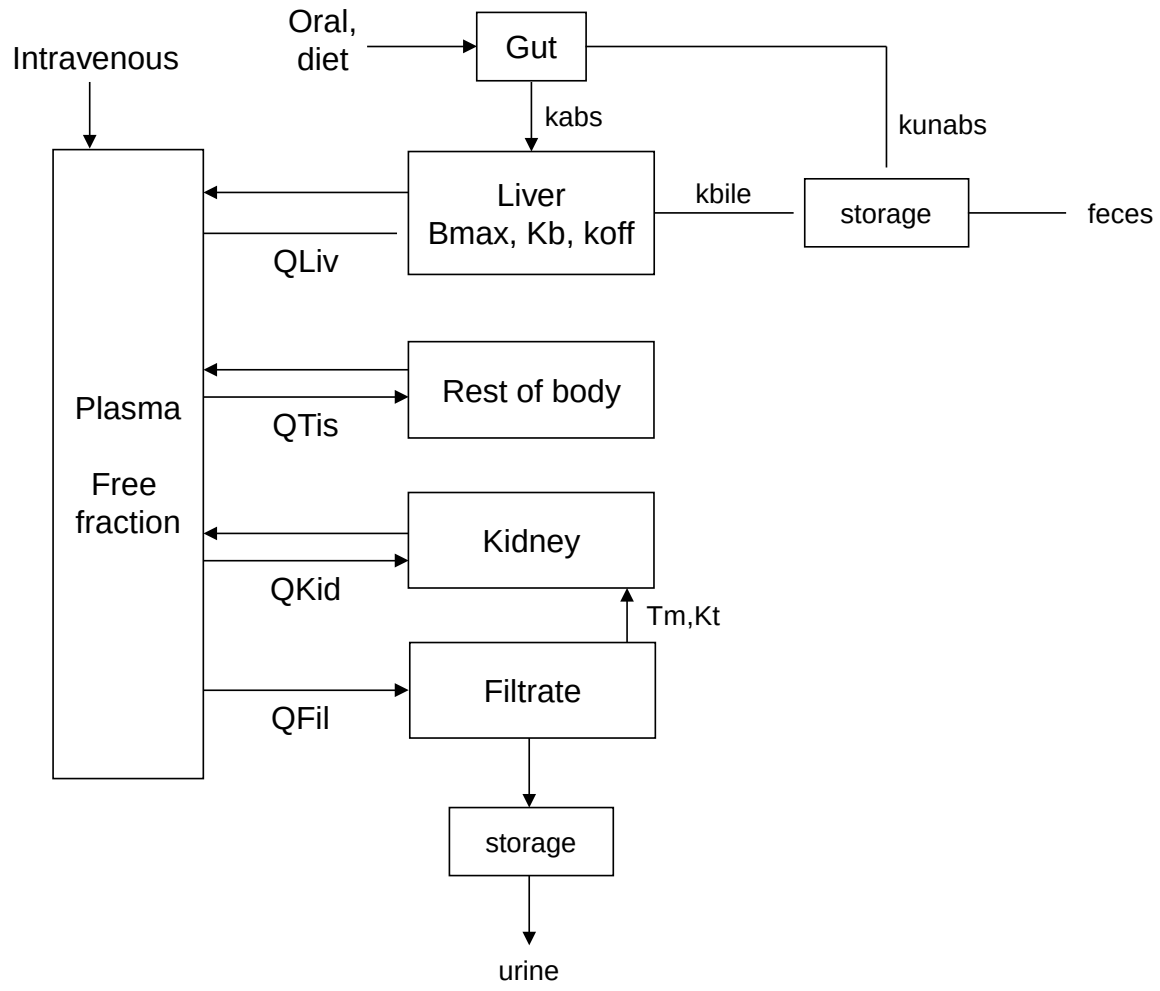
Several PBPK models of PFOA and PFOS have been reported. These include a human model for PFOA and PFOS (Loccisano et al. 2011), models for PFOA and PFOS in rats (Harris and Barton 2008; Loccisano et al. 2012a, 2012b; Tan et al. 2008) and a model for PFOA in mice (Rodriguez et al. 2009). Models of PFOA and PFOS kinetics during gestation and lactation in rats and mice also have been reported (Loccisano et al. 2012a, 2012b; Rodriguez et al. 2009). Various empirical and compartmental models have also been reported (Hoffman et al. 2011; Lorber and Egeghy 2001; Lou et al. 2009; Thompson et al. 2010; Wambaugh et al. 2008). Tardiff et al. (2009) utilized a human pharmacokinetic model to estimate an average daily oral dose corresponding to a Reference Dose for PFOA plasma concentration in humans. The model used in this analysis was described in an abstract presented at the Society of Toxicology (Clewell et al. 2006).

3.4.5.1 Loccisano et al. (2012a, 2012b) Rat Models

Loccisano et al. (2012a) developed a model for simulating the kinetics of PFOA and PFOS in male and female rats. The model was based, in part, on a multi-compartmental model developed by Tan et al. (2008; Andersen et al. 2006). The female rat model (Loccisano et al. 2012a) was subsequently extended to include gestation and lactation (Loccisano et al. 2012b). The general structures of the models are depicted in Figures 3-9, 3-10, and 3-11. A complete list of parameters and parameter values and the bases for parameter values and evaluations of model predictions in comparison to observations are described in Loccisano et al. (2012a, 2012b).

The basic (i.e., adult non-pregnant rat) model includes compartments representing plasma (including a bound and free fraction), kidney and renal glomerular filtrate, liver, and a lumped compartment representing all other tissues. Two storage compartments are included in the model: one receives perfluoroalkyl from the gastrointestinal tract (unabsorbed) and liver (bile) and the other receives perfluoroalkyl from the glomerular filtrate. The storage compartments were included in the model to simulate time delays between elimination from plasma and appearance of perfluoroalkyl in feces or urine. Absorption from the gastrointestinal tract is simulated as the balance between first-order absorption and fecal excretion of unabsorbed chemical. Absorbed PFOA and PFOS are assumed to be delivered to the liver where saturable binding of PFOS (but not PFOA) to liver proteins occurs. Saturable binding of PFOS in liver was included to simulate the relatively long retention times of PFOS in liver that have been observed in rats. Exchanges between PFOA or PFOS in liver (free fraction), kidney, and other tissues with the free pool in plasma are assumed to be flow-limited (governed by blood flow) with equilibrium determined by the tissue:blood partition coefficient. PFOA and PFOS in plasma are simulated as

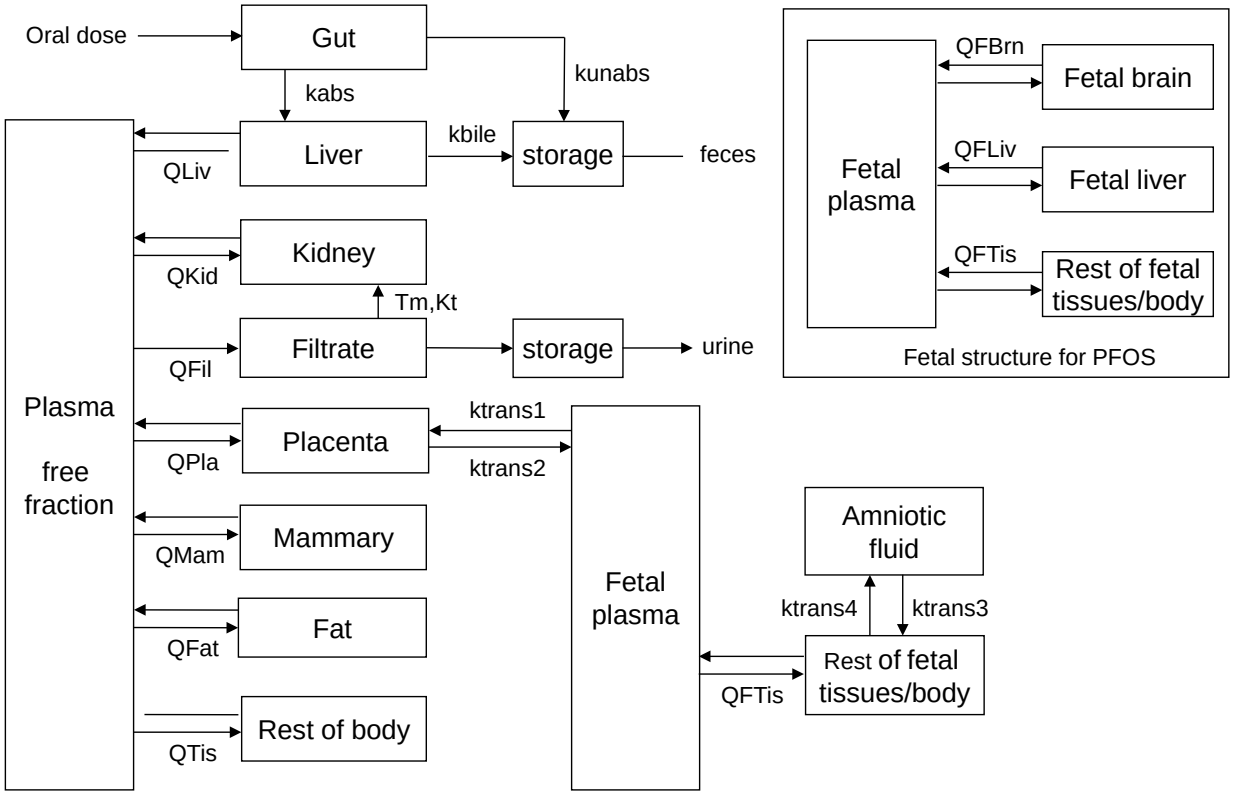
Figure 3-9. Structure of PBPK Model of PFOA and PFOS in the Rat



Bmax = liver binding capacity; kabs = first-order absorption rate constant; Kb = liver binding affinity constant; kbile = biliary excretion rate constant; Koff = liver binding dissocation constant; Kt = affinity constant; kunabs = rate of unabsorbed dose to appear in feces; PBPK = physiologically based pharmacokinetic; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; QFil = clearance from plasma to glomerular filtrate; QKid = blood flow in and out of kidney; QLiv = blood flow in and out of liver; QTis = blood flow in and out of tissues; Tm = transporter maximum

Source: Loccisano et al. 2012a (reproduced with permission of Elsevier Inc. in the format reuse in a government report via Copyright Clearance Center; Reproductive Toxicology by Reproductive Toxicology Center; Washington, DC)

Figure 3-10. PBPK Model Structure for Simulating PFOA and PFOS Exposure During Gestation in the Rat (Dam, Left; Fetus, Right)



kabs = first-order absorption rate constant; kbile = biliary excretion rate constant; Kt = affinity constant; ktrans1/ktrans 2 = transfer between placenta and fetal plasma; ktrans3/ktrans4 = transfer between amniotic fluid and rest of the body; kunabs = rate of unabsorbed dose to appear in feces; PBPK = physiologically based pharmacokinetic; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; QFat = blood flow in and out of fat; QFBrn = blood flow in and out of fetal brain; QFil = clearance from plasma to glomerular filtrate; QFLiv = blood flow in and out of fetal liver; QFTis = blood flow in and out of fetal tissue; QKid = blood flow in and out of kidney; QLiv = blood flow in and out of liver; QMam = blood flow in and out of mammary tissue; QPla = blood flow in and out of placenta; QTis = blood flow in and out of tissues; Tm = transporter maximum

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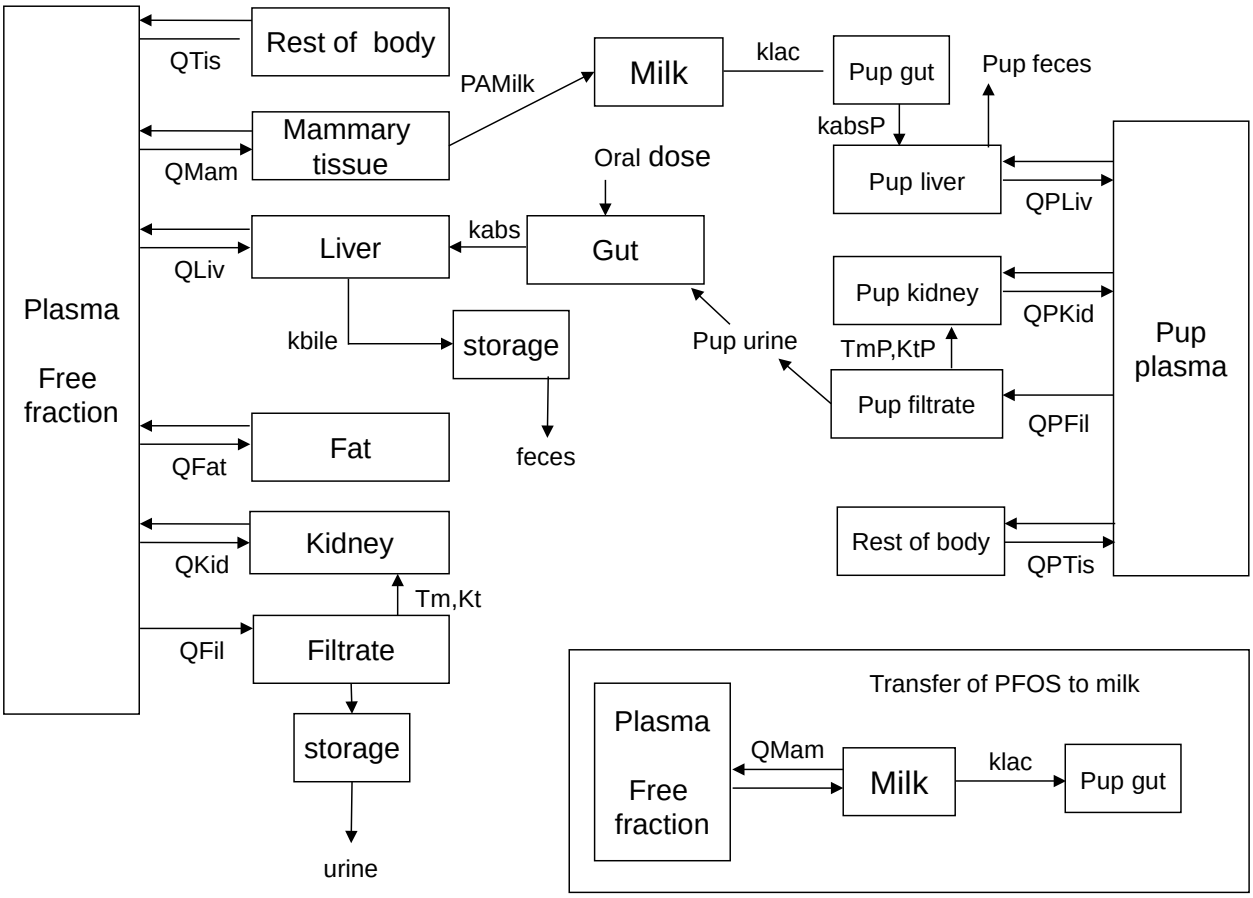
Figure 3-11. PBPK Model Structure for Simulating PFOA/PFOS Exposure During Lactation in the Rat (Dam, Left; Pup, Right)



kabs = first-order absorption rate constant; kabsP = pup first-order absorption rate constant; kbile = biliary excretion rate constant; klac = transfer to pup through milk; Kt = affinity constant; KtP = pup affinity constant; PAMilk = transfer from mammary tissue to liver; PBPK = physiologically based pharmacokinetic; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; QFat = blood flow in and out of fat; QFil = clearance from plasma to glomerular filtrate; QKid = blood flow in and out of kidney; QLiv = blood flow in and out of liver; QMam = blood flow in and out of mammary tissue; QPFil = clearance from pup plasma to glomerular filtrate; QPKid = blood flow in and out of pup kidney; QPLiv = blood flow in and out of pup liver; QPTis = blood flow in and out of pup tissue; QTis = blood flow in and out of tissues; Tm = transporter maximum; TmP = pup transporter maximum

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instantaneous distributions into free and bound fractions. Extensive binding of PFOA and PFOS to plasma proteins has been demonstrated in various animal species including rats (see Section 3.4.2). For PFOA, the free fraction is assigned a constant 4.5% in females and 0.6% in males. These values were optimized to fit observed kinetics of PFOA in plasma and urine of rats following intravenous and oral exposures (Loccisano et al. 2012a). Adequate fit to observed PFOS plasma kinetics following single doses of PFOS required introducing a time-dependence in binding of PFOS to protein (Loccisano et al. 2012a; Tan et al. 2008). The free fraction for PFOS in plasma decreases from an initial value (after dosing) of 2.2% to a minimum of 0.1% with a half-time for the change of approximately 14 hours in a 0.25-kg rat ($k=0.035$ hours^{-1}/kg$^{-0.25}$). The relatively short half-time for the change limits the effects of the time-dependence plasma kinetics over the first 1–2 days of dosing (including peak concentrations) and has no effect on longer-term kinetics or steady state. Although the time-dependence of the free fraction in plasma was needed to simulate short-term plasma PFOS kinetics in rats, the physiological mechanism for a dependence of plasma binding on the time following dosing (i.e., not on concentration of PFOS in plasma or some other dose surrogate) has not been established. Elimination of absorbed chemical occurs by biliary excretion and urinary excretion. Transfer from liver to feces (representing excretion following biliary transfer) is represented as a first-order process acting on the free fraction in liver. Excretion in urine is simulated as the balance between transfer from the free fraction to the glomerular filtrate and renal tubular reabsorption, which removes PFOA and PFOS from the glomerular filtrate and returns it to kidney tissue. Renal tubular reabsorption is simulated as a capacity-limited process with parameters T_m (µg/hour/kg body weight), representing the maximum rate of transport, and K_T (µg/L), representing affinity for the transporter (the concentration in the glomerular filtrate at which reabsorptive transport rate is half of maximum). This representation of renal tubular reabsorption is used to simulate observed sex differences in elimination of PFOA from plasma, which have been attributed to higher reabsorptive capacity in male rats (see Sections 3.4.4.2 and 3.5.1). Values for the maximum and affinity parameters for PFOA result in higher reabsorptive clearances from the glomerular filtrate ($T_m/K_T=4.1$) in male rats compared to female rats ($T_m/K_T=0.045$), and correspondingly lower urinary clearance of PFOA from plasma in male rats. Reabsorption parameters for PFOS are the same in both sexes and result in reabsorptive clearances that are approximately twice that of PFOA in female rats ($T_m/K_T=7.2$).

The basic rat model was extended to simulate gestation with inclusion of additional compartments representing adipose and mammary tissue in the dam, placenta, and fetus (Figure 3-10); Loccisano et al. 2012b). Transfer of PFOA and PFOS to the fetus is simulated as a flow-limited transfer to the placenta, with first-order exchange between the placenta and the free fraction in fetal plasma. The free fraction in fetal plasma is simulated with as a constant fraction for PFOA and PFOS (i.e., no dependence on time as

in the adult). Within the fetus, PFOA in the free fraction of plasma exchanges with a single lumped compartment representing the fetal body, which exchanges with PFOA in amniotic fluid. The fetal PFOS model subdivides fetal tissue into brain, liver, and a lumped compartment for other tissues, all of which undergo flow-limited exchanges with the free fraction of PFOS in fetal plasma. Binding of PFOA and PFOS in fetal liver are assumed to be negligible. Differences in the structure of the fetal models for PFOA and PFOS reflect the differences in the availability of data of for estimating parameter values for the various compartments (e.g., perfluoroalkyl concentrations in amniotic fluid, liver).

The lactation model extends the dam portion of the gestational model to include milk and pup (Figure 3-11; Loccisano et al. 2012b). Transfer of PFOA to milk occurs through the mammary gland with flow-limited exchange between plasma and mammary tissue and diffusion into milk from mammary tissue. Data on PFOS in mammary tissue of rodents were not available to establish parameters for a mammary tissue compartment; therefore, the mammary tissue compartment was left out of the PFOS model, and transfer of PFOS to milk is simulated as diffusion directly from plasma. The pup model includes compartments representing the free fraction in plasma, liver, kidney, glomerular filtrate, and a lumped compartment representing all other pup tissues. This structure is essentially identical to the nonpregnant rat model (Loccisano et al. 2012a) with a few differences. Absorption from the gastrointestinal tract is assumed to be complete in pups, and binding in pup liver is assumed to be negligible in pups. There are no storage compartments for biliary or glomerular filtrate perfluoroalkyl in the pup model. Sex differences in renal tubular reabsorption of PFOA are assumed to develop in response to sexual maturation and, therefore, are not present during lactation (i.e., parameter values are allometrically scaled to pup body weight from the male rat values). Reabsorptive transport parameters for PFOS are allometrically scaled from the lactating dam. The liver/plasma partition coefficient for PFOS in the pups was set lower than that in the dam, based on observations in rats. All other parameters for PFOA and PFOS in the pup were the same or allometrically scaled from values for the dam.

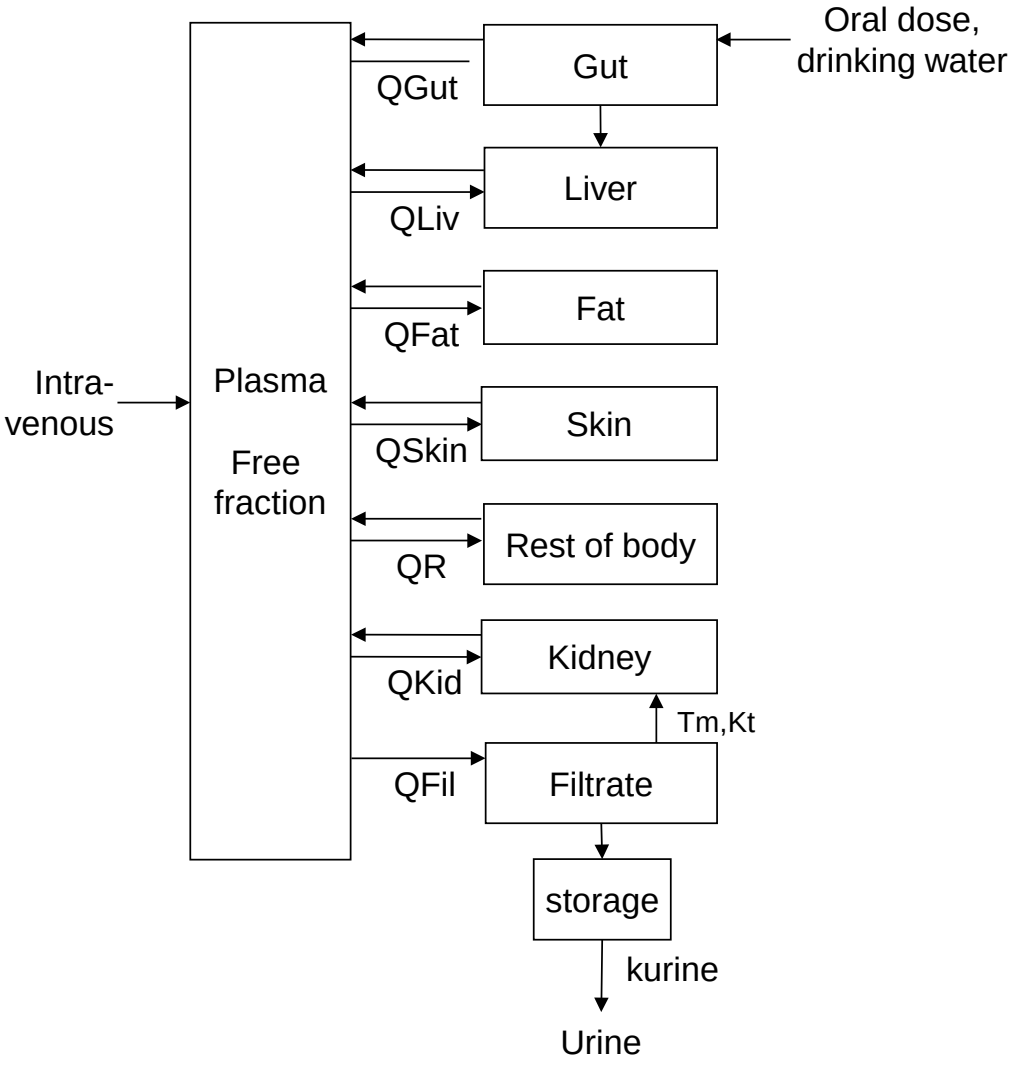
Optimization of parameter values and evaluations of the rat models are described in Loccisano et al. (2012a, 2012b). Data sets utilized in developing and evaluating the nonpregnant rat models included single-dose intravenous and gavage studies and short-term feeding studies (Johnson and Ober 1979; Kemper 2003; Kudo et al. 2007; Perkins et al. 2004). Data used in development and evaluation of the gestation and lactation models included data from gestational and/or lactational exposure studies in rats (Chang et al. 2009; Hinderliter et al. 2005; Kuklenyik et al. 2004; Luebecker et al. 2003, 2005a, 2005b; Thibodeaux et al. 2003).

Applications for Dosimetry Extrapolation and Risk Assessment. The wealth of data on pharmacokinetics of PFOA and PFOS in rats allowed an extensive evaluation of the rat models for predicting plasma urinary and liver PFOA and PFOS following single intravenous or single and repeated oral dosing. Inclusion of renal tubular reabsorption parameters in the model provided accurate simulations of sex differences in elimination rates of PFOA from plasma and excretion in urine, and differences in rates of elimination of PFOA and PFOS. The gestation model successfully predicted fetal plasma and liver PFOA and PFOS at the end (or near the end) of pregnancy. Consistent with observations, the model predicts higher fetal plasma concentrations and lower fetal liver concentrations of PFOS compared to maternal, and lower internal exposure (plasma concentrations) to PFOA in the fetus compared to maternal (fetal liver data were not available for PFOA). The lactation model successfully predicted PFOA and PFOS in pup plasma following dosing of the dam. Predicted plasma concentrations of PFOA in nursing pups were approximately 10–50% lower than maternal concentrations, whereas maternal and pup concentrations of PFOS were similar. The model could be used to estimate liver doses and corresponding plasma profiles resulting from single or repeated dosing of adult male or female rats, and maternal-fetal and maternal-pup transfer of PFOA and PFOS. The rat model was evaluated with data from a 14-week oral dosing study and has not been tested for longer exposures. Harris and Barton (2008) developed a PBPK model for PFOS in the rat and found that time adjustments that increased renal clearance and decreased the liver-plasma partition coefficient as a function of time and dose improved predictions of plasma and liver PFOS in adult rats exposed for a period of 105 weeks. Although the Harris and Barton (2008) model is very different from the Loccisano et al. (2012a) model, these results suggest the possibility that clearance of PFOS may be age- and/or dose-dependent in rats. This may reflect age-related or dose-related changes in kidney function, including tubular reabsorption or secretion of PFOS.

3.4.5.2 Loccisano et al. (2011, 2013) Monkey and Human Models

Loccisano et al. (2011) developed a model for simulating the kinetics of PFOA and PFOS in monkeys and humans. The human model described in Loccisano et al. (2011) was subsequently extended to include simulations of pregnancy and lactation (Loccisano et al. 2013). The monkey model was based, in part, on a multi-compartmental model developed by Tan et al. (2008; Andersen et al. 2006) for simulating the kinetics of plasma and urinary PFOA in monkeys. The structures of the monkey and human models are identical (Figure 3-12) and are very similar to the structure of the rat model (Loccisano et al. 2012a), with inclusion of compartments representing fat and skin, and absence of a storage compartment for biliary transfer. A complete list of parameters and parameter values and the bases for parameter values

Figure 3-12. Structure of PBPK Model for PFOA and PFOS in Monkeys and Humans



Kt = half-saturation constant; kurine = urinary elmination rate; PBPK = physiologically based pharmacokinetic; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; QFat = blood flow in and out of fat; QFil = clearance from plasma to glomerular filtrate; QGut = blood flow in and out of gut; QKid = blood flow in and out of kidney; QLiv = blood flow in and out of liver; QR = blood flow in and out of rest of body; QSkin = blood flow in and out of skin; Tm = transport maximum

Source: Loccisano et al. 2011 (reproduced with permission of Academic Press in the format reuse in a government report via Copyright Clearance Center; Regulatory Toxicology and Pharmacology: RTP by International Society of Regulatory Toxicology and Pharmacology)

and evaluations of model predictions in comparison to observations are reported in Loccisano et al. (2011).

Parameters in the monkey and human models differ in several ways from the rat model. The free fraction in plasma is represented as a constant for both PFOA and PFOS; time-dependency for PFOS in the rat model is absent in the monkey and human models. The parameters for renal tubular reabsorption of PFOA and PFOS are the same for males and females. This is consistent with the absence of evidence for a sex difference in elimination kinetics in monkeys (Butenhoff et al. 2002, 2004a; Seacat et al. 2002). Values for the affinity constant (K_T) and maximum (T_m) for tubular reabsorption were optimized to plasma concentration kinetics in monkeys. The value for K_T in monkeys was used in the human model. The value for T_m for PFOA in humans was set to yield a plasma elimination half-time of 2.3 or 3.8 years. The latter two values derive from estimates of the serum half-time in populations exposed to PFOA in drinking water (2.3 years; Bartell et al. 2010) or in retired fluorochemical workers (3.8 years; Olsen et al. 2007a). The value for T_m for PFOS in humans was set to yield a plasma elimination half-time of 5.4 years, based on observations in retired fluorochemical workers (Olsen et al. 2007a). Binding of PFOA and PFOS in the liver was assumed to be negligible in monkeys and humans. Tissue-plasma partition coefficients used in both models were derived from observations in rodents and were the same in the monkey and human models.

Optimization of parameter values and evaluation of the monkey and human models are described in Loccisano et al. (2011). Data sets utilized in developing and evaluating the monkey model included single-dose intravenous and oral studies and repeated-dose oral studies conducted in Cynomolgus monkeys (Butenhoff et al. 2004c; Noker and Gorman 2003; Seacat et al. 2002). Data used in evaluating the human model consisted of serum measurements in people who experienced environmental exposures (Emmett et al. 2006a; Holzer et al. 2008; Steenland et al. 2009), adult Red Cross donors (Olsen et al. 2003b, 2008), and retired fluorochemical workers (Olsen et al. 2007a). In general, PFOA and PFOS intakes and exposure durations were not known with certainty in these populations and, as a result, these data do not yield confident evaluations of the ability of the human model to predict intake-plasma level relationships. Follow-up monitoring after a cessation or decrease in exposure can provide data that allow evaluation of the ability of the model to accurately simulate elimination kinetics. Predicted declines in serum PFOA concentrations encompassed observed group mean declines when the T_m for renal tubular reabsorption was set to yield elimination half-times of 2.3 or 3.8 years. Group mean declines in serum PFOS were predicted reasonably well for some populations, but not all populations, when the T_m for renal tubular reabsorption was optimized to yield an elimination half-time of 5.4 years.

The human pregnancy model includes additional compartments representing the free fractions in plasma, amniotic fluid, and a lumped compartment for fetal tissue (Loccisano et al. 2013). The same conceptual approach used in rat pregnancy model (Loccisano et al. 2012b, Figure 3-10). Rate constants for placental transfer were initially those from the rat model, adjusted to yield predicated maternal/fetal plasma ratios that agreed with observed maternal/fetal ratios in cord blood (Apelberg et al. 2007b; Fei et al. 2007; Midasch et al. 2007; Washino et al. 2009). Transfers from amniotic fluid to fetus were the same as those used in the rat model, as there were no data on which to base estimates for humans. The lactation model included additional compartments for mammary milk and a lumped compartment representing the infant. Transfer of PFOA to milk is simulated as flow-limited exchange between plasma and milk, governed by mammary tissue blood flow and a milk/plasma partition coefficient. This structure obviated the need to simulate mammary tissue kinetics, for which there were no data in humans. The milk/plasma partition coefficient was calibrated to yield predictions of observed milk/plasma ratios (Fromme et al. 2010; Kärrman et al. 2007). Transfer from maternal milk to infants is the product of the milk concentration and milk production rate assumed to be equal to sucking rate). The pregnancy model was evaluated by comparing predicted maternal/fetal plasma ratios for PFOA and PFOS with observations from various human monitoring studies (Fei et al. 2007; Fromme et al. 2010; Hanssen et al. 2010; Inoue et al. 2004b; Kim et al. 2011; Midasch et al. 2007; Monroy et al. 2008; Tittlemier et al. 2004). The lactation model was evaluated by comparing predicted maternal plasma/milk ratios for PFOA and PFOS with observations from various human monitoring studies (Fromme et al. 2009; Kärrman et al. 2007; Liu et al. 2011). In general, most model predictions were within plus or minus 2-fold of observations.

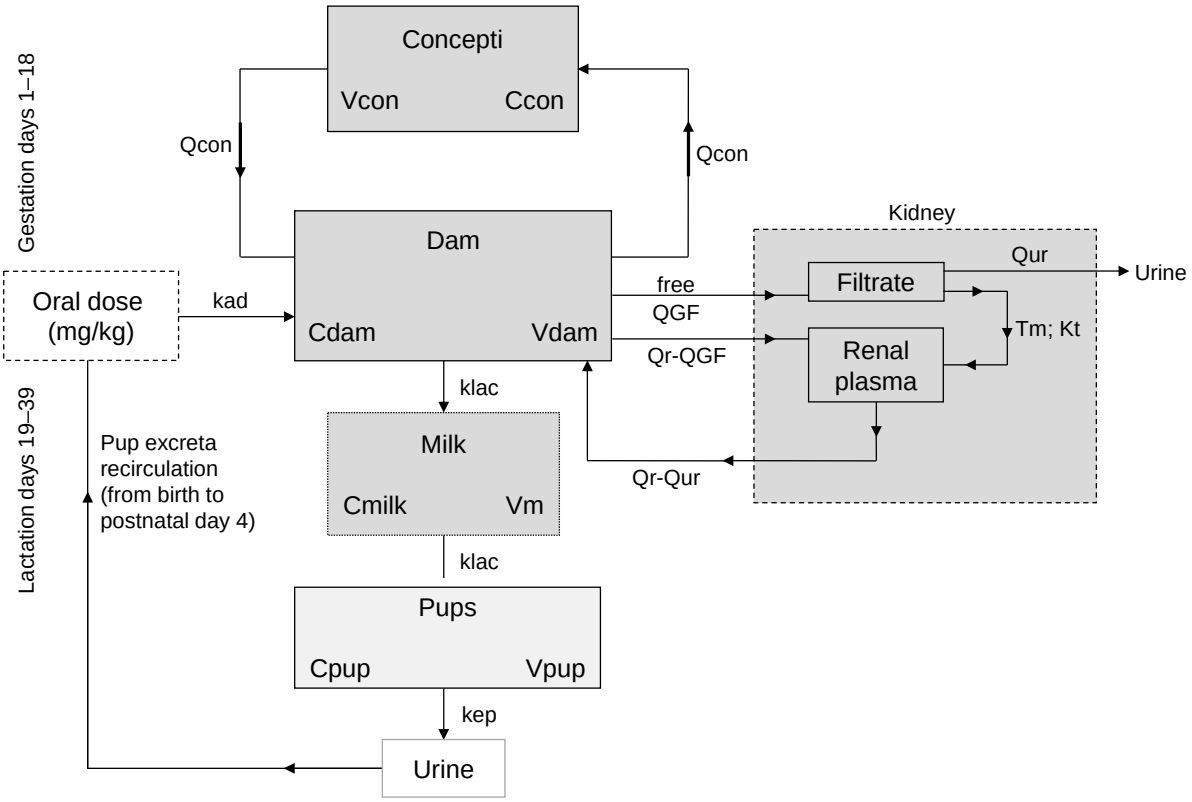
Applications for Dosimetry Extrapolation and Risk Assessment. The model predicts plasma concentrations and tissue levels of PFOA and PFOS following intravenous or oral dosing. A skin compartment is included in the model, which may serve for simulating absorption and distribution following deposition onto the skin surface; however, the dermal absorption model was not evaluated in Loccisano et al. (2011). The human model was calibrated to predict limitation half-times estimated for human populations (e.g., 2.3 or 3.8 years for PFOA, 5.4 years for PFOS). As a result, comparisons made between observed and predicted serum concentrations evaluate whether or not the populations actually exhibit the half-times to which the model was calibrated, and not the validity of the model to predict the internal distribution of PFOA or PFOS. It is not currently possible to assess with confidence whether the human model can accurately predict doses to liver or any other tissues. Fábrega et al. (2014) applied the human adult model to estimate plasma concentrations and tissue levels of PFOA and PFOS in human autopsy samples. Exposure inputs to the model were intakes of PFOA and PFOS estimated from public

water supply concentrations in the local area where the subjects had resided (Catalonia, Spain) and concentrations in local market basket foods (Domingo et al. 2012a, 2012b). The human model predicted levels of PFOA in plasma and liver that were approximately 10- and 5-fold higher, respectively, than observed. Predicted plasma levels of PFOS were approximately 2-fold higher than observed and predicted levels of PFOS in kidney were approximately 25% of observed. Fábrega et al. (2014) explored alternative values for tissue/plasma partition coefficients, determined from human autopsy issues (Maestri et al. 2006). The adjusted partition coefficients improved predictions of observed tissue PFOA and PFOS levels. Although the model could be applied to predicting plasma concentrations of PFOA and PFOS or intakes associated with specific plasma concentrations (e.g., oral MRLs), it is not clear what advantages the model offers over simpler empirical or compartmental models similarly calibrated to predict the serum half-time. The monkey model has been more thoroughly evaluated for predicting plasma and urinary kinetics of PFOA and PFOS. This was possible because of the availability of more extensive experimental data on plasma and urine PFOA and PFOS following intravenous and oral (single and repeated) dosing in male and female monkeys. Nevertheless, data on internal distribution were not available to allow evaluation of how well the monkey model predicts doses to the liver or other tissues. Predictions of plasma PFOA and PFOS concentrations from the monkey (and human) model were highly sensitive to values assigned to the maximum rate for tubular reabsorption (T_m) and other parameters that govern urinary elimination of POFA and PFOS (e.g., free fraction in plasma and glomerular filtration rate; Loccasano et al. 2011). Optimization of the monkey models relied heavily on adjusting these same parameters and, for the human model, target plasma elimination half-times were achieved solely by adjusting T_m. Thus, despite the complexity of the models, their potential to accurately predict plasma elimination kinetics and, therefore, steady-state plasma concentrations and associated oral intakes, depends largely on how well they predict plasma clearance. If plasma clearance and the free-fraction in plasma can be reliably predicted empirically for the animal species of interest, then far simpler compartmental models can be used for dosimetry extrapolation of steady-state free plasma concentrations.

3.4.5.3 Rodriguez et al. (2009) Mouse Model

Rodriguez et al. (2009) developed a model for simulating the maternal-fetal and maternal-pup kinetics of PFOA in mice. The general structure of the model is depicted in Figure 3-13. A complete list of parameters and parameter values and the bases for parameter values and evaluations of model predictions in comparison to observations are reported in Rodriguez et al. (2009). The maternal, fetal and pup systems are simulated as single well-mixed compartments. Absorption from the gastrointestinal tract is

Figure 3-13. Renal Resorption Pharmacokinetic Model of Gestation and Lactation used in the Analysis of CD-1 Mice



Ccon = concentration in concepti; Cdam = concentration in dam; Cmilk = concentration in milk; Cpup = concentration in pup; kad = first-order absorption rate; kep = urinary excretion rate; klac = transfer rate via milk; Kt = half-saturation constant; Qcon = blood flow to and from placenta; QGF = glomerular filtrate; Qr = renal plasma flow; Qur = urine flow; Tm = transport maximum; Vcon = volume in concepti; Vdam = volume in dam; Vmilk = volume in milk; Vpup = volume in pup

Source: Rodriquez et al. 2009 (reproduced with permission of Elsevier Inc. in the format reuse in a government report via Copyright Clearance Center; Reproductive Toxicology by Reproductive Toxicology Center; Washington, DC)

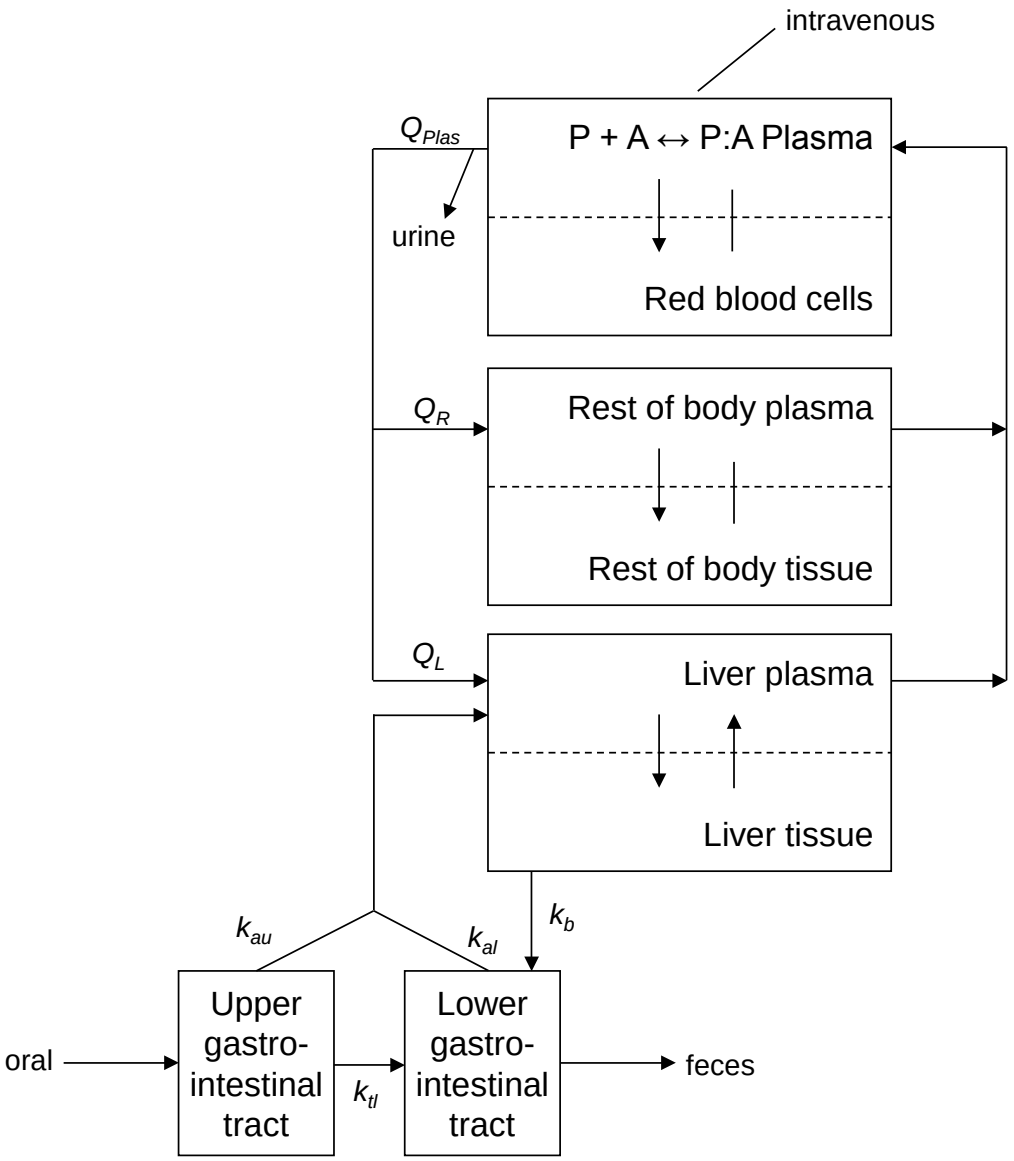
simulated as first-order with complete absorption of the ingested dose. Elimination of absorbed PFOA from the maternal system is simulated as the balance between glomerular filtration and renal tubular reabsorption. The latter is represented as a saturable process with parameters T_m and K_T. Transfer to the fetus is flow-limited and governed by a fetus/maternal partition coefficient and placental blood flow. Transfer from the maternal system to the pup by lactation simulated is first-order governed by a lactation transfer rate constant. Elimination of PFOA from the pup is first-order to urine. Data sets utilized in developing and evaluating the mouse model included oral gestational dosing studies.

Applications for Dosimetry Extrapolation and Risk Assessment. The model predicted observed concentrations of PFOA in maternal, fetal, and pup serum following oral gestational exposures to mice (Abbott et al. 2007; Lau et al. 2006; White et al. 2007). Residuals for predictions are presented, which provide a quantitative measure of how well the model predicted observations (Rodriguez et al. 2009). Similar to the rat, the mouse model predicts higher internal exposure (serum PFOA concentrations) in the maternal system compared to the fetus. It also predicts accelerated loss of PFOA from the maternal system during lactation. The model simulates the maternal, fetal, and pup systems as a single compartments. Although this serves for simulating plasma concentrations (the main objective of the modeling effort), it does not allow for simulation of tissue levels of PFOA in the maternal system, fetus, or pup.

3.4.5.4 Harris and Barton et al. (2008) Rat Model

Harris and Barton (2008) developed a model for simulating the PFOS in adult rats. The general structure of the model is depicted in Figure 3-14. A complete list of parameters and parameter values and the bases for parameter values and evaluations of model predictions in comparison to observations are reported in Harris and Barton (2008). The model includes systemic compartments representing blood (including a bound and free fraction of plasma and red blood cells), liver, and a lumped compartment representing all other tissues. The gastrointestinal tract is simulated as separate compartments representing the upper and lower tracts. Absorption occurs from both the upper and lower tracts, with distinct first-order rate constants assigned to each. Biliary PFOS is transferred from liver to the lower tract. Absorbed PFOS is delivered to the liver where it enters plasma to be distributed to other tissues. Exchanges between PFOS in plasma and all tissues are assumed to be diffusion-limited, with the free pool in plasma participating in the exchange with red blood cells, and the total plasma pool exchanging with liver and all other tissues. Binding of PFOA to plasma albumin is assumed to be saturable with dissociation constant 10^{-7} M and

Figure 3-14. Conceptual Representation of a Physiologically Based Pharmacokinetic Model for PFOS Exposure in Rats



k_{al} = rate of absorption from the lower gastrointestinal tract; k_{au} = rate of absorption from the upper gastrointestinal tract; k_b = maximum rate of biliary elimination; k_{tl} = rate of transfer from upper-lower gastrointestinal tract; P:A = PFOS-bound albumin in plasma; PFOS = perfluorooctane sulfonic acid Q_L = plasma flow rate to the liver; Q_{Plas} = plasma flow rate by the heart; Q_R = plasma flow rate to the rest of body

Source: Harris and Barton 2008 (reproduced with permission of Elsevier Ireland Ltd. in the format reuse in a government report via Copyright Clearance Center; Toxicology Letters by European Societies of Toxicology)

maximum capacity 4.1x 10^{-4} M. This is implemented by assigning bound PFOA to a sub-compartment of plasma in which PFOA enters (binds) or exits (unbinds) at rates governed by binding *on* and *off* rates, respectively, that yield a dissociation constant of 10^{-7} M. Elimination of absorbed chemical occurs by biliary excretion and urinary excretion. Transfer from liver to the lower gastrointestinal tract (representing excretion following biliary transfer) is represented as a first-order process acting on the total amount of PFOS in liver. PFOA is transferred to urine from the free fraction of plasma at a rate governed by a urinary clearance parameter, which is assigned value of 28% of renal plasma flow.

In evaluating performance of the model for simulating PFOS concentrations in a chronic rat feeding study, Harris and Barton (2008) found that the model predicted plasma and liver concentrations measured at 4 and 16 weeks, but over-predicted both at 104 weeks. Performance of the model was improved by having renal clearance increase and the liver/plasma partition coefficient decrease as a function of time (i.e., study duration). These results suggest the possibility that clearance of PFOS may be dependent on age and/or a metric of dose (e.g., cumulative internal dose). This may reflect age-related or dose-related changes in kidney function, including tubular reabsorption or secretion of PFOS.

Applications for Dosimetry Extrapolation and Risk Assessment. The model simulates kinetics of PFOS following oral or intravenous dosing in adult rats and includes several features that are different from other PBPK models of perfluoroalkyls. The Harris and Barton et al. (2008) model includes a red cell compartment that allows predictions of whole-blood concentrations. The utility of this feature remains to be determined; since PFOS does not appreciably concentrate in red blood cells and PFOS (and other perfluoroalkyls) is typically monitored in the central compartment with measurements of plasma or serum concentrations. The model assumes that the total concentration of PFOS (not just the free concentration) in plasma is available for distribution to liver and other tissues, whereas other models assume that only the free pool in plasma exchanges with tissues. The practical consequence of this difference may not be significant in terms of the toxicokinetics of PFOS if the tissue/plasma partition coefficients in the various models were estimated based on the relevant perfluoroalkyl pool in plasma. However, without basing distribution kinetics on the free concentration, it is not possible for concentration-dependent free fraction to be modeled. The model assumes time-dependence in the liver uptake and urinary excretion of PFOS, which were needed to improve predictions of plasma and liver concentrations of PFOS during chronic exposures. Other rat models (Loccisano et al. 2012a) have not been similarly evaluated. A mechanistic understanding of the time-dependent changes in PFOS kinetics will be important for applications of these models for dosimetry extrapolation across exposure durations.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption. Studies conducted in rodents indicate that >93% of an ingested dose of PFOA and PFOS is absorbed and that absorption occurs with an approximate half-time of 0.25–1.5 hours (see Section 3.4.1.2 for discussion of Chang et al. 2008a; Hinderliter et al. 2006b; Hundley et al. 2006; Johnson and Ober 1979, 1980; Kemper 2003). Mechanisms of absorption of perfluoroalkyls have not been elucidated and may involve (1) diffusive transfer of the non-ionized fraction out of the stomach lumen; (2) transport in the small intestine mediated by organic anion transporters; and/or (3) absorption in association with absorptive transport of lipids.

Distribution. Perfluoroalkyls in plasma bind to serum albumin and various other plasma proteins including gamma-globulin, alpha-globulin, alpha-2-macroglobulin, transferrin, and beta-lipoproteins (Bischel et al. 2011; Butenhoff et al. 2012; Chen and Guo 2009; Han et al. 2003, 2005; Kerstner-Wood et al. 2003; Luo et al. 2012; Ohmori et al. 2003; Salvalagio et al. 2010; Vanden Heuvel et al. 1992b; Wu et al. 2009; Ylinen and Auriola 1990; Zhang et al. 2009). The dissociation constant for albumin-bound PFOA in serum is approximately 0.4 mM (0.38 mM, ±0.04 standard deviation for human serum albumin; 0.36 nM, ±0.08 standard deviation for rat serum albumin) and involves 6–9 biding sites (Han et al. 2003). Noncovalent binding appears to be at the same sites as fatty acids (Chen and Guo 2009). Interactions between PFOS and human serum albumin include interaction of PFOS polar sulfonyl groups with albumin hydrophilic sites and interaction of perfluorinated groups with albumin hydrophobic sites (Luo et al. 2012).

Absorbed perfluoroalkyls distribute from plasma to soft tissues, with the highest extravascular concentrations achieved in liver. Mechanisms by which perfluoroalkyls enter the liver have not been elucidated and may involve interactions with organic anion transporters that function in the distribution of fatty acids or other organic anions (Andersen et al. 2008). PFOA appears to be a substrate for organic anion transporters in the luminal and basolateral membranes of renal tubular epithelial cells, which facilitates entry of PFOA into renal tubular cells (Kudo et al. 2002; Vanden Heuvel et al. 1992a). The subcellular distribution of PFOA is sex- and dose-dependent in rats (Han et al. 2005; Kudo et al. 2007) and the association with the membrane fraction of liver cells decreases with increasing dose (Kudo et al. 2007), consistent with limited capacity of membrane proteins that bind PFOA (e.g., membrane transport proteins). Intracellular PFOA binds to proteins; protein complexes formed have not been fully

characterized. PFOA exhibits a low affinity for binding to rat kidney and urine alpha-2μ-globulin (dissociation constants 1.5 and >2 mM, respectively; Han et al. 2004).

Metabolism. Studies conducted in rodents and nonhuman primates have not found quantitatively significant metabolism of perfluoroalkyls PFOA, PFOS, or PFDeA (Goecke et al. 1992; Vanden Heuvel et al. 1991b, 1991c; Ylinen and Auriola 1990). PFOA was not metabolized when incubated with microsomal fractions of human or rat intestine, kidney, or liver homogenates (Kemper and Nabb 2005). Results of these studies suggest that perfluoroalkyls are not metabolized.

Excretion. Urinary excretion of perfluoroalkyls involves glomerular filtration and renal tubular secretion and reabsorption (for PFOA, see Harada et al. 2005a; Kudo et al. 2002; Ohmori et al. 2003). Glomerular filtration of PFOA is limited by extensive binding of PFOA to albumin and other high molecular weight proteins in plasma (Han et al. 2003, 2005; Ohmori et al. 2003; Kerstner-Wood et al. 2003; Vanden Heuvel et al. 1992a, 1992b; Ylinen and Auriola 1990). Elimination of PFOA and other perfluoroalkyls shows pronounced sex differences in rats, with slower elimination in males for PFOA, PFOS, PFNA, PFHxA, PFHxS, PFBA, and PFBuS (Chang et al. 2008a, 2012; Chengelis et al. 2009; Kemper 2003; Kudo et al. 2002; Ohmori et al. 2003; Sundström et al. 2012). The sex difference in elimination PFOA in rats is dependent on testosterone (Hinderliter et al. 2006b; Kudo et al. 2002; Vanden Heuvel et al. 1992a). The significantly slower elimination of PFOA in adult male rats compared to female rats has been attributed to sex hormone modulation of organic anion transporters in kidney. At similar doses administered to male and female rats, PFOA undergoes net tubular reabsorption in male rats (i.e., urinary excretion rate < rate of glomerular filtration of PFOA) and net tubular secretion in female rats (i.e., urinary excretion rate > rate of glomerular filtration of PFOA; Harada et al. 2005a; Kudo et al. 2002; Ohmori et al. 2003). In rats, several transporters have been shown to have affinity for C7–C9 perfluoroalkyl carboxylates. The transporters, Oat1 and Oat3, located on the basolateral membrane of the renal proximal tubule, appear to participate in secretion of C7–C9 perfluoroalkyl carboxylates into the tubular fluid (Nakagawa et al. 2008; Weaver et al. 2010). The transporters, Oatp1a1 (rat), Oat4 (human) and URAT1 (human), located on the apical membrane, appears to mediate reabsorption of C8-C10 perfluoroalkyl carboxylates from the tubular fluid (Katakura et al. 2007; Nakagawa et al. 2009; Weaver et al. 2010; Yang et al. 2009, 2010). In rats and mice, expression of Oat1, Oat3, and Oatp1a1 are controlled by male sex hormones and show higher activities in males (Buist and Klaassen 2004; Gotoh et al. 2002; Kobayashi et al. 2002; Li et al. 2002; Lu et al. 1996; Lubojevic et al. 2004). The slower elimination of PFOA (and other long-chain perfluoroalkyl carboxylates) in male rats has been attributed to Oatp1a1 (Weaver et al. 2010; Yang et al. 2009). Higher activity of Oatp1a1 in male rats results in higher

reabsorptive transport and lower rates of urinary excretion. Affinities of Oastp1a1 (rat), Oat4 (human), and URAT1 (human) are highest for C7–C10 perfluoroalkyl carboxylates (Weaver et al. 2010; Yang et al. 2009, 2010). Affinity of rat Oatp 1a1 is strongly correlated with total clearance in rats (r^2=0.98; Yang et al. 2009).

Although human monitoring studies have not detected sex differences in elimination half-times of perfluoroalkyls, this may reflect limitations in the studies, including numbers and age of subjects (Bartell et al. 2010; Seals et al. 2011). A better metric than serum half-time for evaluating sex differences in elimination for this would be systemic or renal clearance. Harada et al. (2005a) measured renal clearance in a small sample of young adults (five males and five females, age 22–23 years) and found that renal clearance was not different in males and females. Studies that measured systemic clearance in monkeys also have not found significant sex differences in systemic clearance of PFOA (Butenoff et al. 2004c) or PFOS (Chang et al. 2012).

Studies conducted in rats have shown that PFDeA, PFNA, PFOA, PFOS, and PFHxA are secreted in bile and undergo extensive reabsorption from the gastrointestinal tract (Johnson et al. 1984; Kudo et al. 2001; Vanden Heuvel et al. 1991b, 1991c). Biliary secretion rates of PFOA are similar in male and female rats when renal excretion is blocked by ligation of the kidneys (Vanden Heuvel et al. 1991a, 1991b). This lack of sex influence on biliary secretion (compared to the sex influence on renal clearance) may reflect a relative sex insensitivity of OAT2 (or other organic anion transporter) expression in liver, compared to kidney; the latter is approximately 7–8 times higher in adult female rats compared to male rats (Kudo et al. 2002).

3.5.2 Mechanisms of Toxicity

Some information regarding mechanisms of toxicity presented below has been extracted from reviews by Abbott (2009), Cattley et al. (1998), Maloney and Waxman (1999), Corton et al. (2000), Klaunig et al. (2003), and Lau et al. (2007).

Hepatic and developmental toxicity are the most sensitive toxic effects of perfluoroalkyl compounds in animals. Both liver and developmental toxicity in rodents results from the ability of these compounds (with some structural restrictions) to activate the peroxisome proliferator-activated receptor-α (PPARα), a member of the nuclear receptor superfamily that mediates a broad range of biological responses (Issemann and Green 1990). Peroxisome proliferators directly regulate gene transcription through a

heterodimeric receptor complex, composed of PPARα and the retinoid X receptor. The activated receptor complex regulates transcription by binding to a DNA direct repeat motif (also termed PPAR response element or PPRE) located in the promoters of peroxisome proliferators responsive genes. Studies of PPARα in various species have shown that rats and mice are the most sensitive species to PPARα agonists, whereas guinea pigs, nonhuman primates and humans are less responsive, and hamsters fall in between. PPARα cDNA from humans has been cloned and shown to be indistinguishable from the rodent PPARα in overall structure. The DNA binding domains of the human and rodent PPARα are virtually 100% homologous. Several explanations have been offered for the species-specific effects of peroxisome proliferators including: (1) differences in the ability of PPARα to be activated by peroxisome proliferators, (2) differences in the inducibility of PPARα after exposure to peroxisome proliferators (human PPARα required higher PFOA concentrations than mouse PPARα for maximal activation in a COS-1 cell transfection assay), and (3) differences in pattern and levels of tissue-specific expression of PPARα; for example, the level of expression of PPARα in human liver is about 1–10% of the levels found in rat and mouse liver. Although humans are refractory to the many effects induced by peroxisome proliferators in rodents, humans have a functional PPARα as suggested by the pharmacological reductions in serum triglycerides and cholesterol in patients treated with the peroxisome proliferator clofibrate, a response known to be mediated by the PPARα in mice. In addition to PPARα, two other PPAR subtypes encoded by separate genes, PPARβ/δ and PPARγ, have been cloned. It is important to note that although many effects of perfluoroalkyls appear to be mediated through stimulation of PPARα, PPARα-independent mechanisms may also be involved (DeWill et al. 2009; Kleszczynski and Skladanowski 2011).

Several studies show that PFOA- and PFOS-induced developmental toxicity depends upon expression of PPARα (Abbott et al. 2007; 2009; 2012). As discussed in Section 3.2.2.6, developmental effects (e.g., decreased neonatal survival) observed in animals have not been observed in humans (serum perfluoroalkyl concentrations were much higher in the animal studies as compared to the human studies). A gestational exposure study of PFOA conducted using wild-type, PPARα-null, and PPARα-humanized (expressing human PPARα) mice showed that postnatal survival was lower in wild-type, but not null or humanized mice (Albrecht et al. 2013). Results indicate that PPARα mediates developmental effects in mice, but that species differences exist between mice and humans. Abbott et al. (2012) showed that PFOA altered expression of genes that are involved in homeostatic control of lipids and glucose, and postulated that decreased neonatal survival and body weights may be, in part, due to metabolic disruption. However, the critical biological target pathways leading to developmental effects in rodents have not been established.

Some recent studies *in vitro* have provided insights regarding the interaction of PFOA and PFOS with PPARs. For example, PFOS was found to activate both mouse and human PPARα in a COS-1 cell-based luciferase reporter *trans*-activation assay with no significant difference in the responsiveness of two PPARs (Shipley et al. 2004). PFOS activated mouse and human PPARα to the same maximum extent as the prototypical PPARα agonist Wy-14,643, but substantially higher concentrations were required to elicit a PPAR transcriptional response. In a similar study, human, mouse and rat PPARα were activated by PFOA and PFOS, PPARβ/δ was less sensitive, and only PFOA activated the mouse receptor (Vanden Heuvel et al. 2006). Both PFOA and PFOS also activated human, mouse and rat PPARγ, but both chemicals appeared to be only partial agonists of this receptor. In similar experiments conducted by Takacs and Abbott (2007), PFOA had more transactivity than PFOS with both the mouse and human PPARs. In cultured rat, mouse, and human hepatocytes, perfluoroalkyl sulfonate compounds were less potent than perfluoroalkyl carboxylate compounds in stimulating the PPARα-induced gene expression, and the potency of stimulation increases with carbon chain length (Bjork and Wallace 2009; Wolf et al. 2008). PFOA significantly increased the activity of mouse and human PPARα and mouse PPARβ/δ relative to vehicle control, but not the human PPARβ/δ. PFOS significantly increased activation of mouse PPARα and PPARβ/δ, but not the human PPARβ/δ. Neither PFOA nor PFOS activated the mouse or human PPARγ.

As discussed by Vanden Heuvel et al. (2006), although these studies provide valuable information regarding the mechanism of action of PFOA and PFOS, it should be kept in mind that they only measure the first of many steps in the complex regulation of gene transcription. Moreover, the validity of comparing sensitivity across species based on receptor data may be questionable since the comparisons are made between species under conditions where the receptors are equivalently expressed and in the same cellular environment and where ligand-independent potential sources of species differences are removed.

Activation of the receptor in rodents initiates a characteristic sequence of morphological and biochemical events, principally, but not exclusively, in the liver. These events include marked hepatocellular hypertrophy due to an increase in number and size of peroxisomes, a large increase in peroxisomal fatty acid β-oxidation, an increased CYP450-mediated ω-hydroxylation of lauric acid, and alterations in lipid metabolism. PPARα regulates lipid homeostasis through the modulation of expression of genes involved in fatty acid uptake, activation, and oxidation. A toxicogenomics study in rats showed that PFOA and PFOS altered the expression of genes associated with lipid homeostasis and also produced down-

regulation of genes that regulate cholesterol biosynthesis (Martin et al. 2007). In comparison with naturally occurring long-chain fatty acids such as linoleic and α-linoleic acids, PFOA and PFOS are relatively weak ligands for PPARα (Vanden Heuvel et al. 2006). In addition, parenteral exposure of mice to PFOA and PFDeA resulted in the down-regulation of the organic anion transporting polypeptides (Oatps) in liver, likely through multiple mechanisms, including PPARα stimulation (Cheng and Klassen 2008).

Several studies published in recent years have studied the effects of PFOS and PFOA on gene expression with the intent of identifying critical target pathways for the biological effects of these substances. Some examples are summarized below.

Gene expression profiling studies in male and female Sprague-Dawley rats showed that administration of 5 mg/kg/day PFOS by gavage for 3 or 21 days resulted in significant (>3-fold change) induction or suppression of some 400 genes in the liver out of 8,000 functionally annotated genes and expressed sequence tags on the array (Hu et al. 2005). The largest groups of genes induced by PFOS were the cytochrome P450s and genes that coded for lipid metabolizing enzymes. Also induced significantly were genes involved in hormone regulation and other regulatory processes. PFOS suppressed genes involved in signal transduction pathways and in regulating nervous system functions. Of the various pathways represented by the altered genes, the peroxisomal fatty acid β-oxidation pathway seemed to be the pathway most affected by PFOS. In contrast, exposure to PFOS did not enhance the expression of genes involved in mitochondrial fatty acid β-oxidation. The study by Hu et al. (2005) also showed that PFOS also increased the activities of carboxylesterase and CYP2B1, a response characteristic of phenobarbital inducible systems, and it did not induce CYP4A, which is strongly induced by other peroxisome proliferators. This suggested that PFOS may exert its biological effects via other mechanisms of action including being a substrate for fatty acid metabolism, alteration of peroxisomal or mitochondrial membrane permeability, and as a result of surfactant effects (Hu et al. 2002, 2003; Starkov and Wallace 2002).

PFOS significantly (90-fold) induced the activity of the cytosolic enzyme long-chain acyl-CoA hydrolase, an enzyme that cleaves acyl-CoA to free fatty acid and CoA (Hu et al. 2005). The resulting increase in cytosolic free fatty acid concentrations is consistent with observations made in rodents and primates, which exhibit hepatocellular hypertrophy and lipid vacuolation and could be caused by accumulation of free fatty acids (Seacat et al. 2002). In addition, PFOS suppressed (2.5-fold) the activity of HMG CoA reductase, the rate-limiting enzyme in cholesterol synthesis, which is consistent with the earlier findings

of Haughom and Spydevold (1992) who suggested that the hypolipidemic effects of PFOS may result from impaired production of lipoprotein particles due to reduced synthesis and esterification of cholesterol together with enhanced oxidation of fatty acids in the liver. Hu et al. (2005) also conducted experiments in H4IIE rat hepatoma cells *in vitro* and reported differences in gene expression profiles between the *in vitro* and *in vivo* control samples. This, according to the investigators, could be explained by the differences in exposure system, dosage, toxicokinetics, toxicodynamics, and levels of organization and functional integration, which make the *in vivo* exposure more complicated than the *in vitro* exposure.

A study similar to that of Hu et al. (2005) was conducted with PFOA by Guruge et al. (2006) in male Sprague-Dawley rats administered various doses (1–15 mg/kg/day) of PFOA by gavage for 21 days. The largest categories of genes induced were involved in transport and metabolism of fatty acids and lipids. Treatment with PFOA also induced genes involved in cell communication, adhesion, growth, apoptosis, regulation of hormone, proteolysis and peptidolysis, and signal transduction. The largest groups of genes suppressed were related to transport, inflammation and immune response, and cell adhesion. Guruge et al. (2006) also reported significant suppression of several genes involved in apoptosis, regulation of hormone, metabolisms, and G-protein coupled receptor protein signaling pathway. The number of genes induced or suppressed was found to be directly proportional to the dose over the 1–10 mg/kg/day dose range. Comparisons with the PFOS study (Hu et al. 2005) showed that of the 23 genes that were up-regulated by PFOS, 12 genes were also up-regulated by PFOA. Seven genes were unchanged and four could not be found in the PFOA study. Of the 19 genes that were suppressed by PFOS, only one was found to be suppressed and all others were not affected by exposure to PFOA. A more detailed analysis of genes which were up- or down-regulated by all doses of PFOA showed that a large number of genes associated with lipid or fatty acid metabolism were altered by PFOA and some of the genes were linked with pathways of fatty acid degradation and mitochondrial fatty acid β-oxidation. Of interest was the observation that genes responsible for metabolism of unsaturated fatty acid and for the transfer of fatty acids for oxidation were significantly up-regulated suggesting an increased transfer of activated fatty acids or PFOA across the membrane of the mitochondria. Since PFOA significantly induced genes coding for peroxisome proliferation but had no effect on the expression of catalase, Guruge et al. (2006) suggested the possibility that potentially toxic hydrogen peroxide was produced in peroxisomes that could have caused oxidative stress or oxidative damage to proteins and DNA. Also of interest was the suppression of genes that might affect regulation of food intake and energy homeostasis; reduced food intake is commonly seen in studies with PFOA and PFOS in rodents. Similar to PFOS, PFOA down-regulated genes involved in the synthesis of cholesterol, which might affect membrane fluidity and gap junction intercellular communication (Hu et al. 2002; Upham et al. 1998). Lastly, PFOA suppressed

some genes involved in the transport of organic anions that might play a role in the urinary elimination of PFOA, which would result in a negative feedback that would inhibit elimination of PFOA in the male rat.

Recently, Rosen et al. (2008) examined transcript profiles in the livers of wild-type mice and PPARα-null mice exposed orally to 1, 3, or 10 mg/kg/day PFOA for 7 days. The investigators found that in wild-mice, PFOA altered 2.4% of the total number of genes studied (n=45,101), including 641 up-regulated and 451 down-regulated genes. In PPARα-null mice, PFOA altered only 0.3% of the genes studied including 104 up-regulated and 52 down-regulated genes, suggesting that PPARα was required for the majority of transcriptional changes following PFOA exposure in the mouse liver. More than 12% of the PPARα-independent genes regulated by PFOA coded for proteins involved in lipid homeostasis. In general, PFOA increased the expression of these genes in both wild-type mice and PPARα-null mice, but the absolute expression was lower in PPARα-null mice than in wild-mice. PFOA suppressed genes involved in amino acid metabolism in both strains of mice, but to a lesser extent in PPARα-null mice than in wild-mice. In PPARα-null mice, PFOA increased the expression of genes involved in xenobiotic metabolism, including those involved in phase I (oxidation), phase II (conjugation), and phase III (transport) functions. Since PFOA highly induced a gene known to be a target for the nuclear receptor CAR (constitutive activated/androstane receptor), the investigators compared the PFOA transcript profiles with those of livers from mice exposed to CAR activators. The results of experiments in wild-type and CAR-null mice showed a strong similarity in the direction and magnitude of the change between the PFOA PPARα-null genes and genes regulated by CAR activators. This suggested that PFOA can alter a subset of genes through activation of CAR and possibly PPARγ in PPARα-null mice. It should be mentioned that studies in fish have shown that PFOA can also activate the hepatic estrogen receptor (Tilton et al. 2008; Wei et al. 2007b). PFOA acted as a tumor promoter for liver tumors in rainbow trout exposed to an initiator (Tilton et al. 2008).

Overall, the *in vitro* gene profiling experiments summarized above confirm that PPARα plays an important role in the mechanism of action of PFOA and PFOS, indicate that there are similarities and differences in gene modulation between PFOA and PFOS, and provide confirmatory evidence for the existence of PPARα-independent mechanisms. Given the wide range of gene groups affected by PFOA and PFOS, there is the potential for a wide range of biological effects following exposure to these compounds. The results of these studies should not be over interpreted since, as stated by Guruge et al. (2006), alteration of the expression of a particular gene does not necessarily mean that a particular protein or biochemical pathway would be affected *in vivo*. However, alteration of a group of genes involved in a

particular biochemical pathway would provide strong evidence that a compound may affect that particular pathway.

3.5.3 Animal-to-Human Extrapolations

Based on information currently available, extrapolation of animal data to exposure of humans is highly uncertain in part because of large interspecies differences in the toxicokinetics of perfluoroalkyls and some mechanisms of toxicity in animals may not be operant in humans; these issues are strongly interrelated.

The elimination rate for PFOA in female rats is approximately 45 times faster than in male rat, 150 times faster than in Cynomolgus monkeys, and approximately 5000 - 9000 times faster than in humans (Bartell et al. 2010; Butenhoff et al. 2004c; Kemper et al. 2003; Olsen et al. 2007a). Elimination of PFOS in male rats is approximately 3 times faster than in Cynomolgus monkeys, and approximately 40 times faster than in humans (Chang et al. 2001; De Sliva et al. 2009; Olsen et al. 2007a; Seacat et al. 2002). These large differences in elimination rates imply that similar external PFOA or PFOS dosages (i.e., mg/kg/day) in rats, monkeys, or humans would be expected to result in substantially different steady-state internal doses (i.e., body burdens, serum concentrations) of these compounds in each species. In addition, exposure durations required to achieve steady state would be expected to be much longer in humans than in monkeys or rats. Assuming a terminal elimination half-life of 1,400 days for PFOA in humans (Olsen et al. 2007a), a constant rate of intake for 17 years would be required to achieve 95% of steady state. Steady state (i.e., 95%) would be achieved in approximately 110 days in monkeys ($t_{1/2}$ = 25 days, Butenhoff et al. 2004c), 30 days in male rats ($t_{1/2}$=7 days; Kemper et al. 2003), and in 1 day in female rats ($t_{1/2}$=0.2 days; Kemper et al. 2003). As a result of these large differences in kinetics, predicting external doses that yield similar internal doses in animals and humans will require development of validated toxicokinetics models that can simulate elimination rates and internal distribution of perfluoroalkyls in animals and humans (see Section 3.4.5).

Many PFOA- or PFOS-induced effects in rats and mice are mediated through the PPARα and it is generally agreed that humans and nonhuman primates are refractory, or at least less responsive than rodents, to PPARα-mediated effects (Klaunig et al. 2003; Maloney and Waxman 1999). While studies in mice have identified specific effects that require PPARα activation, for example, postnatal viability (Abbott et al. 2007) and some immunological effects (Yang et al. 2002b), other effects such as hepatomegaly were reported to be PPARα-independent (Yang et al. 2002b). Therefore, further studies in

PPARα-null mice are needed to expand the knowledge regarding PPARα-dependent and independent effects that would allow selection of an appropriate animal model for perfluoroalkyls toxicity.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

The available data from epidemiology and animal studies are inconclusive to evaluate whether the toxicity of perfluoroalkyls is mediated through the neuroendocrine axis or whether they have the ability to

mimic or block endogenous hormones. Below is a brief discussion of effects reported in humans and animals exposed to perfluoroalkyls that may be related to a disruption of the endocrine system; a more detailed discussion of individual studies and/or effects is presented in Section 3.2. The effects observed in humans and/or animals exposed to perfluoroalkyls that may be related to a disruption of the endocrine system include alterations in reproductive hormone levels, infertility, development of the reproductive system, alterations of the endometrium or mammary gland, and alterations in the function of endocrine glands such as the thyroid.

A study on male workers found no significant association between PFOA exposure and serum levels of a number of reproductive hormones (dehydroepiandrosterone sulfate, estradiol, FHS, 17α-hydroxy-progesterone, free testosterone, total testosterone, LH, prolactin, and sex hormone-binding globulin) (Olsen et al. 2000b). Workers with serum PFOA levels ≥30 µg/mL had mean estradiol levels 10% higher than workers in other groups, but there were too few subjects in this group to draw any meaningful conclusion. In the cross-sectional study of workers conducted by Sakr et al. (2007b), serum estradiol and testosterone levels were significantly associated with serum PFOA in linear regression models. No consistent findings regarding associations between serum perfluoroalkyl levels and reproductive hormones in males have been found in general population studies (Joensen et al. 2009, 2013; Raymer et al. 2012; Specht et al. 2012). In women aged 43–65 years living in PFOA-contaminated area, serum PFOS levels were negatively associated with serum estradiol levels; no association was found in younger women (Knox et al. 2011). An increase in serum estradiol levels was observed in rats administered ≥2 mg/kg/day PFOA (Biegel et al. 1995, 2001; Cook et al. 1992; Liu et al. 1996). In contrast, significant decreases in serum estradiol levels were observed in male monkeys exposed to ≥0.75 mg/kg/day (Seacat et al. 2002; Thomford 2002a).

Two general population studies found a significant increase in the odds of infertility (time to pregnancy >12 months) in women with higher serum PFOA or PFOS levels (Fei et al. 2009; Whitworth et al. 2012b). No associations between serum perfluoroalkyls and odds of pregnancy were found in a study only monitoring fertility for 6 months (Vestergaard et al. 2012). Conflicting results on sperm parameters were observed in general population studies. A decrease in the proportion of normal sperm was found in men with higher serum PFOS levels (Toft et al. 2012) or with high combined serum PFOA and PFOS levels (Joensen et al. 2009); a third study did not find this effect (Joensen et al. 2013). Multigeneration studies in rats orally exposed to PFOA (Butenhoff et al. 2004b) or PFOS (Luebker et al. 2005a, 2005b) did not report alterations in fertility, and a single generation study did not find fertility effects in rats exposed to PHxS (Butenhoff et al. 2009a; Hoberman and York 2003).

Other reproductive findings that could be related to endocrine disruption include increased odds of experiencing menopause in women 43–65 years of age participating in the C8 Health Studies exposed to high levels of PFOA (Knox et al. 2011). A significant association between serum perfluoroalkyl levels and the odds of endometriosis was observed in a general population study (Buck Louis et al. 2012); it should be noted that the associations were no longer statistically significant when serum perfluoroalkyl levels were adjusted for parity. Substantial delays in mammary gland differentiation (White et al. 2007) or involution (White et al. 2011b) were observed in mice exposed to PFOA during pregnancy. Prenatal exposure to PFOA resulted in delays in the development of the mammary glands in mouse offspring (Macon et al. 2011; White et al. 2007, 2009, 2011b). A cross-fostering study showed that lactation-only exposure to PFOA also resulted in delayed mammary gland development (White et al. 2009).

Three epidemiology studies have examined the possible association between perfluoroalkyls and development of the reproductive system. A study of highly exposed residents found a slight delay (4–5 months) in the onset of puberty in boys and girls with high serum PFOS levels and girls with high serum PFOA levels (Lopez-Espinosa et al. 2011). In contrast, a study of the general population did not find associations between serum PFOA, PFOS, or PFHxS levels and age of puberty (Christensen et al. 2011). A study of males 19–21 years of age found an inverse association between maternal serum PFOA levels and progressive spermatozoa and between maternal PFOS levels and sperm concentration and total sperm count (Vested et al. 2013). Development of the reproductive system has not been examined in animal studies.

Assessments of workers exposed to perfluoroalkyls did not find associations between serum levels of PFOS and PFOA and thyroid hormone levels (Olsen and Zobel 2007; Olsen et al. 2003a; Sakr et al. 2007b). An additional occupational study did not find alterations in thyroid hormones levels in workers exposed to PFNA (Mundt et al. 2007). A study of a population highly exposed to PFOA reported no association between serum PFOA and serum levels of TSH (Emmett et al. 2006b). Similarly, several general population studies did not find significant associations between serum perfluoroalkyl levels and thyroid hormone levels (Bloom et al. 2010; Ji et al. 2012; Wang et al. 2013). A study of pregnant women did not find associations between serum PFOA, PFOS, or PFHxS and the risk of hypthyroxinemia (Chan et al. 2011). Utilizing the NHANES data set, Melzer et al. (2010) found a significant association between serum PFOA levels and the risk of thyroid disease. Studies in animals have reported sporadic alterations in serum levels of thyroid hormones, but for the most part, serum levels of TSH did not change significantly, thus suggesting that a hypothyroid response was not induced (Butenhoff et al. 2002; Chang

et al. 2008b; Luebker et al. 2005b; Seacat et al. 2002; Thibodeaux et al. 2003; Thomford 2001). Transient reductions in serum total T4 reported in various studies have been attributed to a perfluoroalkyl-induced transient increase in tissue availability of thyroid hormones and increased turnover of T4, with a resulting reduction in serum total T4 (Chang et al. 2008b). Reduced serum total T4 were also reported in rats treated with PFDeA by intraperitoneal injection (Gutshall et al. 1988, 1989; Van Rafelghem et al. 1987a).

In vitro studies of PFOA, PFOS, and PFNA using a combination of the E-screen assay, cell cycle analysis, and gene expression analysis of estrogen-responsive biomarker genes showed that these chemicals did not have estrogen-like properties in MCF-7 human Caucasian breast adenocarcinoma cells (Maras et al. 2006). Both PFOA and PFOS showed estrogenic activity in primary cultured hepatocytes from fish (male tilapia), as assessed by induction of vitellogenin (Liu et al. 2007).

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6, Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants

and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The fetus/infant has an immature (developing) blood-brain barrier that past literature has often described as being leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-central nervous system interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the blood-brain barrier, there are differences between fetuses/infants and adults which are toxicologically important. These differences mainly involve variations in physiological transport systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; as it raises a very important toxicological question as to whether these mechanisms provide protection for the developing brain or do they render it more vulnerable to toxic injury. Each case of chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient

tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

The possible association between serum perfluoroalkyl levels in children and health effects has been examined in participants of the C8 Health Project and in the general populations. The studies examined a number of health effects including alterations in serum lipid levels, neurodevelopmental alterations, and reproductive development. Additionally, a large number of studies have examined the possible association of elevated serum perfluoroalkyl levels and adverse birth outcomes.

Similar to adults, significant associations between serum PFOA and PFOS and serum cholesterol levels were observed in a study of over 12,000 children (Frisbee et al. 2010); an increased risk of high cholesterol was also observed in children with higher serum PFOA and PFOS levels. A smaller study of children (n=43) living in the Mid-Ohio Valley did not find associations between serum PFOA levels and hematology parameters, total cholesterol and liver enzymes, indices of kidney function, and serum TSH levels (Emmett et al. 2006b). Another study of highly-exposed residents did not find any significant associations between serum PFOA levels in children aged 6–12 years and IQ, reading and math skills, language, memory, learning, or attention (Stein et al. 2013). Similarly, no association between serum PFOA, PFOS, or PFNA levels in children 5–18 years old and the likelihood of ADHD diagnosis was observed in a study of highly-exposed residents, although the study did find an increased risk associated with higher PFHxS levels (Stein and Savitz 2011). A general population study that utilized the NHANES data found a significant association between serum PFOA, PFOS, and PFHxS levels and the risk of ADHD diagnosis (Hoffman et al. 2010). Another smaller-scale study found significant associations between serum PFOS, PFNA, PFDeA, PFHxS, and PFOSA and impulsivity; no association with PFOA was found (Gump et al. 2011). A study of children 8–18 years of age participating in the C8 studies found reduced odds of reaching puberty at higher serum PFOA levels (Lopez-Espinosa et al. 2011); however, the biological significance of the short delay (4–5 months) is not known.

Hines et al. (2009) showed that *in utero* exposure (GDs 1–17) to low levels of PFOA (0.01–0.3 mg/kg/day) resulted in increases in body weight gain in 10–40-week-old mice; by 18 months of age, the body weights in these mice were similar to controls. Increases in serum insulin and leptin levels were also observed in the mice exposed to 0.01 and 0.1 mg/kg/day. The study also compared body weight and body composition of *in utero* exposed mice (exposed on GDs 1–17) and adult exposed mice (exposed for 17 days starting at 8 weeks of age) and found that *in utero* exposure to 1 mg/kg/day resulted in significantly higher body weight, brown fat weight, and white fat weight; this was not observed in mice exposed to 5 mg/kg/day. The results of the study suggest that gestational exposure to low doses of PFOA may result in increased susceptibility to PFOA toxicity.

A number of studies of highly exposed residents and the general population have examined the potential associations between serum perfluoroalkyl levels and adverse health outcomes. Decreases in birth weight have been found to be associated with higher PFOA (Fei et al. 2007; Lee et al. 2013; Maisonet et al. 2012; Savitz et al. 2012b) or PFOS levels (Maisonet et al. 2012), but not with lower levels of perfluoroalkyls (Fei et al. 2007; Hamm et al. 2010; Inoue et al. 2004b; Kim et al. 2011; Monroy et al. 2008; Washino et al. 2009; Whitworth et al. 2012b). The decreases in birth weight were small and not likely biological relevant. Additionally, no increases in the risk of low birth weight infants were found in highly exposed populations (Darrow et al. 2013; Nolan et al. 2009; Savitz et al. 2012b; Stein et al. 2009). No apparent alterations in the risk of birth defects were found in C8 Health Studies (Darrow et al. 2013; Savitz et al. 2012b; Stein et al. 2009) or in another study of these communities (Nolan et al. 2009).

The developmental toxicity of PFOA and PFOS has been investigated in a number of rat and mouse studies. The observed effects include PFOA- and PFOS-induced increases in prenatal losses and decreases in pup survival, decreases in pup body weight, and neurodevelopmental toxicity (Abbott et al. 2007; Albrecht et al. 2013; Case et al. 2001; Chen et al. 2012b; Era et al. 2009; Fuentes et al. 2006, 2007a, 2007b; Grasty et al. 2003; Hu et al. 2010; Johansson et al. 2008; Lau et al. 2003, 2006; Luebker et al. 2005a, 2005b; Onishchenko et al. 2011; Thibodeaux et al. 2003; White et al. 2007, 2009, 2011b; Wolf et al. 2007; Xia et al. 2011; Yahia et al. 2008, 2010). Additionally, delays in mammary gland development were observed in mice exposed to PFOA (Macon et al. 2011; White et al. 2007, 2009, 2011b). A limited number of developmental end points have been examined in rats and mice exposed to PFDeA, PFHxS, or PFBA (Butenhoff et al. 2009a; Das et al. 2008; Harris and Birnbaum 1989; Hoberman and York 2003; Johansson et al. 2008; Viberg et al. 2013). A more in-depth discussion of the developmental toxicity of perfluoroalkyls in animals is included in Section 3.2.2.6.

Unchanged PFOA and PFOS as well as other perfluoroalkyl compounds are valid biomarkers of exposure to these compounds in children, as they are in adults. No relevant studies were located regarding interactions of perfluoroalkyl compounds with other chemicals in children or adults. No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to perfluoroalkyl compounds, reducing body burden, or interfering with the mechanism of action for toxic effects.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to perfluoroalkyls are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly

adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by perfluoroalkyls are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10, Populations That Are Unusually Susceptible.

The National Report on Human Exposure to Environmental Chemicals provides and ongoing assessment of the exposure of the U.S. population to environmental chemicals using biomonitoring. This report is available at http://www.cdc.gov/exposurereport/. The biomonitoring data for perfluoroalkyls (Calafat et al. 2007a, 2007b) is discussed in Section 6.5.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Perfluoroalkyls

Measurement of serum or whole-blood perfluoroalkyl concentrations is the standard accepted biomarker of perfluoroalkyl exposure in humans. Perfluoroalkyl compounds have been detected in the serum of workers, residents living near perfluoroalkyl facilities, and the general population. As part of NHANES, CDC has been measuring serum levels of perfluoroalkyls in the U.S. general population since 1999. Of the 13 perfluoroalkyls examined in this toxicological profile, blood concentrations of 7 compounds (PFOA, PFOS, PFDeA, PFHxS, PFNA, ME-PFOSA-AcOH, and PFUA) were detected in enough subjects to allow for estimation of the geometric mean. As compared to the general population, serum PFOA and PFOS levels are much higher in individuals with occupational exposure to these compounds (Olsen et al. 2003a; Sakr et al. 2007a) and PFOA levels are much higher in individuals living near a PFOA manufacturing facility (Emmett et al. 2006a; Holzer et al. 2008; Steenland et al. 2009a), suggesting that serum levels are a good biomarker of exposure. Due to the long half-time of some perfluoroalkyl compounds, particularly PFOA and PFOS, elevated serum levels may not be indicative of recent exposure. Although elevated serum levels are likely to be indicative of exposure to the parent compound their presence in blood can also indicate exposure to other perfluoroalkyl compounds. For example, PFOS can be derived from metabolism of Et-PFOSA-AcOH, Me-PFOSA-AcOH, or PFOSA (Olsen et al. 2005; Seacat and Luebker 2000). PFOA can be derived from metabolism of 8-2 fluorotelomer alcohol (Fasano et al. 2006; Henderson and Smith 2007; Kudo et al. 2005; Nabb et al. 2007). Exposure of mice to 8–2 telomer alcohol also generated PFNA as a metabolite (Kudo et al. 2005). Because Et-PFOSA-

AcOH and Me-PFOSA-AcOH are metabolized fairly rapidly and have relatively short serum half-lives, their presence in serum should indicate only recent non-occupational exposure in the general population (Olsen et al. 2005).

3.8.2 Biomarkers Used to Characterize Effects Caused by Perfluoroalkyls

There are no specific biomarkers of effects caused by perfluoroalkyl compounds. Health evaluations of workers exposed to perfluoroalkyl compounds, residents living near a perfluoroalkyl facility, or the general population have found associations between serum PFOA or PFOS levels and increases in serum lipid levels, decreases in birth weight, increases in serum uric acid levels, and alterations in biomarkers of liver damage. None of these biomarkers of effects are specific to PFOA- or PFOS-related effects.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Olestra decreased the absorption of PFOA from the gastrointestinal tract of mice (Jandacek et al. 2010). No additional information was located regarding interactions among chemicals of this class or between perfluoroalkyl compounds and other chemicals. Both PFOA and PFOS (and many other diverse chemicals) can activate the PPARα and other PPARs to a lesser extent (Takacs and Abbott 2007; Vanden Heuvel et al. 2006). Therefore, it is not unreasonable to speculate that interactions at the receptor level might occur; however, there are no experimental data to support or rule out this presumption. Given that the PPARα receptor is much less responsive in humans and rodents, it is unclear if this type of possible interaction would be relevant to humans.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to perfluoroalkyls than will most persons exposed to the same level of perfluoroalkyls in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in compromised function of organs affected by perfluoroalkyls. Populations who are at greater risk due to their unusually high exposure to perfluoroalkyls are discussed in Section 6.7, Populations with Potentially High Exposures.

The available epidemiology data identify several potential targets of toxicity of perfluoroalkyls, and individuals with pre-existing conditions may be unusually susceptible. For example, it appears that exposure to PFOA or PFOS can result in increases in serum lipid levels, particularly cholesterol levels.

Thus, an increase in serum cholesterol may result in a greater health impact in individuals with high levels of cholesterol or with other existing cardiovascular risk factors. Similarly, increases in uric levels have been observed in individuals with higher perfluoroalkyl levels; increased uric acid may be associated with an increased risk of high blood pressure. Thus, individuals with hypertension may be at greater risk. The liver has been shown to be a sensitive target in a number of animal species and there is some indication that it is also a target in humans. Therefore, individuals with compromised liver function may represent a susceptible population.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to perfluoroalkyls. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to perfluoroalkyls. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. No texts were identified that provide specific information about treatment following exposures to perfluoroalkyl compounds.

3.11.1 Reducing Peak Absorption Following Exposure

There are no established methods to reduce absorption of perfluoroalkyl compounds in humans. No relevant information was located from studies in animals.

3.11.2 Reducing Body Burden

No studies were located regarding methods to reduce body burden of perfluoroalkyl compounds in humans. A reduction in exposure levels has been shown to decrease serum PFOA levels in residents with a contaminated public water source (Emmett et al. 2006a). Since breastfeeding has been shown to decrease perfluoroalkyl body burden, it seems logical that breast milk pumping would also reduce the body burden.

In a study in rats, cholestyramine, a bile acid sequestrant which binds bile in the gastrointestinal tract to prevent its reabsorption, was effective in increasing total ^{14}C eliminated in the feces following administration of a single intravenous dose of ^{14}C-APFO or ^{14}C-PFOS (Johnson et al. 1984). Mean cumulative ^{14}C elimination in the feces was increased 9.8-fold for rats administered APFO and 9.5-fold for rats administered PFOS.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

There are no established methods for interfering with the mechanism of toxicity of perfluoroalkyl compounds.

A main effect observed in animals exposed to perfluoroalkyl compounds is liver toxicity. The only relevant information located regarding mitigating liver effects is that pretreatment of mice with fish oil prevented the PFOA-induced increase in hepatic triglyceride content by depressing the formation of triglycerides by docosahexaenoic acid in fish oil (Kudo and Kawashima 1997). The relevance of this finding to occupational or environmental exposures of humans to perfluoroalkyl compounds is unknown.

3.12 ADEQUACY OF THE DATABASE

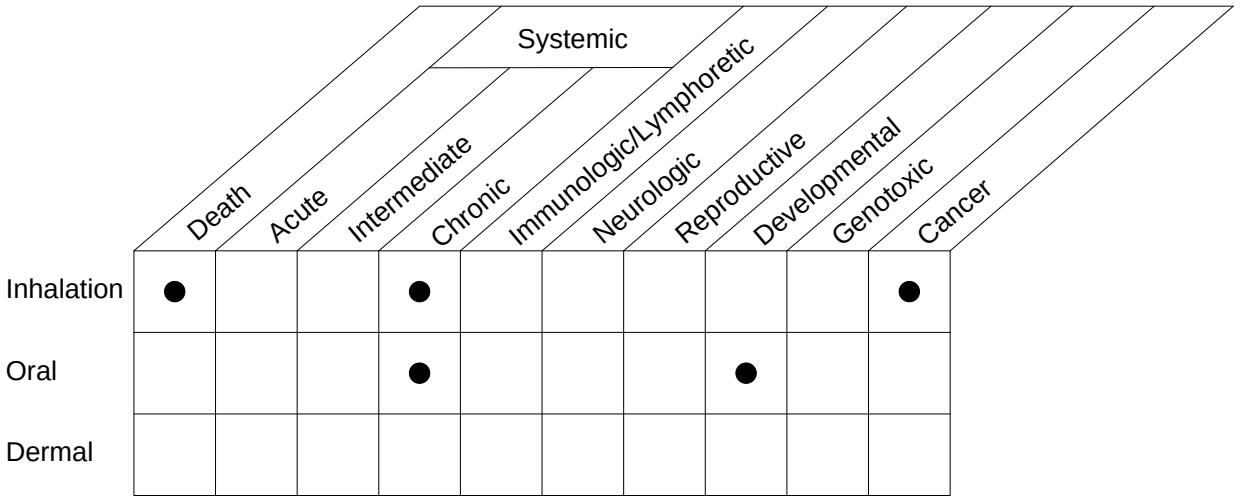
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of perfluoroalkyls is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of perfluoroalkyls.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

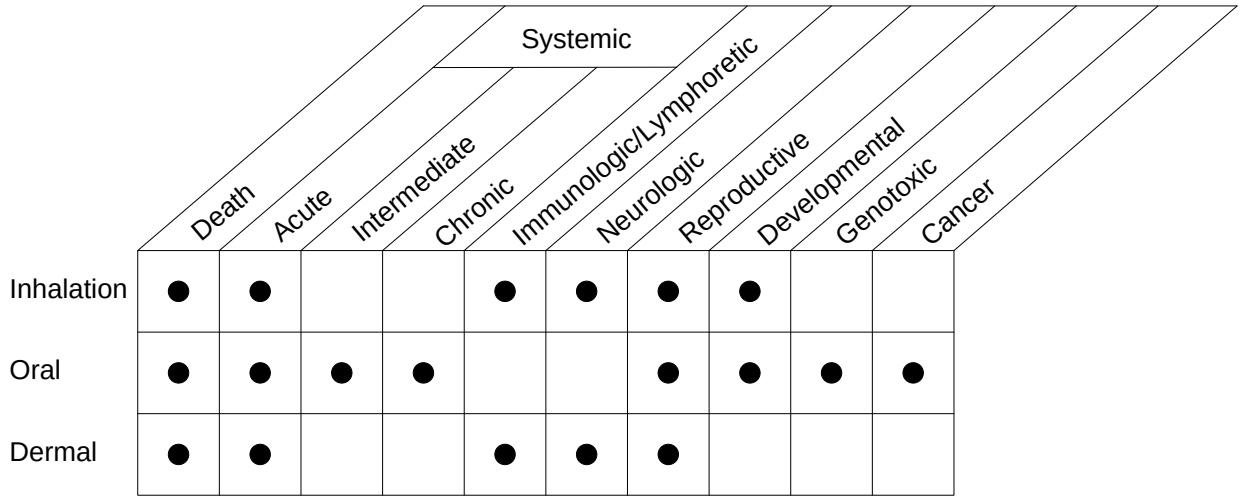
3.12.1 Existing Information on Health Effects of Perfluoroalkyls

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to PFOA and PFOS are summarized in Figures 3-15 and 3-16. Figures for the remaining perfluoroalkyls discussed in this profile are not presented due to the paucity of data for these chemicals, especially data in humans. The purpose of Figures 3-15 and 3-16 is to illustrate the existing information concerning the health effects of perfluoroalkyls. Each dot in the figure indicates that one or more studies provide

Figure 3-15. Existing Information on Health Effects of PFOA



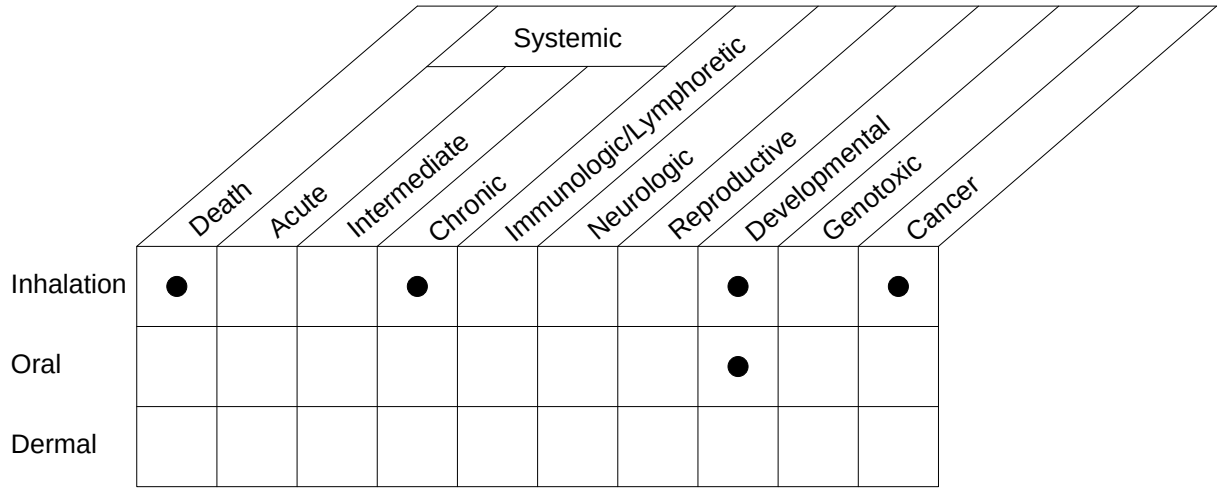
Human



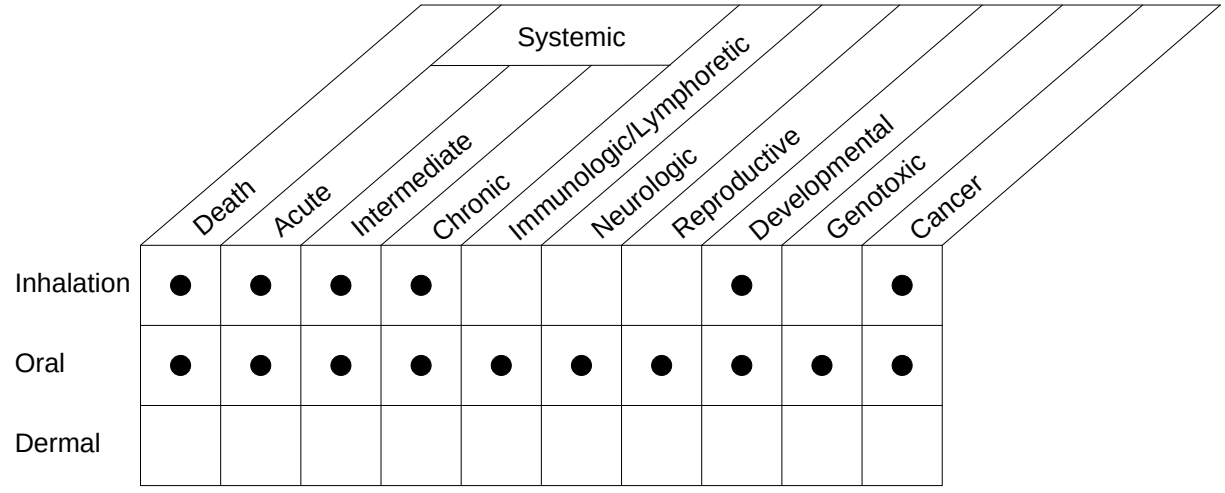
Animal

● Existing Studies

Figure 3-16. Existing Information on Health Effects of PFOS



Human



Animal

● Existing Studies

information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Information regarding the effects of exposure to perfluoroalkyl compounds in humans is derived mainly from health evaluations of subjects exposed in occupational settings, highly exposed residents living near a PFOA facility, and from much more limited data regarding exposures of the general population. Exposure levels are not available, but the concentrations of several perfluoroalkyl compounds have been measured in blood, thus facilitating comparisons with levels measured in studies with experimental animals.

Most of the information regarding the effects of perfluoroalkyl compounds in animals has been derived from oral studies; considerable less information is available from inhalation and dermal exposure studies. It is important to note that the effects of perfluoroalkyl compounds in laboratory animals do not appear to be route-specific. PFOA and PFOS have been the most extensively studied members of this class of chemicals and oral administration has been the preferred route of exposure in animal studies. Acute- and intermediate-duration oral studies in animals have described primarily effects on the liver, body weight, developmental effects, and effects on the immuno/lymphoreticular system. Alterations in liver and kidneys weight as well as increased incidence on tumors in the liver, pancreas, and testes were reported in chronic studies with PFOA in rats. Information regarding other perfluoroalkyls covered in this profile is limited to acute-duration oral studies with PFBA, PFDeA, PFNA, PFDoA, and PFOSA, and intermediate-duration oral studies with PFBA, PFHxS, and PFBuS. An acute-duration-inhalation study with PFNA is also available.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. There are no studies of humans exposed acutely to perfluoroalkyl compounds, although humans are exposed on a daily basis to small amounts of perfluoroalkyls in consumer products and in food and drinking water (Trudel et al. 2008). This also applies to intermediate-duration exposure. Few acute-duration inhalation studies have been conducted in animals. A 2-week

inhalation study with PFOA in rats reported mainly liver and body weight effects (Kennedy et al. 1986) and similar findings were reported in a 4-hour study with PFNA also in rats (Kinney et al. 1989). A need to conduct additional acute-duration inhalation studies in animals with other perfluoroalkyl compounds in animals is not apparent since the main route of exposure for the general population and for environmentally exposed populations is the oral route (Emmett et al. 2006a, 2006b; Trudel et al. 2008). The same can be said for acute dermal exposures, but it should be noted that inhalation of perfluoroalkyl dusts and dermal contact with dusts and or solutions of these compounds can be significant in occupational settings. Extensive information is available from acute-duration oral studies of PFOA and PFOS in animals; much fewer studies are available of PFBA, PFDeA and other perfluoroalkyls. The available studies indicate that the primary targets of PFOA or PFOS toxicity are the liver (i.e., Fuentes et al. 2006; Haughom and Spydevold 1992; Kennedy 1987; Liu et al. 1996; Yahia et al. 2008; Yang et al. 2001) and developmental organism (i.e., Abbott et al. 2007, 2009; Chen et al. 2012b; White et al. 2009; Wolf et al. 2007). Additional oral studies of the comparative potency of perfluoroalkyl compounds of different chain length and functional groups would be useful to try to determine whether a class-risk assessment could be feasible. In addition, further studies with PPARα-null mice can help determine the role of the PPARα in the various toxicities of these compounds. Also, further information on the role of receptors other than PPARα (i.e., PPARβ, PPARγ) in the biological effects induced by perfluoroalkyls would be valuable (Takacs and Abbott 2007; Vanden Heuvel et al. 2006). Studies of simultaneous exposure to mixtures of perfluoroalkyls would be useful to elucidate mechanisms of interaction between these compounds. Toxicity studies should monitor the concentration of perfluoroalkyls in blood and/or in target organs to provide a better basis for interspecies comparisons. Further studies using microarray techniques of gene expression are expected to continue to provide information on genes responsive to perfluoroalkyls that can be used to identify critical target pathways for the biological effects of perfluoroalkyl compounds and provide a basis for understanding similarities and differences in toxicities between compounds and between species (Guruge et al. 2006; Hu et al. 2005). In general, further research with shorter chain perfluoroalkyls, such as PFBA, should be encouraged since data in animals indicate that some effects such as hepatotoxicity and biochemical alterations are less pronounced the shorter the carbon chain (i.e., 3M 2007a; Kudo et al. 2000, 2006; Permadi et al. 1992, 1993). These research recommendations apply to all the specific end points discussed below. The available data were not considered suitable for derivation of inhalation or oral acute-duration MRLs for any perfluoroalkyl compound.

Intermediate-Duration Exposure. Intermediate-duration oral studies in laboratory animals have been conducted with PFOA, PFOS, PFBuS, PFHxS, and PFBA. The liver was a main target (3M 2001;

Albrecht et al. 2013; Butenhoff et al. 2002, 2012a; Elcombe et al. 2012a; Kennedy 1987; Perkins et al. 2004; Seacat et al. 2002, 2003; Son et al. 2008; Thomford 2001, 2002a; van Otterdijk 2007a, 2007b). Pup survival and neurodevelopmental toxicity were also established as a sensitive end point in intermediate-duration oral studies with PFOA (Abbott et al. 2007; Cheng et al. 2013a; Onishchenko et al. 2011) and PFOS (Chen et al. 2012b; Lau et al. 2003; Luebker et al. 2005a, 2005b; Onishchenko et al. 2011; Xia et al. 2011). The same general types of studies suggested above under *Acute-Duration Exposure* can be designed for longer exposure durations. Intermediate-duration oral studies with perfluoroalkyls other than PFOA and PFOS are needed to construct dose-response relationships for these compounds. If future monitoring studies suggest that a specific perfluoroalkyl compound is no longer being detected in the body, conducting further studies on this compound may be unnecessary. Toxicity studies should focus on perfluoroalkyls that are being detected in humans and in the environment with increasing frequency and concentration.

Chronic-Duration Exposure and Cancer. There is information regarding the effects of exposure to perfluoroalkyl compounds in humans derived from health evaluations of subjects exposed in occupational settings and from subjects exposed environmentally. In most of these health assessments the concentrations of perfluoroalkyl compounds (mostly PFOA and PFOS) have been measured in blood, thus facilitating comparisons with levels measured in studies with experimental animals. Although the human studies do not establish causality, there are data to suggest associations between serum PFOA or PFOS and increases in serum lipid levels and small decreases in birth weight (Château-Degat et al. 2010; Costa 2004; Costa et al. 2009; Eriksen et al. 2013; Frisbee et al. 2010; Nelson et al. 2010; Olsen et al. 1999, 2003a; Sakr et al. 2007a, 2007b; Steenland et al. 2009). It is assumed that health assessments will continue to be conducted in these cohorts and in any newly identified cohort exposed to perfluoroalkyl compounds. Two chronic-duration oral studies in rats are available for PFOA (3M 1983; Biegel et al. 2001). The study by Biegel et al. (2001) investigated the role of peroxisome proliferation on hepatic, Leydig cell, and pancreatic acinar cells tumorigenesis. The study conducted by 3M (1983) was a standard 2-year bioassay in male and female rats dosed with 0, 1.5, or 15 mg/kg/day PFOA. Additional chronic-duration studies with PFOA do not seem necessary at this time. A 2-year dietary study of PFOS in rats that identified the liver as a main target is available (Butenhoff et al. 2012b; Thomford 2002b); additional chronic studies with PFOS are not necessary at this time. The need to conduct chronic-duration studies for other perfluoroalkyl compounds should depend on the results of 90-day studies as they become available. If specific targets are identified in intermediate-duration studies, conduction of longer-term studies with lower doses may be warranted. Data were not considered adequate for derivation of inhalation or oral chronic-duration MRLs for any perfluoroalkyl compound.

Occupational exposure studies, studies of the general population, and studies of communities living in areas with known perfluoroalkyl contamination have examined the potential association between cancer and perfluoroalkyl compounds. Studies of highly exposed individuals have found increases in several cancer types; however, the results are not consistent across studies. Increases in the risk of prostate cancer (Gilliland and Mandel 1993; Lundin et al. 2009), kidney cancer (Steenland and Woskie 2012; Vieira et al. 2013), and testicular cancer (Barry et al. 2013; Vieira et al. 2013) have been reported in some groups of workers or residents living near a facility and exposed to high levels of PFOA in the drinking water. The lack of consistent findings across studies may be due to the lack of control for potential confounders, especially exposure to non-perfluoroalkyl compounds. Follow-up assessments of perfluoroalkyl workers and highly exposed populations living near manufacturing facilities are needed; these studies should attempt to control for potential confounding variables, particularly smoking, which has been associated with an increased risk of kidney and testicular cancer. In a 2-year bioassay, PFOA induced a "tumor triad" in rats, that is, liver tumors, Leydig cell tumors, and tumors in pancreatic acinar cells, characteristic of PPARα-agonist activation in rats (3M 1983; Biegel et al. 2001). The relevance of these findings to humans has been questioned by some since humans are considered refractory to most, but not all PPARα-activation effects (Klaunig et al. 2003). It is possible that PPARα agonism may not be the only mode of action for PFOA and further studies are needed to investigate this possibility and the potential involvement of the estrogen receptor or other nuclear receptors. PFOA also increased the incidence of mammary gland fibroadenomas (3M 1983); however, an independent review of the pathology slides resulted in a re-classification of lesions and the incidences of fibroadenomas and other mammary gland tumors were no longer statistically significant (Hardisty et al. 2010). In a 2-year dietary bioassay of PFOS in rats, there was an increased incidence of liver hepatocellular adenoma and thyroid follicular cell adenoma (Butenhoff et al. 2012; Thomford 2002b). No cancer studies were located for the remaining perfluoroalkyl compounds covered in this profile. PFDeA, PFOA, PFHxS, and PFBuS are listed as chemicals nominated to the NTP for in-depth toxicological evaluation for carcinogenesis testing in fiscal years 1988–2003 (NTP 2005).

Genotoxicity. Both PFOA and PFOS have been tested for mutagenic activity in standard tests and, for the most part, both chemicals gave negative results (EPA 2005a; Griffith and Long 1980; Oda et al. 2007; OECD 2002). A study in rats suggested that PFOA and PFDeA induced oxidative damage in liver DNA, but not in kidney DNA; PFBA had no significant effect on DNA from either tissue (Takagi et al. 1991). PFOA was also reported to cause DNA strand breaks and the incidence of micronuclei in human hepatoma HepG2 cells (Yao and Zhong 2005). Further studies on the mechanism of DNA damage

caused by PFOA and possibly by other perfluoroalkyl compounds seem warranted. No information was located regarding the mutagenicity of the perfluoroalkyls covered in this profile other than PFOA and PFOS. Although these chemicals have been detected in much smaller concentrations than PFOA and PFOS in serum samples from the general population (Calafat et al. 2007b), a screening battery of genotoxicity tests would provide useful additional information.

Reproductive Toxicity. The only relevant information regarding reproductive effects in humans following exposure to perfluoroalkyl compounds is that of a positive association between PFOA levels in serum and levels of estradiol and testosterone in serum from male workers (Sakr et al. 2007b). In another occupational study, serum estradiol but not other sex hormones was elevated in a small group of male workers who had the highest serum PFOA levels (Olsen et al. 1998b). Studies in the general population have not consistently found associations between PFOA or PFOS serum levels and alterations in reproductive hormone levels (Joensen et al. 2009, 2013; Raymer et al. 2012; Specht et al. 2012). Conflicting results have also been found in general population studies examining an association with sperm parameters (Joensen et al. 2009, 2013; Raymer et al. 2012; Toft et al. 2012) and impaired fertility (Fei et al. 2009, 2012; Vestergaard et al. 2012; Whitworth et al. 2012b). A study of highly exposed residents found an association between serum PFOA and PFOS levels and earlier onset of menopause (Knox et al. 2011). Further studies of workers, highly exposed populations, and members of the general population environmentally exposed to perfluoroalkyl compounds could evaluate end points related to fertility such as sperm characteristic and time to pregnancy. Studies with PFOA in rats have reported increased levels of estradiol in serum (Biegel et al. 1995, 2001; Cook et al. 1992; Liu et al. 1996). Acute treatment of male rats with PFDoA also resulted in elevated serum estradiol (Shi et al. 2007). Multi-generation studies have been conducted in rats dosed with PFOA, PFOS, and PFHxS; these studies have not provided evidence of alterations in fertility parameters or of histopathology of the reproductive organs (Butenhoff et al. 2004b, 2009a; Hoberman and York 2003; Luebker et al. 2005a, 2005b), but a single intraperitoneal dose of 50 mg/kg PFDeA caused atrophy and degeneration of the seminiferous tubules in the testes from rats (George and Andersen 1986). Thus, further studies with lower doses PFDeA administered orally that evaluate reproductive parameters may be warranted. In general, acute- and intermediate-duration studies with PFOA or PFOS did not find morphological alterations in the sex organs from rats or monkeys (Butenhoff et al. 2002; Griffith and Long 1980; Seacat et al. 2002, 2003). In a 2-year-dietary study, PFOA significantly increased the incidences of Leydig cell hyperplasia, vascular mineralization in the testes, and tubular hyperplasia in the ovaries in rats in 2-year dietary studies (3M 1983; Biegel et al. 2001). Little is known regarding reproductive effects of other perfluoroalkyl compounds; therefore studies that examine the effects of these compounds on the microscopic

morphology of the reproductive organs and serum levels of sex hormones, as well as in *in vitro* tests that evaluate effects on the estrogen and androgen receptors would be valuable.

Developmental Toxicity. A number of studies have examined the potential of PFOA and PFOS to induce developmental toxicity in highly exposed residents or the general population by examining the association between serum perfluoroalkyl levels and developmental end points. The epidemiology studies provide evidence that higher serum PFOA or PFOS levels are associated with small decreases in birth weight (Fei et al. 2007; Lee et al. 2013; Maisonet et al. 2012; Savitz et al. 2012b). Although studies of highly exposed residents and the general population have reported alterations in growth (Andersen et al. 2010; Halldorsson et al. 2012; Maisonet et al. 2012), neurodevelopment (Fei et al. 2008b; Gump et al. 2011; Hoffman et al. 2010; Stein and Savitz 2011), reproductive development (Christensen et al. 2011; Lopez-Espinosa et al. 2011; Vested et al. 2013), and immunological end points (Okada et al. 2012), the effects were not consistently found across studies or were only examined in a single study. The available studies are cross-sectional, account for a limited number of potential confounders, and do not establish causality. Longitudinal studies would be useful for establishing whether there are associations between PFOA or PFOS exposure and developmental toxicity in humans. Prospective evaluation of women with elevated levels of perfluoroalkyl compounds in serum such as female perfluoroalkyl workers or of women that are environmentally exposed to perfluoroalkyls who became pregnant would provide valuable information regarding the pharmacokinetics of these chemicals during pregnancy, placental transfer to the fetus, and transfer to neonates via maternal milk. Some data are available from studies of the general population in which serum levels of PFOA and PFOS were significantly lower than in perfluoroalkyl workers (Inoue et al. 2004b; Kärrman et al. 2007; Midasch et al. 2007; So et al. 2006b). Prospective evaluation of children born to women with higher body burden of perfluoroalkyls during pregnancy would also provide valuable information on potential delayed developmental effects or other effects.

Studies in animals have provided information mostly on developmental effects of PFOS and PFOA in rodents, a small number of studies have examined the other perfluoroalkyls. Standard gestational exposure studies with other perfluoroalkyl compounds would be valuable. Specific effects reported in studies with PFOA and PFOS include prenatal loss, decreased pup viability, reduced neonate weight, and delays in mammary gland differentiation, eye opening, vaginal opening, and first estrus and generally occurred in the absence of maternal toxicity (Abbott et al. 2007, 2009; Albrecht et al. 2013; Butenhoff et al. 2004b, 2009a; Case et al. 2001; Chang et al. 2009; Chen et al. 2012b; Cheng et al. 2013a; Era et al. 2009; Fuentes et al. 2007; Grasty et al. 2003, 2005; Hines et al. 2009; Hu et al. 2010; Johansson et al. 2008; Keil et al. 2008; Lau et al. 2006; Luebker et al. 2005a, 2005b; Macon et al. 2011; Onishchenko et

al. 2011; Thibodeaux et al. 2003; White et al. 2007; Wolf et al. 2007, 2009, 2011b; Xia et al. 2011; Yu et al. 2009b; Yahia et al. 2008, 2010). Studies with PFOA have also demonstrated impaired development of the mammary gland (Macon et al. 2011; White et al. 2009) and increases in body weight gains at 3–10 months following *in utero* exposure to low doses (Hines et al. 2009). PFHxS had no significant effects on a wide range of developmental parameters evaluated in rats (Butenhoff et al. 2009a; Hoberman and York 2003), but did result in neurodevelopmental effects (Viberg et al. 2013). In contrast, PFDeA did not result in neurodevelopmental effects (Johansson et al. 2008), but did result in a decrease in fetal weight (Harris and Birnbaum 1989). In a study with PFBA, the chemical had no significant effect on neonatal weight gain or viability (Das et al. 2008). Wolf et al. (2007) reported that developmental effects (i.e., delayed eye opening) were more severe in mice as the exposure began earlier, but could not determine whether this was due to a higher cumulative dose of PFOA or to a developmentally sensitive period. A study with PFOS reported that dosing late during gestation caused significantly more lethality than dosing early (Grasty et al. 2003). Studies have also shown that gestational exposure alone is sufficient to induce postnatal deficits in body weight and developmental delays (Wolf et al. 2007) and that in mice, PPARα is required for PFOA-induced increased postnatal lethality (Abbott et al. 2007). The mechanism(s) by which PFOA and PFOS induce developmental effects is not known. A study in rats suggested that impaired lung development could be the cause of early pup death following maternal exposure to PFOS (Grasty et al. 2003, 2005). Rosen et al. (2007) reported that exposure to PFOA during gestation altered the expression of genes related to fatty acid catabolism in both the fetal liver and lung. Further studies of gene expression analysis following exposure to other perfluoroalkyl compounds and gene expression analysis in organs other than the liver and lungs may provide additional insight into the mechanisms of developmental effects of perfluoroalkyls. Also, additional studies are needed to examine the role of PPARα and other nuclear receptors on developmental toxicity induced by perfluoroalkyl compounds.

Immunotoxicity. Limited information is available on the immunotoxicity of perfluoroalkyl compounds in humans. A study in highly exposed residents found an association between serum PFOA levels and the risk of ulcerative colitis, but not with other autoimmune diseases (Steenland et al. 2013); the study did not establish whether the ulcerative colitis was due to immunotoxicity. Another study of highly exposed residents found an altered response to antibody production following influenza vaccination in residents with high serum PFOA levels, but there was no increase in the frequency of self-reported colds or flu (Looker et al. 2014). Two studies of the general population examined the dose-response relationship between serum PFOA and PFOS levels and serum childhood vaccine antibody concentrations in children (Grandjean et al. 2012; Granum et al. 2013). A study in mice reported increased airway reactivity following dermal exposure to PFOA and suggested that PFOA might increase

the IgE response to environmental allergens (Fairley et al. 2007). Thus, examination of possible associations between exposure to perfluoroalkyls and health conditions such as asthma, particularly in children, could be conducted. Acute oral studies in mice exposed to PFOA have reported immunological alterations characterized by thymus and spleen atrophy, alterations in thymocytes and splenocytes and in parameters of humoral immunity (Dewitt et al. 2008; Yang et al. 2000, 2002a). The mechanism of these effects is unknown and further research in this area is needed. Information on levels of perfluoroalkyls in lymphoreticular organs would be valuable. Experiments in PPARα-null mice showed that the effects of PFOA on the spleen were PPARα-dependent, whereas those in the thymus were only partially dependent (Yang et al. 2002b). This line of research should be extended to examine the role of PPARα on other immunological end points and the role of other PPARs. Very little information is available regarding immunological effects of other perfluoroalkyl compounds. Single lethal (160 and 320 mg/kg) gavage doses of PFDeA induced atrophy and lymphoid depletion in the thymus and spleen of female C57BL/6N mice (Harris et al. 1989). Also, a single intraperitoneal injection of 50 mg/kg PFDeA caused thymic atrophy in male rats (George and Andersen 1986). Dietary studies with lower doses and of various durations are necessary to establish dose-response relationships for immunological effects of perfluoroalkyls other than PFOA.

Neurotoxicity. Neurological examinations were not conducted (or at least it was not explicitly indicated) in the studies of perfluoroalkyl workers (Gilliland and Mandel 1996; Mundt et al. 2007; Olsen and Zobel 2007; Olsen et al. 1998b, 1999, 2003a; Sakr et al. 2007a, 2007b); it is reasonable to assume that no frank clinical signs were detected in the groups examined. A general population study (Power et al. 2013) and a study of highly-exposed residents (Gallo et al. 2013) have examined the possible association between serum perfluoroalkyl levels and memory and found conflicting results; no other epidemiology studies examining neurological effects were identified. Studies in animals have not provided evidence that the nervous system is a sensitive target for perfluoroalkyl compounds based on clinical observations and morphological examinations of the nervous system; however, no comprehensive neurological testing has been conducted except for a study with PFHxS in rats in which a functional observation battery and tests for motor activity provided no indication of adverse neurological effects (Butenhoff et al. 2009a; Hoberman and York 2003) and one with PFBuS, also in rats, that reported a decrease in tail flick latency test in males (3M 2001). Some neurological testing should be conducted as part of routine testing of workers and of groups identified as having had high exposure in the past or currently undergoing high exposure to perfluoroalkyl compounds.

Epidemiological and Human Dosimetry Studies. As previously mentioned, information is available regarding the effects of exposure to perfluoroalkyl compounds in humans derived from health evaluations of subjects exposed in occupational settings (Alexander et al. 2003; Alexander and Olsen 2007; Costa 2004; Costa et al. 2009; Gilliland and Mandel 1996; Grice et al. 2007; Leonard 2006; Leonard et al. 2008; Lundin et al. 2009; Mundt et al. 2007; Olsen and Zobel 2007; Olsen et al. 1998b, 1999, 2000; 2003a, 2012; Sakr et al. 2007a, 2007b, 2009; Steenland and Woskie 2012), residents living near a PFOA manufacturing facility with high levels of PFOA in the drinking water (Anderson-Mahoney et al. 2008; Darrow et al. 2013; Emmett et al. 2006a, 2006b; Eriksen et al. 2010; Frisbee et al. 2010; Gallo et al. 2013; Knox et al. 2011; Looker et al. 2014; MacNeil et al. 2009; Nolan et al. 2009; Savitz et al. 2012b; Steenland et al. 2009, 2013; Stein et al. 2009; Watkins et al. 2013), and the general population (Bloom et al. 2010; Buck Louis et al. 2012; Chan et al. 2011; Dong et al. 2013; Fei et al. 2009, 2012; Fisher et al. 2013; Ji et al. 2012; Joensen et al. 2009, 2013; Kvist et al. 2012; Maisonet et al. 2012; Lee et al. 2013; Lin et al. 2010; Min et al. 2012; Nelson et al. 2010; Raymer et al. 2012; Power et al. 2012; Shankar et al. 2011; Uhl et al. 2013; Wang et al. 2013; Whitworth et al. 2012b). Although many studies found significant associations between serum perfluoroalkyl levels and the occurrence of an adverse health effect, the findings were not consistent across studies. For an effect on serum lipids and birth weight, the weight of evidence suggests an association with serum PFOA and PFOS. There is also some indication that increased levels of PFOA or PFOS could influence blood pressure and liver enzymes. Interpretation of the human data is limited by the reliance of cross-sectional studies, which do not establish causality, and the lack of exposure data. Studies on serum lipids suggest that the dose-response curve is steeper at lower concentrations and flattens out at higher serum perfluoroalkyl concentrations (Steenland et al. 2010a); additional studies that could be used to establish dose-response relationships would be valuable. Mechanistic studies examining the association between perfluoroalkyl exposure and serum lipid levels would also provide valuable insight. Clarification of the significance and dose-response relationships for other observed effects is also is needed. Longitudinal studies examining a wide-range of end points would be useful for identifying critical targets of toxicity in humans exposed to perfluoroalkyls. The available human studies have identified some potential targets of toxicity; however, cause-and-effect relationships have not been established for any of the effects and the effects have not been consistently found in all studies. Mechanistic studies would useful for establishing causality. When possible, health assessments should include subjects of different race/ethnicity and age to determine potential race/ethnicity-based and age-based susceptibilities.

Biomarkers of Exposure and Effect.

Exposure. Data are available regarding levels of perfluoroalkyl compounds in serum from the general population (Calafat et al. 2007a, 2007b; CDC 2013; Emmett et al. 2006a, 2006b; Olsen et al. 2003c, 2003b, 2004b, 2007b), highly exposed residents (Frisbee et al. 2010; Steenland et al. 2009), and perfluoroalkyl workers (Gilliland and Mandel 1996; Olsen and Zobel 2007; Olsen et al. 1999, 2003b, 2003c; Sakr et al. 2007a, 2007b; Steenland and Woskie 2012). Information is needed regarding the toxicokinetics (see also below) of perfluoroalkyl compounds in humans to be able to relate levels of these compounds in serum to exposure to specific perfluoroalkyls; data on matched serum and urine samples would be valuable. Also needed is further information on the relationship between serum and liver concentrations of perfluoroalkyl compounds in humans. Data on serum levels in young children are lacking, but presumably will be available in future NHANES reports (Calafat et al. 2007b).

Effect. Health evaluations of perfluoroalkyl workers (i.e., Olsen and Zobel 2007; Olsen et al. 1999, 2003a; Sakr et al. 2007a, 2007b) or of people undergoing high environmental exposure (Emmett et al. 2006b) have provided little evidence of adverse effects, although there has been suggestive evidence of changes in sex hormones levels and lipids in some studies of perfluoroalkyl workers (Olsen et al. 1998b; Sakr et al. 2007b). Although no specific studies to identify effects unique to perfluoroalkyls can be suggested at this time, as indicated above, clarification of the details, significance, and dose-response relationships of the observed changes is needed.

Absorption, Distribution, Metabolism, and Excretion. Several population studies have examined the kinetics of serum perfluoroalkyl concentrations following a change in environmental or occupational exposure, from which estimates of terminal elimination half-times in adults are available for PFOA, PFOS, PFHxS, PFBA, and PFBuS (see Table 3-14). Renal clearances of PFOA and PFOS were estimated in a population study of adults (Harada et al. 2005a). Binding of PFOA, PFOS, and PFHxS to human plasma protein has been measured and a dissociation constant for binding of PFOA to human plasma albumin has been estimated (Han et al. 2003; Kerstner-Wood et al. 2003). Studies of perfluoroalkyl levels in tissues from human cadavers have provided information on serum and liver concentrations of PFOS (Olsen et al. 2003c). Detection limits precluded reliable estimates of serum and liver levels of PFOA, PFOSA, or PFHxA. Population studies have measured perfluoroalkyls in maternal and fetal cord serum (see Table 3-11) and in mammary milk (see Table 3-12). Results of these studies confirm maternal-fetal and maternal-infant transfer of various long-chain perfluoroalkyls in humans (see Section 3.4.2). Data on other aspects of the toxicokinetics of perfluoroalkyls in humans are not available

and could serve to improve predictions of internal dosimetry associated with exposures to perfluoroalkyls (bioavailability, kinetics of tissue distribution and elimination, binding in tissues, external-internal dose relationships, all aspects of toxicokinetics in children and aging populations).

Toxicokinetics of perfluoroalkyls have been studied much more extensively in rodents (rats and mice) and less extensively in Cynomolgus monkeys. These studies have shown that elimination kinetics, and therefore, internal dose-external dose relationships, are dependent on structure, including the terminal acid group (carboxylate or sulfonate), carbon chain length, and carbon chain branching. These structural features affect plasma and tissue protein binding, renal and biliary clearances, tissue levels, maternal-fetal transfer, and lactational transfer of perfluoroalkyls. Elimination kinetics of some perfluoroalkyls (e.g., PFOA) are also sex-dependent in certain animal species (e.g., rat).

Toxicokinetic studies have provided information on distributions of PFOA and PFOS in rodents (Bogdanska et al. 2011; Chang et al. 2012; Curran et al. 2008; Griffith and Long 1980; Hundley et al. 2006; Johnson and Ober 1980, 1999b; Kemper 2003; Seacat and Luebker 2000; Vanden Heuvel et al. 1991b, 1991c; Ylinen et al. 1990) and PFOA in nonhuman primates (Butenhoff et al. 2004c). These studies have identified the liver as a site of relatively high concentrations of PFOA and PFOS and have found marked animal species and sex differences as well as dose dependencies of tissue distribution (e.g., tissue levels that change disproportionately with dose). These differences have been attributed, in part, to species and sex differences in elimination kinetics of absorbed perfluoroalkyls and dose dependence of elimination kinetics (see Section 3.4.2). Toxicokinetic studies have found sex- and dose-dependent subcellular distribution of PFOA in rats (Han et al. 2005; Kudo et al. 2007). Further studies on the mechanisms for dose-dependency, characterization of subcellular binding proteins, and mechanistic linkages between subcellular distribution and toxicity of perfluoroalkyls are needed.

The distribution and elimination of PFOA and PFOS are greatly influenced by binding interactions with albumin and other high molecular weight plasma proteins. Interactions with albumin have been partially characterized to the extent that binding capacity and affinity constants have been estimated (Han et al. 2003). Attempts to simulate plasma and excretion kinetics of PFOA and PFOS with PBPK models suggest that binding to plasma proteins, as well as the volume of distribution may be sex- and species-specific (Andersen et al. 2006; Loccisano et al. 2012a, 2012b; Tan et al. 2008). Liver uptake and renal clearance of PFOS also appeared to be time-dependent in a PBPK model used to predict plasma and liver in concentrations of PFOS in a chronic rat study (Harris and Barton et al. 2008). Mechanisms underlying these time dependencies have not been elucidated. Although affinity constants for binding of PFOA and

PFOS have been estimated, rates of association and dissociation have not been reported. Knowledge of the binding kinetics would be useful for evaluating whether or not binding equilibrium is achieved within capillary transit times.

Rates of elimination of perfluoroalkyls vary substantially across chemical species and animal species, and show sex differences and age dependencies within certain species (see Section 3.4.4.2). Slower elimination of PFOA in male rats compared to female rats has been attributed to sex hormone-modulated renal tubular transport of PFOA that results in markedly lower renal clearance of PFOA, and other long-chain perfluoroalkyls (C8-C10) in the sexually mature male rat (see Section 3.5.1, Excretion). These differences appear to be less relevant to nonhuman primates; studies conducted in Cynomolgus monkeys have not found sex differences in elimination rates. Sex differences in elimination rates of perfluoroalkyls in humans have not been demonstrated in population studies of serum elimination kinetics or renal clearance. Although the few studies that have estimated elimination half-times or renal clearances in male and female humans have not found significant sex differences (Harada et al. 2005a; Olsen et al. 2007a), these outcomes may reflect the relatively low serum concentrations in these subjects compared with studies that have been conducted in nonhuman primates and rodents (i.e., sex differences in elimination may vary with dose and/or plasma concentration). Additionally, the failure to account for the influence of reduced estrogen levels (in postmenopausal women) and reduced testosterone levels (in older males) in occupational and/or site-related epidemiology studies may also account for the lack of finding of sex-related differences.

A single study was located that provides direct evidence for absorption of PFOA in rats following exposure to an aerosol (MMAD=1.9–2.1 μm) of 1–25 mg ammonium PFOA/m^3 and some information on the rate of absorption (i.e., time to highest plasma concentration, Hinderliter et al. 2006a). Studies of inhalation absorption of other perfluoroalkyls were not located, although a study in rats exposed to PFNA provided indirect evidence of absorption of this compound (Kinney et al. 1989). Toxicokinetic studies conducted in rodents provide estimates of absorption fractions and absorption rates for ingested PFOA, PFOS, and PFBA (see Section 3.4.1.2 for discussion of Chang et al. 2008a; Hinderliter et al. 2006b; Hundley et al. 2006; Johnson and Ober 1979, 1999a; Kemper 2003). Mechanisms of pulmonary and gastrointestinal absorption have not been elucidated; therefore, appropriate studies are needed.

Comparative Toxicokinetics. Toxicokinetic studies conducted in various rodent species (mice, rats, hamsters, rabbits) and in Cynomolgus monkeys have revealed profound species and sex differences as well as dose dependencies in the tissue distribution and elimination kinetics of PFOA and PFOS (see

Sections 3.4.2 and 3.4.4.2). Studies conducted in rats have revealed contributing mechanisms for sex differences in elimination of PFOA; slower elimination of PFOA in male rats compared to female rats has been attributed to sex hormone-modulated renal tubular transport of PFOA that results in markedly lower renal clearance of PFOA in the sexually mature male rat (see Section 3.5.1, Excretion). Sex differences in elimination of PFOA have also been observed in hamsters; unlike the rat, male hamsters excreted absorbed PFOA more rapidly than female hamsters. Sex differences in elimination of PFOA have not been observed in other rodent species, in Cynomolgus monkeys, or in limited observations made in humans. Additional data are needed to provide a mechanistic explanation for the species differences in sex-specificity of elimination kinetics of PFOA.

Methods for Reducing Toxic Effects. As previously mentioned, health evaluations of workers exposed to perfluoroalkyl compounds, residents living in communities near perfluoroalkyl facilities, or members of the general population have reported effects which appear to related to PFOA or PFOS exposure. The effects include increases in serum lipid levels, decreases in birth weight, increases in serum uric acid levels, and alterations in biomarkers of liver damage. The mechanisms associated with these effects are not known. Therefore, it is difficult to design studies or methods for reducing toxic effects without reliable mechanistic data. Studies that examine the issue of how to reduce body burden by increasing the elimination rate of some perfluoroalkyls would be valuable.

Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

It is not known whether children are more or less susceptible than adults to the effects of exposure to perfluoroalkyl compounds because there are no studies that specifically addressed this question. Several studies have examined the possible associations between perfluoroalkyl exposure and health outcome in children living in an area with high PFOA contamination and in the general population. Studies of children living near a PFOA facility have examined several systemic end points (hematology, serum lipids, liver enzymes, kidney function, and TSH levels) (Emmett et al. 2006b), serum lipid levels (Frisbee et al. 2010), the likelihood of ADHD diagnosis (Stein and Savitz 2011), IQ and learning (Stein et al. 2013), and the age of puberty in boys and girls (Lopez-Espinosa et al. 2011). General population studies have also examined the association between serum perfluoroalkyl levels and ADHD diagnosis (Stein and Savitz 2011) or impulsivity (Hoffman et al. 2010).

Although some studies have found significant associations, they are not adequate for establishing causality. Follow-up studies of the C8 population could allow for a longitudinal assessment of health effects in children and would be useful in determining whether the observed effects are due to perfluoroalkyl exposure. Toxicokinetics information in children is needed. Half-life studies have been conducted in adults; there is the need to understand if these are applicable to children. There are no studies that have examined whether young animals are more or less susceptible than adults to perfluoroalkyls toxicity. Additional information on this issue would be useful.

Child health data needs relating to exposure are discussed in Section 6.8.1, Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

The following ongoing studies pertaining to perfluoroalkyls have been identified in the National Institutes of Health (NIH) RePORTER (2014) database.

Aimin Chen at the University of Cincinnati is examining the associations between polybrominated diphenyl ethers and perfluoroalkyl chemicals on fetal, infant, and child neurobehavioral development, as assessed by measuring thyroid function, cognition, learning and memory, motor skills, attention and executive function, and behavior in children aged 1–8 years. This investigation is part of the Health Outcomes and Measures of the Environment Study.

Stephanie Frisbee at West Virginia University is investigating the association of non-8-carbon chain perfluoroalkyls (e.g., PFHxS, PFHpA, PFDeA) on serum parameters of lipid, liver, and kidney function in children. The study will utilize data collected from the C8 Health Project.

The National Toxicology Program is conducting a study to evaluate the chronic toxicity and carcinogenicity of PFOA in rats exposed via the diet. The study will compare chronic toxicity in rats with or without perinatal exposure to PFOA.

Sharon Sagive at Boston University Medical Campus is investigating the effect of prenatal perfluoroalkyl exposure on growth and development in children. The study will measure PFOA, PFOS, PFHxS, and PFNA levels in maternal blood samples and examine the possible associations with fetal and infant growth, childhood adiposity, metabolic outcome (e.g., serum cholesterol levels, insulin resistance), and

neurodevelopment (e.g., cognition and behavior). The study will utilize data collected in Project Viva, which is a longitudinal study examining pregnant women and their children from birth through 7 years of age.

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of perfluoroalkyls is located in Table 4-1. This information includes synonyms, chemical formulas and structures, and identification numbers. The perfluoroalkyls discussed in this profile exist as linear and branched isomers depending upon the method of production (see Chapter 5) and the reported values for the physical-chemical properties are typically reflective of the mixtures rather than a single specific isomer.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of perfluoroalkyls is located in Table 4-2.

Perfluoroalkyl compounds are very stable owing to the strength of the carbon-fluorine bonds, the presence of the three electron pairs surrounding each fluorine atom, and the shielding of the carbon atoms by the fluorine atoms (3M 1999; Kissa 2001; Schultz et al. 2003). Perfluoroalkyl carboxylates and sulfonates are resistant to direct photolysis, reaction with acids, bases, oxidants, and reductants (3M 2000; EPA 2008f; OECD 2002, 2006a, 2007; Schultz et al. 2003). APFO was shown to decompose starting at 196°C (Krusic 2004) and PFOA was shown to decompose rapidly in the presence of crushed borosilicate glass at 307°C (Krusic 2005).

Perfluoroalkyl carboxylates and sulfonates are made of a long perfluorocarbon tail that is both hydrophobic and oleophobic and a charged end that is hydrophilic (3M 1999; de Vos et al. 2008; Kissa 2001; Schultz et al. 2003). This combination of hydrophobic and oleophobic character makes these substances very useful as surfactants. The ability of these substances to repel oil, fat, and water has resulted in their use in surface protectants (Kissa 2001). Their ability to reduce the surface tension of aqueous systems to below 20 mN/m has resulted in their use as wetting agents (Kissa 2001). Based on the behavior of some perfluoroalkanes, perfluoroalkyls are expected to form separate layers when mixed with hydrocarbons and water; therefore, measurement of the n-octanol water partition coefficient is not practical (3M 1999; EPA 2005a).

With the exception of PFOSA, estimated pKa values for the perfluoroalkyls listed in Table 4-2 range from -0.17 to 3.92 (SPARC 2008). This pKa range indicates that these substances will exist in anion form when in contact with water at environmental pH. An estimated pKa of 6.24 indicates that PFOSA

Table 4-1. Chemical Identity of Perfluoroalkyls

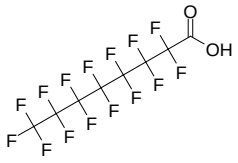
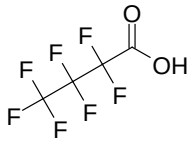
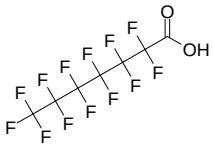
Characteristic	Information		
Chemical name	Perfluorooctanoic acid	Perfluorobutyric acid	Perfluoroheptanoic acid
Synonym(s)	PFOA; pentadecafluoro-1-octanoic acid; pentadecafluoro-n-octanoic acid; pentadecaflurooctanoic acid; perfluorocaprylic acid; perfluoroctanoic acid; perfluoroheptanecarboxylic acid; octanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8, 8-pentadecafluoro-	PFBA; heptafluoro-1-butanoic acid; heptafluorobutanoic acid; heptafluorobutyric acid; perfluorobutanoic acid; perfluorobutyric acid; perfluoropropanecarboxylic acid	PFHpA; perfluoro-n-heptanoic acid; tridecafluoro-1-heptanoic acid; heptanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7, 7-tridecafluoro-
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_8HF_{15}O_2$	$C_4HF_7O_2$	$C_7HF_{13}O_2$
Chemical structure			
Identification numbers:			
CAS registry	335-67-1	375-22-4	375-85-9
NIOSH RTECS	RH0781000	ET4025000	No data
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	UN3261	No data	No data
HSDB	7137	No data	No data
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Perfluoroalkyls

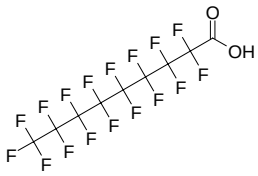
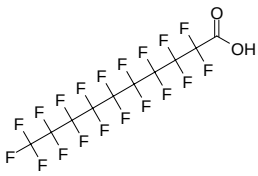
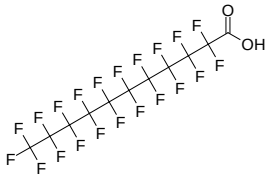
Characteristic	Information		
Chemical name	Perfluorononanoic acid	Perfluorodecanoic acid	Perfluoroundecanoic acid
Synonym(s)	PFNA; perfluoro-n-nonanoic acid; perfluoro-nonan-1-oic acid; heptadecafluoro-nonanoic acid; nonanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-	PFDA; PFDeA; Ndfda; nonadecafluoro-n-decanoic acid; nonadecafluorodecanoic acid; perfluoro-n-decanoic acid; decanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-nonadecafluoro-	PFUA; perfluoro-n-undecanoic acid; henicosafluoroundecanoic acid
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_9HF_{17}O_2$	$C_{10}HF_{19}O_2$	$C_{11}HF_{21}O_2$
Chemical structure			
Identification numbers:			
CAS registry	375-95-1	335-76-2	2058-94-8
NIOSH RTECS	No data	HD9900000	No data
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	No data	No data	No data
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Perfluoroalkyls

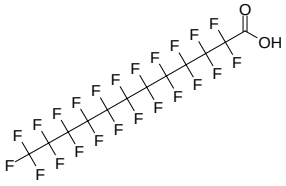
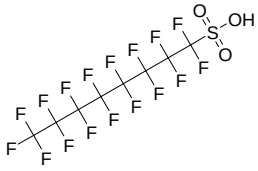
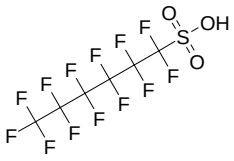
Characteristic	Information		
Chemical name	Perfluorododecanoic acid	Perfluorooctane sulfonic acid	Perfluorohexane sulfonic acid
Synonym(s)	PFDoA; tricosafluoro-dodecanoic acid; dodecanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-tricosafluoro-	PFOS; 1-perfluoro-octanesulfonic acid; heptadecafluoro-1-octane-sulfonic acid; heptadecaf-luorooctan-1-sulphonic acid; perfluorooctane sulfonate; perfluoro-octylsulfonic acid; 1-Octanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8, 8-heptadecafluoro-	PFHxS; perfluorohexane-1-sulphonic acid; 1-hexanesulfonic acid, 1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluoro-; 1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexane-1-sulfonic
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_{12}HF_{23}O_2$	$C_8HF_{17}O_3S$	$C_6HF_{13}O_3S$
Chemical structure			
Identification numbers:			
CAS registry	307-55-1	1763-23-1	355-46-4
NIOSH RTECS	No data	RG9701600	No data
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	No data	7099	No data
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Perfluoroalkyls

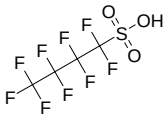
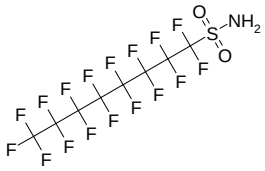
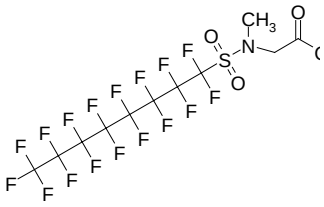
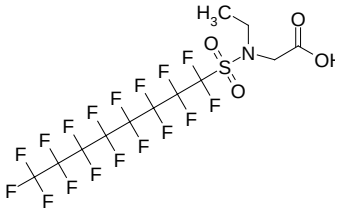
Characteristic	Information		
Chemical name	Perfluorobutane sulfonic acid	Perfluroroocatane-sulfonamide	2-(N-methyl-perfluorooctane sulfonamido) acetic acid
Synonym(s)	PFBuS; 1-perfluorobutane-sulfonic acid; nonafluoro-1-butanesulfonic acid; nonafluorobutanesulfonic acid; pentyl perfluoro-butanoate; 1,1,2,2,3,3,4,4,4-nona-fluoro-1-butanesulfonic acid; 1,1,2,2,3,3,4,4,4-nona-fluorobutane-1-sulphonic acid; 1-butanesulfonic acid, nonafluoro- (6Cl,7Cl,8Cl)	PFOSA; perfluoroctyl-sulfonamide; perfluoro-octanesulfonic acid amide; heptadecafluorooctane-sulphonamide; 1-octane-sulfonamide, 1,1,2,2,3,3,4,4,5,5,6,6,7,7,8 ,8,8-heptadecafluoro-	Me-PFOSA-AcOH
Registered trade name(s)	No data	No data	No data
Chemical formula	$C_4HF_9O_3S$	$C_8H_2F_{17}NO_2S$	$C_{11}H_6F_{17}NO_4S$
Chemical structure			
Identification numbers:			
CAS registry	375-73-5	754-91-6	2355-31-9
NIOSH RTECS	EK5930000	RG9701400	No data
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMDG shipping	No data	No data	No data
HSDB	No data	No data	No data
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Perfluoroalkyls

Characteristic	Information
Chemical name	2-(N-ethyl-perfluorooctane sulfonamido) acetic acid
Synonym(s)	Et-PFOSA-AcOH
Registered trade name(s)	No data
Chemical formula	$C_{12}H_8F_{17}NO_4S$
Chemical structure	
Identification numbers:	
CAS registry	2991-50-6
NIOSH RTECS	No data
EPA hazardous waste	No data
OHM/TADS	No data
DOT/UN/NA/IMDG shipping	No data
HSDB	No data
NCI	No data

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Source: Calafat et al. 2007a, 2007b; CAS 2008; ChemIDplus 2008; RTECS 2008

Table 4-2. Physical and Chemical Properties of Perfluoroalkyls

Property	PFOA	PFBA	PFHpA	PFNA
Molecular weight	414.069[a]	214.039[a]	364.06[b]	464.08[b]
Color	No data	No data	No data	No data
Physical state	Solid[c]	Liquid[a]	No data	No data
Melting point	54.3°C[a]	-17.5°C[a]	24-30°C[d]	No data
Boiling point	188°C[a]	121°C[a]	175°C at 742 mm Hg[e]	No data
Density at 20°C	1.8 g/cm^{3}[f]	1.651 g/cm^{3}[a]	No data	No data
Odor	No data	No data	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water	9.5x10^{3} mg/L at 25°C[e]	No data	No data	No data
Organic solvents	No data	Soluble in ethanol and toluene; insoluble in petroleum ether[a]	No data	No data
Partition coefficients:				
Log K_{ow}	Not applicable[g]	Not applicable[g]	Not applicable[g]	Not applicable[g]
K_{oc}	17–230[h]	No data	No data	No data
pKa	3.8[i]	0.08 (estimated)[j]	-0.15 (estimated)[j]	-0.17 (estimated)[j]
Vapor pressure	0.017 mm Hg at 20°C (extrapolated); 0.962 mm Hg at 59.25°C (measured)[k]	44 mm Hg at 56°C[e]	No data	4.83 x 10^{-3} mm Hg at 20°C (extrapolated); 8.4 mm Hg at 99.63°C (measured)[l]
Henry's law constant	Not applicable[m]	Not applicable[m]	Not applicable[m]	Not applicable[m]
Autoignition temperature	Not applicable[n]	Not applicable[n]	Not applicable[n]	Not applicable[n]
Flashpoint	Not applicable[n]	Not applicable[n]	Not applicable[n]	Not applicable[n]
Flammability limits	Not applicable[n]	Not applicable[n]	Not applicable[n]	Not applicable[n]
Conversion factors	1 ppm=17.21 mg/m^{3}; 1 mg/m^{3}=0.058 ppm[c]	1 ppm=8.90 mg/m^{3}; 1 mg/m^{3}=0.11 ppm[o]	1 ppm=15.14 mg/m^{3}; 1 mg/m^{3}=0.07 ppm[o]	1 ppm=19.29 mg/m^{3}; 1 mg/m^{3}=0.05 ppm[o]
Explosive limits	Not applicable[n]	Not applicable[n]	Not applicable[n]	Not applicable[n]

Table 4-2. Physical and Chemical Properties of Perfluoroalkyls

Property	PFDeA	PFUA	PFDoA
Molecular weight	514.084[a]	564.085[p]	614.1[b]
Color	No data	No data	No data
Physical state	No data	No data	No data
Melting point	No data	97.9–100.3°C[d]	No data
Boiling point	219°C	No data	No data
Density at 20°C	No data	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	No data	No data	No data
Organic solvents	No data	No data	No data
Partition coefficients:			
Log K_{ow}	Not applicable[g]	Not applicable[g]	Not applicable[g]
K_{oc}	No data	No data	No data
pKa	-0.17 (estimated)[j]	-0.17 (estimated)[j]	-0.17 (estimated)[j]
Vapor pressure	7.62×10^{-4} mm Hg at 20°C (extrapolated); 23.5 mm Hg at 129.56°C (measured)[q]	3.44×10^{-4} mm Hg at 20°C (extrapolated); 4.62 mm Hg at 112.04°C (measured)[q]	5.11×10^{-60} mm Hg at 20°C (extrapolated)[q]
Henry's law constant at 25°C	Not applicable[m]	Not applicable[m]	Not applicable[m]
Autoignition temperature	Not applicable[n]	Not applicable[n]	Not applicable[n]
Flashpoint	Not applicable[n]	Not applicable[n]	Not applicable[n]
Flammability limits	Not applicable[n]	Not applicable[n]	Not applicable[n]
Conversion factors	1 ppm=21.37 mg/m^3; 1 mg/m^3=0.05 ppm[o]	1 ppm=23.45 mg/m^3; 1 mg/m^3=0.04 ppm[o]	1 ppm=25.53 mg/m^3; 1 mg/m^3=0.04 ppm[o]
Explosive limits	Not applicable[n]	Not applicable[n]	Not applicable[n]

Table 4-2. Physical and Chemical Properties of Perfluoroalkyls

Property	PFOS	PFHxS	PFBuS
Molecular weight	500.03[b]	400.12[b]	300.1[b]
Color	No data	No data	No data
Physical state	No data	No data	No data
Melting point	≥400°C (potassium salt)[q]	No data	No data
Boiling point	No data	No data	No data
Density at 20°C	No data	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	570 mg/L (potassium salt in pure water)[q]	No data	No data
Organic solvents	No data	No data	No data
Partition coefficients:			
Log K_{ow}	Not applicable[g]	Not applicable[g]	Not applicable[g]
K_{oc}	No data	No data	No data
pKa	0.14 (estimated)[j]	0.14 (estimated)[j]	0.14 (estimated)[j]
Vapor pressure	2.48×10^{-6} mm Hg at 20°C (potassium salt)[c]	No data	No data
Henry's law constant at 25°C	Not applicable[m]	Not applicable[m]	Not applicable[m]
Autoignition temperature	Not applicable[n]	Not applicable[n]	Not applicable[n]
Flashpoint	Not applicable[n]	Not applicable[n]	Not applicable[n]
Flammability limits	Not applicable[n]	Not applicable[n]	Not applicable[n]
Conversion factors	1 ppm=20.79 mg/m^3; 1 mg/m^3=0.05 ppm[o]	1 ppm=16.63 mg/m^3; 1 mg/m^3=0.06 ppm[o]	1 ppm=12.48 mg/m^3; 1 mg/m^3=0.08 ppm[o]
Explosive limits	Not applicable[n]	Not applicable[n]	Not applicable[n]

Table 4-2. Physical and Chemical Properties of Perfluoroalkyls

Property	PFOSA	Me-PFOSA-AcOH	Et-PFOSA-AcOH
Molecular weight	499.15[b]	571.21 (from structure)	585.24[b]
Color	No data	No data	No data
Physical state	No data	No data	No data
Melting point	No data	No data	No data
Boiling point	No data	No data	No data
Density at 20°C	No data	No data	No data
Odor	No data	No data	No data
Odor threshold:			
Water	No data	No data	No data
Air	No data	No data	No data
Solubility:			
Water	No data	No data	No data
Organic solvents	No data	No data	No data
Partition coefficients:			
Log K_{ow}	Not applicable[g]	Not applicable[g]	Not applicable[g]
K_{oc}	No data	No data	No data
pKa	6.24 (estimated)[j]	3.92 (estimated)[j]	3.92 (estimated)[j]
Vapor pressure	No data	No data	No data
Henry's law constant	Not applicable[m]	Not applicable[m]	Not applicable[m]
Autoignition temperature	Not applicable[n]	Not applicable[n]	Not applicable[n]
Flashpoint	Not applicable[n]	Not applicable[n]	Not applicable[n]
Flammability limits	Not applicable[n]	Not applicable[n]	Not applicable[n]

Table 4-2. Physical and Chemical Properties of Perfluoroalkyls

Property	PFOSA	Me-PFOSA-AcOH	Et-PFOSA-AcOH
Conversion factors	1 ppm=20.75 mg/m^3; 1 mg/m^3=0.05 ppm[o]	1 ppm=23.75 mg/m^3; 1 mg/m^3=0.04 ppm[o]	1 ppm=24.33 mg/m^3; 1 mg/m^3=0.04 ppm[o]
Explosive limits	Not applicable[n]	Not applicable[n]	Not applicable[n]

[a]Lide 2005.
[b]EPA 2008h.
[c]3M 2008c.
[d]Kunleda and Shinoda 1976.
[e]Kauck and Diesslin 1951.
[f]Kroschwitz and Howe-Grant 1994.
[g]The log K_{ow} is not measureable since these substances are expected to form multiple layers in an octanol-water mixture (3M 1999, 2008c; EPA 2005a).
[h]Prevedouros et al. 2006).
[i]Burns et al. 2008.
[j]SPARC 2008.
[k]Kaiser et al. 2005.
[l]Kaiser et al. 2005.
[m]Henry's law constant is not applicable for these substance since they are dissociated in the environment.
[n]Perfluorocarboxylates and perfluorosulfonates are nonflammable (3M 1999, Kissa 2001, OECD 2007). However, they readily degrade via incineration (Krusic and Roe 2004; Krusic et al. 2005; Yamada et al. 2005).
[o]Calculated using molecular weight.
[p]ChemID Plus 2008.
[q]3M 2000.

Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid; Me-PFOSA-AcOH = 2-(N-methyl-perfluorooctane sulfonamide) acetic acid; PFBA = perfluorobutyric acid; PFBuS = perfluorobutane sulfonic acid; PFDeA = perfluorodecanoic acid; PFDoA = perfluorododecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide; PFUA = perfluoroundecanoic acid

will exist as both the anion and the neutral species (SPARC 2008). Perfluoroalkyl salts, such as APFO, will form the corresponding anions when dissolved in water. Prevedouros et al. (2006) report a Krafft point of 22°C and critical micelle concentration of $3.7x10^3$ mg/L for the perfluorooctanoate anion (PFO). At temperatures above the Krafft point, the solubility of PFO is expected to increase abruptly due to the formation of micelles.

Vapor pressures at 25°C were extrapolated for PFOA, PFNA, PFDeA, PFUA, and PFDoA using Antoine coefficients. Experimental vapor pressures were as follows: 0.962–724 mm Hg (59.25–190.80°C) for PFOA; 8.40–750 mm Hg (99.63–203.12°C) for PFNA; 23.5–750 mm Hg (129.56–218.88°C) for PFDeA; 4.62–750 mm Hg (112.04–237.65°C) for PFUA; and 6.42–750 mm Hg (127.58–247.36°C) for PFDoA (Kaiser et al. 2005).

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

No information is available in the TRI database on facilities that manufacture or process perfluoroalkyls because this chemical is not required to be reported under Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986) (EPA 2005b).

Perfluoroalkyls have been manufactured for their direct use in commercial products as well as for their use in industrial process streams. The most important perfluoroalkyl compounds in terms of production and use have been PFOS and PFOA; however, these substances and related perfluoroalkyl compounds are currently being phased out as a joint effort by EPA and industry.

The 3M Company, which was the principal worldwide manufacturer of PFOS and related chemicals, completed the phase-out of its PFOS production in 2002 (3M 2008a; EPA 2008f). During the same year, EPA finalized the significant new use rule for 88 perfluoroalkyl sulfonate compounds, which requires manufacturers to notify EPA 90 days prior to commencing manufacture or import of these substances for a significant new use to allow time for evaluation (EPA 2002, 2007c, 2008f). The purpose of this rule was to limit future manufacturing and importation of these substances. According to EPA, the rule allows for the continuation of a few limited, highly technical uses for which no alternatives are available, and which are characterized by very low volume, low exposure, and low releases. The significant new use rule was amended in 2007 to include 183 additional perfluoroalkyl sulfonate compounds (EPA 2007c, 2008f). Included on the current list are PFOS, PFHxS, PFOSA, and Et-PFOSA-AcOH. EPA believed that the perfluoroalkyl sulfonate compounds listed under the significant new use rule were no longer manufactured in the United States; however, during the comment period of the 2007 amendment, EPA learned of the ongoing use of tetraethylammonium perfluorooctanesulfonate as a fume/mist suppressant in metal finishing and plating baths (EPA 2007c). EPA has since excluded this from the list of significant uses. The only nation that still has manufacturers producing PFOS is China (Lim et al. 2011).

In 2006, the eight major companies of the perfluoropolymer/fluorotelomer industry agreed to participate in EPA's PFOA Stewardship Program (EPA 2008f). This included voluntary commitments from these companies to reduce facility emissions and product content of PFOA and related chemicals on a global basis by 95% no later than 2010, and to work toward elimination of these substances by 2015. Progress

reports were provided in 2007. Data from these reports that list the content and percent reduction of PFOA, PFOA precursors, and higher PFOA homologues in products are listed in Table 5-1.

According to DuPont, PFOA is produced at trace levels as a byproduct during the manufacture of fluorotelomer products; however, DuPont specifies that PFOA is not used to manufacture its fluorotelomer products (DuPont 2008). DuPont has announced that a new manufacturing process has been developed for its fluorotelomer products that are based on short-chain chemistry. The company claims that this new process will remove >97% of trace levels of PFOA, its homologues, and direct precursors from DuPont fluorotelomer products. The chemicals that will be involved in DuPont's new manufacturing process are not identified. Based on statements made by the 3M Chemical Company, the short chain perfluoroalkyl, PFBuS, may play a role in new technologies that will be used to reformulate products affected by the phase out of PFOA and related perfluoroalkyls (3M 2008a).

U.S. production volume data for PFOA, PFBA, and PFOS reported by manufacturers under the EPA Inventory Update Rule (IUR) are provided in Table 5-2. Production volume ranges for the ammonium salt of PFOA, ammonium perfluorooctanoate (APFO), are also listed. During the reporting year 2002, manufacturers reported that the production volumes were within the range of 15,000–500,000 pounds (6–227 metric tons) for PFOS and PFOA and within the range of 500,000–1,000,000 pounds (227–454 metric tons) for APFO (EPA 2008g). PFBA was reported as having a production volume within the range of 15,000–500,000 pounds (6–227 metric tons) during 1986; however, PFBA production volumes were not reported for subsequent years (EPA 2008g). None of the other perfluoroalkyl compounds were listed in EPA's IUR database. Current U.S. production volume data for perfluoroalkyl compounds are not available; however, the production volume of PFBA and the production volumes of PFOS and related perfluoroalkyl sulfonate compounds are expected to be zero since 3M ceased production of these substances in 1998 and 2002, respectively (3M 2008a; Agency for Toxic Substances and Disease Registry 2008; EPA 2007c). Similarly, the current production volumes of PFOA and APFO are expected to be much less as a result of efforts by companies to reduce PFOA emissions and develop alternatives for this chemical so that it can be completely removed from process streams (EPA 2008f).

Perfluorocarboxylates have been manufactured industrially by electrochemical fluorination (ECF), fluorotelomer iodide oxidation, fluorotelomer olefin oxidation, and fluorotelomer iodide carboxylation.(Prevedouros et al. 2006; Schultz et al. 2003). During the ECF process, an organic acyl or

Table 5-1. Content (ppm) and Percent Reduction of PFOA, PFOA Homologues, or PFOA Precursors in Products from the 2006 U.S. Operations of Fluoropolymer/Fluorotelomer Companies

		Dispersions		Other fluoropolymers		Telomers	
Company	Chemicals	Content	Percent reduction[a]	Content	Percent reduction[a]	Content	Percent reduction[a]
Arkema, Inc.	PFOA and higher homologues	>500–1,000	0%	>70–150	30	Not applicable	Not applicable
	Precursors	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Asahi Glass Company	PFOA, PFOA salts, and higher homologues	500–1,570	12%	0.12	Not applicable	Not applicable	Not applicable
	Precursors	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Ciba Specialty Chemicals Corporation	PFOA	0.05 kg	>99%	0.05 kg	>99%	0.05 kg	>99%
	Higher homologues	0.05 kg	>99%	0.05 kg	>99%	0.05 kg	>99%
	Precursors	0	>99%	0	>99%	0	>99%
Clariant International Ltd.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Daikin America, Inc.	PFOA	280	34%	2; 300	0%	0.28	72%
	Precursors and higher homologues	Not applicable	Not applicable	Not applicable	Not applicable	2,500	78%
E.I. DuPont de Nemours and Company	PFOA, PFOA salts	547	44%	69	80%	246 kg	50%
	Direct precursors	Not applicable	Not applicable	Not applicable	Not applicable	57 kg	14%
3M/Dyneon	PFOA	0	100%	Not reported	Not reported	Not applicable	Not applicable
Solvay Solexis	PFOA and PFOA salts	600–700	59%	Not applicable	Not applicable	Not applicable	Not applicable
	Higher homologues	Not applicable	Not applicable	170–200	0%	Not applicable	Not applicable
	Precursors	0	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

[a]Percent reduction in product content of these compounds from baseline year levels. The baseline year is the year nearest to the year 2000 for which company data are available.

PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Source: EPA 2008f

Table 5-2. U.S. Production Volume Ranges for Perfluoroalkyls (1986–2002) Reported under the EPA Inventory Update Rule

Perfluoro-alkyl	Reporting year production volume range (pounds)				
	1986	1990	1994	1998	2002
PFOA	10,000–500,000	Not reported	10,000–500,000	10,000–500,000	10,000–500,000
APFO	10,000–500,000	10,000–500,000	10,000–500,000	10,000–500,000	500,000–1,000,000
PFBA	10,000–500,000	Not reported	Not reported	Not reported	Not reported
PFOS	Not reported	Not reported	10,000–500,000	Not reported	10,000–500,000

APFO = ammonium perfluorooctanoate; EPA = Environmental Protection Agency; PFBA = perfluorobutyric acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Source: EPA 2008g

sulfonyl fluoride backbone structure is dissolved in a solution of aqueous hydrogen fluoride (Savu 1994b; Siegemund et al. 2005). A direct electrical current is then passed through the solution, which replaces all of the hydrogens on the molecule with fluorines. Perfluoroacyl fluorides produced by ECF are hydrolyzed to form the perfluorocarboxylic acid, which is then separated via distillation. This method was used extensively by 3M in the production of perfluoroalkylsulfonates such as PFOS (3M 1999; Hekster et al. 2003; Schultz et al. 2003).

$$R_hCOF + HF \longrightarrow R_fCOF + H_2 + \text{byproducts}$$

$$R_fCOF + H_2O \longrightarrow R_fCOOH + HF$$

Perfluoroalkanesulfonyl fluorides produced by ECF are hydrolyzed under alkaline conditions to form the corresponding salt (Savu 1994b; Siegemund et al. 2005). Acidification followed by distillation yields the anhydrous perfluoroalkanesulfonic acid.

$$R_hSO_2F + HF \longrightarrow R_fSO_2F + H_2$$

$$R_fSO_2F + KOH \longrightarrow R_fSO_3K + HF$$

$$R_fSO_3K + H_2SO_4 \longrightarrow R_fSO_3H + KHSO_4$$

Perfluorosulfonamido compounds, such as PFOSA, can be formed by reacting the perfluoroalkane-sulfonyl fluoride with a primary or secondary amine (3M 1999; Hekster et al. 2003; Siegemund et al. 2005).

The fluorotelomer iodide oxidation process was developed by DuPont and has served as the basis for their fluoropolymer production chemistry (Hekster et al. 2003; Savu 1994a; Siegemund et al. 2005). It begins with the preparation of pentafluoroiodoethane from tetrafluoroethane. Tetrafluoroethane is then added to this product at a molar ratio that gives a product of desired chain length. Finally, the product is oxidized to form the carboxylic acid. The process produces linear perfluorocarboxylic acids of even carbon numbers as illustrated below.

$$5C_2F_4 + IF_5 + 2I_2 \xrightarrow{\text{catalyst}} 5C_2F_5I$$

$$C_2F_5I + nC_2F_4 \longrightarrow C_2F_5(C_2F_4)_nI$$

$$C_2F_5(C_2F_4)_nI \xrightarrow{SO_3} C_2F_5(C_2F_4)_{n-1}CF_2COOH$$

Ammonium perfluorononanoate is currently manufactured in Japan through fluorotelomer olefin oxidation (Prevedouros et al. 2006). Fluorotelomer iodide carboxylation has also been used to produce ammonium perfluorononanoate (Prevedouros et al. 2006). The ECF process resulted in a mixture of linear and branched isomers, whereas the telomerization processes yielded predominantly linear products. It has been reported that the 3M ECF process resulted in approximately 70% linear and 30% branched isomers for PFOS and 78% linear and 22% branched isomers for PFOA (Benskin et al. 2009).

5.2 IMPORT/EXPORT

Information regarding the import and export of perfluoroalkyl compounds are limited; however, some PFBA is may be imported for commercial use (ATSDR 2008; 3M 2008a).

5.3 USE

Applications of perfluoroalkyl compounds have made use of their unique surfactant properties (Schultz et al. 2003). The alkyl tails of perfluoroalkyls make these substances both hydrophobic (water-repelling) and oleophobic (oil-repelling) (3M 1999; Kissa 2001; Schultz et al. 2003). Because of these properties, perfluoroalkyls have been used extensively in surface coating and protectant formulations (Kissa 2001). Major applications have included protectants for paper and cardboard packaging products, carpets, leather products, and textiles that enhance water, grease, and soil repellency (Hekster et al. 2003; Schultz et al. 2003). These compounds have been widely used in industrial surfactants, emulsifiers, wetting agents, additives, and coatings as well (3M 1999; Schultz et al. 2003). Perfluoroalkyls have been used in fire-fighting foams since they are effective in extinguishing hydrocarbon fueled fires (Schultz et al. 2003). Perfluoroalkyls have also been used as processing aids in the manufacture of fluoropolymers such as nonstick coatings on cookware, membranes for clothing that are both waterproof and breathable, electrical wire casing, fire and chemical resistant tubing, and plumbing thread seal tape (DuPont 2008; EPA 2008f).

5.4 DISPOSAL

Information concerning disposal of individual perfluoroalkyl products may be found on Material Safety Data Sheets (MSDS) from the manufacturers of the chemicals. Two methods are generally recommended for the disposal of fluoropolymer dispersions. The first method involves precipitation, decanting, or filtering to separate solids from liquid waste. The dry solids are then disposed of in an approved industrial solid waste landfill or incinerated, while the liquid waste is discharged to a waste water

treatment facility (Plastics Europe 2012). The second method involves incineration at temperatures >800°C using a scrubber to remove hydrogen fluoride (Plastics Europe 2012). Currently, several companies under the direction of EPA are performing incineration testing on commercially available fluoropolymers and fluorotelomers to determine whether these disposal processes result in the formation and release of perfluoroalkyl compounds into the environment (EPA 2008f). According to perfluorochemical facility assessment reports, historical disposal of perfluoroalkyl containing waste has been through onsite and offsite landfills, through sludge incorporation (subsurface injection), and through incineration (3M 2007b, 2008a; Agency for Toxic Substances and Disease Registry 2005). Pilot scale studies in which carpet samples were incinerated using a rotary kiln incinerator indicated that most perfluoroalkyls were effectively destroyed in combustors (Lemieux et al. 2007). Similar conclusions were reached by Yamada et al. (2005) when studying the incineration of textiles and paper treated with fluorotelomer-based acrylic polymers.

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6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Perfluoroalkyls have not been reported at EPA National Priorities List (NPL) sites; however, it is unknown how many of the 1,699 current or former NPL sites have been evaluated for the presence of perfluoroalkyls (HazDat 2008).

Since the early 2000s, companies in the fluorochemical industry have been working with EPA to phase-out the production and use of several perfluoroalkyl compounds (3M 2008a; DuPont 2008; EPA 2007c, 2008f). 3M ceased production of PFOS and related chemicals in 2002 (3M 2008a; EPA 2007c). PFOA, PFOA precursors, and higher homologues are currently being phased out by DuPont and other members of EPA's PFOA Stewardship Program (DuPont 2008; EPA 2008f). Industrial releases of these perfluoroalkyls in the United States are declining based on company reports submitted to EPA (EPA 2008f). In the past, large amounts of perfluoroalkyls were released to the air, water, and soil in and around fluorochemical facilities (3M 2007b, 2008a, 2008b; Barton et al. 2007; Davis et al. 2007; DuPont 2008; EPA 2008f).

Other sources of perfluoroalkyls in the environment have also been considered. Perfluorocarboxylates and sulfonates may be formed from the oxidation of precursors such as fluorotelomer alcohols and perfluoroalkyl sulfonamides in air, water, and soil (D'eon et al. 2006; Ellis et al. 2004; Gauthier and Mabury 2005; Liu et al. 2007; Martin et al. 2006; Wallington et al. 2006; Wang et al. 2005a, 2005b; Wania 2007). The use of perfluoroalkyls in surface protectants such as treatments for carpets and textiles is expected to result in the release of these substances to the air (Barber et al. 2007; Jahnke et al. 2007a; Kubwabo et al. 2005; Moriwaki et al. 2003; Prevedouros et al. 2006; Shoeib et al. 2004). The former use of perfluoroalkyls in aqueous fire-fighting foams has resulted in the release of these substances to soil and groundwater (Moody and Field 1999; Moody et al. 2003).

Perfluoroalkyl carboxylic acids and sulfonic acids are expected to dissociate in the environment based on measured and estimated pKa values of <3 (Kissa 2001; SPARC 2008). Perfluoroalkyl anions will not volatilize from water or soil surfaces (Prevedouros et al. 2006). The unique surfactant properties of these substances may prevent total dissociation of perfluoroalkyls in water (EPA 2005a; Kissa 2001; Prevedouros et al. 2006). Therefore, some volatilization of perfluoroalkyls may occur since the neutral forms of these substances are considered to be highly volatile (Barton et al. 2007; EPA 2005a; Kim and Kannan 2007). Perfluoroalkyls have been detected in air both in the vapor phase and as adsorbed to

particulates (Kim and Kannan 2007). Perfluoroalkyl sulfonamides may partially dissociate in the environment, especially under acidic conditions and are therefore expected to have a higher rate of volatilization compared to the carboxylic acids and sulfonic acids (Martin et al. 2006; SPARC 2008).

Perfluoroalkyls are very stable compounds and are resistant to biodegradation, direct photolysis, atmospheric photooxidation, and hydrolysis (3M 2000; EPA 2008f; OECD 2002, 2007; Schultz et al. 2003). Atmospheric photooxidation half-lives determined for representative perfluoroalkyl sulfonamides ranging from 20 to 50 days indicate that this may be an important degradation mechanism for this group of perfluoroalkyls (D'eon et al. 2006; Martin et al. 2006). Perfluoroalkyls released to the atmosphere are expected to adsorb to particles and settle to the ground through wet or dry deposition (Barton et al. 2007; Hurley et al. 2004; Prevedouros et al. 2006). The chemical stability of perfluoroalkyls and the low volatility of these substances in ionic form indicate that perfluoroalkyls will be persistent in water and soil (3M 2000; Prevedouros et al. 2006). K_{oc} values ranging from 17 to 230 indicate that PFOA will be mobile in soil and can leach into groundwater (Davis et al. 2007; Prevedouros et al. 2006).

Perfluoroalkyls have been detected in environmental media and biota of the Arctic region and in other remote locations such as open ocean waters (Barber et al. 2007; Prevedouros et al. 2006; Yamashita et al. 2005, 2008; Wei et al. 2007a). Proposed source pathways include long-range atmospheric transport of precursor compounds followed by photooxidation to form perfluoroalkyls, direct long-range transport of perfluoroalkyls via oceanic currents, and transport of perfluoroalkyls in the form of marine aerosols (Armitage et al. 2006; Barber et al. 2007; Prevedouros et al. 2006; Wania 2007). Direct transport of perfluoroalkyls in the atmosphere has also been proposed as a source pathway since these substances were recently detected in the vapor phase in outdoor air samples (CEMN 2008; Prevedouros et al. 2006). The actual source of perfluoroalkyls in remote locations is likely to be a combination of these pathways.

PFOA and PFOS have been measured in outdoor urban air samples at concentrations as high as 46 and 919 pg/m^3, respectively (Barber et al. 2007; Harada et al. 2005b, 2006; Kim and Kannan 2007). Concentrations of other perfluoroalkyls measured in outdoor air are generally <1 pg/m^3. Reported concentrations of perfluoroalkyls measured in four indoor air samples were <5 pg/m^3 (Barber et al. 2007). PFOA, PFOS, and PFHxS have been detected in indoor dust samples at concentrations ranging from <2.29–3,700, <4.56–5,065, and <4.56–4,305 ng/g, respectively (Kubwabo et al. 2005; Moriwaki et al. 2003). Reported concentrations of perfluoroalkyls measured in surface water samples are generally below 50 ng/L (Boulanger et al. 2004; Kannan et al. 2005; Kim and Kannan 2007; Nakayama et al. 2007; Simcik and Dorweiler 2005; Sinclair et al. 2004, 2006). Background concentrations of perfluoroalkyls in

groundwater, drinking water, soil, and sediment have not been located. Perfluoroalkyls have been detected in different types of foods at reported concentrations ranging from 0.05 to 10,000 ng/g fresh weight (3M 2001; Food Standards Agency 2006; Fromme et al. 2007b; Tittlemier et al. 2007). Perfluoroalkyls have also been detected in consumer products such as treated carpeting, treated apparel, and paper food packaging (Begley et al. 2005; Washburn et al. 2005). Elevated concentrations of perfluoroalkyls have been measured in air, water, soil, and sediment near fluorochemical industrial facilities (3M 2007b, 2008b, 2008c; Barton et al. 2006; Davis et al. 2007; Hansen et al. 2002).

The highest concentrations of perfluoroalkyls in animals are measured in apex predators, such as polar bears, which indicates that these substances biomagnify in food webs (de Vos et al. 2008; Houde et al. 2006b; Kannan et al. 2005; Kelly et al. 2007; Smithwick et al. 2005a, 2005b, 2006). The bioaccumulation potential of perfluoroalkyls is reported to increase with increasing chain length (de Vos et al. 2008; Furdui et al. 2007; Martin et al. 2004b). In living organisms, perfluoroalkyls bind to protein albumin in blood, liver, and eggs and do not accumulate in fat tissue (de Vos et al. 2008; Kissa 2001).

Mean PFOA, PFOS, and PFHxS serum concentrations reported in various studies from the United States were 2.1–9.6, 14.7–55.8, and 1.5–3.9 ng/mL, respectively (Calafat et al. 2006b, 2007a, 2007b; De Silva and Mabury 2006; Kuklenyik et al. 2004; Olsen et al. 2003a, 2003b, 2004c, 2005, 2007a). Mean concentrations of PFHpA, PFNA, PFDeA, PFUA, PFDoA, PFBuS, PFBA, PFOSA, Me-PFOSA-AcOH, and Et-PFOSA-AcOH are generally <1 ng/mL in these studies. Major PFOS exposure pathways proposed for the general population include food and water ingestion, dust ingestion, and hand-to-mouth transfer from mill-treated carpets (Trudel et al. 2008). For PFOA, the major exposure pathways are proposed to be oral exposure resulting from general food and water ingestion, inhalation from impregnated clothes, and dust ingestion. While migration of residual PFOA in paper packaging and wrapping into food is also a potential route of exposure (Trudel et al. 2008), precursor substances in food packaging can also be metabolized in the body to PFOA (D'eon and Mabury 2007; D'eon et al. 2009). Polyfluoroalkyl phosphoric acids (PAPs) are fluorinated surfactant substances used to greaseproof food-containing paper products. Biotransformation of the 8:2 PAP and the 8:2 fluorotelomer alcohol into PFOA has been demonstrated (D'eon et al. 2009). Based on these proposed exposure pathways, Trudel et al. (2008) estimated that adult uptake doses for high-exposure scenarios were approximately 30 and 47 ng/kg body weight/day for PFOS and PFOA, respectively. The estimated dosage for children under the age of 12 under a high-exposure scenario were estimated to be 101–219 and 65.2–128 ng/kg body weight/day, for PFOS and PFOA, respectively (Trudel et al. 2008). Estimated daily doses for the general population were also estimated by Vestergren et al. (2008) to range from 3.9 to 520 ng/kg body

weight/day for PFOS and from 0.3 to 150 ng/kg body weight/day for PFOA. Infants and toddlers had the highest estimated dosages due to greater hand-to-mouth contact with treated carpeting, mouthing activities of clothes, and greater dust ingestion. Under certain exposure scenarios, it was estimated that up to 80% of the intake could be attributable to exposure to precursor substances followed by subsequent metabolism to PFOS or PFOA. Exposure pathways of perfluorocarboxylate homologues for different exposure settings were modeled by Vestergren and Cousins (2009). Food intake was determined to be the major exposure pathway for the general population, while inhalation of indoor air was reported to be the primary exposure route for occupationally exposed individuals employed in fluorochemical plants. Ingestion of contaminated drinking water was determined to be the primary exposure pathway for individuals residing in communities with high point source contamination of water supplies.

Perfluoroalkyls have been detected in human breast milk and umbilical cord blood. The reported maximum concentrations of PFOS and PFOA measured in human breast milk samples were 0.360–0.685 and 0.210–0.609 ng/mL, respectively (Kärrman et al. 2007; Llorca et al. 2010; So et al. 2006b; Völkel et al. 2008). Maximum concentrations of other perfluoroalkyl compounds were <0.18 ng/mL. PFOS and PFOA have been detected in most umbilical cord blood samples with reported concentrations of 4.9–11.0 and 1.6–3.7 ng/mL, respectively (Apelberg et al. 2007a, 2007b; Fei et al. 2007; Inoue et al. 2004b; Midasch et al. 2007). Other perfluoroalkyls have been detected less frequently, with maximum concentrations of <2.6 ng/mL.

Individuals who perform jobs that require frequent contact with perfluoroalkyl-containing products, such as individuals who install and treat carpets, are expected to have occupational exposure to these substances. Individuals who work at fluorochemical facilities may have higher exposure to perfluoroalkyl compounds than the general population based on elevated concentrations of these substances measured in air, soil, sediment, surface water, groundwater, and vegetation surrounding these facilities (3M 2007b, 2008b, 2008c; Barton et al. 2006; Davis et al. 2007). Studies of individuals living near fluorochemical facilities indicate that drinking water is the major exposure pathway (Emmett et al. 2006a; Holzer et al. 2008; Wilhelm et al. 2009). Estimated off-site exposure of local residents that live near a fluorochemical facility to PFOA from contaminated environmental media ranged from 0.011 to 260 ng/kg/day (3M 2008c).

6.2 RELEASES TO THE ENVIRONMENT

There is no information listed in EPA's Toxic Release Inventory (TRI) on releases of perfluoroalkyls to the environment from manufacturing and processing facilities because these releases are not required to be reported within this program (EPA 2005b).

Perfluoroalkyls are man-made compounds that are not naturally occurring in the environment. Perfluoroalkyls such as PFOS and PFOA have been widely used in the manufacturing of consumer products (Hekster et al. 2003; Schultz et al. 2003). These substances are now detected in both environmental and biological media around the world as well as in serum samples collected from the general population (Calafat et al. 2006b, 2007a, 2007b; De Silva and Mabury 2006; Kuklenyik et al. 2004; Olsen et al. 2003b, 2003c, 2004b, 2004c, 2005, 2007a; Prevedouros et al. 2006). These findings have prompted efforts to reduce and even eliminate emissions of these substances from industrial process streams.

In 2006, the eight major companies of the perfluoropolymer/perfluorotelomer industry agreed to participate in EPA's PFOA Stewardship Program (EPA 2008f). This included voluntary commitments from these companies to reduce facility emissions and product content of PFOA and related chemicals on a global basis by 95% no later than 2010, and to work toward elimination of these substances by 2015 (EPA 2008f). Progress reports were provided in 2007. Data from these reports regarding releases of PFOA, PFOA precursors, and higher PFOA homologues to all media as well as percent reduction in releases are listed in Table 6-1. Total releases of these substances by these companies are uncertain since some of the data are listed as confidential business information.

Prevedouros et al. (2006) estimated the total global historical emissions of perfluoroalkyl carboxylates into the environment from both direct and indirect sources. These data are provided in Table 6-2. Based on these estimations, direct emissions (3,200–6,900 metric tons) have far exceeded indirect emissions (30–350 metric tons). The largest direct emissions identified are from industrial processes such as the manufacture of perfluoroalkyl carboxylates (470–900 metric tons), fluoropolymer manufacture (2,200–5,400 metric tons), and fluoropolymer processing (210–320 metric tons). Direct release of perfluoroalkyl carboxylates from use of aqueous firefighting foams and consumer and industrial products were estimated to be 20–100 and 40–200 metric tons, respectively. The largest indirect emissions identified were from perfluoroalkyl carboxylate residual impurities in perfluorooctylsulfonyl fluoride products (20–130 metric tons) and fluorotelomer-based precursor degradation (6–130 metric tons).

Table 6-1. Reported Emissions of PFOA, PFOA Homologues, or PFOA Precursors in Products from the 2006 U.S. Operations of Fluoropolymer/Fluorotelomer Companies

		Releases to all media from fluorotelomer and telomer manufacturing		
Company	Chemicals	kg	kg of release/100 kg of product produced	Percent reduction in emissions[a]
Arkema, Inc.	PFOA and higher homologues	>1,000–10,000	For fluorotelomer production: >0.1–1	22%
	Precursors	Not applicable	Not applicable	Not applicable
Asahi Glass Company	PFOA, PFOA salts, and higher homologues	4,922	For fluorotelomer production: <1	6%
	Precursors	Not applicable	Not applicable	Not applicable
Ciba Specialty Chemicals Corporation	PFOA	0.05[b]		>99%
	Higher homologues	0.05[b]		>99%
	Precursors	0[b]		>99%
Clariant International Ltd.	Not applicable	Not applicable	Not applicable	Not applicable
Daikin America, Inc.	PFOA	Confidential business information	For fluorotelomer production: 8.0×10^{-3}; for telomer production: 6.4×10^{-7}	94% for FP production; 92% for telomer production
	Precursors and higher homologues	Confidential business information	For telomer production: 6.4×10^{-7}	22% for telomer production
E.I. DuPont de Nemours and Company	PFOA, PFOA salts	1,100	Not reported	98%
	Direct precursors	Confidential business information	Not reported	Confidential business information
3M/Dyneon	PFOA	0	0	100%
Solvay Solexis	PFOA and PFOA salts	Not applicable	Not applicable	Not applicable
	Higher homologues	>1,000–10,000	For fluorotelomer production: 0.161	28%
	Precursors	Not applicable	Not applicable	Not applicable

[a]Percent reduction in product content of these compounds from baseline year levels. The baseline year is the year nearest to the year 2000 for which company data are available.
[b]Total for emissions and product content

PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Source: EPA 2008f

Table 6-2. Global Historical PFCA Production and Emissions Summary[a]

Environmental input source	Historical time period (years)	Estimated total global historical PFCA emissions (t)
Direct PFCA sources		
PFCA manufacture		
PFO/APFO	1951–2004	400–700
PFN/APFN	1975–2004	70–200
Total manufactured		470–900
Industrial and consumer uses		
Fluoropolymer manufacture (APFO)	1951–2004	2,000–4,000
Fluoropolymer dispersion processing (APFO)	1951–2004	200–300
Fluoropolymer manufacture (APFN)	1975–2004	400–1,400
Fluoropolymer processing (APFN)	1975–2004	10–20
Aqueous firefighting foams (AFFF)	1965–1974	50–100
Consumer and industrial products	1960–2000	40–200
Total direct		3,200–6,900
Indirect PFCA sources		
POSF-based products		
PFCA residual impurities	1960–2002	20–130
POSF-based precursor degradation	1960–2002	1–30
POSF-based AFFF	1970–2002	3–30
Fluorotelomer-based products		
PFCA residual impurities	1974–2004	0.3–30
Fluorotelomer-based precursor degradation	1974–2004	6–130
Fluorotelomer-based AFFF	1975–2004	<1
Total indirect		30–350
Total source emissions (direct and indirect)		3,200–7,300

[a]Low and high estimated values as well as the period of use/production for each source are based upon publicly available information cited in the text.

AFFF = aqueous firefighting foams; APFN = ammonium perfluorononanoate; APFO = ammonium perfluoro-octanoate; PFCA = perfluorinated carboxylic acid; PFO = perfluorooctanoate; POSF = perfluorooctanesulfonyl fluoride

Source: Prevedouros et al. 2006

3M ceased production of PFOS and related chemicals in 2002 (3M 2008a; EPA 2008f). EPA has since established the significant new use rule to limit future manufacturing and importation of these substances (EPA 2002, 2007c, 2008f). Included on the current list are PFOS, PFHxS, PFOSA, and Et-PFOSA-AcOH. Therefore, current industrial releases of these perfluoroalkyl sulfonates in the United States are expected to be negligible. In limited applications, products containing PFOS-containing chemicals may be exempted by EPA. Certain chrome plating applications, for example, utilize surfactants containing PFOS to help reduce emissions of hexavalent chromium (Agency for Toxic Substances and Disease Registry 2008b). Information regarding current releases of shorter-chain perfluoroalkyls that are not included under phase-out regulations, such as PFBA and PFBuS, have not been located. Production of PFBA in the United States appears to have ceased, although some is reportedly imported for commercial use (3M 2008a; Agency for Toxic Substances and Disease Registry 2008b).

6.2.1 Air

There is no information listed in the TRI on releases of perfluoroalkyls to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported within this program (EPA 2005b).

According to 3M, PFOA was released to air during manufacturing processes at the Decatur, Alabama facility until use of this substance ceased in 2004 (3M 2008b). This company states that there are currently no air emissions of PFOA at this facility (3M 2008b). PFOA concentrations (75,000–900,000 pg/m^3) measured at the fence line of the DuPont Washington Works facility near Parkersburg, West Virginia in 2004 correlated with values modeled from wind speeds and trajectories surrounding this facility (Barton et al. 2006; Davis et al. 2007; Prevedouros et al. 2006). Based on current EPA regulations and information submitted by companies under EPA's PFOA Stewardship Program, industrial emissions of perfluoroalkyls to air are expected to be decreasing (EPA 2008f). High volume air samples collected at several monitoring stations near the Washington Works facility during nine events between August and October of 2005 contained PFOA at reported concentrations ranging from 10 to 75,900 pg/m^3 (EPA 2007d). The mean and median of these reported concentrations are 5,500 and 240 pg/m^3.

The presence of perfluoroalkyl compounds in indoor air and dust indicates that perfluoroalkyl-containing consumer products such as treated carpets and textiles are sources of release to air (Barber et al. 2007; Jahnke et al. 2007b; Kubwabo et al. 2005; Moriwaki et al. 2003; Prevedouros et al. 2006; Shoeib et al.

2004; Strynar and Lindstrom 2008). Perfluoroalkyl compounds have also been identified on both indoor and outdoor window films (Gewurtz et al. 2009). Disposal of perfluoroalkyl-containing consumer products is also expected to be a source of release to air (Prevedouros et al. 2006). Harada et al. (2005a, 2006) proposed that automobiles may be a source of PFOA in urban air based on elevated levels measured near heavy traffic areas and the widespread use of this substance in automobile materials.

Perfluoroalkyl carboxylic acids and perfluoroalkyl sulfonic acids may be formed by the atmospheric photooxidation of precursor compounds such as fluorotelomer alcohols and perfluoroalkyl sulfonamides (D'eon et al. 2006; Ellis et al. 2004; Martin et al. 2006; Wallington et al. 2006; Wania 2007). Perfluoroalkyl carboxylic acids including PFOA, PFNA, PFHpA, and PFBA were observed as products during a laboratory study involving the photooxidation of 4:2, 6:2, and 8:2 fluorotelomer alcohols (Ellis et al. 2004). D'eon et al. (2006) observed both perfluoroalkyl carboxylic acids and perfluorobutane sulfonate among products of the photooxidation of N-methyl perfluorobutane sulfonamidoethanol.

6.2.2 Water

There is no information listed in the TRI on releases of perfluoroalkyls to water from manufacturing and processing facilities because these releases are not required to be reported within this program (EPA 2005b).

Waste water discharge is also indicated as a release pathway for ammonium perfluorooctanoate (APFO) from the DuPont Washington Works facility (Davis et al. 2007). The average monthly concentrations of APFO measured in surface water from three outlets at the Washington Works facility during 2007 and early 2008 ranged from 3.65 to 377 µg/L (EPA 2008i). Reported concentrations of APFO and PFOA measured in surface water from four separate outlets at this facility during the same period were 3–64 and 2.3–61 µg/L, respectively.

During perfluorochemical operations at the 3M Cottage Grove facility in Minnesota, waste water treatment plant effluent containing perfluoroalkyl compounds was discharged to the Mississippi River. Discharge into Bakers Creek from the waste water treatment plant at the 3M Decatur facility was considered to be a principal source of PFOA release from this facility (3M 2008b). Based on current EPA regulations and information submitted by companies under EPA's PFOA Stewardship Program, industrial emissions of perfluoroalkyls to water are expected to be decreasing (EPA 2008f).

Levels of perfluoroalkyls measured in groundwater near fire-training areas are attributed to the use of these substances in aqueous fire-fighting foams (Moody and Field 1999; Moody et al. 2003). Use and disposal of perfluoroalkyl-containing consumer products is expected to be a source of release to water (Prevedouros et al. 2006).

Both PFOA and PFNA were among the identified products of the aqueous photooxidation of 8:2 fluorotelomer alcohol (Gauthier and Mabury 2005). Wang et al. (2005a, 2005b) measured PFOA as a product of the biodegradation of 8:2 fluorotelomer alcohol in an activated sludge inoculum. These results indicate that both aqueous photooxidation and biodegradation of fluorotelomer alcohols may result in the formation of perfluoroalkyl carboxylic acids in water.

A 2007 study identified perfluoroalkyl compounds in waste water from various waste water treatment plants in Minnesota. Influent, effluent, and sludge samples from 28 public and private facilities were analyzed for 13 perfluoroalkyl compounds. Several facilities, primarily urban treatment plants, were found to have higher concentrations of perfluoroalkyl compounds. Influent, effluent, and sludge from a treatment plant in Brainerd had the highest PFOS levels of all sampled facilities. The PFOS concentration in effluent was found to be 1.51 µg/L. The high levels were attributed to a chrome plating facility using a surfactant containing fluorosulfonate to control hexavalent chromium emissions (Kelly and Solem 2009). Based on these findings, EPA Region 5 began an investigation of whether chromium electroplating facilities were significant sources of PFOS and other perfluoroalkyls in the environment (EPA 2009b). Effluent samples were obtained from seven facilities located in Chicago, Illinois and four facilities in Cleveland, Ohio. It was determined that perfluoroalkyls were being discharged from all 11 facilities at quantifiable levels and that PFOS was detected in waste water from 10 out of 11 facilities at levels of 0.0314–39 µg/L (EPA 2009b). PFOA and PFOS were detected in effluents of six waste water treatment plants located in New York at levels of 0.058–1.05 and 0.003–0.068 µg/L, respectively (Sinclair and Kannan 2006). PFOS and PFOA were detected in effluents of two waste water treatment plants located in Singapore at levels of 0.0053–0.5609 and 0.0112–1.057 µg/L, respectively (Yu et al. 2009c). PFOA, PFOS, and several other perfluoroalkyls were detected in effluent samples of 21 waste water treatment plants and 9 industrial point sources (Clara et al. 2009). PFOA and PFOS were reportedly identified in the effluents of all of the facilities monitored at an average level of 0.060 µg/L for both substances. Polyfluoroalkyl phosphoric acids, a potential precursor to perfluoroalkyls such as PFOA, have also been measured in waste water treatment plant sludge (D'eon et al. 2009).

6.2.3 Soil

There is no information listed in the TRI on releases of perfluoroalkyls to soil from manufacturing and processing facilities because these releases are not required to be reported within this program (EPA 2005b).

Amounts of perfluoroalkyl compounds released to soil from industrial facilities were not located. Between 1978 and 1998, 3M disposed of PFOA-containing sludge from its waste water treatment plant at the Decatur Facility in Alabama through subsurface injection in on-site area fields (3M 2008b). The total amount of sludge applied to the former sludge incorporation area during this time period was 43,149 metric tons, dry weight. Sludge from the Decatur facility has also been disposed of at off-site landfills. During fluorochemical operations at its Cottage Grove facility in Minnesota, 3M disposed of perfluoroalkyl-containing waste at both on- and off-site locations (3M 2007b). Off-site disposal locations included the Washington County Landfill, the Oakdale Dump, and the Woodbury Disposal Site (3M 2008a). Based on current EPA regulations and information submitted by companies under EPA's PFOA Stewardship Program, industrial emissions of perfluoroalkyls to soil are expected to be decreasing (EPA 2008f).

Liu et al. (2007) measured PFOA as a product of the biodegradation of 8:2 fluorotelomer alcohol in soil. This result, along with similar findings in activated sludge tests, indicates that biodegradation of fluorotelomer alcohols may result in the formation of perfluoroalkyl carboxylic acids in soil (Liu et al. 2007; Wang et al. 2005a, 2005b).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

Based on the low pKa values (<3) for the perfluoroalkyl carboxylic acids and sulfonic acids, these compounds are expected to exist primarily as anions in the environment (Kissa 2001; SPARC 2008). Volatilization of perfluoroalkyl anions such as perfluorooctanoate (PFO) from water surfaces is expected to be negligible since ions do not volatilize (Prevedouros et al. 2006). However, due to the surfactant nature of the perfluoroalkyl compounds, some of the amount released to water may form micelles and exist in the associated form despite the low pKa values of these substances (EPA 2005a; Prevedouros et al. 2006). Perfluoroalkyl compounds that associate on water and soil surfaces may volatilize into the

atmosphere (EPA 2005a; Kim and Kannan 2007). The extrapolated vapor pressure of PFOA is 0.017 mm Hg at 20°C, indicating that the neutral form of this substance may be volatile (Barton et al. 2007).

Barton et al. (2007) explored the atmospheric partitioning of PFOA during rain events near an industrial facility and concluded that this substance will be primarily adsorbed to particles in the air since PFOA was not detected in the vapor phase (detection limit of 0.2 ng/m^3). Concentrations of PFOA in raindrops and as particulates were 11.3–1,660 ng/L and 0.09–12.40 ng/m^3. The authors proposed that PFOA or APFO released into air from industrial facilities will be scavenged by atmospheric particles (including aqueous aerosols and raindrops) and dissociate to form the perfluorooctanoate anion. Although Barton et al. (2007) did not detect PFOA in the vapor phase during rain events, low concentrations (<0.12–3.16 pg/m^3) of vapor-phase perfluoroalkyl compounds measured by Kim and Kannan (2007) in urban air provide evidence of a partitioning equilibrium. Wet and dry deposition are expected to be the principal removal mechanisms for perfluoroalkyl carboxylic acids and sulfonic acids in particulate form from the atmosphere. Residence times with respect to these processes are expected to be days to weeks (Barton et al. 2007; Hurley et al. 2004; Kim and Kannan 2007).

Estimated pKa values of 3.92 for Me- and Et-PFOSA-AcOH and 6.24 for PFOSA indicate that these compounds may exist partially in the undissociated form in the environment, especially under acidic conditions (SPARC 2008). Volatilization information are not available for these substances; however, a vapor pressure of 0.05 mm Hg at 25°C for n-ethylperfluorooctane sulfonamide (Et-PFOSA) indicates that undissociated perfluoroalkyl sulfonamides may volatilize into the atmosphere (Martin et al. 2006). Assuming that wet and dry deposition is not important for gas-phase perfluoroalkyl sulfonamides and an atmospheric photooxidation lifetime of 20–50 days, Martin et al. (2006) concluded that perfluoroalkyl sulfonamides could possibly undergo long-range transport in the atmosphere.

K_{oc} values of 17–230 measured for perfluorooctanoate in soils of various organic carbon content indicate that PFOA will be mobile in soil and will not adsorb to suspended solids and sediment in the water column (Davis et al. 2007; Prevedouros et al. 2006). This is supported by the presence of PFOA in groundwater at the Decatur, Cottage Grove, and Washington Works fluorochemical industrial facilities (3M 2007b, 2008b; Davis et al. 2007). In addition to migration to groundwater from plumes near industrial facilities, air emissions followed by atmospheric deposition to soils and subsequent leaching may also contaminate nearby groundwater (Davis et al. 2007). Low volatility, high water solubility (9,500 mg/L at 25°C), and low sorption to solids indicate that the perfluorooctanoate anion will

accumulate in surface waters, especially oceans (Armitage et al. 2006; Kauck and Diesslin 1951; Prevedouros et al. 2006; Wania 2007).

Perfluoroalkyl carboxylic acids and sulfonic acids have been widely detected in both environmental media and biota of the Arctic region (see Table 6-3) and other remote locations. The source of the perfluoroalkyl compounds at these locations is not clear. A number of source pathways for perfluoroalkyl compounds in these remote areas have been proposed and it is likely that the actual source is a combination of these (Barber et al. 2007; Prevedouros et al. 2006).

Long-range atmospheric transport of precursor compounds such as fluorotelomer alcohols and perfluoroalkyl sulfonamides followed by the atmospheric photooxidation of these substances to form perfluoroalkyl carboxylic acids and perfluoroalkyl sulfonic acids results in PFOA and PFOS contamination in remote locations with no direct point sources for these compounds (Barber et al. 2007; D'eon et al. 2006; Dinglasan-Panlilio and Mabury 2006; Ellis et al. 2004; Martin et al. 2006; Simcik 2005; Small et al. 2009; Wallington et al. 2006; Wania 2007). Fluorotelomer alcohols and perfluoroalkyl sulfonamides are relatively volatile and possess long enough atmospheric residence times for long-range transport to be possible (Barber et al. 2007; Yarwood et al. 2007). The presence of fluorotelomer alcohols and perfluoroalkyl sulfonamides in urban and Arctic air offers evidence of long-range atmospheric transport (Loewen et al. 2005; Shoeib et al. 2006; Stock et al. 2004). Photooxidation studies have demonstrated the conversion of these substances to perfluoroalkyl carboxylic acids and sulfonates (see Section 6.2.1). According to Young et al. (2007), the presence of perfluorodecanoic acid and perfluoroundecanoic acid in an Arctic ice cap indicate atmospheric oxidation as a source.

A second source of perfluoroalkyls in remote areas is direct oceanic transport of these substances (Armitage et al. 2006; Barber et al. 2007; Simcik 2005; Wania 2007; Yamashita et al. 2005, 2008). This hypothesis is supported by the presence of perfluoroalkyl compounds measured in ocean water, analysis of ocean currents directed toward the Arctic Ocean, and elevated perfluoroalkyl concentrations measured in coastal waters near industrial regions (Armitage et al. 2006; Barber et al. 2007; Prevedouros et al. 2006; Saito et al. 2003, 2004; Wania 2007; Wei et al. 2007a; Yamashita et al. 2004, 2005, 2008). A third possibility is the transport of perfluoroalkyls in the form of marine aerosols (Barber et al. 2007; CEMN 2008; Prevedouros et al. 2006). This mechanism may be especially relevant for perfluoroalkyl compounds since surfactants have been shown to accumulate in upper sea layers and at water surfaces (Prevedouros et al. 2006). Although direct atmospheric transport of perfluoroalkyl carboxylic acids and sulfonic acids was initially discounted, some researchers are suggesting that this may be a contributing

Table 6-3. Biological Monitoring of PFOA and PFOS in the Arctic

Location and organism	Concentration (ng/g) PFOA	PFOS	Reference
Northeastern Canada, 1996–2002; wet weight[a]			Tomy et al. 2004
Zooplankton (n=5)	2.6	1.8	
Clams (n=5)	ND	0.28	
Shrimp (n=7)	0.17	0.35	
Arctic cod (n=6)	0.16	1.3	
Redfish (n=7)	1.2	1.4	
Walrus (n=5)	0.34	2.4	
Narwhal (n=5)	0.9	10.9	
Beluga (n=5)	1.6	12.6	
Black-legged kittiwake (n=4)	ND	10.0	
Glaucous gulls (n=5)	0.14	20.2	
Northern Canada, 1992–2002[a]			Martin et al. 2004a
Polar bear (n=7)	8.6	3,100	
Arctic fox (n=10)	<2	250	
Ringed seal (n=9)	<2	16	
Mink (n=10)	<2	8.7	
Common loon (n=5)	<2	20	
Northern fulmar (n=5)	<2	1.3	
Black guillemot (n=5)	<2	ND	
White sucker (n=3)	<2	7.6	
Brook trout (n=2)	<2	39	
Lake whitefish (n=2)	<2	12	
Lake trout (n=1)	<2	31	
Northern pike (n=1)	<2	5.7	
Arctic sculpin (n=1)	<2	12	
Northwestern Canada, 2004			Powley et al. 2008
Zooplankton (n=3)	ND	ND–0.2	
Arctic cod (n=5)	ND	0.3–0.7	
Ringed seal (n=5)		2.5–8.6	
Bearded seal (n=1)	ND	1.3	
Northern Norway; ng/g wet weight[a]			Verreault et al. 2005, 2007
Herring gull eggs	<0.091–0.652	21.4–42.2	
Glaucous gulls			
Eggs (n=10)	<0.70	104	
Plasma (n=20)	<0.70–0.74	134	

Table 6-3. Biological Monitoring of PFOA and PFOS in the Arctic

	Concentration (ng/g)		
Location and organism	PFOA	PFOS	Reference
Nanavut, Canada			Butt et al. 2007a, 2007b
Thick-billed murres	<MDL[b]–0.16	<0.40–0.76	
Northern fulmars	<MDL[b]–0.09	<0.40–0.60	
Ringed seals	<0.85–6.2	2–20	
Northern Canada, 2002–2005			Butt et al. 2008
Ringed seal livers (n=110)	<0.7–13.9	0.89–189	
Greenland			Bossi et al. 2005
Ringed seals	<1.2	12.5–95.6	
North American and European Arctic, 1999–2002			Smithwick et al. 2005a
Polar bears (n>72)	<2.3–57.1	263–6,340	
Greenland, 1999–2001			Smithwick et al. 2005b
Polar bears (n=29)[a]	10	2,470	
Greenland, 1972–2002			Smithwick et al. 2006
Polar bears	1.6–4.4	120–1,400	

[a]Reported as mean values
[b]Minimum detection limits for study analytes ranged from 0.03 to 2.3 ng/g. To calculate means, concentrations less than the MDL were replaced with a random value that was less than half the MDL.

MDL = maximum detection limit; ND = not detected; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

source pathway based on recent atmospheric measurements of these compounds in both the vapor phase and as particulates (Barber et al. 2007; Prevedouros et al. 2006).

Perfluoroalkyls compounds have been measured in invertebrates, fish, amphibians, reptiles, birds, bird eggs, and mammals located around the world (Dai et al. 2006; Giesy and Kannan 2001; Houde et al. 2005, 2006a, 2006b; Keller et al. 2005; Kannan et al. 2001a, 2001b, 2002a, 2002b, 2002c, 2002d, 2005, 2006; Sinclair et al. 2006; So et al. 2006a; Wang et al. 2008). The highest concentrations of PFOA and PFOS in animals are measured in apex predators, such as polar bears (Table 6-3), which indicates that these substances biomagnify in food webs (de Vos et al. 2008; Houde et al. 2006b; Kannan et al. 2005; Kelly et al. 2007). The bioaccumulation potential of perfluoroalkyls increases with increasing chain length from 4 to 8 carbon units and then declines with further increases in chain length (Conder et al. 2008; de Vos et al. 2008; Furdui et al. 2007; Martin et al. 2004b). In living organisms, perfluoroalkyls bind to protein albumin in blood, liver, and eggs and do not accumulate in fat tissue, which may explain why bioconcentration factors (BCFs) are lower than expected in aquatic organisms (de Vos et al. 2008; Kissa 2001).

6.3.2 Transformation and Degradation

Perfluoroalkyl compounds are considered to be environmentally persistent chemicals (EPA 2008f; OECD 2002, 2007; Schultz et al. 2003). The carbon atoms of the perfluoroalkyl chain are protected from attack by the shielding effect of the fluorine atoms; furthermore, environmental degradation processes generally do not possess the energy needed to break apart the strong fluorine-carbon bonds (3M 2000; Hekster et al. 2003; Schultz et al. 2003). Perfluoroalkyl compounds are resistant to biodegradation, direct photolysis, atmospheric photooxidation, and hydrolysis (OECD 2002, 2007; Prevedouros et al. 2006).

6.3.2.1 Air

Although transport and partitioning information indicates that air will not be a sink for perfluoroalkyl compounds in the environment, low concentrations of perfluoroalkyl carboxylic acids, sulfonic acids, and sulfonamides have been measured in air both in the vapor phase and as bound to particulates (Barton et al. 2007; Kim and Kannan 2007). Available information indicates that photodegradation will not compete with wet deposition as an atmospheric removal process for perfluoroalkyls (Barton et al. 2007; Hurley et al. 2004; Prevedouros et al. 2006). However, photooxidation may be an important degradation mechanism for perfluoroalkyl sulfonamides (D'eon et al. 2006; Martin et al. 2006).

PFOA does not absorb UV light at environmentally relevant wavelengths (>290 nm); Hori et al. (2004a) reports a weak absorption band for PFOA that ranges from 220 to 270 nm. Based on the measured absorption wavelength of PFOA, perfluoroalkyl carboxylic acids are not expected to undergo direct photolysis. Following irradiation of the potassium salt of PFOS with light of wavelength 290–800 nm for 67–167 hours, it was concluded that there was no evidence of direct photolysis of PFOS under any of the test conditions (OECD 2002). Based on these test results for PFOS, perfluoroalkyl sulfonic acids are not expected to undergo direct photolysis in the atmosphere. Direct photolysis data were not located for perfluoroalkyl sulfonic acids.

A measured photooxidation rate constant is not available for PFOA. Hurley et al. (2004) measured the reaction of short-chain (C1–C4) perfluoroalkyl carboxylic acids with photochemically generated hydroxyl radicals. The proposed mechanism begins with abstraction of the carboxyl hydrogen, which is followed by the removal of the carboxyl group and generation of a perfluoroalkyl radical. Finally, the perfluoroalkyl chain is broken down one carbon atom at a time through an unzipping sequence. The same rate constant, 1.69×10^{-13} cm^3/molecule-second, was measured for the photooxidation of the C2, C3, and C4 molecules, indicating that the chain length may have little effect on the reactivity of perfluoroalkyls with hydroxyl radical. According to the authors, this rate constant corresponds to a half-life of 130 days. Based on the data for the short chain structures, the authors concluded that atmospheric photooxidation of perfluoroalkyl carboxylic acids is not expected to compete with wet and dry deposition, which is predicted to occur on a time scale of the order of 10 days.

Atmospheric photooxidation data are not available for perfluoroalkyl sulfonic acids. Atmospheric photooxidation studies involving n-methyl perfluorobutane sulfonamidoethanol (Me-FBSE) and n-ethyl perfluorobutanesulfonamide (Et-FBSA) indicate possible mechanisms for the reaction of these substances with atmospheric hydroxyl radicals (D'eon et al. 2006; Martin et al. 2006). Products observed from the photooxidation of these compounds indicate the following pathways: removal of an alkyl from the amide (cleavage of the N-C bond); removal of the amido group (cleavage of the S-N bond); and removal of the sulfonamido group (cleavage of the S-C bond) (D'eon et al. 2006; Martin et al. 2006). Each of these pathways would be applicable to the photooxidation of Me- and Et-PFOSA-AcOH. The last two pathways indicate that PFOSA may be photooxidized through removal of the amido or sulfonamido group. The third pathway, cleavage of the S-C bond, also indicates a photooxidation mechanism for perfluoroalkyl sulfonic acids. Martin et al. (2006) proposes an unzipping sequence for the perfluoroalkyl chain following removal of the sulfonyl group.

Measured rate constants for the reaction of Me-FBSE and Et-FBSA with atmospheric hydroxyl radicals are $5.8x10^{-12}$ and $3.74x10^{-13}$ cm^3/molecule-second, respectively (D'eon et al. 2006; Martin et al. 2006). Atmospheric half-lives calculated using these rate constants were 2 days for Me-FBSE and 20–50 days for Et-FBSA.

6.3.2.2 Water

PFOS and PFOA are expected to be stable to hydrolysis in the environment based on half-lives of 41 and 92 years, respectively, calculated from experimental hydrolysis data that were measured over pH 5, 7, and 9 (OECD 2002, 2006b). Based on the data for PFOS and PFOA, hydrolysis is not expected to be an important degradation process for perfluorinated carboxylates and sulfonates in the environment. Hydrolysis data were not located for perfluoroalkyl sulfonamides.

Available information indicates that perfluoroalkyl compounds are resistant to aerobic biodegradation. PFOA and PFNA were not biodegraded during an OECD guideline manometric respirometry screening test for ready biodegradability; 0% of the theoretical oxygen demand was reached after 28 days (Stasinakis et al. 2008). Meesters and Schröder (2004) reported that PFOA and PFOS were not degraded from an initial concentration of 5 mg/L in aerobic sewage sludge in a laboratory scale reactor.

Substances such as perfluorotelomer alcohols and perfluoroalkyl sulfonamides, which are used in a variety of products, are degraded to other substances such as PFOA and PFOS in water and can be considered a source of these substances in the environment (Liu et al. 2007).

6.3.2.3 Sediment and Soil

Data are not available regarding the transformation and degradation of perfluoroalkyl compounds in sediment and soil. Based on the chemical stability of these substances and their resistance to biodegradation in screening tests, environmental degradation processes are not expected to be important removal mechanisms for perfluoroalkyl compounds in sediment and soil (3M 2000; EPA 2008f; Hekster et al. 2003; OECD 2002, 2007; Prevedouros et al. 2006; Schultz et al. 2003).

Substances such as perfluorotelomer alcohols and perfluoroalkyl sulfonamides, which are used in a variety of products, are degraded to other substances such as PFOA and PFOS in soil and sediment and can be considered a source of these substances in the environment (Liu et al. 2007).

6.3.2.4 Other Media

Data are not available regarding the transformation and degradation of perfluoroalkyl compounds in other media.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to perfluoroalkyls depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of perfluoroalkyls in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on perfluoroalkyls levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring perfluoroalkyls in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Perfluoroalkyl levels have been measured in outdoor air at a few locations in the United States, Europe, Japan, and over the Atlantic Ocean (Barber et al. 2007; Barton et al. 2006; Harada et al. 2005a, 2006; Kim and Kannan 2007). Concentrations reported in these studies are provided in Table 6-4.

Mean PFOA levels ranged from 1.54 to 15.2 pg/m^3 in air samples collected in the urban locations in Albany, New York; Fukuchiyama, Japan; and Morioka, Japan and in the rural locations in Kjeller, Norway and Mace Head, Ireland. Higher mean concentrations (101–552 pg/m^3) were measured at the urban locations in Oyamazaki, Japan and Manchester, United Kingdom, and semirural locations in Hazelrigg, United Kingdom. Maximum reported concentrations at Oyamazaki and Hazelrigg were 919 and 828 pg/m^3, respectively. The authors attributed the elevated concentrations at the Hazelrigg location to emissions from a fluoropolymer production plant located 20 km upwind of this semirural community.

PFOA concentrations were above the method quantitation limit (70,000–170,000 pg/m^3) in 6 out of 28 air samples collected along the fence line of the DuPont Washington Works fluoropolymer manufacturing facility, which is located near Parkersburg, West Virginia, in the Ohio River valley (Barton et al. 2006).

Table 6-4. Concentrations of Perfluoroalkyl in Outdoor Air

Location	Mean (range) concentration (pg/m^3)			Reference
	PFOA	PFHpA	PFNA	
Urban				
Albany, New York				
Gas phase (n=8)	3.16 (1.89–6.53)	0.26 (0.13–0.42)	0.21 (0.16–0.31)	Kim and Kannan 2007
Particulate phase (n=8)	2.03 (0.76–4.19)	0.37 (<0.12–0.81)	0.13 (<0.12–0.40)	Kim and Kannan 2007
Oyamazaki, Japan (n=12)	262.7 (72–919); 3,412.8 ng/g in dust	—	—	Harada et al. 2005b
Fukuchiyama, Japan	15.2; 314 ng/g in dust	—	—	Harada et al. 2006
Morioka, Japan (n=8)	2.0 (1.59–2.58)	—	—	Harada et al. 2005b
Manchester, United Kingdom (n=2,1)[a]	341, 15.7	8.2, 0.2	<26.6, 0.8	Barber et al. 2007
Rural				
Kjeller, Norway (n=2)	1.54	0.87	0.12	Barber et al. 2007
Mace Head, Ireland (n=4)	8.9	<0.001	<3.3	Barber et al. 2007
Hazelrigg, United Kingdom (semi-rural) (n=10)	101, 552[b,c]	1.6, 14.4[b]	0.9	Barber et al. 2007
Marine air				
Near Europe (northwest) (n=3)	1.22 (0.5–2.0)	<0.6 (ND–<0.6)	0.3 (ND–0.5)	Jahnke et al. 2007a
Near Africa (east coast) (n=5)	<0.5 (ND–0.7)	ND	<0.2 (ND–0.3)	Jahnke et al. 2007a
Source dominated				
DuPont Washington Works Facility; Parkersburg, West Virginia (n=28)	430,000 (75,000–900,000)[d]	—	—	Barton et al. 2006
DuPont Washington Works Facility; Parkersburg, West Virginia (n=90)	55,260 (10–75,900)	—	—	EPA 2007d

Table 6-4. Concentrations of Perfluoroalkyl in Outdoor Air

Location	Mean (range) concentration (pg/m^3)			Reference
	PFDeA	PFUA	PFDoA	
Urban				
Albany, New York				
Gas phase (n=8)	0.63 (0.24–1.56)	<0.12 (ND–0.16)	0.27 (0.14–0.43)	Kim and Kannan 2007
Particulate phase (n=8)	0.27 (0.13–0.49)	ND	0.12 (<0.12–0.38)	Kim and Kannan 2007
Oyamazaki, Japan (n=12)	—	—	—	Harada et al. 2005b
Fukuchiyama, Japan	—	—	—	Harada et al. 2006
Morioka, Japan (n=8)	—	—	—	Harada et al. 2005b
Manchester, UK (n=2,1)[a]	5.4, <0.8	<0.01, <0.4	<0.01, <0.01	Barber et al. 2007
Rural				
Kjeller, Norway (n=2)	<0.15	<0.12	<0.12	Barber et al. 2007
Mace Head, Ireland (n=4)	<2.8	<0.002	<0.003	Barber et al. 2007
Hazelrigg, United Kingdom (semi-rural) (n=10)	1.0, 8.3[b]	0.7	<0.01	Barber et al. 2007
Marine air				
Near Europe (northwest) (n=3)	<0.6 (ND–0.6)	ND	<0.14 (ND–0.17)	Jahnke et al. 2007a
Near Africa (east coast) (n=5)	ND	0.03 (ND–0.2)	ND	Jahnke et al. 2007a
Source dominated				
DuPont Washington Works Facility – Parkersburg, West Virginia (n=28)	—	—	—	Barton et al. 2006
DuPont Washington Works Facility; Parkersburg, West Virginia (n=90)	—	—	—	EPA 2007d

Table 6-4. Concentrations of Perfluoroalkyl in Outdoor Air

Location	Mean (range) concentration (pg/m^3)				Reference
	PFOS	PFBuS	PFHxS	PFOSA	
Urban					
Albany, New York					
Gas phase (n=8)	1.70 (0.94–3.0)	—	0.31 (0.13–0.44)	0.67 (0.22–2.26)	Kim and Kannan 2007
Particulate phase (n=8)	0.64 (0.35–1.16)	—	<0.12	0.29 (<0.12–0.79)	Kim and Kannan 2007
Oyamazaki, Japan (n=12)	5.2 (2.51–-9.80); 72.2 ng/g in dust	—	—	—	Harada et al. 2005b
Fukuchiyama, Japan	2.2; 46.0 ng/g in dust	—	—	—	Harada et al. 2006
Morioka, Japan (n=8)	0.7 (0.46–1.19)	—	—	—	Harada et al. 2005b
Manchester, United Kingdom (n=2,1)[a]	46, 7.1	2.2, <1.6	1.0, 0.1	<1.6, <0.2	Barber et al. 2007
Rural					
Kjeller, Norway (n=2)	1.0	<0.09	0.05	0.78	Barber et al. 2007
Mace Head, Ireland (n=4)	<1.8	<1.0	0.07	<0.56	Barber et al. 2007
Hazelrigg, United Kingdom (semi-rural) (n=10)	1.6	2.6	0.04	0.2	Barber et al. 2007
Marine air					
Near Europe (north west) (n=3)	1.36 (0.4–2.5)	ND	0.12 (0.02–0.3)	ND	Jahnke et al. 2007a
Near Africa (east coast) (n=5)	0.544 (0.05–1.9)	ND	0.013 (ND–0.05)	ND	Jahnke et al. 2007a

Table 6-4. Concentrations of Perfluoroalkyl in Outdoor Air

Location	Mean (range) concentration (pg/m^3)				Reference
	PFOS	PFBuS	PFHxS	PFOSA	
Source dominated					
DuPont Washington Works Facility, Parkersburg, West Virginia (n=28)	—	—	—	—	Barton et al. 2006
DuPont Washington Works Facility; Parkersburg, West Virginia (n=90)	—	—	—	—	EPA 2007d

[a]Mean values were reported for separate sampling sessions.
[b]The second concentration reported was measured during an earlier sampling session (n=2).
[c]A maximum PFOA concentration of 828 pg/m^3 was measured in air at Hazelrigg, United Kingdom.
[d]Average and range of concentrations in 6 out of 28 samples that contained PFOA above the quantitation limit (70,000–170,000 pg/m^3).

ND = not detected; PFBuS = perfluorobutane sulfonic acid; PFDeA = perfluorodecanoic acid; PFDoA = perfluorododecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide; PFUA = perfluoroundecanoic acid

The reported concentrations in these six samples ranged from 75,000 to 900,000 pg/m^3. The highest concentrations were measured at locations downwind of the facility. High volume air samples collected at several monitoring stations near the Washington Works facility contained PFOA at reported concentrations ranging from 10 to 75,900 pg/m^3 (EPA 2007d). The mean and median of these reported concentrations are 5,500 and 240 pg/m^3.

PFOS was detected above quantitation limits in most of the studies, but concentrations were generally below 5 pg/m^3. A concentration of 46 pg/m^3 was reported in samples from Manchester, United Kingdom. Reported concentrations of other perfluoroalkyls (PFHpA, PFNA, PFDeA, PFUA, PFDoA, PFBuS, PFHxS, and PFOSA) were generally <1 pg/m^3 in these studies. PFHpA was detected at slightly higher concentrations (8.2 and 14.4 pg/m^3) at Manchester and Hazelrigg, United Kingdom, respectively.

Jahnke et al. (2007a) collected eight marine air samples during a cruise between Germany and South Africa (53°N to 33°S). Perfluoroalkyl concentrations steadily declined as the sampling moved further from Europe and toward less industrialized regions. Only PFOS was detected in the two samples collected over the Atlantic Ocean east of southern Africa.

Measurements of perfluoroalkyls in snow samples collected from Canadian Arctic ice caps indicate that these substances may be generated in the atmosphere at these locations (Young et al. 2007). Reported concentrations in these snow samples were 2.6–86 pg/L for PFOS, 12–147 pg/L for PFOA, 5.0–246 ng/L for PFNA, <8–22 pg/L for PFDeA, and <6–27 pg/L for PFUA.

The concentration of PFOS measured in rainwater collected during a rain event in Winnipeg, Manitoba was 0.59 ng/L (Loewen et al. 2005). PFOA, PFNA, PFDeA, PFUA, and PFDoA were not detected in the rainwater. Reported method detection limits for these compounds were 7.2, 3.7, 1.7, 1.2, and 1.1 ng/L, respectively.

Studies of perfluoroalkyl concentrations in indoor environments are available (Table 6-5). The reported mean concentrations of perfluoroalkyls measured in four indoor air samples collected from Tromso, Norway were 0.2 pg/m^3 for PFOSA, <0.5 for PFBuS, <4.1 pg/m^3 for PFHxS, <47.4 pg/m^3 for PFOS, 0.8 pg/m^3 for PFHpA, 4.4 pg/m^3 for PFOA, 2.7 ng/m^3 for PFNA, 3.4 ng/m^3 in PFDeA, <1.3 ng/m^3 for PFUA, and 1.2 ng/m^3 for PFDoA (Barber et al. 2007).

Table 6-5. Concentrations of Perfluoroalkyl in Indoor Air

	Concentration: mean (range); median			
Location	PFOA	PFHpA	PFNA	Reference
Indoor air (pg/m^3)				
Tromso, Norway (n=4)	4.4	0.8	2.7	Barber et al. 2007
Indoor dust (ng/g)				
Ottawa, Canada (n=67)	106.00 (<2.29–1,234); 19.72[a]	—	—	Kubwabo et al. 2005
Japan (n=16)	380 (70–3,700); 165	—	—	Moriwaki et al. 2003
North Carolina and Ohio (n=112)	296 (<10.2–1960); 142 [b]	109 (<12.5–1150); 50.2[b]	22.1 (<11.3–263); 7.99[b]	Strynar and Lindstrom 2008

	Mean (range) concentration (pg/m^3)			
Location	PFDeA	PFUA	PFDoA	Reference
Indoor air (pg/m^3)				
Tromso, Norway (n=4)	3.4	<1.3	1.2	Barber et al. 2007
Indoor dust (ng/g)				
Ottawa, Canada (n=67)	—	—	—	Kubwabo et al. 2005
Japan (n=16)	—	—	—	Moriwaki et al. 2003
North Carolina and Ohio (n=112)	15.5 (<9.40–267); 6.65[b]	30.4 (<10.7–588); 7.57[b]	18.0 (<11.0–520); 7.78[b]	Strynar and Lindstrom 2008

	Mean (range) concentration (pg/m^3)				
Location	PFOS	PFBuS	PFHxS	PFOSA	Reference
Indoor air (pg/m^3)					
Tromso, Norway (n=4)	<47.4	<0.5	<4.1	2.8	Barber et al. 2007
Indoor dust (ng/g)					
Ottawa, Canada (n=67)	443.68 (<4.56–5,065); 37.8[a]	ND[a]	391.96 (<4.56–4,305); 23.1[a]	<1.38[a]	Kubwabo et al. 2005
Japan (n=16)	200 (11–2,500); 24.5	—	—	—	Moriwaki et al. 2003
North Carolina and Ohio (n=112)	761 (<8.93–12,100); 201[b]	41.7 (<12.5–1,150); 9.11[b]	874 (<12.9–35,700); 45.5[b]	—	Strynar and Lindstrom 2008

[a]Method detection limits (MDL) and percent below MDL are as follows: PFOA (2.29 ng/g, 37%), PFOS (4.56 ng/g, 33%), PFBuS (1.38 ng/g, 100%), PFHxS (4.56, 15%), and PFOSA (0.99 ng/g, 90%).
[b]Limit of quantitation (LOQ) and percent above LOQ are as follows: PFHpA (12.5 ng/g, 74.1%), PFOA (10.2 ng/g, 96.4%), PFNA (11.3 ng/g, 42.9%), PFDeA (9.40 ng/g, 30.4%), PFUA (10.7 ng/g, 36.6%), PFDoA (11.0 ng/g, 18.7%), PFOS (8.93 ng/g, 94.6%), PFHxS (12.9 ng/g, 77.7%), PFBuS (12.5 ng/g, 33.0%). Values below the LOQ were assigned a value of LOQ/1.412 when calculating the median.

ND = not detected; PFBuS = perfluorobutane sulfonic acid; PFDeA = perfluorodecanoic acid; PFDoA = perfluorododecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide

Kubwabo et al. (2005) measured the concentrations of selected perfluoroalkyls in dust samples from 67 Canadian homes. PFOA, PFOS, and PFHxS were each detected in 37, 33, and 15% of these samples, respectively (detection limits of 2.29, 4.56, and 4.56 ng/g, respectively). Mean, median, and range of concentrations in these samples were 106, 19.72, and 1.15–1,234 ng/g, respectively, for PFOA; 443.68, 37.8, and 2.28–5,065 ng/g, respectively, for PFOS; and 391.96, 23.1, and 2.28–4,305 ng/g, respectively, for PFHxS. Concentrations were not reported for PFOSA, which was detected above 0.99 ng/g in 10% of the samples. PFBuS was not detected in any of the samples. Moriwaki et al. (2003) measured PFOS and PFOA concentrations in vacuum cleaner dust samples collected from 16 Japanese homes. PFOS and PFOA were detected in every sample with reported concentrations of 11–140 and 69–380 ng/g, respectively, in 15 of the 16 samples. One of the samples contained 2,500 ng/g PFOS and 3,700 ng/g PFOA.

Strynar and Lindstrom (2008) measured perfluoroalkyl levels in 112 indoor dust samples collected from homes and daycare centers in North Carolina and Ohio. These authors detected PFHpA, PFOA, PFNA, PFDeA, PFUA, PFDoA, PFOS, PFHxS, and PFBuS. Mean values ranged from 15.5 to 874 ng/g. PFOS and PFOA were detected in 94.6 and 96.4% of the samples, respectively. Maximum detections in the samples were as high as 12,100 ng/g for PFOS and 35,700 ng/g for PFHxS. Household dust samples collected from the United Kingdom, Australia, Germany, and the United States showed the presence of perfluoroalkyl substances (Kato et al. 2009a). These data are summarized in Table 6-6.

Median levels of PFOS in dust samples collected in homes, apartments, daycare centers, offices, and cars in Sweden were 39, 85, 31, 110, and 12 ng/g, respectively (Bjorklund et al. 2009). Median PFOA levels in dust samples from the same study were 54, 93, 41, 70, and 33 ng/g in homes, apartments, daycare centers, offices, and cars, respectively. The authors concluded that while dietary intake was the major PFOA/PFOS exposure pathway for adults and toddlers in the general population, dust ingestion could become an important pathway under a worst-case scenario (high dust ingestion and maximum dust levels).

6.4.2 Water

PFOS and PFOA have been widely detected in surface water samples collected from various rivers, lakes, and streams in the United States (Boulanger et al. 2004; Kannan et al. 2005; Kim and Kannan 2007; Nakayama et al. 2007; Simcik and Dorweiler 2005; Sinclair et al. 2004, 2006). Less data are available regarding the concentrations of other perfluoroalkyl compounds in surface water. PFHpA and PFHxS

Table 6-6. Concentration (ng/g) of Perfluoroalkyls in 39 Dust Samples[a]

Analyte	25th percentile	50th percentile	75th percentile	Maximum	Frequency of detection (%)
PFBuS	86.3	359.0	782.1	7718	92.3
PFHxS	47.7	185.5	632.2	43,765	79.5
PFOS	31.7	479.6	1,456.6	18,071	74.4
PFHpA	33.9	97.3	532.5	5,195	61.2
PFOA	<LOQ	96.5	667.7	9,818	64.1
PFNA	<LOQ	<LOQ	26.2	832	25.6
PFDeA	<LOQ	<LOQ	61.0	1,965	38.5
PFUA	<LOQ	<LOQ	<LOQ	732	20.5
PFDoA	<LOQ	<LOQ	37.6	1,048	43.6
PFOSA	<LOQ	<LOQ	16.1	184	23.1
Me-PFOSA-AcOH	<LOQ	<LOQ	110.3	4,520	33.3
Et-PFOSA-AcOH	92.4	243.5	417.9	3,795	87.2

[a]The LOQs are 2.6 ng/g except for PFHpA, which is 4.0 ng/g.

Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid; LOQ = limit of quanitification; Me-PFOSA-AcOH = 2-(N-methyl-perfluorooctane sulfonamide) acetic acid; PFBuS = perfluorobutane sulfonic acid; PFDeA = perfluorodecanoic acid; PFDoA = perfluorododecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide; PFUA = perfluoroundecanoic acid

were commonly detected in the few studies that analyzed surface water for these compounds (Kim and Kannan 2007; Nakayama et al. 2007; Simcik and Dorweiler 2005). Concentrations of perfluoroalkyls measured in surface water are listed in Tables 6-7 and 6-8. Reported concentrations of perfluoroalkyls in surface water samples are generally below 50 ng/L. Maximum concentrations of PFOS, PFOA, PFHpA, PFNA, PFDeA, PFUA, PFDoA, PFBuS, and PFHxS measured in surface water collected from the Cape Fear Basin, North Carolina were 287, 132, 329, 194, 120, 52.1, 4.46, 9.41, and 35.1 ng/L, respectively (Nakayama et al. 2007). Much higher concentrations of PFOS (198–1,090 ng/L) have been measured in Onondaga Lake in Syracuse, New York (Sinclair et al. 2006). Onondaga Lake is a Superfund site that has become contaminated through industrial activity along its banks. High levels were also reported around Dalton, Georgia, an area with a high density of carpet manufacturing locations (Konwick et al. 2008).

Levels of some perfluoroalkyl compounds measured in surface water and groundwater surrounding perfluorochemical industrial facilities are listed in Table 6-9. Maximum PFOS and PFOA concentrations measured in surface water downstream of the 3M Decatur, Alabama facility were 144 and 598 ng/L, respectively (Hansen et al. 2002).

The average monthly concentrations of APFO measured in surface water from three outlets at the Washington Works facility during 2007 and early 2008 ranged from 3.65 to 377 µg/L (EPA 2008i). Reported concentrations of APFO and PFOA measured in surface water from four separate outlets at this facility during the same period were 3–64 and 2.3–61 µg/L, respectively. Levels of APFO and PFOA measured in groundwater samples collected from three wells at the Washington Works facility during 2007 and early 2008 were 2.9–100 and 2.8–100 µg/L, respectively (EPA 2008i). Information regarding background concentrations of perfluoroalkyls in groundwater in the United States has not been located. PFOS was routinely detected in groundwater samples from the Tokyo, Japan metropolitan area, with its occurrence being traced to the degradation of precursors released to the environment and waste water treatment plants (Murakami et al. 2009).

Yamashita et al. (2005) measured PFOA, PFOS, PFNA, and PFHxS concentrations in ocean water collected from locations in the Atlantic Ocean, Pacific Ocean, and areas near China, Korea, and Japan. These concentrations are listed in Table 6-10. Wei et al. (2007a) measured perfluoroalkyl concentrations in surface seawaters from the western Pacific Ocean, Indian Ocean, and near-Antarctic region. PFOS and PFOA were detected in 60 and 40% of the samples, respectively, with maximum concentrations of 71.7 and 441.6 pg/L, respectively. Concentrations of other perfluoroalkyls (PFHxS, PFBuS, PFDoA, PFDeA, PFNA, PFHpA) were generally below detection in most samples, with the exceptions being in

Table 6-7. Concentrations of PFOA and PFOS in Surface Water (ng/L)

Location	Concentration		Reference
	PFOA	PFOS	
Great Lakes			Boulanger et al. 2004
Lake Ontario (n=8)	15–70	6–121	
Lake Erie (n=8)	21–47	11–39	
New York State waters			Sinclair et al. 2006
Lake Ontario (n=13)	18–34	2.9–30	
Niagara River (n=3)	18–22	3.3–6.7	
Lake Erie (n=3)	13–27	2.8–5.5	
Finger Lakes (n=13)	11–20	1.3–2.6	
Onondaga Lake (n=3)	39–64	198–1,090 (median=756)	
Oneida Lake (n=1)	19	3.5	
Erie Canal (n=3)	25–59	5.7–13	
Hudson River (n=8)	22–173 (median=35)	1.5–3.4	
Lake Champlain (n=4)	10–46	0.8–7.7	
Albany, New York			Kim and Kannan 2007
Lake water (n=11)	3.27–15.8 (median=7.20)	ND–9.30 (median=2.88)	
Surface water runoff (n=14)	0.51–29.3 (median=3.80)	<0.25–14.6 (median=0.81)	
Michigan water regions			Sinclair et al. 2004
Detroit (n=10)	<8–16.14	<0.08–6.13	
Flint (n=4)	<8–23.01	1.50–12.31	
Saginaw Bay (n=5)	<8–24.08	3.10–12.69	
Northeastern Michigan (n=2)	<8	0.87–6.34	
Upper Peninsula (n=7)	<8–13.77	<0.8–3.09	
Northwestern Michigan (n=2)	11.96	<0.8–4.48	
Western Michigan (n=6)	<8–15.17	<0.8–5.32	
Southwestern Michigan (n=5)	8.74–35.86	7.22–29.26	
Lansing (n=3)	<8–13.37	1.04–4.96	

Table 6-7. Concentrations of PFOA and PFOS in Surface Water (ng/L)

Location	Concentration		Reference
	PFOA	PFOS	
Minnesota Waters and Lake Michigan			Simcik and Dorweiler 2005
Remote (n=4)			
Loiten	0.7	ND	
Little Trout	0.3	1.2	
Nipisiquit	0.1	ND	
Tettegouche	0.5	0.2	
Urban (n=4)			
Calhoun	20	47	
Lake Harriet	3.5	21	
Lake of the Isles	0.5	2.4	
Minnesota River	1.2	9	
Lake Michigan (n=4)	<0.6–0.5	1–3.2	
Cape Fear Basin, North Carolina			Nakayama et al. 2007
80 Sites (n=100)			
Mean	43.4	31.2	
Median	12.6	28.9	
Minimum	ND	<1	
Maximum	287	132	
Percent not detected[a]	7.6	0	
Raisin and St. Clair Rivers, Michigan			Kannan et al. 2005
Raisin River	14.7	3.5	
St. Clair River (n=3)	4.0–5.0	1.9–3.9	
Conasauga River, Georgia	253–1,150	192–318	Konwick et al. 2008
Dalton, Georgia	49.9–299	15.8–120	
Several rivers in Japan	0.1–67,000	0.3–59	Harada and Koizumi 2009
Lake Victoria Gulf, Kenya	0.4–96.4 (rivers) 0.4–11.6 (lakes)	<0.4–13.23 (rivers); <0.4–2.53 (lakes)	Orata et al. 2009
River Po, Italy	1–1,270	1–25	Loos et al. 2008

[a]Detection limit is 0.05 ng/L

ND = not detected; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Table 6-8. Concentrations of Other Perfluoroalkyls in Surface Water

	Concentration (ng/L)								
Location (reference)[a]	PFHpA	PFNA	PFDeA	PFUA	PFDoA	PFBuS	PFHxS	PFOSA	Et-PFOSA-AcOH
Great Lakes (Boulanger et al. 2004)									
Lake Ontario (n=8)	—	—	—	—	—	—	—	—	<0.3–10
Lake Erie (n=8)	—	—	—	—	—	—	—	—	3–11
New York State waters (Sinclair et al. 2006)									
Onondaga Lake (n=3)	—	—	—	—	—	—	4.2–8.5	—	—
Erie Canal (n=3)	—	—	—	—	—	—	2.5–5.6	—	—
Other lakes and rivers	—	—	—	—	—	—	0.9–2.8	—	—
Albany, New York (Kim and Kannan 2007)									
Lake water (n=11)	1.15–12.7	ND–3.51	0.25–3.58	ND–1.45	ND–<0.25	—	<0.25–4.05	<0.25	—
Surface water runoff (n=14)	<0.25–6.44	<0.25–5.90	ND–8.39	ND–1.99	ND–1.60	—	ND–13.5	ND–2.14	—
Minnesota waters and Lake Michigan (Simcik and Dorweiler 2005)									
Remote (n=4)									
Loiten	10	ND	ND	—	—	—	—	—	—
Little Trout	4.8	ND	ND	—	—	—	—	—	—
Nipisiquit	0.9	<0.3	ND	—	—	—	—	—	—
Tettegouche	3.1	ND	ND	—	—	—	—	—	—
Urban (n=4)					—	—	—	—	—
Calhoun	11	0.6	0.5	—	—	—	—	—	—
Lake Harriet	2.6	ND	ND	—	—	—	—	—	—
Lake of the Isles	0.4	ND	ND	—	—	—	—	—	—
Minnesota River	0.7	1.9	ND	—	—	—	—	—	—
Lake Michigan (n=4)	<0.6–4.1	<0.6–3.1	ND	–	—	—	—	—	—
Cape Fear Basin, North Carolina (Nakayama et al. 2007)									
80 Sites (n=100)									
Mean	38.7	33.6	22.1	10.4	2.17	2.58	7.29	—	—
Median	14.8	5.70	13.2	5.67	1.95	2.46	5.66	—	—
Maximum	329	194	120	52.1	4.46	9.41	35.1	—	—

Table 6-8. Concentrations of Other Perfluoroalkyls in Surface Water

Location (reference)[a]	Concentration (ng/L)								
	PFHpA	PFNA	PFDeA	PFUA	PFDoA	PFBuS	PFHxS	PFOSA	Et-PFOSA-AcOH
Percent not detected[b]	32.9	10.1	15.2	17.7	53.2	38.0	45.6	—	—
Raisin and St. Clair Rivers, Michigan (Kannan et al. 2005)									
Raisin River	—	—	—	—	—	—	<1	<10	—
St. Clair River (n=3)	—	—	—	—	—	—	<1	<10	—

[a]See Table 6-7 for numbers of samples collected at these locations.
[b]Detection limit = 0.05 ng/L.

Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid; ND = not detected; PFBuS = perfluorobutane sulfonic acid; PFDeA = perfluorodecanoic acid; PFDoA = perfluorododecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOSA = perfluorooctane sulfonamide; PFUA = perfluoroundecanoic acid

Table 6-9. Concentrations of Perfluoroalkyls in Surface Water and Groundwater at Fluorochemical Industrial Facilities

	Percent detection and concentration (µg/L)					
Location	PFOA	PFBA	PFOS	PFHxS	PFBuS	Reference
DuPont Washington Works Facility, West Virginia						
Groundwater						
Borings (n=18)						Davis et al. 2007
Percent detected	89%[a]	—	—	—	—	
Minimum	0.0912[a]	—	—	—	—	
Maximum	78[a]	—	—	—	—	
Wells (n=14)			—	—	—	Davis et al. 2007
Percent detected	100%[a]	—	—	—	—	
Minimum	0.081[a]	—	—	—	—	
Maximum	37.1[a]	—	—	—	—	
Wells (n=3)			—	—	—	EPA 2008i
Percent detected	100%	—	—	—	—	
Minimum	2.8	—	—	—	—	
Maximum	100	—	—	—	—	
Surface water						
Outlets (n=4)						EPA 2008i
Percent detected	100%	—	—	—	—	
Minimum	2.3	—	—	—	—	
Maximum	61	—	—	—	—	
3M Cottage Grove Facility, Minnesota						
Groundwater						
Wells (n=1–7)						3M 2007b
Percent detected	100%	100%	100%	100%	100%	
Minimum	24.6	23.3	26.0	6.47	2.11	
Maximum	619	318	26.0	40.0	26.1	
Surface water						
East and West Cove (n=3–9)						3M 2007b
Percent detected	100%	100%	100%	100%	78%	
Minimum	0.172	0.803	0.227	0.0936	0.304	
Maximum	2.79	1.01	3.12	4.58	9.69	
Mississippi River Shoreline (n=52–80)						3M 2007b
Percent detected	60%	52%	43%	28%	56%	
Maximum	0.760	6.92	0.539	1.04	3.05	
Mississippi River Transect (n=34–44)						3M 2007b
Percent detected	14%	12%	0%	0%	0%	
Maximum	0.0501	0.0530	ND	ND	ND	

Table 6-9. Concentrations of Perfluoroalkyls in Surface Water and Groundwater at Fluorochemical Industrial Facilities

	Percent detection and concentration (µg/L)					
Location	PFOA	PFBA	PFOS	PFHxS	PFBuS	Reference
3M Decatur Facility, Alabama						
Groundwater						
Off-site groundwater (n=18)						3M 2008c
Percent detected	94%	—	—	—	—	
Mean	1.87	—	—	—	—	
Range	0.083–19.8	—	—	—	—	
Surface water						
On-site surface water (n=7)						3M 2008c
Percent detected	100%	—	—	—	—	
Median	2.66	—	—	—	—	
Range	0.32–127	—	—	—	—	
Off-site surface water (n=60)						3M 2008c
Percent detected	98%	—	—	—	—	
Range	0.026–27.7	—	—	—	—	
Tennessee River						Hansen et al. 2002
Upstream of facility (n=19)						
Percent detected	0%	—	100%	—	—	
Range	<25	—	16.8–52.6	—	—	
Downstream of facility (n=21)				—	—	
Percent detected	0%	—	100%	—	—	
Median	355	—	107	—	—	
Range	<25–598	—	30.3–144	—	—	

[a]Analyte was reported as APFO.

APFO = ammonium perfluorooctanoate; ND = not detected; PFBA = perfluorobutyric acid; PFBuS = perfluorobutane sulfonic acid; PFHxS = perfluorohexane sulfonic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Table 6-10. Concentrations of PFOA and PFOS in Ocean Water

	Concentration (pg/L)			
Location	PFOA	PFOS	PFNA	PFHxS
North Atlantic (n=9)	160–338	8.6–36	15–36	4.1–6.1
Mid Atlantic (n=7)	100–439	37–73	—	2.6–12
Central to Eastern Pacific (n=14)	15–62	1.1–20	1.0–16	0.1–1.6
Western Pacific (n=2)	136–142	54–78	—	2.2–2.8
Tokyo Bay (n=8)	1,800–192,000	338–57,700	163–71,000	17–5,600
Offshore Japan (n=4)	137–1,060	40–75	–	3.0–6.1
Coastal Hong Kong (n=12)	673–5450	70–2,600	22–207	<5–311
Coastal China (n=14)	243–15,300	23–9,680	2.0–692	<5–1,360
Coastal Korea (n=10)	239–11,350	39–2,530	15–518	<5–1,390
Sulu Sea (n=5)	88–510	<17–109	—	<0.2
South China Sea (n=2)	160–420	8–113	—	<0.2

PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Source: Yamashita et al. 2005

samples collected near Shanghai, the Philippines, and Indonesia. Maximum concentrations of these perfluoroalkyls ranged from 3.1 to 70.2 pg/L near Shanghai. PFOA, PFOS, and other perfluoroalkyl species were monitored in waste water effluents and 20 rivers located in Japan (Murakami et al. 2008). Perfluoroalkyls were ubiquitous in the river water samples, with concentrations of PFOA as large as 0.054–0.192 µg/L in seven of the river samples with low waste water effluent sources.

The widespread presence of PFOA and PFOS at low concentrations in surface water in the United States indicates that drinking water taken from these sources may contain detectable levels of these substances. PFOA was detected in 12 out of 13 samples collected from four municipal drinking water treatment plants that draw water from the Tennessee River and are located downstream from the 3M Decatur Facility in Alabama. Reported concentrations range from 0.025 to 0.16 µg/L (3M 2008c). PFOA was not detected in any samples collected from a fifth plant located upstream of the 3M Decatur facility (3M 2008c).

Based on a memorandum of understanding with the EPA, DuPont began collecting water monitoring data of both public and private wells near the Washington Works chemical plant. The quarterly reports and monitoring data affiliated with these reports may be obtained from the regulations.gov portal (http://www.regulations.gov/#!home). In samples of water collected at 17 public water facilities from 2002 to 2009 in West Virginia and Ohio, PFOA levels ranged from below the detection limit (0.0023 µg/L) to nearly 100 µg/L in a few test wells in Little Hocking, Ohio (EPA 2010). Emmett et al. (2006a) reported an average PFOA concentration of 3.55 µg/L in residential drinking water from the Little Hocking community, which is located across the Ohio River from the DuPont Washington Works Facility.

According to the Agency for Toxic Substances and Disease Registry (2008), PFOA, PFOS, PFBA, PFHxS, and PFBuS have been detected in the municipal drinking water of communities located near the 3M Cottage Grove fluorochemical facility. According to Chang et al. (2008a), concentrations of PFBA were generally in the low ng/L range in effluent at these locations, but could be in the µg/L range in public and private wells.

PFOS concentrations ranging from 0.1 to 4 ng/L were measured in tap water samples collected from the areas of Morioka City, Iwate, Tokyo, and Kyoto in Japan (Harada et al. 2003).

Concentrations of 43.7 and 50.9 ng/L were measured in samples of tap water originating from the PFOS-contaminated Tama River. PFOA was detected in 65% of the public drinking water systems tested in

New Jersey in 2006 at concentrations ranging from 5 to 39 ng/L (Post et al. 2009). PFOA and PFOS were detected in tap water from 21 cities located in China at concentrations of <0.1–45.9 and <0.1–14.8 ng/L, respectively (Jin et al. 2009). Mak et al. (2009) published a study comparing detections of perfluoroalkyls including PFOA and PFOS in tap water collected in China, Japan, India, Canada and the United States. PFOA and PFOS were the predominant species measured, accounting for 40–50% of the total perfluoroalkyls present in water, with the exception of certain location of India where PFOS or PFOA may not have been present or were present at low levels.

6.4.3 Sediment and Soil

Background environmental levels of perfluoroalkyl compounds in sediment and soil were not located. Levels of some perfluoroalkyl compounds measured in soil and sediment surrounding perfluorochemical industrial facilities are listed in Table 6-11. PFOA was detected in most soil and sediment samples collected on- and off-site at the 3M Decatur facility in Alabama. Maximum soil concentrations were as high as 14,750 ng/g on-site and 7.85 ng/g off-site, and maximum sediment concentrations were as high as 347 on-site and 2,385 ng/g off-site (3M 2008c). The highest levels of PFOA were measured in soil from on-site fields formerly injected with PFOA-containing sludge. Grazing land polluted with perfluoroalkyl-contaminated sludge potentially resulted in contamination of the food supply. Studies of tissue levels of perfluorinated compounds in cattle are ongoing.

PFOA, PFOS, and PFHxS were detected in 90–100% of soil samples collected from a former tar neutralization area, a former sludge disposal area, a former solids burn pit area, a former waste water treatment plant area, and a former fire training area at the 3M Cottage Grove facility in Minnesota (3M 2007b). PFBuS was detected in 60–73% of these samples. Maximum concentrations for these substances were 21,800, 104,000, 3,470, and 139 ng/g, respectively. Levels of PFBuA were only reported for soil in the fire training area; it was detected in 9 out of 11 samples from this location at 0.306–9.07 ng/g. The percent detection of these compounds in sediment from the East and West Cove sites was similar to that in soil. Maximum concentrations of PFOA and PFOS were 1,845 and 65,450 ng/g, respectively. These perfluoroalkyls were also analyzed for in Mississippi River sediment near the Cottage Grove Facility. Levels of these compounds were much greater along the facility shoreline compared to levels in transect samples collected at points crossing the river. Maximum shoreline concentrations for PFOA, PFBuA, PFOS, PFHxS, and PFBuS were 341, 124, 79.0, 11.5, and 29.4 ng/g, respectively. PFHxS, PFBuS, and PFBuA were not detected in any of the transect samples and PFOA was found in only 18%. Although the maximum concentration of PFOS was 3.16 ng/g, it was still detected in 82% of the transect samples.

Table 6-11. Concentrations of Perfluoroalkyls in Soil and Sediment at Fluorochemical Industrial Facilities

	Percent detection and concentration (ng/g)					
Location	PFOA	PFBA	PFOS	PFHxS	PFBuS	Reference
DuPont Washington Works Facility, West Virginia						
Soil						
Boring samples (n=22)						Davis et al. 2007
Percent detected	36%[a]	—	—	—	—	
Minimum	<0.17[a]	—	—	—	—	
Maximum	170[a]	—	—	—	—	
3M Cottage Grove Facility, Minnesota						
Soil						
Boring samples (n=50–108)						3M 2007b
Percent detected	100%	—	95%	90%	60%	
Maximum	21,800	—	104,000	3,470	139	
Fire training area (n=8–11)						3M 2007b
Percent detected	91%	82%	100%	100%	73%	
Maximum	262	11.5	2,948	62.2	24.6	
Sediment						
East and West Cove (n=21–28)						3M 2007b
Percent detected	100%	93%	100%	96%	65%	
Minimum	0.764	ND	40.0	ND	ND	
Maximum	1,845	94.6	65,450	126	9.14	
Mississippi River shoreline (n=84–92)						3M 2007b
Percent detected	70%	44%	80%	28%	29%	
Maximum	341	124	79.0	11.5	29.4	
Mississippi River transect (n=38–40)						3M 2007b
Percent detected	18%	0%	82%	0%	0%	
Maximum	1.09	ND	3.16	ND	ND	

Table 6-11. Concentrations of Perfluoroalkyls in Soil and Sediment at Fluorochemical Industrial Facilities

	Percent detection and concentration (ng/g)					
Location	PFOA	PFBA	PFOS	PFHxS	PFBuS	Reference
3M Decatur Facility, Alabama						
Soil						
On-site former sludge incorporation area (n=357)						3M 2008c
Percent detected	99%	—	—	—	—	
Mean	885–929					
Range	2.91–14,750	—	—	—	—	
On-site background (n=18)						3M 2008c
Percent detected	100%	—	—	—	—	
Mean	3.53–4.1					
Range	1.61–6.03	—	—	—	—	
Off-site soil (n=23)						3M 2008c
Percent detected	100%	—	—	—	—	
Mean	3.68–4.6					
Range	0.72–7.85	—	—	—	—	
Sediment						
On-site sediment (n=8)						3M 2008c
Percent detected	88%	—	—	—	—	
Median	16.8					
Range	1.64–347	—	—	—	—	
Off-site sediment (n=30)						3M 2008c
Percent detected	93%	—	—	—	—	
Range	0.39–2,385	—	—	—	—	

[a]Analyte was reported as APFO.

APFO = ammonium perfluorooctanoate; ND = not detected; PFBA = perfluorobutyric acid; PFBuS = perfluorobutane sulfonic acid; PFHxS = perfluorohexane sulfonic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Paustenbach et al. (2007) estimated PFOA concentrations in environmental media for communities located near the DuPont Washington Works chemical manufacturing facility. From this analysis, the authors concluded that much of the PFOA detected in groundwater near the facility was attributed to deposition to soil surfaces following atmospheric emissions from the plant followed by subsequent leaching into groundwater.

6.4.4 Other Environmental Media

Limited data are available regarding the concentrations of perfluoroalkyl compounds in food. One study has been located that analyzed foods in the United States for PFOS, PFOA, and PFOSA (3M 2001). During this study, over 200 food items were collected from grocery stores in three U.S. test cities having commercial perfluoroalkyl manufacturing or use and from grocery stores in three U.S. control cities that do not have this type of activity. Twelve samples contained perfluoroalkyls above the limit of quantification. Eight of the positive detections were collected in test cities. PFOSA was not detected in any of the food samples. PFOS was detected in four whole milk samples (0.573–0.852 ng/g) and 3 ground beef samples (0.570–0.587 ng/g). PFOA was detected in two ground beef samples (0.504, 1.09 ng/g), two bread samples (0.524, 14.7 ng/g), two apple samples (1.13, 2.35 ng/g), and one green bean sample (0.543 ng/g). The author's state that concentration of 14.7 ng/g measured for PFOA in the one bread sample may have resulted from contamination.

Concentrations of perfluoroalkyls have been reported in foods sampled in Canada, the United Kingdom, and Germany (Food Standards Agency 2006; Fromme et al. 2007b; Tittlemier et al. 2007). Perfluoroalkyls were detected in only 9 out of 54 food composites collected during Canadian Total Diet Studies from 1992 to 2004 (Tittlemier et al. 2007). PFOS was detected in beef steak, ground beef, luncheon meats, marine fish, freshwater fish, and microwave popcorn at concentrations ranging from 0.98–2.7 ng/g, wet weight. PFOA was detected in roast beef, pizza, and microwave popcorn at 0.74–3.6 ng/g, wet weight. PFHpA was detected in pizza and microwave popcorn at 1.5–2.0 ng/g, wet weight. PFNA was detected only in beef steak at 4.5 ng/g, wet weight. PFDeA, PFUA, and PFDoA were analyzed for but not detected in any of the food composites. During the U.K. Food Standards Agency Total Diet Study, PFOS was detected in eggs, sugars and preserves, potatoes, and canned vegetables at 1, 1, 10, and 2 μg/kg, respectively (Food Standards Agency 2006). PFOA was detected only in potatoes at 1 μg/kg. Neither substance was detected in the bread, miscellaneous cereals, carcass meats, offal, meat

products, poultry, fish, oils and fats, green vegetables, other vegetables, fresh fruit, fruit products, beverages, milk, dairy products, or nuts categories. Fromme et al. (2007b) detected PFOS, PFOA, and PFHxS in 33, 45, and 3% of 214 daily duplicate food portions for 31 adults in the city of Munich, Germany. Concentrations were 0.025–1.03 ng/g fresh weight for PFOS, 0.025–118.29 ng/g fresh weight for PFOA, and 0.05–3.03 ng/g fresh weight for PFHxS. Reported 90th percentile values were 0.11 and 0.21 ng/g fresh weight for PFOS and PFOA, respectively (Fromme et al. 2007b).

Limited data are available regarding the levels of perfluoroalkyls in food packaging; however, some measurements have been performed. PFOA was detected in the packaging paper of two microwave popcorn bags at 0.3–4.7 ng/cm^2 uncooked and 0.5–4.3 ng/cm^2 cooked (Sinclair et al. 2007). The mean mass of PFOA in the gas phase of popcorn vapors following popping was 16–17 ng/cm^2. PFHpA, PFNA, PFDeA, PFUA, and PFDoA were detected in one of the bags at 0.4–3.2 ng/cm^2 uncooked and 0.5–4.3 ng/cm^2 cooked; however, these perfluoroalkyls were not detected (<0.2 ng/cm^2) in the second bag. Begley et al. (2005) measured PFOA concentrations of 6–290 μg/kg in microwave popcorn bags. These authors also tested a hamburger wrapper, a sandwich wrapper, a French fry box, and soak-proof paper plates and did not find PFOA above the detection limit in these products. These paper products were not necessarily coated with fluorochemicals. The concentration of PFOA measured in undiluted perfluoro paper coating formulations ranged from 88,000 to 160,000 μg/kg (Begley et al. 2005).

Washburn et al. (2005) measured the concentration of the perfluorooctanoate anion in fluorotelomer treated consumer articles as well as the fluorotelomer formulations used for the treatments. PFOA was detected in mill-treated carpeting (0.2–0.6 mg/kg), carpet-care solution-treated carpeting (0.2–2 mg/kg), treated apparel (<0.02–1.4 mg/kg), treated home textiles (<0.02–1.4 mg/kg), industrial floor waxes and wax removers (0.0005–0.06 mg/kg), latex paint (0.02–0.08 mg/kg), and home and office cleaners (0.005–0.05 mg/kg). The concentrations of PFOA measured in the formulations used for these applications were 30–80, 1–50, <1–40, <1–40, 5–120, 50–150, and 50–150 mg/L, respectively. PFOA was not detected in treated upholstery (<0.034 mg/kg), treated technical textiles (<0.034 mg/kg), treated nonwoven medical garments (<0.034 mg/kg), or stone, tile, and wood sealants (<0.1 mg/kg).

PTFE is a fluoropolymer used in applications such as nonstick cookware coatings and plumbing sealant tape; PFOA has been used as a processing aid in the manufacture of PTFE (DuPont 2008). DuPont states that PFOA is removed from the fluoropolymer material during the baking and curing step of nonstick cookware coatings in a high temperature oven and that there may be trace amounts of residual PFOA in the final coatings (DuPont 2008). Begley et al. (2005) has measured PFOA concentrations of 4–75 μg/kg

in PTFE cookware, 3 µg/kg in PTFE-based dental floss, 4 µg/kg in PTFE-based dental tape, and 1,800 µg/kg in PTFE film/sealant tape. PFOA was not detected in tubing made of a fluoro-ethylene-propene copolymer (Begley et al. 2005).

Studies have been conducted that investigated the release of PFOA from PTFE cookware when heated. Sinclair et al. (2007) reported PFOA release concentrations ranging from 19–287 pg/cm^2 measured using four nonstick frying pans. These concentrations were measured at normal cooking temperatures–within the range of 180–229°C. PFOA was detected in water (7 and 75 ng) boiled for 10 minutes in two out of five non-stick pans (Sinclair et al. 2007). PFOA was not found above the detection limit (0.1 ng/cm^2) during 40 extraction tests on PTFE cookware using an ethanol/water mixture (Washburn et al. 2005). Likewise, Powley et al. (2005) conducted extraction texts on commercial fluoropolymer-treated cookware using water and water/ethanol mixtures at 100 and 125°C. Under simulated cooking conditions, PFOA was not identified above the detection limit of 100 pg/cm^2. Begley et al. (2005) reported that additional PFOA was not generated in the PTFE coating of three empty pans heated to 320°C (DuPont 2008). According to DuPont, the non-stick coating on a pan may begin to deteriorate if the pan is accidentally heated above 348°C, which is well above the maximum recommended cooking temperature of 260°C (DuPont 2008). Although it is possible for an unattended empty pan to reach these high temperatures, overheating non-stick cookware is expected to be prevented in most cases because food oils begin to generate smoke around 190°C (Begley et al. 2005).

Perfluoroalkyl compounds have been identified on both indoor and outdoor window films at urban, suburban, and rural locations near Toronto, Ontario, Canada. The sum of perfluoroalkyls contaminant (ΣPFC) concentrations on outdoor window films ranged from 0.04 to 0.75 pg/cm^2 in winter and from 0.04 to 0.92 pg/cm^2 in summer, with higher values found in urban and suburban locations than in rural locations. Indoors, ΣPFC concentrations on window film ranged from less than the detection limit (which ranged from 25 to 50 pg) to 2.1 pg/cm^2 in winter and from 0.08 to 4.3 pg/cm^2 in summer, although there were no distinct trends between urban and rural for indoor concentrations (Gewurtz et al. 2009).

A comprehensive study that examined 116 articles of commerce (AOC) found perfluorocarboxylic acids, including PFOA, in many commercially available substances, such as carpet care products and waxes (EPA 2009c). Levels of PFOA ranged from nondetectable to 6,750 ng/g, and levels of total perfluorocarboxylic acids (the sum of C5–C12 acids) ranged from nondetectable to 47,100 ng/g. Perfluoroalkyl compounds, including PFOA, have been detected at low levels in personal care products such as cosmetics and sunscreens (Fujii et al. 2013).

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

As a group of compounds, perfluoroalkyls appear to be ubiquitous in human blood based on the widespread detection of these substances in human serum samples (Calafat et al. 2006b, 2007a, 2007b; De Silva and Mabury 2006; Kuklenyik et al. 2004; Olsen et al. 2003b, 2003c, 2004b, 2004c, 2005, 2007a). Tables 6-12 and 6-13 list concentrations of perfluoroalkyl compounds measured in serum samples collected from the general population in the United States. Mean PFOA, PFOS, and PFHxS serum concentrations reported in various studies from the United States were 2.1–9.6, 9.32–55.8, and 1.5–3.9 ng/mL, respectively. Mean concentrations of PFHpA, PFNA, PFDeA, PFUA, PFDoA, PFBuS, PFOSA, Me-PFOSA-AcOH, and Et-PFOSA-AcOH are generally <1 ng/mL in these studies. Biomonitoring data for PFBA in the general population have not been located.

The widespread presence of perfluoroalkyl compounds in blood is well illustrated in studies by Calafat et al. (2007a, 2007b). These authors reported perfluoroalkyl levels in human serum collected during the 1999–2000 and 2003–2004 periods of the National Health and Nutrition Examination Survey (NHANES). The numbers of individuals included in the analyses for each survey period were 1,562 and 2,094, respectively. PFOA, PFOS, PFNA, and PFHxS were detected in 95–100% of serum samples collected during both survey periods. Mean concentrations for PFOA, PFOS, and PFHxS declined by 10–30% in the 2003–2004 survey, while PFNA values doubled from 0.5 to 1.0 ng/mL. NHANES survey data from 2005–2006, 2007–2008, and 2009–2010, have generally continued to show declining levels of PFOA and PFOS in human serum samples (CDC 2014). A dramatic difference in detection frequency was observed for PFOSA, Me-PFOSA-AcOH, and Et-PFOSA-AcOH which were widely detected (91–100%) during the 1999–2000 survey period but were present in only 3.4–27.5% of samples collected during the 2003–2004 survey period. PFDoA and PFBuS were detected in <1% of the NHANES samples. Olsen et al. (2008) reported a nearly 60% decline in PFOS blood levels when comparing data from 2001 to 2006 American Red Cross surveys of participants.

The widespread detection of perfluoroalkyl compounds in the blood of U.S. residents demonstrates that exposure of the general population to these substances is common. Levels of perfluoroalkyl compounds have been measured in indoor air, outdoor air, dust, food, surface water, and various consumer products. Possible exposure pathways have been proposed; however, the relative importance of these pathways including their association with the accumulation of perfluoroalkyls in blood remains unclear (Apelberg

Table 6-12. Concentrations of PFOA and PFOS in Human Serum Collected in the United States

	Detection and concentration (ng/mL [ppb])[a]		
Location	PFOA	PFOS	Reference
U.S. residents—NHANES			
1999–2000 (n=1,562)			Calafat et al. 2007a
Percent >LOD	100%	100%	
Geometric mean	5.2	30.4	
95th percentile	11.9	75.6	
2003–2004 (n=2,094)			Calafat et al. 2007b
Percent >LOD	99.7%	99.9%	
Geometric mean	3.9	20.7	
95th percentile	9.8	54.6	
U.S. residents—NHANES			
Percent >LOD	NR	NR	
Geometric mean	3.07	9.32	
95th percentile	7.50	32.0	
U.S. residents			Calafat et al. 2006b
1990–2002 (n=23)			
Percent >LOD	100%	100%	
Geometric mean	9.6	30.0	
95th percentile	23.0	52.3	
U.S. blood donors			Olsen et al. 2003b
2000–2001 (n=645)			
Percent >LLOQ	100%	92.5%	
Geometric mean	4.6	34.9	
95th percentile[b]	12.1	88.5	
Maximum	52.3	1,656.0	
U.S. residents			Olsen et al. 2003c
(n=24)			
Percent >LLOQ	Not reported	98%	
Geometric mean	2.5	14.7	
Minimum	<3.0	<6.1	
Maximum	7.0	58.3	
Midwestern United States			De Silva and Mabury 2006
2004–2005 (n=16)[c]			
Percent detected	100%	Not detected	
Mean	4.4		
Maximum	8.6		

Table 6-12. Concentrations of PFOA and PFOS in Human Serum Collected in the United States

	Detection and concentration (ng/mL [ppb])[a]		
Location	PFOA	PFOS	Reference
Minneapolis-St. Paul blood donors (plasma)			Olsen et al. 2007b
2005 (n=40)			
Percent >LLOQ	95%	100%	
Geometric mean	2.2	15.1	
75th percentile	3.5	20.2	
Maximum	4.7	36.9	
Atlanta, Georgia			Kuklenyik et al. 2004
2003 (n=20)			
Percent >LOD	100%	100%	
Mean	4.9	55.8	
Minimum	0.2	3.6	
Maximum	10.4	164.0	
Seattle, Washington elderly individuals			Olsen et al. 2004c
(n=238)			
Percent >LLOQ	99.2%	99.5%	
Geometric mean	4.2	31.0	
95th percentile[b]	9.7	84.1	
Maximum	16.7	175.0	
Washington County, Maryland			Olsen et al. 2005
1974 (n=178)			
Percent >LLOQ	71%	100%	
Geometric mean	2.1	30.1	
75th percentile	3.0	40.2	
1989 (n=178)			
Percent >LLOQ	99%	100%	
Geometric mean	5.5	33.3	
75th percentile	6.7	44.0	

Table 6-12. Concentrations of PFOA and PFOS in Human Serum Collected in the United States

	Detection and concentration (ng/mL [ppb])[a]		
Location	PFOA	PFOS	Reference
Boston, Massachusetts; Charlotte, North Carolina; Hagerstown, Maryland; Los Angeles, California; Minneapolis-St. Paul, Minnesota; Portland, Oregon			Olsen et al. 2008
2006 (n=600)	99%	99%	
Percent >LLOQ			
Geometric mean	3.4	14.5	
95th percentile CI geometric mean	3.3–3.6	13.9–15.2	

[a]"Less than" values indicate that the concentration was reported as below the LOD or LLOQ. For cases where samples had concentrations below the limit of detection or lower limit of quantification, a value between zero and the LOD or LLOQ was assigned when calculating the mean concentration.
[b]Reported as bias-corrected estimates.
[c]One sample purchased separately with no origin information supplied.

CI = confidence interval; LLOQ = lower limit of quanitification; LOD = limit of detection; NR = not reported; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Table 6-13. Concentrations of Other Perfluoroalkyls in Human Serum Collected in the United States

	Detection and concentration (ng/mL [ppb])[a]									
Sample population	PFHpA	PFNA	PFDeA	PFUA	PFDoA	PFBuS	PFHxS	PFOSA	Me-PFOSA-AcOH	Et-PFOSA-AcOH
U.S. residents NHANES										
1999–2000 (n=1,562) (Calafat et al. 2007a)										
Percent >LOD	10%	95%	25%	12%	<1%	—	100%	100%	96%	91%
Geometric mean	<0.4	0.5	<0.2	<0.2	<0.2		2.1	0.4	1.0	0.6
95th percentile	NR	1.7	0.5	NR	NR		8.7	1.4	3.2	2.2
2003–2004 (n=2,094) (Calafat et al. 2007b)										
Percent >LOD	6.2%	98.8%	31.3%	9.7%	<0.1%	<0.4%	98.3%	22.2%	27.5%	3.4%
Geometric mean	<0.3	1.0	<0.3	<0.3	<1.0	<0.4	1.9	<0.2	<0.6	<0.4
95th percentile	0.4	3.2	0.8	0.6	<1.0	<0.4	8.3	0.2	1.3	<0.4
2005–2006 (n=2,120) (CDC 2013)										
Percent >LOD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Geometric mean	—	1.09	0.355	—	—	—	1.67	—	0.41	—
95th percentile	0.7	3.6	1.5	0.7	<LOD	0.1	8.3	0.3	1.57	0.3
2007–2008 (n=2,100) (CDC 2013)										
Percent >LOD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Geometric mean	—	1.22	0.286	—	—	—	1.95	—	0.301	—
95th percentile	0.5	3.28	0.9	0.6	<LOD	<LOD	9.8	<LOD	1.31	<LOD
2009–2010 (n=2,233) (CDC 2013)										
Percent >LOD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Geometric mean	—	1.26	0.279	0.172	—	—	1.66	—	0.189	—
95th percentile	0.2	3.77	0.9	0.9	<LOD	<LOD	6.9	<LOD	0.96	0.1
U.S. residents (Calafat et al. 2006b)										
1990–2002 (n=23)										
Percent >LOD	0%	8.7%	0%	13%	0%	—	91.3%	26.1%	13%	56.5%
Geometric mean	NA	<0.3	NA	<0.3	NA		1.6	<0.4	<0.6	<0.4
95th percentile	NA	0.3	NA	1.3	NA		2.7	0.7	1.9	2.5

Table 6-13. Concentrations of Other Perfluoroalkyls in Human Serum Collected in the United States

	Detection and concentration (ng/mL [ppb])[a]									
Sample population	PFHpA	PFNA	PFDeA	PFUA	PFDoA	PFBuS	PFHxS	PFOSA	Me-PFOSA-AcOH	Et-PFOSA-AcOH
U.S. blood donors (Olsen et al. 2003b)										
2000–2001 (n=645)										
Percent >LLOQ	—	—	—	—	—	—	64%	2%	49%	58%
Geometric mean							1.9	NR	<1.8	<2.8
95th percentile[b]							9.5	NR	5.0	7.6
Maximum							66.3	NR	16.4	60.1
U.S. residents (Olsen et al. 2003c)										
(n=24)										
Geometric mean	—	—	—	—	—	—	1.8	3.0	—	—
Minimum							<1.2	<1.3		
Maximum							5.9	22.1		
Midwestern United States (De Silva and Mabury 2006)										
2004–2005 (n=16)										
Percent detected	—	100%	100%	13%	0%	—	—	—	—	—
Mean		0.77	0.17	NR	NA					
Maximum		1.2	0.25	0.067	NA					
Atlanta, Georgia (Kuklenyik et al. 2004)										
2003 (n=20)										
Percent >LOD	10%	100%	75%	85%	10%	—	100%	75%	100%	90%
Mean[b]	<0.3	2.6	0.7	0.8	<1		3.9	0.34	1.7	0.9
Maximum	8.5	3.9	1.2	1.4	1.6		11.2	0.7	5.2	1.4
Seattle, Washington (Olsen et al. 2004c)										
(n=238)										
Percent >LLOQ	—	—	—	—	—	—	76%	"Few"	65%	52%
Geometric mean							2.2	NR	1.2	<1.6
95th percentile[b]							8.3	NR	3.8	7.8
Maximum							40.3	NR	6.6	21.1

Table 6-13. Concentrations of Other Perfluoroalkyls in Human Serum Collected in the United States

	Detection and concentration (ng/mL [ppb])[a]									
Sample population	PFHpA	PFNA	PFDeA	PFUA	PFDoA	PFBuS	PFHxS	PFOSA	Me-PFOSA-AcOH	Et-PFOSA-AcOH
Washington County, Maryland (Olsen et al. 2005)										
1974 (n=178)										
Percent >LLOQ	—	—	—	—	—	—	63%	0%	4%	33%
Geometric mean							1.5	NA	0.5	1.2
75th percentile							2.5	NA	<1.0	1.8
1989 (n=178)										
Percent >LLOQ	—	—	—	—	—	—	82%	0%	38%	93%
Geometric mean							2.5	NA	0.8	3.6
75th percentile							1.6	NA	1.3	4.7

[a]"Less than" values indicate that the concentration was reported as below the LOD or LLOQ. For cases where samples had concentrations below the limit of detection or lower limit of quantification, a value between zero and the LOD or LLOQ was assigned when calculating the mean concentration.
[b]Reported as bias-corrected estimates.
[c]Arithmetic mean of positive concentrations.

Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid; LLOQ = lower limit of quanitification; LOD = limit of detection; Me-PFOSA-AcOH = 2-(N-methyl-perfluorooctane sulfonamide) acetic acid; NA = not applicable; NR = not reported; PFBuS = perfluorobutane sulfonic acid; PFDeA = perfluorodecanoic acid; PFDoA = perfluorododecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOSA = perfluorooctane sulfonamide; PFUA = perfluoroundecanoic acid

et al. 2007b; Begley et al. 2005; Calafat et al. 2006b; Trudel et al. 2008; Washburn et al. 2005). For populations that have elevated levels of perfluoroalkyls in water supplies, the primary route of exposure is expected to be ingestion of contaminated drinking water. Using a stratified random sample of residents in the Little Hocking Water district in Ohio between July 2004 and February 2005, Emmett et al. (2006a) reported median serum PFOA levels of 329 ng/mL in residents' drinking water, with a mean PFOA concentration of 3.55ng/mL. Median serum PFOA levels were 371 ng/mL in residents for whom this was the only residential water source, and 71 ng/mL in those who used bottled, cistern, or spring water. Increased serum PFOA was associated with increasing number of drinks of tap water daily and also with increasing use of water for making soups and stews and in-home canning of fruits and vegetables. Use of a carbon water filter reduced PFOA levels by about 25%. In a follow-up study, 231 study participants in the Little Hocking Water District were evaluated 15 months later with 88% using bottled water exclusively; 8% had made other changes to their ingestion of residential water including use of activated carbon water filters. PFOA levels had decreased an average of 26% from the initial levels (Emmett et al. 2009).

A study conducted by the Minnesota Department of Health reported higher PFOA and PFOS serum levels in residents of two communities with contaminated water supplies as compared to the general population (MN EPHT 2009). Similar findings have been reported by Steenland et al. (2009) in a study of residents in six water districts in the mid-Ohio Valley located near the DuPont Washington Works facility in Washington, West Virginia. The Minnesota Department of Health instituted a program to reduce levels of perfluoroalkyls in drinking water that included using granulated activated carbon (GAC) filters for home use in areas where private wells showed high levels of contamination and large GAC filters for the municipal water supplies (MN EPHT 2009). In two Mid-Ohio Valley locations with PFOA-contaminated drinking water, blood serum levels of PFOA in residents declined significantly following the implementation of GAC filtration of the public water supply (Bartell et al. 2010). The Lubeck, West Virginia and Little Hocking, Ohio public water systems, which were contaminated with PFOA from the DuPont Washington Works facility, began GAC treatment to remove PFOA from the potable water supply in 2007. The average decrease in serum PFOA levels for Lubeck, West Virginia residents primarily consuming public water at home (n=130) was 26% a year after treatment began. Similar trends were reported for residents of Little Hocking, Ohio. The average decrease in PFOA serum levels for residents primarily consuming public water (n=39) was about 11% 6 months after treatment began (Bartell et al. 2010).

Trudel et al. (2008) provide a thorough analysis of general population exposure to PFOS and PFOA based on the available information and have proposed the following possible exposure pathways: food and water consumption, ingestion of house dust, hand-to-mouth transfer from treated carpets, migration into food from PFOA-containing paper or cardboard, inhalation of indoor and ambient air, and inhalation of impregnation spray aerosols. Other pathways proposed to be less significant included oral exposure from hand-to-mouth contact with clothes and upholstery, migration into food prepared with PTFE-coated cookware, dermal exposure from wearing treated clothes, deposition of spray droplets on skin while impregnating, skin contact with treated carpet and upholstery, and deposition of dust onto skin (Trudel et al. 2008). The strong correlation between PFOA and PFOS concentrations in human serum samples indicates that common exposure pathways for these two substances are possible (Calafat et al. 2007a).

In order to estimate human uptake and the major pathways for human exposure to PFOS and PFOA, reported levels of these compounds in various environmental media, including food and consumer products, were analyzed with respect to product use patterns, personal activity patterns, and personal intake rates (Trudel et al. 2008). For PFOS, the major exposure pathways in a high-exposure scenario were proposed to be food and water ingestion, dust ingestion, and hand-to-mouth transfer from mill-treated carpets. Relative contributions of these pathways to the total uptake of PFOS in adults were estimated to be approximately 80, 15, and 5%, respectively (Trudel et al. 2008). For PFOA, the major exposure pathways in a high-exposure were proposed to be oral exposure resulting from migration from paper packaging and wrapping into food, general food and water ingestion, inhalation from impregnated clothes, and dust ingestion. Relative contributions of these pathways to the total uptake of PFOA in adults were estimated to be approximately 60, 15, 15, and 10%, respectively (Trudel et al. 2008). Major exposure pathways for the intermediate and low exposure scenarios were proposed to be through food and drinking water (PFOA and PFOS) and ingestion of house dust (PFOA only).

Based on these proposed exposure pathways, adult uptake doses estimated for low, medium, and high exposure scenarios were approximately 7, 15, and 30 ng/kg body weight/day, respectively, for PFOS and approximately 0.4, 2.5, and 41–47 ng/kg body weight/day, respectively, for PFOA (Trudel et al. 2008). The estimated uptake values were similar for men and women.

Fromme et al. (2009) assessed human exposure to perfluoroalkyls for adults in the general population of western countries. These authors determined average daily exposure levels of 1.6 ng/kg body weight/day for PFOS and 2.9 ng/kg body weight/day for PFOA. Upper daily exposure levels were determined to be 8.8 ng/kg body weight/day for PFOS and 12.6 ng/kg body weight/day for PFOA. These authors

concluded that the oral route, especially diet, was the primary route of exposure to perfluoroalkyls (Fromme et al. 2007a, 2007b, 2009). The geometric mean adult daily intakes for PFOA and PFOS were estimated as 92.6 and 83.3 ng/day, respectively, for residents in Kansai, Japan and 53.7 and 63.8 ng/day, respectively, for residents in Tohoku, Japan (Harada and Koizumi 2009). The most important exposure pathway for both compounds was food ingestion.

Limited information has been located regarding pathways of human exposure to PFBA, PFHpA, PFNA, PFUA, PFDoA, PFBuS, PFHxS, PFOSA, Me-PFOSA-AcOH, and Et-PFOSA-AcOH.

Limited monitoring data are available for PFBA. Monitoring efforts conducted in Washington County, Minnesota near the 3M Cottage Grove Facility revealed widespread contamination of this substance in the groundwater of that area in 2006. This compound has since also been detected along with PFOA, PFOS, PFHxS, and PFBuS in municipal drinking water in Washington County (Agency for Toxic Substances and Disease Registry 2008). Chang et al. (2008a) measured concentrations of PFBA in the serum of 127 former employees and 50 current employees of the 3M Cottage Grove Facility in Minnesota. PFBA serum concentrations were below the detection limit in 73.2% of the former employees and 68.0% of the current employees. Only 4% of the serum samples contained PFBA above 2 ng/mL with maximum concentrations of 6.2 ng/mL for the former employees and 2.2 ng/mL for the current employees.

Another possible source for perfluoroalkyls in human blood is through uptake of precursor compounds and then conversion of these within the human body (Trudel et al. 2008). For example, Me-PFOSA-AcOH and Et-PFOSA-AcOH are the oxidation products of 2-(N-methyl-per-fluorooctane sulfonamido) ethanol and 2-(N-ethyl-per-fluorooctane sulfonamido) ethanol, which have been used in surface treatment applications (Calafat et al. 2006a). Concentrations of Me- and Et-PFOSA-AcOH measured in human serum may have resulted from exposure of individuals to these perfluoroalkyl sulfonamido ethanols and then conversion of the ethanols to the perfluoroalkyl sulfonamido acetates within the body.

Levels of perfluoroalkyl compounds measured in the blood of occupationally exposed individuals are listed in Table 6-14. 3M has estimated doses for various on-site exposure scenarios based on monitoring information collected at the Decatur Facility in Alabama (3M 2008c). Occupational exposure scenarios included groundskeeper/maintenance worker and construction/utility worker exposed to on-site soils, surface water, and sediment. According to 3M, estimated on-site exposure to PFOA ranges from $3.2x10^{-6}$ to 2.4 ng/kg/day, with the highest estimated exposure corresponding to construction/utility

Table 6-14. Concentrations of PFOA, PFOS, and PFHxS in Human Serum for Occupationally Exposed Individuals

	Concentration (µg/mL [ppm])			
Location	PFOA	PFOS	PFHxS	Reference
Decatur, Alabama				
1993 (n=111)	0.00–80.00; 89% <8.92	—	—	Olsen et al. 1998
1995 (n=80)	0.00–114.10; 81% <8.20	—	—	Olsen et al. 1998
1995 (n=90)	—	96% <6.00	—	Olsen et al. 1999
1997 (n=84)	—	94% <6.00	—	Olsen et al. 1999
2000 (n=263)	1.78; 0.04–12.70	1.32; 0.06–10.06	—	Olsen et al. 2003a
1999–2004 (n=26)[a]				Olsen et al. 2007a
Initial	0.691 (0.072–5.1)	0.799 (0.145–3.49)	0.290 (0.016–1.30)	
Final	0.262 (0.017–2.44)	0.403 (0.037–1.74)	1.85 (0.01–0.791)	
Cottage Grove, Minnesota				
1993 (n=111)	0.00–80.00; 88% <8.92	—	—	Olsen et al. 2000
1995 (n=80)	0.00–114.1; 81% <8.20	—	—	Olsen et al. 2000
1997 (n=74)	0.05–81.35; 85% <7.66	—	—	Olsen et al. 2000
2000 (n=122)	4.63 (0.01–92.03)	0.86 (0.03–4.79)	—	Olsen and Zobel 2007
Washington Works, Little Hocking, Ohio				
2004–2005				Emmett et al. 2006a
No occupational exposure (n=312)	0.423 (0.175–0.537)[b]	—	—	
Potential occupational exposure (n=48)	0.406 (0.168–0.623)[b]	—	—	
Substantial occupational exposure (n=18)	0.824 (0.422–0.999)[b]	—	—	
Antwerp, Belgium				
1995 (n=88)	—	75% <6.00	—	Olsen et al. 1999
1997 (n=65)	—	86% <6.00	—	Olsen et al. 1999
2000 (n=255)	0.84 (0.01–7.04)	0.80 (0.04–6.24)	—	Olsen et al. 2003a
Miteni, Trissino, Italy				
2007				
Current occupational exposure (n=39)	5.71[c] (0.20–47.04)	—	—	Costa et al. 2009

Table 6-14. Concentrations of PFOA, PFOS, and PFHxS in Human Serum for Occupationally Exposed Individuals

	Concentration (µg/mL [ppm])			
Location	PFOA	PFOS	PFHxS	Reference
Former occupational exposure (n=11)	4.43[c] (0.53–18.66)	—	—	Costa et al. 2009
2000 (n=25)	11.92[c] (1.54–86.3)	—	—	Costa et al. 2009
2001 (n=42)	11.07[c] (0.73–91.9)	—	—	Costa et al. 2009
2002 (n=46)	10.15[c] (0.34–91.9)	—	—	Costa et al. 2009
2003 (n=41)	6.25[c] (0.38–74.7)	—	—	Costa et al. 2009
2004 (n=34)	6.82[c] (0.54–46.3)	—	—	Costa et al. 2009
2006 (n=49)	5.27[c] (0.54–41.9)	—	—	Costa et al. 2009
2007 (n=50)	3.89[c] (0.20–47.0)	—	—	Costa et al. 2009
Washington Works				
2004				
Current occupational exposure (n=259)	0.494 (0.0174–9.550)	—	—	Sakr et al. 2007b
Intermittent current occupational exposure (n=160)	0.176 (0.0081–2.070)	—	—	Sakr et al. 2007b
Past occupational exposure (n=264)	0.195 (0.0086–2.590)	—	—	Sakr et al. 2007b
No occupational exposure (n=342)	0.114 (0.0046–0.963)	—	—	Sakr et al. 2007b

[a]Data include results from three retirees from the 3M plant in Cottage Grove, Minnesota.
[b]Reported as the interquartile range.
[c]Reported as the median value.

PFHxS = perfluorohexane sulfonic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

workers engaged in projects that involve contact with soil from an onsite field. Individuals who perform jobs that require frequent contact with perfluoroalkyl containing products, such as fire fighters, waste handlers, and individuals who install and treat carpets, are also expected to have occupational exposure to these substances (Emmett et al. 2006a). However, Emmett et al. (2006a) determined that levels of PFOA in the serum of these types of individuals were only slightly higher than the non-occupational exposure group (388 ng/mL compared to 329 ng/mL, respectively) while serum levels in workers at a fluoropolymer manufacturing facility were much higher (775 ng/mL).

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Perfluoroalkyl compounds have been detected in childhood serum samples, human breast milk, and umbilical cord blood; reported concentrations are listed in Tables 6-15 and 6-16. Measurements of perfluoroalkyl compounds in amniotic fluid, meconium, neonatal blood, or other tissues have not been located.

A few studies are available that report serum levels of perfluoroalkyls measured in children. Calafat et al. (2007a, 2007b) reported perfluoroalkyl serum concentrations measured in 543–640 adolescents who make up the 12–19-year-old age subpopulation in the 1999–2000 and 2003–2004 NHANES surveys. Olsen et al. (2003a) measured PFOA, PFOS, PFHxS, PFOSA, Me-PFOSA-AcOH, and Et-PFOSA-AcOH in the serum of 598 children of ages 2–12 from various locations in the United States who have been diagnosed with group A streptococcal infections. Mean serum concentrations of perfluoroalkyl compounds

Table 6-15. Percent Detection and Levels of PFOA and PFOS in Children's Serum, Umbilical Cord Blood, and Breast Milk

	Detection and concentration (ng/mL [ppb])		
Location	PFOA	PFOS	Reference
Serum			
U.S. adolescents—NHANES (ages 12–19)			
1999–2000 (n=543)			Calafat et al. 2007a
Percent >LOD	100%	100%	
Geometric mean	5.5	29.1	
95th percentile	11.2	56.8	
2003–2004 (n=640)			Calafat et al. 2007b
Percent >LOD	99.7%[a]	99.9%[a]	
Geometric mean	3.9	19.3	
95th percentile	8.6	42.2	
2005–2006 (n=640)			CDC 2013
Percent >LOD	NR	NR	
Geometric mean	3.59	15.0	
95th percentile	8.40	38.5	
2007–2009 (n=357)			CDC 2013
Percent >LOD	NR	NR	
Geometric mean	3.91	11.3	
95th percentile	7.30	28.0	
2009–2010 (n=364)			CDC 2013
Percent >LOD	NR	NR	
Geometric mean	2.74	6.84	
95th percentile	5.00	18.1	
U.S. children (ages 2–12)			
1994–1995 (n=598)			Olsen et al. 2004b
Percent >LLOQ	97–99%	100%	
Geometric mean	4.9	37.5	
95th percentile[b]	10	89	
U.S. Children (ages 6–11)			Kato et al. 2009b
2001–2002 (n=936)			
Percent >LLOQ	NR	NR	
Arithmetic mean	6.1–7.6	30.45–42.45	
95th percentile	95th percentile	36.51–48.51	

Table 6-15. Percent Detection and Levels of PFOA and PFOS in Children's Serum, Umbilical Cord Blood, and Breast Milk

	Detection and concentration (ng/mL [ppb])		
Location	PFOA	PFOS	Reference
Umbilical cord blood			
Baltimore THREE Study			Apelberg et al. 2007a, 2007b
Cord serum (n=299)			
Percent >LOD	100%	99%	
Geometric mean	1.6	4.9	
Minimum	0.3	<0.2	
Maximum	7.1	34.8	
Maternal serum (n=293)			
Median	1.4–1.6	4.1–5.0	
Germany			Midasch et al. 2007
Cord plasma (n=11)			
Percent detected	100%	100%	
Median	3.4	7.3	
Maternal plasma (n=11)			
Percent detected	100%	100%	
Median	2.6	13.0	
Danish National Birth Cohort			Fei et al. 2007
Cord blood (n=50)			
Mean	3.7	11.0	
Maternal blood (n=200)			
Mean	4.5	29.9	
Japan			Inoue et al. 2004b
Cord serum (n=15)			
Percent detected	0%	100%	
Minimum	<0.5	1.6	
Maximum	No data	5.3	
Maternal serum (n=15)			
Percent detected	20%	100%	
Minimum	<0.5	4.9	
Maximum	2.3	17.6	

Table 6-15. Percent Detection and Levels of PFOA and PFOS in Children's Serum, Umbilical Cord Blood, and Breast Milk

	Detection and concentration (ng/mL [ppb])		
Location	PFOA	PFOS	Reference
Breast milk			
Massachusetts (n=45)			Tao et al. 2008
Milk			
Percent >LOQ	89%	96%	
Median	0.0361	0.106	
Minimum	<0.0301	<0.032	
Maximum	0.161	0.617	
Sweden (n=12)			Kärrman et al. 2007
Milk			
Percent >LOD	8%[c]	100%	
Minimum	<0.209	0.060	
Maximum	0.492	0.470	
Maternal serum			
Percent >LOD	100%	100%	
Minimum	2.4	8.2	
Maximum	5.3	48.0	
China (n=19)			So et al. 2006b
Percent >LOD	100%	100%	
Minimum	0.047	0.045	
Maximum	0.210	0.360	
Germany/Hungary (n=70)			Völkel et al. 2008
Percent >LOQ	16%	100%	
Minimum	<0.200	0.028	
Maximum	0.460	0.639	

[a]Percent detection for the adolescent age group was not specified for the 2003–2004 NHANES samples. Percentages listed here are for the total sample population.
[b]Reported as bias-corrected estimates.
[c]All 12 samples were above the detection limit (0.01 ng/mL); however, levels were only reported for one sample due to a high blank level for this substance (0.209 ng/mL).

LLOQ = lower limit of quantification; LOD = limit of detection; LOQ = limit of quantification; NR = not reported; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Table 6-16. Percent Detection and Levels of Other Perfluoroalkyls in Children's Serum, Umbilical Cord Blood, and Breast Milk

	Detection and concentration (ng/mL [ppb])[a]									
Sample population	PFHpA	PFNA	PFDeA	PFUA	PFDoA	PFBuS	PFHxS	PFOSA	Me-PFOSA-AcOH	Et-PFOSA-AcOH
Serum										
U.S. NHANES (ages 12–19)										
1999–2000 (n=543) (Calafat et al. 2007a)										
Percent >LOD	10%[a]	96%	15%	12%[a]	<1%[a]	—	100%	100%	100%	98%
Geometric mean	—	0.5	<0.2	—	—	—	2.7	0.4	1.3	0.8
95th percentile	—	1.1	0.5	—	—	—	12.9	1.5	3.7	2.4
2003–2004 (n=640) (Calafat et al. 2007b)										
Percent >LOD	6.2%[a]	98.8%[a]	31.3%[a]	9.7%[a]	<0.1%[a]	<0.4%[a]	98.3%[a]	22.2%[a]	27.5%[a]	3.4%[a]
Geometric mean	<0.3	0.9	<0.3	<0.3	<1.0	<0.4	2.4	<0.2	<0.6	<0.4
95th percentile	0.5	2.7	0.7	<0.3	<1.0	<0.4	13.1	0.3	1.4	<0.4
2005–2006 (n=640) (CDC 2013)										
Percent >LOD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Geometric mean	—	0.929	0.295	—	—	—	2.09	—	0.432	—
95th percentile	1.10	2.7	0.8	0.5	<LOD	0.1	14.1	0.3	1.48	0.2
2007–2008 (n=357) (CDC 2013)										
Percent >LOD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Geometric mean	—	0.929	0.295	—	—	—	2.09	—	0.432	—
95th percentile	1.10	2.7	0.8	0.5	<LOD	0.1	14.1	0.3	1.48	0.2
2009–2010 (n=357) (CDC 2013)										
Percent >LOD	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Geometric mean	—	1.1	0.22	—	—	—	2.03	—	0.225	—
95th percentile	0.4	2.62	0.6	0.4	<LOD	<LOD	12.3	<LOD	0.87	<LOD

Table 6-16. Percent Detection and Levels of Other Perfluoroalkyls in Children's Serum, Umbilical Cord Blood, and Breast Milk

	Detection and concentration (ng/mL [ppb])[a]									
Sample population	PFHpA	PFNA	PFDeA	PFUA	PFDoA	PFBuS	PFHxS	PFOSA	Me-PFOSA-AcOH	Et-PFOSA-AcOH
U.S. children (ages 2–12)										
1994–1995 (n=598) (Olsen et al. 2004b)										
Percent >LLOQ	—	—	—	—	—	—	85%	14%	77%	92%
Geometric mean	—	—	—	—	—	—	4.5	<2.0	1.9	3.3
95th percentile[b]	—	—	—	—	—	—	65	<2.0	12	10
Umbilical cord blood										
Baltimore THREE Study (Apelberg et al. 2007a, 2007b)										
Cord serum (n=299)										
Percent >LOD	2%	—	24%	34%	5%	3%	—	26%	40%	1%
Minimum	<0.4	—	<0.2	<0.2	<0.2	<0.1	—	<0.05	<0.2	<0.2
Maximum	2.6	—	1.1	1.9	1.7	0.2	—	0.8	1.8	0.5
Japan (Inoue et al. 2004b)										
Cord serum (n=15)										
Percent detected	—	—	—	—	—	—	—	0%	—	—
Maternal serum (n=15)										
Percent detected	—	—	—	—	—	—	—	0%	—	—
Breast milk										
Massachusetts (n=45) (Tao et al. 2008)										
Milk										
Percent >LOQ	<1%	64%	<1%	<1%	<1%	<1%	51%	—	—	—
Minimum	<0.010	<0.0052	<0.00772	<0.00499	<0.00440	<0.0100	<0.0120	—	—	—
Maximum	0.0234	0.0184	0.0111	0.00884	0.00974	0.0198	63.8	—	—	—

Table 6-16. Percent Detection and Levels of Other Perfluoroalkyls in Children's Serum, Umbilical Cord Blood, and Breast Milk

	Detection and concentration (ng/mL [ppb])[a]									
Sample population	PFHpA	PFNA	PFDeA	PFUA	PFDoA	PFBuS	PFHxS	PFOSA	Me-PFOSA-AcOH	Et-PFOSA-AcOH
Sweden (n=12) (Karrman et al. 2007a)										
Milk										
Percent >LOD	—	17%	0%	0%	—	—	100%	67%	—	—
Minimum	—	<0.005	<0.008	<0.005	—	—	0.031	<0.007	—	—
Maximum	—	0.020	<0.008	<0.005	—	—	0.172	0.030	—	—
Maternal serum		—				—	—			—
Percent >LOD	—	100%	100%	100%	—	—	100%	75%	—	—
Minimum	—	0.43	0.27	0.20	—	—	1.8	<0.10	—	—
Maximum	—	2.5	1.8	1.5	—	—	11.8	0.49	—	—
China (n=19) (So et al. 2006b)										
Percent >LOD	37%	100%	100%	100%	—	11%	100%	—	—	—
Minimum	<0.005	0.01	0.0038	0.0091	—	<0.001	0.004	—	—	—
Maximum	0.0067	0.062	0.011	0.056	—	0.0025	0.10	—	—	—

[a]Percent detection for the adolescent age group was not specified for these samples. Percentages listed here are for the total sample population.
[b]Reported as bias-corrected estimates.

Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid; LLOQ = lower limit of quantification; LOD = limit of detection; Me-PFOSA-AcOH = 2-(N-methyl-perfluorooctane sulfonamide) acetic acid; ND = no data; NR = not reported; PFBuS = perfluorobutane sulfonic acid; PFDeA = perfluorodecanoic acid; PFDoA = perfluorododecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOSA = perfluorooctane sulfonamide; PFUA = perfluoroundecanoic acid

measured in children from these studies are similar to mean concentrations reported for adults (Calafat et al. 2007a, 2007b; Olsen et al. 2003a). For example, geometric mean concentrations of PFOA and PFOS measured during the NHANES surveys were 3.9–5.5 and 19.3–29.1 ng/mL, respectively, in adolescent serum and 3.9–5.2 and 20.7–30.4 ng/mL, respectively, in serum of the total population. Emmett (2006a) found that 2–5-year-old children had a higher serum PFOA (median 600 ng/mL) in the Little Hocking Water Association district compared with residents in all other age groups (median 321 ng/dL) except for the group aged >60 years, whose levels were similar to those in young children. Several factors may have contributed to the observed high levels in children: infants and young children proportionally drink more water per kg of body weight than adults; children (and also the elderly) tend to spend more time at home with exclusive use of residential water than other age groups; and trans-placental and breast milk exposures could also contribute to levels in children.

Kato et al. (2009b) reported serum levels in children aged 3–5 and 6–11 years from the 2001–2002 NHANES survey for PFNA, PFOA, PFOS, and PFOSA. Highest levels were typically observed for PFOS. The least square mean (LSM is equivalent to arithmetic mean) serum concentrations for PFOS ranged from 30.45 ng/mL for Mexican Americans to 42.45 ng/mL for non-Hispanic whites aged 6–11 years (Kato et al. 2009b). The LSM for PFOA ranged from 6.1 ng/mL for Mexican Americans to 7.6 ng/mL for non-Hispanic whites aged 6–11 years. Among 3–5 year olds, specific data from pooled samples were only presented for PFNA. The LSM serum PFNA serum concentrations for this age group were 0.9, 1.2, and 0.6 ng/mL for non-Hispanic whites, non-Hispanic blacks, and Mexican Americans, respectively (Kato et al. 2009b).

Blood serum levels of PFOA, PFOS, and PFHxS obtained in 2006–2007 from children residing in Australia were reported by Toms et al. (2009). The highest levels tended to occur for PFOS. Mean PFOS serum levels (combined male and female) ranged from 7.0 ng/mL for infants 0–0.5 years of age to 18.3 ng/mL for 6–9 year olds while mean PFOA serum levels ranged from 4.5 ng/mL for infants 0–0.5 years of age to 8.2 ng/mL for 6–9 year olds. Mean serum PFHxS levels ranged from 0.9 ng/mL for infants 0–0.5 years of age to 5.8 ng/mL for 6–9 year olds (Toms et al. 2009).

Although mean serum concentrations of perfluoroalkyl compounds are reported to be similar for older children (12–19 years of age) and adults, estimated 95th percentile values of PFHxS measured in childhood serum were noted to be higher than values estimated for adults. Olsen et al. (2003a) reported bias-corrected 95th percentile estimates of 65 ng/mL for PFHxS in the serum of children ages 2–12. This value is higher than bias-corrected 95th percentile estimates of 9.5 and 8.3 ng/mL based on PFHxS

measurements in the serum of 645 U.S. adult blood donors and 238 elderly individuals from the Seattle, Washington area, respectively (Olsen et al. 2003b, 2004b, 2004c). The difference is less extreme in the NHANES data, with PFHxS 95th percentile values of 12.9–13.1 ng/mL reported for children compared to values of 8.3–8.7 ng/mL reported for the total population. Olsen et al. (2004b) also noted statistically higher levels of Me-PFOSA-AcOH measured in children citing estimated 95th percentile values of 12.0, 5.0, and 3.8 ng/mL for serum concentrations of this substance measured in children, adult donors, and elderly individuals, respectively (Olsen et al. 2003b, 2004b, 2004c).

Reasons for the observed differences of PFHxS and Me-PFOSA-AcOH levels in childhood serum samples compared to adult samples have not been determined. Olsen et al. (2004b) states that different exposure and activity patters between children and adults should be considered. For example, children may have a higher exposure than adults to PFHxS, a substance that has been used in postmarket carpet cleaning applications, since they are lower to the ground and have increased contact with carpeted floors (Calafat et al. 2007a; Olsen et al. 2004b).

When estimating PFOS and PFOA uptake doses for children, Trudel et al. (2008) assumes the same exposure pathways for children as were proposed for adults, but considers exposure from hand-to-mouth transfer from treated carpets to be much larger in children. This pathway was estimated to contribute 40–60% of the total uptake of both PFOS and PFOA in infants (0–1 years), toddlers (1–4 years), and children (5–11 years) in the high exposure scenario. Exposure via human breast milk was included in the food consumption pathway for infants. Exposure via mouthing of clothes, carpet, and upholstery was also considered for children <12; however, this was considered to be a minor pathway of exposure. PFOS uptake doses estimated for the low, medium, and high exposure scenarios were 18.1–219 ng/kg body weight/day for infants, 14.8–201 ng/kg body weight/day for toddlers, and 9.7–101 ng/kg body weight/day for children. PFOA uptake doses estimated for the low, medium, and high exposure scenarios were 2.2–121 ng/kg body weight/day for infants, 1.2–128 ng/kg body weight/day for toddlers, and 0.8–65.2 ng/kg body weight/day for children. In contrast with the estimates for children under age 12, relative exposure pathways and uptake doses estimated for teenagers (12–20 years) were approximately the same as for adults.

Tao et al. (2008) measured perfluoroalkyl concentrations in 45 human breast milk samples collected from Massachusetts. PFOS, PFOA, PFHxS, and PFNA were each detected in 96, 89, 51, and 64% of the samples, respectively, with median concentrations of 106, 36.1, 12.1, and 6.97 pg/mL, respectively. PFHpA, PFDeA, PFUA, PFDoA, and PFBuS were each detected in <1% of the samples. Perfluoroalkyls

have also been measured in the human breast milk of individuals from Sweden, China, and Germany/ Hungary (Kärrman et al. 2007; So et al. 2006b; Völkel et al. 2008). PFOS was detected in all samples while detection of PFOA ranged from 8–100% in these studies. The reported maximum concentrations of PFOS and PFOA measured in human breast milk samples collected during these studies were 0.360–0.639 and 0.210–0.490 ng/mL, respectively (Kärrman et al. 2007; So et al. 2006b; Völkel et al. 2008). Other perfluoroalkyls detected in human breast milk included PFHpA, PFNA, PFDeA, PFUA, PFBuS, PFHxS, and PFOSA. Maximum concentrations of these compounds were reported to be <0.18 ng/mL.

The presence of perfluoroalkyl compounds in umbilical cord blood indicates that these substances can cross the placental barrier resulting in the exposure of babies *in utero* (Apelberg et al. 2007a, 2007b; Fei et al. 2007; Inoue et al. 2004b; Midasch et al. 2007). In most studies, PFOS and PFOA have been detected in 99–100% of umbilical cord blood samples with reported concentrations were 4.9–11.0 and 1.6–3.7 ng/mL, respectively (Apelberg et al. 2007a, 2007b; Fei et al. 2007; Inoue et al. 2004b; Midasch et al. 2007). Inoue et al. (2004b) did not detect PFOA in 15 cord blood samples from Japan; however, this compound was only detected in the maternal serum of three mothers. Apelberg et al. (2007a) also reported concentrations of other perfluoroalkyl compounds measured in 299 cord serum samples collected during the Baltimore THREE Study. Of these compounds, PFDeA, PFUA, PFOSA, and Me-PFOSA-AcOH were detected most frequently (24, 34, 26, and 40%, respectively). Maximum concentrations in these samples ranged from 1.1 to 1.8 ng/mL. PFHpA, PFDoA, PFBuS, and Et-PFOSA-AcOH were each detected in <6% of the samples with maximum concentrations ranging from 0.2 to 2.6 ng/mL.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Individuals who work at or are located near fluorochemical facilities may have higher exposure to perfluoroalkyl compounds than the general population based on elevated concentrations of these substances measured in air, soil, sediment, surface water, groundwater, and vegetation surrounding these facilities (3M 2007b, 2008b, 2008c; Barton et al. 2006; Davis et al. 2007). PFOA, PFOS, PFBA, PFBuS, and PFHxS have been detected in the municipal drinking water of some communities located near fluorochemical facilities (3M 2008c; Agency for Toxic Substances and Disease Registry 2008; Emmett et al. 2006a; Holzer et al. 2008; Steenland et al. 2009; Wilhelm et al. 2009). Emmett et al. (2006a) compared PFOA serum levels to various types of exposure for individuals living in the Little Hocking community (near DuPont's Washington Works facility) and concluded that residential water source was the primary determinant of serum PFOA at this location. These authors reported that the mean human serum PFOA level was 105 times the level in residential drinking water. In residents with residential

drinking water but without occupational exposure, the model of best-fit for serum PFOA also varied significantly by age (highest in children ≤5 years old, and those over 60 years old), use of carbon home water filters (negative effect), number of servings of home-grown fruits and vegetables (positive effect), and number of tap water-based drinks per day (positive effect). Median PFOA serum levels for residents currently residing in six water districts located in the mid-Ohio Valley near the Washington Works facility ranged from 12.1 to 224.1 ng/mL, while the median concentration ranged from 10.5 to 33.7 ng/mL for residents who previously worked or resided in these districts (Steenland et al. 2009). PFOA serum levels tended to be highest for children aged 0–9 years and persons over 50 years old. These authors also reported that former employees at the chemical plant had much higher levels (median=75 ng/mL) than people who had not worked at the plant (median=24 ng/mL), but lower levels than those who continued to be employed at the plant during the monitoring period (median=148 ng/mL). The serum levels of the 69,030 residents participating in this study categorized by age are provided in Table 6-17. Additional blood serum levels of PFOA and PFOS for residents in selected areas of Ohio, West Virginia, New Jersey, and Minnesota whose residential source of drinking water may have been contaminated are available from the EPA docket on PFOA and related perfluoroalkyl substances (EPA-HQ-OPPT-2003-0012) (Bilott 2004, 2005a, 2005b, 2007).

Individuals involved in activities with prolonged use of perfluoroalkyl-containing products, such as the application of protective coatings for fabrics and carpet and the use of paper coatings, may have higher levels of exposure to perfluoroalkyl compounds than the general population (Calafat et al. 2006a).

3M estimated doses for various off-site exposure scenarios based on monitoring information collected at the Decatur Facility in Alabama (3M 2008c). Exposure scenarios include local children and adult residents exposed to PFOA in off-site soils, groundwater, municipal water, fish from the Tennessee River, and surface water and sediments in the Tennessee River. According to 3M, estimated off-site exposure of local residents to PFOA ranges from 0.011 to 260 ng/kg/day with the highest estimated exposure corresponding to children whose source of drinking water is groundwater adjacent to the southern side of the facility.

6.8 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether

Table 6-17. Blood Serum Levels for 69,030 Current and Former Residents of Six Water Districts in the Mid-Ohio Valley (2005–2006)

Age (years)	Number (percentage of total)	Median PFOA level (ng/mL)
0–9	4,915 (7.1)	32.8
10–19	9,658 (14.0)	26.6
20–29	10,073 (14.6)	21.0
30–39	10,547 (15.3)	22.7
40–49	12,113 (17.6)	28.0
50–59	10,515 (15.2)	33.6
60–69	6,881 (10)	42.9
≥70	4,328 (6.3)	40.1

PFOA = perfluorooctanoic acid

Source: Steenland et al. 2009

adequate information on the health effects of perfluoroalkyls is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of perfluoroalkyls.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. Perfluoroalkyl compounds have unique and complex physical and chemical properties (Kissa 2001; Schultz et al. 2003). Sources are available that provide helpful insights into the structural aspects and surfactant nature of these substances; however, many of the properties are still not well understood (CEMN 2008; Kissa 2001; Schultz et al. 2003). In general, specific properties such as physical state, melting point, boiling point, density, solubility, vapor pressure, micelle formation, and acid dissociation in water have not been determined or are not well described for these compounds. Measurements of these end points are needed. Information regarding the potential association of these species in water would be useful. Where determination of a particular end point is not possible, a thorough description of the physical and chemical properties as they relate to that end point would be helpful. Perfluoroalkyl substances discussed in this profile exist as a mixture of linear and branched isomers. Isomer-specific data would also be useful for the various physical-chemical properties.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2006, became available in May of 2008. This database is updated yearly and should provide a list of industrial production facilities and emissions.

United States production volume ranges as of 2002 are available for PFOA, APFO (PFOA salt), PFBA, and PFOS (EPA 2008g). Production volume information for other perfluoroalkyls has not been located.

Perfluoroalkyl production is expected to be declining since companies have begun phasing out these substances (EPA 2008f). Continued reporting on perfluoroalkyl production is expected to provide evidence of this decline.

No information has been located regarding the import and export of perfluoroalkyl compounds. Uses of perfluoroalkyls are well described in the literature; no further information is needed (3M 1999; DuPont 2008; EPA 2008f; Hekster et al. 2003; Schultz et al. 2003). Recommended methods for the disposal of perfluoroalkyl compounds have not been located. In the past, perfluoroalkyl-containing waste has been disposed of in on- and off-site landfills, through sludge incorporation, and through incineration (3M 2007b, 2008b; Agency for Toxic Substances and Disease Registry 2005). New disposal methods that avoid release of these substances into the open environment and prevent contamination of nearby soil, sediment, and groundwater should be developed.

Environmental Fate. Perfluoroalkyls are very stable compounds and are resistant to biodegradation, direct photolysis, atmospheric photooxidation, and hydrolysis (3M 2000; EPA 2008f; OECD 2002, 2007; Schultz et al. 2003). The chemical stability of perfluoroalkyls and the low volatility of these substances in ionic form indicate that perfluoroalkyls will be persistent in water and soil (3M 2000; Prevedouros et al. 2006). K_{oc} values ranging from 17 to 230 indicate that PFOA will be mobile in soil and can leach into groundwater (Davis et al. 2007; Prevedouros et al. 2006). Environmental fate and potential pathways of PFOA exposure at and near the DuPont Washington Works site have been discussed (Small et al. 2009).

Bioavailability from Environmental Media. Perfluoroalkyls are widely detected in humans and animals indicating that these substances are bioavailable. The bioaccumulation potential of perfluoroalkyls is reported to increase with increasing chain length (de Vos et al. 2008; Furdui et al. 2007; Martin et al. 2004b). In living organisms, perfluoroalkyls bind to protein albumin in blood, liver, and eggs and do not accumulate in fat tissue (de Vos et al. 2008; Kissa 2001). The mechanism of perfluoroalkyl uptake in animals is not fully understood; additional study would be helpful (de Vos et al. 2008). Perfluoroalkyl substances discussed in this profile exist as a mixture of linear and branched isomers. Data regarding the bioavailability of branched versus linear substances would be useful.

Food Chain Bioaccumulation. High levels of certain perfluoroalkyls in animals have been measured in apex predators, such as polar bears, which indicates that some perfluoroalkyls possess the ability to bioaccumulate (de Vos et al. 2008; Houde et al. 2006a; Kannan et al. 2005; Smithwick et al. 2005a, 2005b, 2006). Perfluoroalkyl sulfonates with carbon chain length lower than 8 tend to

bioaccumulate less than PFOS. Ongoing monitoring of perfluoroalkyl levels in animals may help to determine whether efforts to phase out these substances will have had an effect on their biomagnification.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of perfluoroalkyls in contaminated media at hazardous waste sites are needed so that the information obtained on levels of perfluoroalkyls in the environment can be used in combination with the known body burden of perfluoroalkyls to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Concentrations of perfluoroalkyls have been measured in surface water from several locations across the United States (Boulanger et al. 2004; Kannan et al. 2005; Kim and Kannan 2007; Nakayama et al. 2007; Simcik and Dorweiler 2005; Sinclair et al. 2004, 2006). Continued monitoring for perfluoroalkyls in surface water would be useful. Data are available regarding levels of perfluoroalkyls in outdoor air, indoor air, indoor dust, food, food packaging, and consumer products (3M 2001; Barber et al. 2007; Begley et al. 2005; Food Standards Agency 2006; Fromme et al. 2007b; Harada et al. 2005b, 2006; Jogsten et al. 2009; Kim and Kannan 2007; Kubwabo et al. 2005; Moriwaki et al. 2003; Tittlemier et al. 2007; Washburn et al. 2005). Comprehensive studies monitoring for perfluoroalkyls in these matrices within the United States are needed. Background concentrations of perfluoroalkyls in groundwater, drinking water, soil, and sediment have not been located and therefore are a data need. Elevated concentrations of perfluoroalkyls have been measured in air, water, soil, and sediment near fluorochemical industrial facilities (3M 2007b, 2008b, 2008c; Barton et al. 2006; Davis et al. 2007; Hansen et al. 2002). Continued monitoring for perfluoroalkyls in these matrices are needed to assess exposure of individuals working at these locations and individuals who live near these facilities.

Exposure Levels in Humans. Trudel et al. (2008) provided a thorough assessment of the exposure of the general population to PFOS and PFOA. 3M (2008b) provided an assessment of exposure of individuals to PFOA on-site at a fluoropolymer facility. Uptake values and exposure pathways determined in these studies should be examined further. Conclusions made in these assessments are expected to be adjusted as future monitoring data are made available. Large-scale monitoring of perfluoroalkyls in human serum in the United States is ongoing (Calafat et al. 2006a). Future results of human monitoring studies would be useful for assessing human exposure to these substances over time. The results of these studies can be examined for correlations between human perfluoroalkyl levels and the phasing out of perfluoroalkyl compounds by companies of the fluorochemical industry. Concentrations of perfluoroalkyls measured in urine have not been located. Higher exposure levels for individuals who

reside in areas where substances such as PFOA contaminated both public and private water supplies have been documented (Emmett et al. 2006a, 2009).

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Trudel et al. (2008) provided a thorough assessment of the exposure of children to PFOS and PFOA. These conclusions should be reexamined with respect to future biomonitoring data when they become available. Data are available regarding the levels of perfluoroalkyls in young children (Kato et al. 2009b; Olsen et al. 2004b; Toms et al. 2009). The recent NHANES surveys did not include perfluoroalkyl serum levels for children below 12 years of age (Calafat et al. 2007a, 2007b). Future NHANES efforts are scheduled to include children of ages 3–11 years in the sample population (Calafat et al. 2007a). Data provided from these efforts will be useful in assessing the exposure of young children to perfluoroalkyls.

Concentrations of perfluoroalkyls have been measured in human breast milk and cord blood (Apelberg et al. 2007a, 2007b; Fei et al. 2007; Inoue et al. 2004b; Kärrman et al. 2007; Midasch et al. 2007; So et al. 2006b; Völkel et al. 2008). Additional monitoring for perfluoroalkyls in these media would be useful.

Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. No exposure registries for perfluoroalkyls were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

6.8.2 Ongoing Studies

The NIH RePORTER (2014) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-18.

As part of the EPA PFOA Stewardship Program, member companies have agreed to reduce facility emissions and product content of PFOA and related chemicals on a global basis by 95% no later than 2010, and to work toward elimination of these substances by 2015. These companies have also agreed to provide progress reports to EPA on a regular basis. DuPont and 3M are currently working with EPA to develop thorough assessments of perfluoroalkyl environmental contamination and human exposure to these substances surrounding major fluorochemical facilities such as the Decatur, Alabama facility and the Washington Works facility (3M 2008a, 2008b, 2008c, 2008d; DuPont 2008; EPA 2008f).

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, will be analyzing human blood samples for perfluoroalkyls. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

Table 6-18. Ongoing Studies on Perfluoroalkyls

Investigator	Affiliation	Research description	Sponsor
Shankar, A	West Virginia University	Perfluoroalkyl chemicals (PFC) are detectable in the blood of >98% of U.S. adults. This project will study the association between blood PFCs and kidney disease and cardiovascular disease.	National Institute of Environmental Health Sciences (NIEHS)
Frisbee, SJ	West Virginia University	The primary objective of this proposal is to determine the associations between non-8-carbon perfluoroalkyl acids (PFAAs) and serum parameters of lipid, liver, and kidney function in children. The proposed study will perform secondary analysis on data collected as part of the C8 Health Project, a community cohort study with 69,030 participants, including more than 12,000 children.	National Institute of Environmental Health Sciences (NIEHS)
Sagiv, SK	Boston University Medical Campus	This study ill measure levels of four perfluorinated compounds—perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), perfluorohexane sulfonate (PFHxS), and perfluorononanoate (PFNA) —in prenatal maternal plasma collected in early gestation and estimate associations with fetal and infant somatic growth, childhood adiposity, and metabolic outcomes such as serum cholesterol and insulin resistance, and neurodevelopment, including cognition and behavior.	National Institute of Environmental Health Sciences (NIEHS)

Source: NIH RePORTER 2014

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring perfluoroalkyls, their metabolites, and other biomarkers of exposure and effect to perfluoroalkyls. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

Although analytical methods sensitive to ppt/ppb levels have been developed for detecting perfluoroalkyls in biological and environmental media, these methods have not yet been standardized (Longnecker et al. 2008; van Leeuwen et al. 2006). Both EPA (2009) and the International Organization for Standardization (ISO 2009) have published methods for determining perfluoroalkanoic acids in water matrices. The EPA method reports a single laboratory lowest concentration minimal reporting level (LCMRL) in drinking water of 3.7–5.5 ng/L for C6–C13 carboxylic acids. The applicable levels in the ISO method are 10 ng/L for PFOA and 2 ng/L for PFOS in unfiltered water samples. As part of EPA's PFOA Stewardship Program, member companies have agreed to "work with EPA, other PFOA Stewardship Program participants, and others in order to establish scientifically credible analytical standards and laboratory methods for measuring the chemicals in the program by 2010" (EPA 2008f). This effort will be useful for ensuring accuracy and reproducibility across studies monitoring for perfluoroalkyls. Analytical techniques currently in use are summarized in the following sections (Longnecker et al. 2008; van Leeuwen et al. 2006). Summaries of the analytical methods and challenges of measuring highly fluorinated compounds exist in the literature (de Voogt 2006; Jahnke and Berger 2009; Larsen and Kaiser 2007; Martin et al. 2010). The results of an interlaboratory study on perfluorinated compounds in human and environmental matrices were published in 2006 (van Leeuwen et al. 2006). The perfluoroalkyls that were reported most frequently and had the best agreement within the interlaboratory results were PFOS and PFOA. Poor agreement was reported for perfluoroalkyl levels in fish liver extract, fish tissue, and water samples due to challenges with matrix matched calibration standards, extraction, and cleanup procedures within these matrices (van Leeuwen et al. 2006). Moreover, most laboratories reported the

sum of the branched and linear isomers; however, some laboratories reported the concentration of the linear isomer only, which further confounded the results.

7.1 BIOLOGICAL MATERIALS

Detection of individual perfluoroalkyls in biological materials was not possible until the 1980s, when methods were developed based on gas chromatographic (GC) techniques (Belisle and Hagen 1980; Kärrman et al. 2005). These techniques, however, required derivitization of the analytes to methyl esters or other moieties (Belisle and Hagen 1980; Flaherty et al. 2005; Kärrman et al. 2005; Kudo et al. 1998). This involved complex and tedious sample preparation and resulted in low sensitivity. The introduction of high-performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (MS/MS) allowed for more sensitive determination of individual perfluoroalkyls in biological materials and much simpler sample preparation (Flaherty et al. 2005; Hansen et al. 2001; Kärrman et al. 2005; Ohya et al. 1998). Most perfluoroalkyl detection methods currently in use are forms of HPLC-MS/MS (van Leeuwen et al. 2006). Methods of sample preparation used for perfluoroalkyls have included solvent extraction, ion-pair extraction, solid-phase extraction, and column-switching extraction (Flaherty et al. 2005). Analytical methods for detecting perfluoroalkyls in biological materials are listed in Table 7-1.

Calafat et al. (2007a, 2007b) reported a summary of the method that was developed to measure perfluoroalkyls in NHANES serum samples. Serum samples were stored at -70°C prior to analysis. Serum samples (1 mL) were then analyzed using automated solid phase extraction coupled to reversed-phase HPLC-MS/MS. The limits of detection, accuracy, and precision determined for the perfluoroalkyl analytes were 0.1–1.0 µg/L, 84–135%, and 10–26%, respectively.

Kuklenyik et al. (2004) described a method for measuring perfluoroalkyls in human breast milk samples. The milk samples were stored at -40°C. Sample preparation included combining 3 mL of 0.1 M formic acid, 50 µL of internal standard solution, and 1 mL of milk. This solution was then analyzed using automated solid-phase extraction followed by HPLC-MS/MS. Limits of detection, recovery, and accuracy reported for the perfluoroalkyl analytes ranged from 0.1–1.0 µg/L, 26–102%, and 70–118%, respectively.

Table 7-1. Analytical Methods for Determining Perfluoroalkyls in Biological Samples

Sample matrix	Preparation method	Detection method	Analytes	Sample detection limit	Percent recovery	Reference
Human Plasma	Solvent extraction, derivatization with diazomethane	GC-ECD	PFOA	15 ng/mL	97–113%	Belisle and Hagen 1980
Human Urine	Solvent extraction, derivatization with diazomethane	GC-ECD	PFOA	1.5 ng/mL	100%	Belisle and Hagen 1980
Rat and monkey liver	Homogenization, solvent extraction, derivatization with diazomethane	GC-ECD	PFOA	0.145 µM/5 g liver (60 ppb)	98%	Belisle and Hagen 1980
Rat liver	Homogenization, solvent extraction, derivatization with diazomethane	GC-ECD	PFOA, PFNA, PFDeA	40–60 µg/g liver	30–60%	Kudo et al. 1998
Rat liver	Homogenization, ion pair extraction using tetrabutylammonium ion, derivatization with 3-bromoacetyl-7-methoxycoumarin	HPLC-FD	PFHpA, PFOA, PFNA, PFDeA	50 pmol/ 50 mg liver	92–98%	Ohya et al. 1998
Human serum	Ion pair extraction using tetrabutylammonium hydrogen sulfate	HPLC-ESMSMS	PFOS, PFOA, PFHxS, PFOSA	1–3 ng/mL	85–101%	Hansen et al. 2001
Human serum, milk	Automated solid-phase extraction	HPLC-MS/MS	PFOSA, Me-PFOSA-AcOH, Et-PFOSA-AcOH, PFHxS, PFOS, PFHpA, PFOA, PFNA, PFDeA, PFUA, PFDoA	0.1–1.0 ng/mL (serum); 0.1–1.0 ng/mL (milk)	30–91% (serum); 26–89% (milk)	Kuklenyik et al. 2004
Human plasma	Centrifugation, Column-switching extraction, backflushing into analytical column	LC-ESI-MS/MS	PFOS, PFOA, PFOSA	0.05–0.25 ng/mL	82.2–98.7%	Inoue et al. 2004a

Table 7-1. Analytical Methods for Determining Perfluoroalkyls in Biological Samples

Sample matrix	Preparation method	Detection method	Analytes	Sample detection limit	Percent recovery	Reference
Human plasma	Protein precipitation using acetonitrile, extraction via large volume injection capillary column switching, backflushing into analytical column	LC-IT-MS	PFOS, PFOA, PFHpA	0.2–0.5 ng/mL	NR	Holm et al. 2004
Human serum/ plasma	Protein precipitation using acetonitrile in a column arrayed in a 96-well plate format	LC-MS/MS	PFOA	0.5 ng/mL[a]	91–109%	Flaherty et al. 2005
Human whole blood	Treatment with formic acid, sonication, solid phase extraction	LC-MSD	PFBuS, PFHxS, PFOA, PFOS, PFNA, PFDeA, PFOSA, PFUA, PFDoA	0.1–2 ng/mL	26–112%	Kärrman et al. 2005
Human whole blood	Samples collected in heparin or EDTA, solid phase extraction	HPLC-MS/MS	PFBuS, PFHxS, PFOS, PFOA	5–10 ng/mL[a]	93.2–99.7%	Ehresman et al. 2007

[a]Limit of quantitation.

GC = gas chromatography; ECD = electron capture detection; EDTA = ethylenediamine tetraacetic acid; ESMSMS = negative ion electrospray tandem mass spectrometry; HPLC-FD = high performance liquid chromatography with fluorescence detection; Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid; LC-ESI-MS = liquid chromatography with electrospray mass spectrometry; LC-IT-MS = liquid chromatography coupled to electrospray ionization mass spectrometry; LC-MSD = liquid chromatography coupled to mass spectrometric detector; Me-PFOSA-AcOH = 2-(N-methyl-perfluorooctane sulfonamide) acetic acid; MS = mass spectrometry; PFBuS = perfluorobutane sulfonic acid; PFDeA = perfluorodecanoic acid; PFDoA = perfluoro-dodecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluoro-nonanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide; PFUA = perfluoroundecanoic acid

One of the greatest challenges with regard to trace-level analysis of perfluoroalkyl compounds is avoiding sample contamination (Flaherty et al. 2005; Longnecker et al. 2008; Van Leeuwen et al. 2006; Yamashita et al. 2004). Perfluoroalkyl compounds may be present at trace levels in reagents, labware, sample collection implements, and instrumentation; therefore, these items must be carefully screened prior to analysis to avoid contamination.

Jahnke and Berger (2009) have published a comprehensive review article for the trace analysis of perfluoroalkyl compounds in both biological and environmental matrices. Readers are encouraged to examine this article for details regarding instrumental methods, extraction techniques, detection limits, and strengths and weaknesses of the methods with respect to the analysis of individual perfluoroalkyl compounds in a wide variety of matrices.

7.2 ENVIRONMENTAL SAMPLES

As with biological matrices, methods developed for analysis of perfluoroalkyls in environmental samples such as air, water, and soil are primarily based on HPLC-MS/MS technology (Harada et al. 2006; Jahnke et al. 2007b; Kubwabo et al. 2005; Schroder 2003; Schultz et al. 2006; Taniyasu et al. 2005; Tseng et al. 2006; Washington et al. 2008; Yamashita et al. 2004). Some studies have measured perfluoroalkyls in air samples using GC-MS (Barber et al. 2007; Barton et al. 2006; Martin et al. 2002). Available methods report sensitivities of low pg/m^3 levels in air, high pg/L to low ng/L levels in water, and high pg/g to low ng/g levels in soil (Jahnke et al. 2007b; Martin et al. 2002; Schultz et al. 2006; Taniyasu et al. 2005; Washington et al. 2008). Analytical methods for detecting perfluoroalkyls in environmental samples are listed in Table 7-2. A more comprehensive listing is provided in Jahnke and Berger (2009).

7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of perfluoroalkyls is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of perfluoroalkyls.

Table 7-2. Analytical Methods for Determining Perfluoroalkyls in Environmental Samples

Sample matrix	Preparation method	Detection method	Analytes	Sample detection limit	Percent recovery	Reference
Air	Collection using high volume sampler and glass fibers or XAD resin followed by extraction with methanol, acetone, dichloromethane, and hexane	LC/MS	Et-PFOSA-AcOH; PFOSA; PFOS; PFOA	pg/m^3 (range)	61–116	Boulanger et al. 2005
Air	Collection with cascade impact sampler with quartz membrane filter followed by accelerated solvent extraction	LC/MS	PFOA; PFOS	0.1 pg/m^3	No data	Harada et al. 2006
Dust	Dispersion using 0.1 M formic acid and methanol followed by SPE	SPE-HPLC-MS/MS	PFBuS; PFHxS; PFOS; PFHpA; PFOA; PFNA; PFDeA; PFUA; PFDoA; PFOSA; Me-PFOSA-AcOH; Et-PFOSA-AcOH	4.0 ng/g for PFHpA; all others 2.6 ng/g	73.2–100.2	Kato et al. 2009a
Water	SPE followed by elution with methanol	LC/MS/MS	Me-PFOSA-AcOH; Et-PFOSA-AcOH; PFBuS; PFDeA; PFDoA; PFHxS; PFNA; PFOS; PFOA; PFUA	0.5–6.5 ng/L	93–120	EPA 2009 Method 537
Soil	Alkaline pretreatment followed by acetonitrile/water extraction	LC/MS/MS	PFOA; PFDoA; PFHpA; PFNA; PFBA	270 ag/µL (ppq)	28–152	Washington et al. 2008

Table 7-2. Analytical Methods for Determining Perfluoroalkyls in Environmental Samples

Sample matrix	Preparation method	Detection method	Analytes	Sample detection limit	Percent recovery	Reference
Fish	Acetonitrile followed by SPE cleanup extraction	UPLC/MS/MS and GC/MS	PFOS; PFBuS; PFHxS; PFOSA; Et-PFOSA-AcOH; Me-PFOSA-AcOH	Sub to single-digit pg/g range	50–102	Ullah et al. 2014
Plants	Homogenize sample followed by solvent extraction	HPLC/MS/MS	PFOA; PFOS;	No data	No data	Stahl et al. 2009

Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid; HPLC = high performance liquid chromatography; LC = liquid chromatography; Me-PFOSA-AcOH = 2-(N-methyl-perfluorooctane sulfonamide) acetic acid; MS = mass spectrometry; MS/MS = tandem mass spectrometry; PFBuS = perfluorobutane sulfonic acid; PFDeA = perfluorodecanoic acid; PFDoA = perfluorododecanoic acid; PFHpA = perfluoroheptanoic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide; PFUA = perfluoroundecanoic acid; SPE = solid phase extraction; UPLC = ultra performance liquid chromatography;

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. The presence of perfluoroalkyls in blood and other human biological matrices are biomarkers of exposure to these substances. The presence of some perfluoroalkyls in the blood may also be the result of exposure to precursor compounds. For example, PFOSA, Me-PFOSA-AcOH, and Et-PFOSA-AcOH are expected to be oxidized in the body to form PFOS (Olsen et al. 2005; Seacat and Luebker 2000). Exposure to 8–2 fluorotelomer alcohol may result in the formation of PFOA as a metabolite within the body (Fasano et al. 2006; Henderson and Smith 2007; Kudo et al. 2005; Nabb et al. 2007).

Analytical methods that identify perfluoroalkyl compounds in blood or other biological matrices are available; however, these have not been standardized. Two studies have been performed that assessed interlaboratory variability in the analysis of perfluoroalkyls. According to Longnecker et al. (2008), assays of identical plasma specimens from six different laboratories were relatively precise. However, van Leeuwen et al. (2006) stated that 38 laboratories were not able to produce consistent data when analyzing for perfluoroalkyls in provided samples of human plasma, whole blood, fish muscle tissue, and fish liver extract, although agreement was better for the human matrices than for the fish matrices and water. These authors suggested that laboratories need to address poor extraction efficiency, suitability of external calibration, suitability of native perfluorinated compounds as internal standards, quality of standards used, matrix effects, and selectivity of MS/MS technique. Both interlaboratory studies concluded that standardized methods are needed for the analysis of perfluoroalkyls (Longnecker et al. 2008; van Leeuwen et al. 2006).

Effect. There are no known biomarkers of effect for perfluoroalkyl compounds.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. As mentioned for analytical methods for measuring perfluoroalkyls in biological materials,

standardization is needed for methods for measuring these substances in environmental media as well. According to van Leeuwen et al. (2006), 38 laboratories were not able to produce consistent data when analyzing for perfluoroalkyls in provided samples of water.

7.3.2 Ongoing Studies

No ongoing studies regarding analytical methods for measuring perfluoroalkyls in biological materials or environmental media were located.

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.

ATSDR has derived an intermediate-duration oral MRL of $2x10^{-5}$ mg/kg/day for PFOA based on a BMDL of $1.54x10^{-3}$ mg/kg/day for increased absolute liver weight in monkeys administered PFOA via a capsule for 26 weeks (Butenhoff et al. 2002). The BMDL was estimated using serum PFOA levels as a dose metric; a HED was estimated using an empirical clearance model. The $BMDL_{HED}$ was divided by an uncertainty factor of 90 (3 for animal to human extrapolation with dosimetric adjustment, 10 for human variability, and 3 for database deficiencies, particularly the lack of developmental and immunological studies in monkeys).

ATSDR has derived an intermediate-duration oral MRL of $3x10^{-5}$ mg/kg/day for PFOS based on a NOAEL of $2.52x10^{-3}$ mg/kg/day for increased absolute liver weight in monkeys administered PFOS via a capsule for 6 months (Seacat et al. 2002). The NOAEL was estimated using serum PFOS levels as a dose metric; a HED was estimated using an empirical clearance model. The $NOAEL_{HED}$ was divided by an uncertainty factor of 90 (3 for animal to human extrapolation with dosimetric adjustment, 10 for human variability, and 3 for database deficiencies, particularly the lack of developmental and immunological studies in monkeys).

EPA has not derived reference dose (RfD) or reference concentration (RfC) values of perfluoroalkyl compounds (IRIS 2014).

The international and national regulations and guidelines regarding perfluoroalkyls in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Perfluoroalkyls

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2014
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	No data	ACGIH 2013
	APFO	0.1 mg/m^3	
AIHA	ERPGs	No data	AIHA 2013
DOE	PFOA		DOE 2012
	PAC-1[a]	0.015 mg/m^3	
	PAC-2[a]	16 mg/m^3	
	PAC-3[a]	75 mg/m^3	
	PFBA		
	PAC-1[a]	0.5 mg/m^3	
	PAC-2[a]	5.5 mg/m^3	
	PAC-3[a]	33 mg/m^3	
EPA	AEGLs	No data	EPA 2013a
	Second AEGL chemical priority list	No data	EPA 2014a
	Hazardous air pollutant	No data	EPA 2014b 42 USC 7412
	NAAQS	No data	EPA 2014e
NIOSH	REL (10-hour TWA)	No data	NIOSH 2014
	IDLH	No data	
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2013 29 CFR 1910.1000, Table Z-1
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2013c 40 CFR 116.4
	Drinking water contaminant candidate list		EPA 2009e 74 FR 51850
	PFOA	Yes	
	PFOS	Yes	

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Perfluoroalkyls

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Provisional drinking water health advisories for short-term exposure		EPA 2012
	PFOA	0.4 µg/L	
	PFOS	0.2 µg/L	
	Master Testing List	No data	EPA 2014d
	Monitoring requirements for unregulated contaminants		EPA 2013e 40 CFR 141.40
	PFOA		
	Minimum reporting level	0.02 µg/L	
	Sampling location	EPTDS	
	Period during which monitoring to be completed	1/1/2013–12/31/2015	
	PFHpA		
	Minimum reporting level	0.01 µg/L	
	Sampling location	EPTDS	
	Period during which monitoring to be completed	1/1/2013–12/31/2015	
	PFNA		
	Minimum reporting level	0.02 µg/L	
	Sampling location	EPTDS	
	Period during which monitoring to be completed	1/1/2013–12/31/2015	
	PFOS		
	Minimum reporting level	0.04 µg/L	
	Sampling location	EPTDS	
	Period during which monitoring to be completed	1/1/2013–12/31/2015	
	PFHxS		
	Minimum reporting level	0.03 µg/L	
	Sampling location	EPTDS	
	Period during which monitoring to be completed	1/1/2013–12/31/2015	
	PFBuS		
	Minimum reporting level	0.09 µg/L	
	Sampling location	EPTDS	
	Period during which monitoring to be completed	1/1/2013–12/31/2015	
	National primary drinking water standards	No data	EPA 2009f
	National recommended water quality criteria: human health for the consumption of	No data	EPA 2014f

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Perfluoroalkyls

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2013f 40 CFR 117.3
c. Food			
FDA	EAFUS[b]	No data	FDA 2014
d. Other			
ACGIH	APFO	A3[c]	ACGIH 2013
EPA	Carcinogenicity classification	No data	IRIS 2014
	RfC	No data	
	RfD	No data	
	Endocrine disruptor screening program; final second list of chemicals and substances for Tier 1 screening		EPA 2013b 78 FR 35922
	PFOA	Yes	
	PFOS	Yes	
	Identification and listing of hazardous waster	No data	EPA 2013d 40 CFR 261, Appendix VIII
	Inert pesticide ingredients in pesticide products	No data	EPA 2014c
	RCRA waste minimization PBT priority chemical list	No data	EPA 1998 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	No data	EPA 2013h 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity	No data	EPA 2013i 40 CFR 302.4
	Effective date of toxic chemical release reporting	No data	EPA 2013k 40 CFR 372.65
	Extremely hazardous substances and its threshold planning quantity	No data	EPA 2013l 40 CFR 355, Appendix A
	Significant new uses for specific chemical substances		EPA 2013g 40 CFR 721.336
	PFOS	Yes	
	PFHxS	Yes	
	PFOSA	Yes	
	Et-PFOSA-AcOH	Yes	
	TSCA chemical lists and reporting periods	No data	EPA 2013l 40 CFR 712.30

Table 8-1. Regulations, Advisories, and Guidelines Applicable to Perfluoroalkyls

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	TSCA health and safety data reporting	No data	EPA 2013m 40 CFR 716.120
NTP	Carcinogenicity classification	No data	NTP 2011
	Nominations to the Report on Carcinogens		NTP 2013 78 FR 57868
	PFOA	Yes	

[a]PAC-1: mild, transient health effects; PAC-2: irreversible or other serious health effects that could impair the ability to take protective action; PAC-3: life-threatening health effects.
[b]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS.
cA3: confirmed animal carcinogen with unknown relevance to humans.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; APFO = ammonium perfluorooctanoate; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; EPTDS = entry points to the distribution system; ERPG = emergency response planning guidelines; Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid; FDA = Food and Drug Administration; FR = Federal Register; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PBT = Persistent, Bioaccumulative, and Toxic; PEL = permissible exposure limit; PFBA = perfluorobutyric acid; PFHpA = perfluoroheptanoic acid; PFBuS = perfluorobutane sulfonic acid; PFHxS = perfluorohexane sulfonic acid; PFNA = perfluorononanoic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid; PFOSA = perfluorooctane sulfonamide; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Organophosphate or Organophosphorus Compound—A phosphorus-containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a

variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL, from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The absorption, distribution, and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Perfluorooctanoic acid (PFOA)
CAS Number: 335-67-1
Date: December 2014
Profile Status: Final for Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 48
Species: Monkey

Minimal Risk Level: $2x10^{-5}$ [X] mg/kg/day [ ] ppm

Reference: Butenhoff J, Costa G, Elcombe C, et al. 2002. Toxicity of ammonium perfluorooctanoate in male Cynomolgus monkeys after oral dosing for 6 months. Toxicol Sci 69:244-257.

Experimental design: Groups of male Cynomolgus monkeys were administered ammonium PFOA (purity 95.2%) by daily capsule at doses of 0 (n=6), 3 (n=4), 10 (n=6), or 30 (n=6) mg/kg/day, once per day for 26 weeks. Two monkeys from the control and 10 mg/kg/day groups were observed for 90 days posttreatment period. Assessments included clinical observations body weight, food consumption, clinical chemistry (days 31, 63, 91, and 182 of treatment and recovery days 217, 245, and 275), determination of key hormones (cholecystokinin, testosterone, estradiol, estrone, estriol, TSH, and total and free T4 and T3), gross and microscopic pathology, organ weights, and serum and liver PFOA concentrations.

Effect noted in study and corresponding doses: During treatment week 1, all monkeys in the 30 mg/kg/day dose group exhibited decreased food consumption and weight loss. Dosing of this group was suspended from treatment day 12 until treatment day 22, at which time dosing was reinstated, but at 20 mg/kg/day. One monkey in this dose group was sacrificed moribund on day 29; cessation of dosing for three of the remaining five monkeys occurred on treatment days 43, 66, or 81, respectively, due to continued weight loss, no to low food consumption, and few or no feces. Some recovery was noted upon cessation of treatment. Clinical signs, body weights, and food consumption were normal in the 3 and 10 mg/kg/day groups, with the exception of a single 3 mg/kg/day monkey that was sacrificed moribund on treatment day 137 for reasons not clearly related to ammonium PFOA dosing. There were no signs of treatment-related ophthalmologic effects. No major treatment-related effects on clinical chemistry, hematology, or urinalysis were seen in the 3 and 10 mg/kg/day dose groups, but serum triglycerides were significantly increased in the high-dose group on days 31, 63, and 91. Dose-related increases in absolute liver weight (associated with mitochondrial proliferation) occurred in all ammonium PFOA-treated groups, in the absence of histopathologic evidence of hepatotoxicity (36, 38, 50%). However, the 30/20 mg/kg/day monkey that was sacrificed moribund on exposure day 29 exhibited histopathologic liver lesions (hepatocellular degeneration, vacuolation, and basophilia), as well as indications of dosing error in esophagus and stomach. Relative liver weights were increased 19, 22, and 57% in the treated groups after 6 months of dosing. The absolute and relative liver weights are summarized in Table A-1. There were no significant effects on serum levels of estriol, estrone, testosterone, or cholecystokinin. Free T4 and TT4 were significantly reduced at 10 mg/kg/day during the study, but no significant changes were seen in levels of free T3, total T3, or TSH. Except for the high-dose group, there were no significant changes in hepatic DNA content or enzymes that are specific markers of subcellular fractions. The high-dose group showed a significant increase in sorbitol dehydrogenase activity (mitochondrial marker). Other than the liver, there were no significant effects of treatment on organ weights. At ≤10 mg/kg/day, there were no significant gross or microscopic alterations in the organs examined. There were no indications of treatment-related differences in cell proliferation in liver, pancreas, or testes.

Table A-1. Liver Weights of Male Cynomolgus Monkeys Exposed to PFOA for 6 Months

Dose (mg/kg/day)	Serum PFOA level[a] (µg/mL)	Number of animals	Absolute liver weight (g)	Relative liver weight (%)
0	0.203±0.154[b]	4	60.2±6.9	1.5±0.1
3	77±39 (10–154)[c]	3	81.8±2.8*	1.8±0.1
10	86±33 (10–180)	4	83.2±9.7*	1.9±0.1
30/20	158±100 (20–467)	2	90.4±4.2*	2.4±0.5*

[a]Average serum PFOA levels measured every 2 weeks beginning at study week 6.
[b]Mean ± standard deviation.
[c]Range of values.
*Statistically significant when compared to controls, $p<0.01$.

PFOA = perfluorooctanoic acid

Source: Butenhoff et al. 2002

Dose and end point used for MRL derivation: The $BMDL_{HED}$ of $1.54x10^{-3}$ mg/kg/day for increases in absolute liver weight was used as the POD for the MRL.

[ ] NOAEL [ ] LOAEL [X] $BMDL_{RD10\%}$

Using the dose levels from the Butenhoff et al. (2002) study is problematic due to species differences in the toxicokinetics of PFOA, particularly the difference in half-times. An alternative approach is to use the serum concentration as an internal dosimetric and the assumption that a serum concentration level that would result in an effect in monkeys would also result in an effect in humans. Using serum PFOA level as the internal dosimetric, the absolute and relative liver weight data were fit to all available continuous models in EPA's BMDS (version 2.4.0). Due to the toxicity observed in the high dose group, this dose group was dropped from the benchmark dose modeling. The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p\geq0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p>0.1$); visual inspection of the dose-response curve; and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMCLs estimated from these models was more than 3-fold; otherwise, the BMDL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. If the test for constant variance was negative, then the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p\geq0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and POD selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. Three BMRs were considered: 1 SD change from the control; 2 SD change from the control; and 10% increase in liver weight. Although a 1 SD change is the typical BMR used for continuous variable models without a biological basis to

establish a cut-point for biological significance, a 2 SD BMR was also used due to the small number of animals tested. The results of the BMD modeling for absolute liver weight are summarized in Tables A-2, A-3, and A-4.

Table A-2. Absolute Liver Weights of Male Cynomolgus Monkeys Exposed to PFOA for 6 Months (Butenhoff et al. 2002)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{1SD} (µg/mL)	$BMDL_{1SD}$ (µg/mL)
Constant variance									
Exponential (model 2)[d]	0.0007	0.116	0.765	-0.029	0.238	0.238	57.69	26.17	18.43
Exponential (model 3)[d]	0.0007	0.116	0.765	-0.029	0.238	0.238	57.69	26.17	18.43
Exponential (model 4)[d]	0.0007	0.116	NA	0.00	0.00	0.00	59.60	ND	ND
Linear[e,f]	**0.0007**	**0.12**	**0.82**	**-0.0156**	**0.172**	**1.72**	**57.64**	**23.29**	**15.87**
Polynomial[e]	0.0007	0.116	0.827	-0.0156	0.172	1.72	57.64	23.29	15.87
Power[d]	0.0007	0.116	0.827	-0.0156	0.172	1.72	57.64	23.29	15.87

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); ND = not determined, model does not provide adequate fit to the data; PFOA = perfluorooctanoic acid; SD = standard deviation

Table A-3. Absolute Liver Weights of Male Cynomolgus Monkeys Exposed to PFOA for 6 Months (Butenhoff et al. 2002)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c]			AIC	BMD_{2SD} (µg/mL)	$BMDL_{2SD}$ (µg/mL)
				Dose below BMD	Dose above BMD	Overall largest			
Constant variance									
Exponential (model 2)[d]	0.0007	0.116	0.765	-0.029	0.238	0.238	57.69	49.95	35.50
Exponential (model 3)[d]	0.0007	0.116	0.765	-0.029	0.238	0.238	57.69	49.95	35.50
Exponential (model 4)[d]	0.0007	0.116	NA	0.00	0.00	0.00	59.60	ND	ND
Linear[e,f]	**0.0007**	**0.116**	**0.827**	**-0.0156**	**0.172**	**0.172**	**57.64**	**46.57**	**31.73**
Polynomial[e]	0.0002	0.116	0.827	-0.0156	0.172	0.172	57.64	46.57	31.73
Power[d]	0.0002	0.116	0.827	-0.0156	0.172	0.172	57.64	46.57	31.73

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); ND = not determined, model does not provide adequate fit to the data; PFOA = perfluorooctanoic acid; SD = standard deviation

Table A-4. Absolute Liver Weights of Male Cynomolgus Monkeys Exposed to PFOA for 6 Months (Butenhoff et al. 2002)

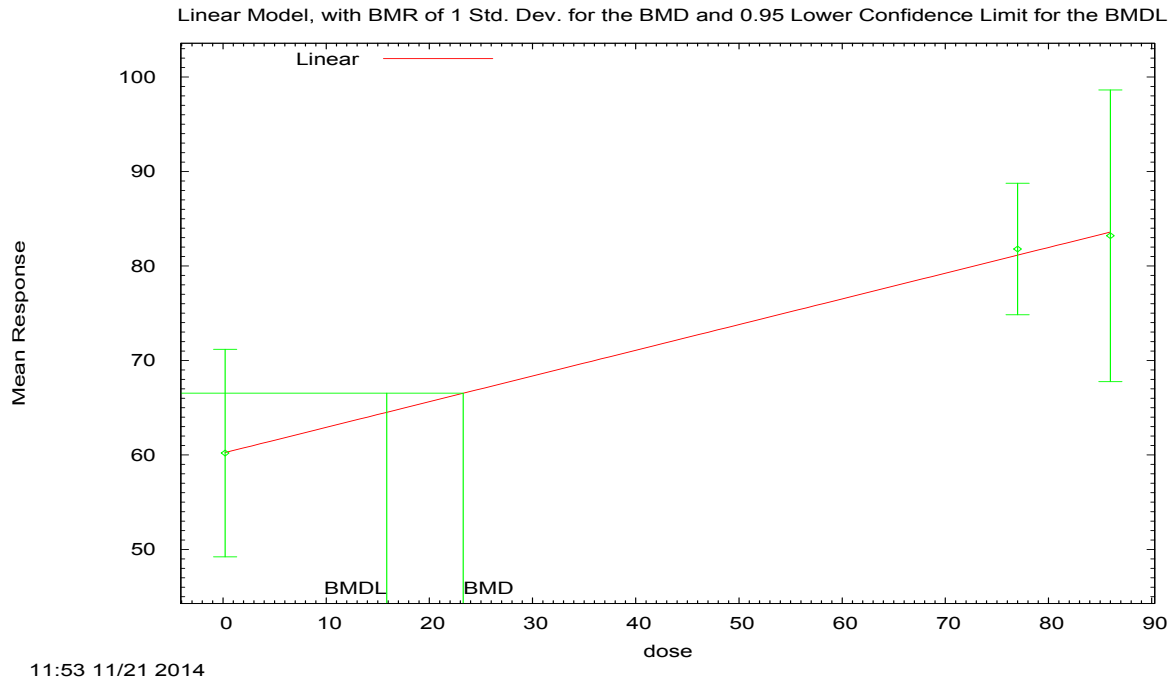
Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	$BMD_{RD10\%}$ (µg/mL)	$BMDL_{RD10\%}$ (µg/mL)
Constant variance									
Exponential (model 2)[d]	0.0007	0.116	0.765	-0.029	0.238	0.238	57.69	24.87	18.52
Exponential (model 3)[d]	0.0007	0.116	0.765	-0.029	0.238	0.238	57.69	24.87	18.52
Exponential (model 4)[d]	0.0007	0.116	NA	0.00	0.00	0.00	59.60	ND	ND
Linear[e,f]	**0.0002**	**0.116**	**0.827**	**-0.016**	**0.172**	**0.172**	**57.64**	**22.01**	**15.53**
Polynomial[e]	0.0002	0.116	0.827	-0.016	0.172	0.172	57.64	22.01	15.53
Power[d]	0.0002	0.116	0.827	-0.016	0.172	0.172	68.67	22.01	15.53

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); ND = not determined, model does not provide adequate fit to the data; PFOA = perfluorooctanoic acid; RD = relative deviation

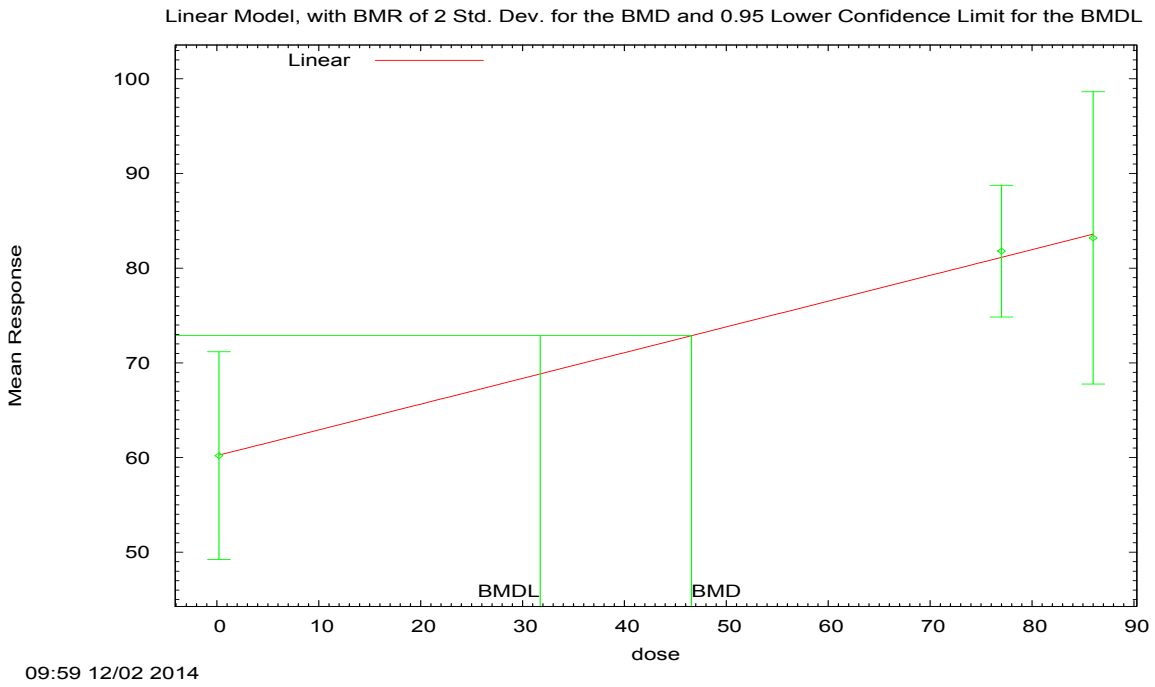
The AIC values were virtually the same for the remaining models with adequate fit; the linear model was selected because it was the simplest model. The linear models for each BMR are presented in Figures A-1, A-2, and A-3.

Figure A-1. Predicted (Linear Model with Constant Variance, High Dose Dropped, 1 Standard Deviation Benchmark Response) and Observed Absolute Liver Weights



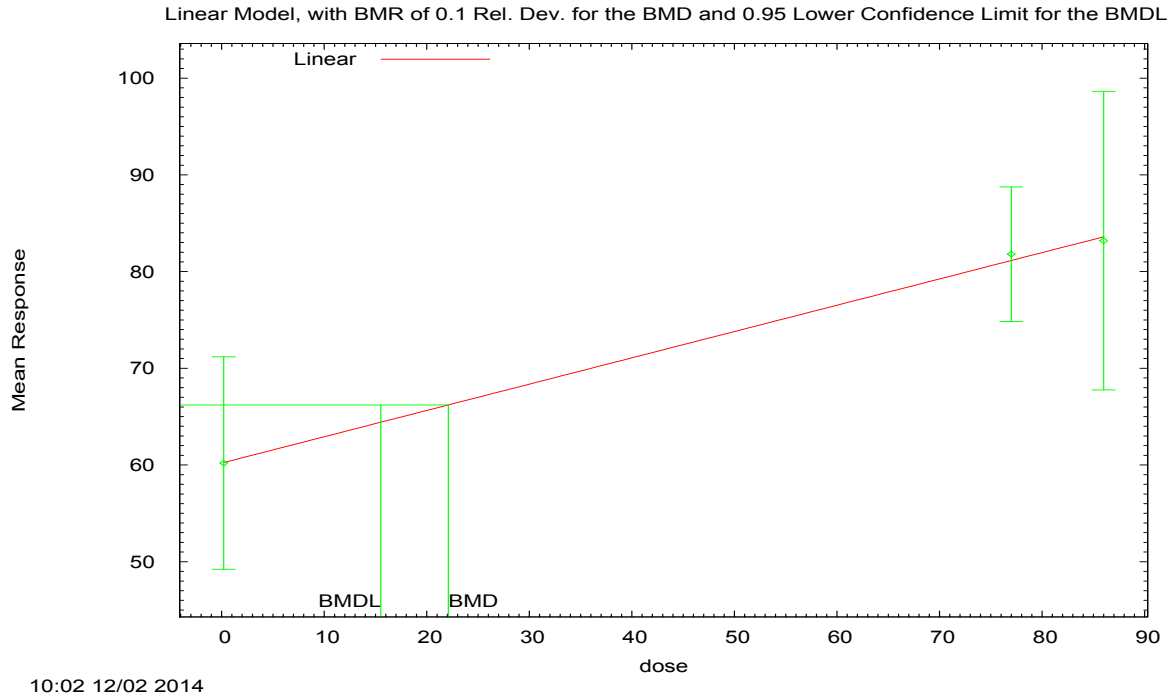
*The x-axis represents the serum PFOA level (µg/mL).

Figure A-2. Predicted (Linear Model with Constant Variance, High Dose Dropped, 2 Standard Deviation Benchmark Response) and Observed Absolute Liver Weights



*The x-axis represents the serum PFOA level (µg/mL).

Figure A-3. Predicted (Linear Model with Constant Variance, High Dose Dropped, 10% Relative Deviation BMR) and Observed Absolute Liver Weights



*The x-axis represents the serum PFOA level (µg/mL).

The results of the BMD modeling for relative liver weight are presented in Tables A-5, A-6, and A-7.

Table A-5. Relative Liver Weights of Male Cynomolgus Monkeys Exposed to PFOA for 6 Months (Butenhoff et al. 2002)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{1SD} (µg/mL)	$BMDL_{1SD}$ (µg/mL)
Constant variance									
Exponential (model 2)[d]	0.0011	0.99	0.39	0.074	-0.663	-0.663	-36.44	21.64	15.27
Exponential (model 3)[d]	0.0011	0.99	NA	0.00	0.00	0.00	-35.16	ND	ND
Exponential (model 4)[d]	0.0011	0.99	NA	0.064	-0.705	-0.705	-34.33	ND	ND
Linear[f]	0.0011	0.99	0.36	0.064	-0.705	-0.705	-36.33	20.07	13.89
Polynomial[e,f]	**0.0011**	**0.99**	**0.73**	**0.047**	**-0.276**	**-0.276**	**-37.04**	**40.13**	**33.45**
Power[d]	0.0011	0.99	NA	0.00	0.00	0.00	-35.16	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive
[f]Selected model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable; ND = not determined, model does not provide adequate fit to the data; PFOA = perfluorooctanoic acid; SD = standard deviation

Table A-6. Relative Liver Weights of Male Cynomolgus Monkeys Exposed to PFOA for 6 Months (Butenhoff et al. 2002)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{2SD} (µg/mL)	$BMDL_{2SD}$ (µg/mL)
Constant variance									
Exponential (model 2)[d]	0.0011	0.99	0.39	0.074	-0.663	-0.663	-36.44	42.12	29.90
Exponential (model 3)[d]	0.0011	0.99	NA	0.00	0.00	0.00	-35.16	ND	ND
Exponential (model 4)[d]	0.0011	0.99	NA	0.064	-0.705	-0.705	-34.33	ND	ND
Linear[f]	0.0011	0.99	0.36	0.064	-0.705	-0.705	-36.33	40.14	27.79
Polynomial[e,f]	**0.0011**	**0.99**	**0.73**	**0.047**	**-0.276**	**-0.276**	**-37.04**	**56.75**	**47.31**
Power[d]	0.0011	0.99	NA	0.00	0.00	0.00	-35.16	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e] Coefficients restricted to be positive.
[f]Selected model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable; ND = not determined, model does not provide adequate fit to the data; PFOA = perfluorooctanoic acid; SD = standard deviation

Table A-7. Relative Liver Weights of Male Cynomolgus Monkeys Exposed to PFOA for 6 Months (Butenhoff et al. 2002)

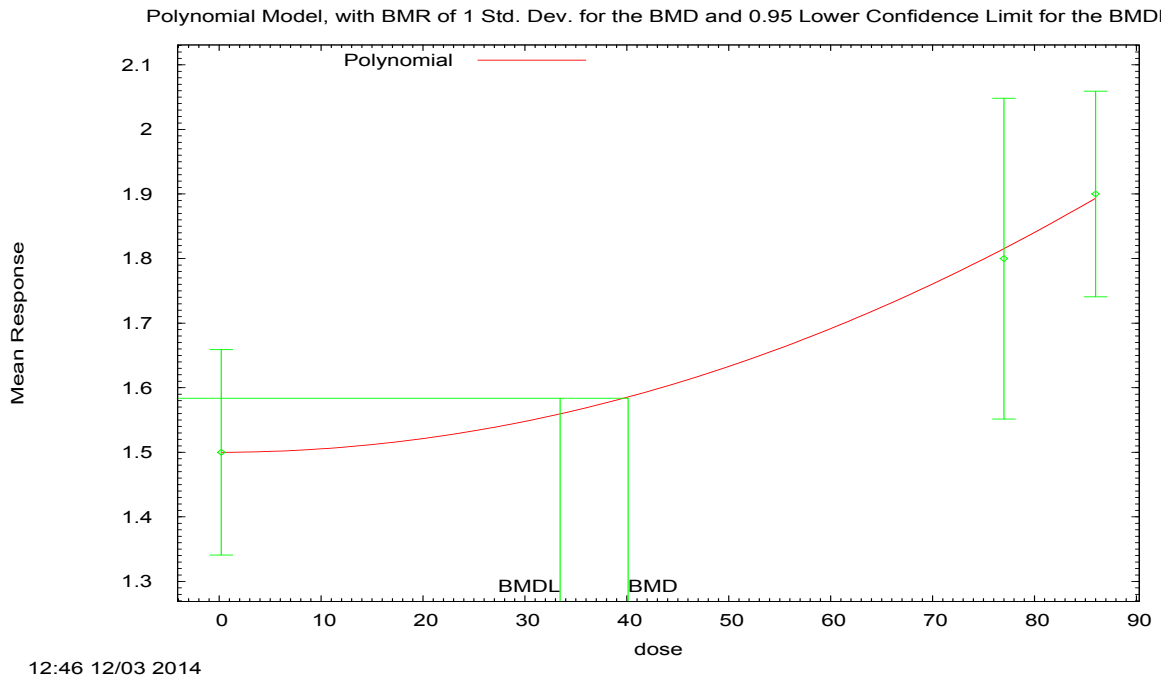
Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Dose above BMD	Overall largest	AIC	$BMD_{RD10\%}$ (µg/mL)	$BMDL_{RD10\%}$ (µg/mL)
Constant variance									
Exponential (model 2)[d]	0.0011	0.99	0.39	0.074	-0.663	-0.663	-36.44	36.05	28.13
Exponential (model 3)[d]	0.0011	0.99	NA	0.00	0.00	0.00	-35.16	ND	ND
Exponential (model 4)[d]	0.0011	0.99	NA	0.064	-0.705	-0.705	-34.33	ND	ND
Linear[f]	0.0011	0.99	0.36	0.064	-0.705	-0.705	-36.33	33.91	25.59
Polynomial[e,f]	**0.0011**	**0.99**	**0.73**	**0.047**	**-0.276**	**-0.276**	**-37.04**	**53.04**	**46.31**
Power[d]	0.0011	0.99	NA	0.00	0.00	0.00	-35.16	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable; ND = not determined, model does not provide adequate fit to the data; PFOA = perfluorooctanoic acid; RD = relative deviation

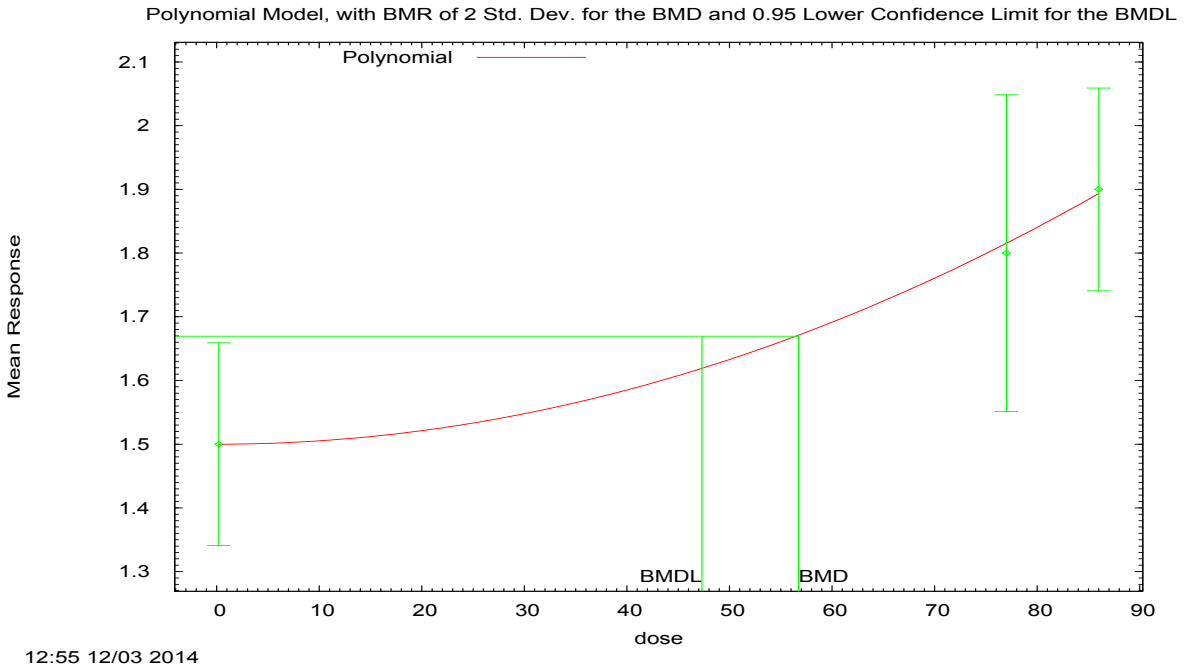
For the relative liver weights, the difference in BMDL values for the BMD models with adequate fit was <2-fold and the model with the lowest AIC was selected. The polynomial plots are presented in Figures A-4, A-5, and A-6.

Figure A-4. Predicted (Polynomial Model, High Dose Dropped with Constant Variance, 1 Standard Deviation Benchmark Response) and Observed Relative Liver Weights



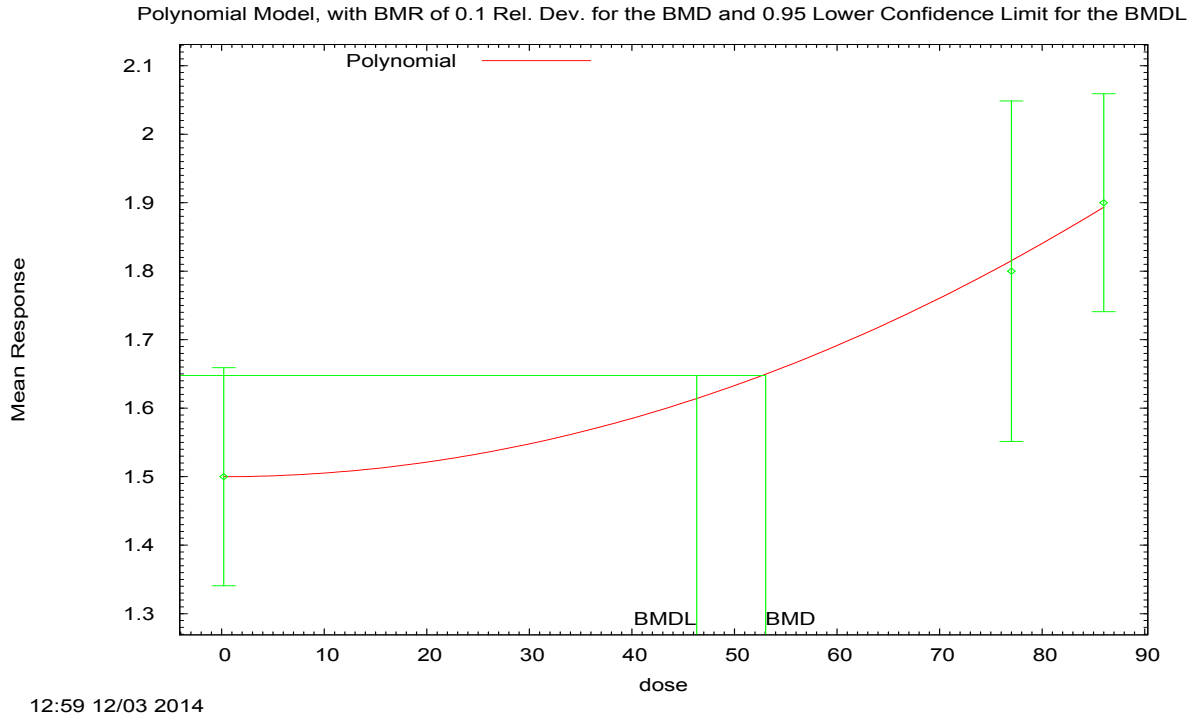
*The x-axis represents the serum PFOA level (µg/mL).

Figure A-5. Predicted (Polynomial Model, High Dose Dropped with Constant Variance, 2 Standard Deviation Benchmark Response) and Observed Relative Liver Weights



*The x-axis represents the serum PFOA level (µg/mL).

Figure A-6. Predicted (Polynomial Model, High Dose Dropped with Constant Variance, 10% Relative Deviation Benchmark Response) and Observed Relative Liver Weights



*The x-axis represents the serum PFOA level (µg/mL).

The BMDL serum concentrations can be converted to an equivalent dose in humans, defined as the continuous ingestion dose (mg/kg/day) that would result in steady-state serum concentrations of PFOA equal to the serum concentration (µg/mL) selected as the POD.

The relationship between PFOA external dosage (mg/kg/day) and steady-state serum concentration in humans can be estimated assuming a single-compartment first-order model in which elimination kinetics are adequately represented by observed serum elimination half-time for PFOA (≈1,400 days) in retired workers (e.g., Olsen et al. 2007a) and an assumed apparent volume of distribution (e.g., 0.2 L/kg, Butenhoff et al. 2004c; Harada et al. 2005a) and gastrointestinal absorption fraction (e.g., 1.0; based on studies in rodents and non-human primates). In the first-order single-compartment model, continuous exposure will result in a steady-state body burden (BB_{SS}, mg/kg) for PFOA, which will be distributed in a single volume of distribution (V_d, L/kg) to yield a steady-state serum concentration (CC_{SS}, mg/L, Equation A-1):

$$C_{SS} = \frac{BB_{SS}}{V_d} \quad \text{Eq. (A-1)}$$

At steady state, the rate of first-order elimination (a constant fraction of the body burden, k_e per day) will equal the absorbed dosage (mg/kg/day, Equation A-2):

$$D_{SS} \cdot AF = BB_{SS} \cdot k_e \quad \text{Eq. (A-2)}$$

Rearrangement of Equation A-2 allows calculation of the steady-state body burden corresponding to a given external dosage (Equation A-3):

$$BB_{SS} = \frac{D_{SS} \cdot AF}{k_e} \quad \text{Eq. (A-3)}$$

The relationship between the elimination rate constant (k_e, day^{-1}) and the elimination half-time ($t_{1/2}$, day), is given in Equation A-4:

$$k_e = \frac{\ln(2)}{t_{1/2}} \quad \text{Eq. (A-4)}$$

Combining Equations A-1 and A-2 yields an expression relating the external steady state dosage and steady-state serum concentration (Equation A-5):

$$D_{SS} = \frac{C_{SS} \cdot k_e \cdot V_d}{AF} \quad \text{Eq. (A-5)}$$

Equation A-5 can be used to calculate an external dosage (mg/kg/day) that would be equivalent to any given steady-state serum concentration (mg/L).

The above estimates of C_{SS}/D_{SS} are sensitive to the input parameters, $t_{1/2}$, AF, and V_d. Several studies have estimated PFOA half-times ($t_{1/2}$) in workers (Costa et al. 2009; Olsen et al. 2007a) or highly exposed residents (Bartell et al. 2010). Estimates of the half-time based on Olsen et al. (2007a) were derived from longitudinal measurements of serum concentrations of PFOA in a group of fluorochemical production workers (24 males, 2 females); the estimated half-time was 3.8 years (1,387 days). Costa et al. (2009) reported a half-time for PFOA of 5.1 years (1,862 days) for a group of workers (n=16) following their cessation of PFOA production work. A longitudinal study by Bartell et al. (2010) followed serum PFOA concentrations in 200 subjects recruited from the Lubeck Public Service District and Little Hocking Water Association and followed for a period of 6–12 months after mitigation of exposures from drinking water. The estimated half-time for PFOA was 2.3 years (840 days). A fourth study estimated half-times in a cross-sectional study of residents served by the Lubeck Public Service District and Little Hocking Water Association (Seals et al. 2011). The estimated half-times ranged from 2.9 to 10.1 years (1,059–3,687 days) for PFOA. Results from the longitudinal studies are shown in Table A-8. For the MRL calculations, the PFOA half-time estimated by Olsen et al. (2007a) was selected over the half-time estimated by Bartell et al. (2010) because the Olsen et al. (2007a) study had a longer follow-up time (>5 years compared to 6–12 months) and estimates of the terminal half-time appear to increase with longer follow-ups because slower kinetics make a larger contribution to the terminal half-time (Seals et al. 2011). Estimates of the $t_{1/2}$ for PFOA are most applicable to serum concentrations within the above ranges and would be less certain if applied to serum concentrations substantially below or above these ranges. The serum concentrations during the 5-year observation period in the Olsen et al. (2007a) study ranged from 72 to 5,100 ng/mL (mean 408 ng/mL) at the initial measurements and from 17 to 2,435 ng/mL (mean 148 ng/mL) at the final measurements.

Table A-8. Half-Time Perfluorooctanoic Acid (PFOA) Levels in Humans

PFOA $t_{1/2}$ (days)	Exposure type	Number of subjects	Reference
1,387	Occupational	26	Olsen et al. (2007a)
1,862	Occupational	16	Costa et al. (2009)
840	Environmental	200	Bartell et al. (2010)

Estimates of volume of distribution (V_d) are based on non-compartmental modeling of serum concentration kinetics in monkeys and are assumed to be applicable to humans at the above serum concentrations (Table A-9).

Table A-9. Apparent Volume of Distribution for Perfluorooctanoic Acid (PFOA)

PFOA V_d (L/kg)	Source
0.18 (male) 0.20 (female)	Butenhoff et al. (2004c)
0.3	Harada et al. (2005a)

Numerous studies conducted in various animal models provide evidence for approximately complete absorption of oral doses of PFOA (i.e., AF≈1, see Section 3.4.1).

The first-order one-compartment model input parameters ($t_{1/2}$, V_d, and AF) are given in Table A-10.

Table A-10. PFOA Model Parameters for Humans

Parameter		Unit	PFOA
Serum elimination half-time[a]	$t_{1/2}$	day	1,400
Serum elimination rate constant[b]	k_e	day^{-1}	$4.95x10^{-4}$
Gastrointestinal absorption fraction[c]	AF	--	1
Apparent volume of distribution[d]	V_d	L/kg	0.2

[a]Estimates from Olsen et al. (2007a).
[b]Calculated using Equation A-4.
[c]Based on studies in rodents and nonhuman primates.
[d]Estimates based on studies in nonhuman primates (Butenhoff et al. 2004c; Chang et al. 2012; Harada et al. 2005a).

PFOA = perfluorooctanoic acid

Human equivalent doses (HEDs) were calculated for each potential point of departure (POD) for the absolute and relative liver weights. The HEDs, presented in Table A-11, were calculated using Equation A-5 and the model parameters in Table A-10. The increased absolute liver weight was selected as the critical effects because it was the more sensitive end point and was significantly increased as all three dose levels. The BMDL value of $1.54x10^{-3}$ mg/kg/day predicted with the 10% relative deviation was selected as the POD because it had the lowest HED for increased absolute liver weight.

Table A-11. Human Equivalent Doses for PFOA

	POD (µg/mL)	HED (mg/kg/day)
Absolute liver weight, $BMDL_{1SD}$; linear model	15.87	$1.57x10^{-3}$
Absolute liver weight, $BMDL_{2SD}$; linear model	31.73	$3.14x10^{-3}$
Absolute liver weight, $BMDL_{RD10\%}$; linear model	15.53	$1.54x10^{-3}$
Relative liver weight, $BMDL_{1SD}$; polynomial model	33.45	$3.31x10^{-4}$
Relative liver weight, $BMDL_{2SD}$; polynomial model	47.31	$4.68x10^{-3}$
Relative liver weight, $BMDL_{RD10\%}$; polynomial model	46.31	$4.59x10^{-3}$

BMDL = lower confidence limit on the benchmark dose; HED = human equivalent dose; PFOA = perfluorooctanoic acid; POD = point of departure

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment
[X] 10 for human variability
[X] 3 for database deficiencies particularly studies examining developmental and immunological end points in monkeys.

Intermediate-duration studies in rats and mice have demonstrated that the developing organism and the immune system are also sensitive targets of PFOA toxicity. The lowest LOAEL for developmental effects in mice (0.01 mg/kg/day; Hines et al. 2009) was lower than lowest LOAEL for liver effects in 21-day mouse studies (0.5 mg/kg/day; Kennedy 1987; Son et al. 2008). The lowest LOAEL for immune effects (0.49 mg/kg/day; Son et al. 2009) was similar to the lowest LOAEL for liver effects. A database uncertainty factor was used to account for the lack of studies examining the possible developmental and immune toxicity of PFOA in monkeys and to allow for a more thorough evaluation of the most sensitive target of PFOA toxicity in humans.

Was a conversion factor used from ppm in food or water to mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The identification of the liver as one of the critical targets of toxicity is well supported by studies in rats and mice. In rodents, increases in liver weight, hepatocellular hypertrophy, and decreases in serum cholesterol levels have been observed following intermediate-duration exposure (Abbott et al. 2007; Albrecht et al. 2013; Biegel et al. 2001; Butenhoff et al. 2004b; Griffith and Long 1980; Kennedy 1987; Lau et al. 2006; Loveless et al. 2008; Perkins et al. 2004; Son et al. 2008; Tan et al. 2013; Wolf et al. 2007),

Other sensitive effects observed in rodents, but not adequately examined in monkeys, include immunotoxicity and developmental toxicity. No alterations in spleen or thymus morphology or the response to T-dependent antigens were observed in rats (Iwai and Yamashita 2006; Loveless et al. 2008). However, intermediate-duration exposure in mice resulted in decreases in the number of splenocytes and thymocytes and their phenotypes, splenic atrophy, and impaired response to T-dependent antigens (Dewitt

et al. 2008; Loveless et al. 2008; Son et al. 2009). In monkeys, no morphological alterations were observed in the spleen after a 4-week exposure to 20 mg/kg/day (Thomford 2001); however, atrophy of the lymphoid follicles was observed in the spleen and bone marrow of Rhesus monkeys exposed to 30 mg/kg/day for 90 days (Griffith and Long 1980).

At doses similar to those inducing liver effects, developmental effects, including decreases in postnatal survival, decreases in pup body weight, increased spontaneous activity, and impaired mammary gland development, have been observed in rats and mice (e.g., Abbott et al. 2007; Albrecht et al. 2013; Hu et al. 2010; Johansson et al. 2008; Lau et al. 2006; Onishchenko et al. 2011; White et al. 2007, 2009, 2011b; Wolf et al. 2007).

Studies in humans provide suggestive evidence that chronic exposure to PFOA can result in increases in serum cholesterol levels (Costa 2004; Costa et al. 2009; Eriksen et al. 2013; Frisbee et al. 2010; Olsen et al. 2003a; Sakr et al. 2007a, 2007b; Steenland et al. 2009b). Increases in serum ALT and bilirubin levels have been observed in highly exposed residents (Gallo et al. 2012), but studies in workers have not consistently found alterations in serum liver enzymes (Costa et al. 2009; Olsen et al. 1999, 2000, 2003a, 2012; Sakr et al. 2007a, 2007b).

Agency Contact (Chemical Manager): Selene Chou

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Perfluorooctane sulfonic acid (PFOS)
CAS Number: 1763-23-1
Date: December 2014
Profile Status: Final for Pre-Public Comment
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 27
Species: Monkey

Minimal Risk Level: $3x10^{-5}$ [X] mg/kg/day [ ] ppm

Reference: Seacat AM, Thomford PJ, Hansen KJ, et al. 2002. Subchronic toxicity studies on perfluorooctanesulfonate potassium salt in Cynomolgus monkeys. Toxicol Sci 68:249-264.

Experimental design: Potassium PFOS (86.9% pure) was administered to groups of Cynomolgus monkeys in a capsule at doses of 0 (6/sex), 0.03 (4/sex), 0.15 (6/sex), or 0.75 (6/sex) mg/kg/day for at least 26 weeks. Two monkeys/sex in the control, 0.15, and 0.75 mg/kg/day groups were monitored for 1 year after dosing ceased (recovery phase). End points monitored twice weekly during the study included mortality, morbidity, clinical signs, and qualitative food consumption; body weights were monitored predosing and weekly thereafter. PFOS levels in the serum were determined predosing and at multiple times during dosing and through the recovery period; PFOS levels in the liver were measured at necropsy. Blood samples for comprehensive hematology and clinical chemistry testing were also collected several times predosing and during the study. Hormones measured in serum included cortisol, testosterone, estradiol, estrone, estriol, total T3, total T4, free T3 and T4, and TSH. Urine was also analyzed at various time points. All major organs and tissues were processed for microscopic examination. Hepatic peroxisomal proliferation was evaluated by measuring palmitoyl CoA oxidase activity and cell proliferation by immunohistochemistry.

Effect noted in study and corresponding doses: Two high-dose males died or were sacrificed *in extremis* during treatment. The specific cause of the death and morbidity was not determined; histological and clinical chemistry evaluations of these animals suggest that the causes of death and morbidity were probably pulmonary inflammation and hyperkalemia, respectively, and do not appear to be related to dosing with PFOS. After 183 days of treatment, body weight in mid- and high-dose males was decreased 11 and 13.5%, respectively relative to controls. Body weight of high-dose females was decreased 7% relative to controls. Absolute liver weight in high-dose males and females was increased 55 and 47%, respectively, relative to controls. Liver weight relative to body and brain weight was also significantly increased in high-dose males and females. The absolute and relative liver weights are reported in Table A-12. No anatomic pathology occurred in low- or mid-dose animals. The average liver/serum PFOS concentration ranged from 0.9/1 to 2.7/1, without a dose-response relationship. The average percent of the cumulative dose of PFOS found in the liver at termination ranged from 4.4 to 8.7% without apparent correlation to dose or sex. The mean concentrations of PFOS in serum in low-dose males and females were 15.8 and 13.2 ppm, respectively. The only significant treatment-related, but not biologically significant, hematological change was a reduction in hemoglobin in high-dose males at termination. Significant clinical chemistry changes consisted of decrease in total cholesterol in high-dose males and females on days 91, 153, and 182. On day 182, total cholesterol decreased to 35 and 53% of predosing values in males and females, respectively. HDL was significantly lower in low- and high-dose males on days 153 and 182 and in mid- and high-dose females at days 153 and 182. Serum bilirubin was significantly lower in high-dose males at days 91, 153, and 182; however, they were within the normal

range. The only significant change in urinalysis was a lower pH value in high-dose females on day 62. Significant changes in hormone levels included the following: increased TSH and decreased total T3 in high-dose males and females on day 182 and reduced mean estradiol in high-dose males at day 182. The TSH levels were within the normal range and T3 levels were within the normal range for Rhesus monkeys. Liver peroxisome proliferation was significantly increased in high-dose females, but not enough to be considered biologically significant. Cell proliferation in liver, pancreas, and testes was not significantly altered at day 182. Light microscopy of liver sections showed centrilobular vacuolation, hypertrophy, and mild bile stasis in some high-dose monkeys. Electron microscopy showed lipid-droplet accumulation in some high-dose males and females. Increased glycogen content was also noted in the high-dose group. The following was reported in the recovery phase. The elimination of PFOS from serum of high-dose monkeys appeared to be multiphasic, whereas that for the mid-dose group was linear. For both groups, the elimination half-life was approximately 200 days. There were no differences between males and females. PFOS in liver decreased substantially during the recovery period. One year after cessation of treatment, PFOS in liver from mid-dose monkeys were approximately 19% of the concentration measured at the end of treatment. Serum cholesterol in high-dose monkeys returned to pre-treatment levels by day 36; HDL values returned to control levels within 61 days of cessation of treatment in the mid- and high-dose groups. All hormone values returned to normal between day 33 and 61 of recovery. Samples of liver collected at 7 months of recovery showed complete recovery of pathology by light or electron microscopy. The same observations were made after 1 year of recovery.

Table A-12. Liver Weights of Male and Female Cynomolgus Monkeys Exposed to PFOS for 6 Months

Nominal dose[a] (mg/kg/day)	Serum PFOS level[b] (µg/mL)	Number of animals	Absolute liver weight (g)	Relative liver weight (%)
Males				
0	0.05	3	54.9±8.1	1.6±0.2
0.03	8.6	4	62.1±5.3	1.7±0.3
0.150	43.5	4	57.3±5.5	1.8±0.1
0.75	140	2	85.3±38.4	2.7±0.3*
Females				
0	0.05	4	51.1±9.4	1.8±0.2
0.03	7.8	4	56.8±12.6	1.9±0.0
0.150	36.4	4	57.0±3.1	2.1±0.2
0.75	131	4	75.3±13.3*	2.9±0.3*

[a]KPFOS (86.9%) purity was administered; capsules for the 0.75 mg/kg/day group contained 72±35% of target dose for 0.75 mg/kg/day group and 103±25% for the 0.150 and 0.75 mg/kg/day groups).
[b]Time-weighted average of mean serum concentrations for the 6-month period; data taken from Figure 1 of the Seacat et al. (2002) paper.
*Statistically significant when compared to controls, $p<0.01$.

PFOS = perfluorooctane sulfonic acid

Source: Seacat et al. 2002

Dose and end point used for MRL derivation: The $NOAEL_{HED}$ of $2.52x10^{-3}$ mg/kg/day for increases in absolute liver weight in female monkeys was used as the POD for the MRL.

[X] NOAEL [ ] LOAEL [ ] BMDL

Using the dose levels from the Seacat et al. (2002) study is problematic due to species differences in the toxicokinetics of PFOS, particularly the difference in half-times. An alternative approach is to use the serum concentration as an internal dosimetric and the assumption that a serum concentration level that would result in an effect in monkeys would also result in an effect in humans. Using the calculated time-weighted average mean serum PFOS level as the internal dosimetric, the absolute and relative liver weight data were fit to all available continuous models in EPA's BMDS (version 2.4.0). The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$); visual inspection of the dose-response curve; and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMDL was selected as the POD when the difference between the BMCLs estimated from these models were more 3-fold; otherwise, the BMDL from the model with the lowest AIC was chosen. If the test for constant variance was negative, then the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, exponential, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and point of departure selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. Three BMRs were considered: 1 SD change from the control; 2 SD change from the control; and 10% increase in liver weight. Although a 1 SD change is the typical BMR used for continuous variable models without a biological basis to establish a cut-point for biological significance, a 2 SD BMR was also used due to the small number of animals tested. The results of the BMD modeling for absolute liver weight are summarized in Tables A-13, A-14, and A-15.

Table A-13. Absolute Liver Weights of Male and Female Cynomolgus Monkeys Exposed to PFOS for 6 Months (Seacat et al. 2002)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{1SD} (µg/mL)	$BMDL_{1SD}$ (µg/mL)
Male monkeys									
Constant variance									
Linear[e]	0.001	0.002	0.38	-1.01	0.37	-1.01	84.90	ND	ND
Nonconstant variance									
Exponential (model 2)[d,e]	**0.001**	**0.38**	**0.10**	**-0.98**	**0.68**	**1.26**	**76.83**	**55.27**	**23.21**
Exponential (model 3)[d]	0.001	0.38	0.20	-0.36	0.00	1.23	75.81	129.03	47.37
Exponential (model 4)[d]	0.001	0.38	0.03	-0.91	0.78	1.23	79.06	ND	ND
Exponential (model 5)[d]	0.001	0.38	NA	-0.36	0.00	1.23	77.81	ND	ND
Hill[d]	0.001	0.38	NA	-0.36	0.00	1.23	77.81	ND	ND
Linear[f]	0.001	0.38	0.09	-0.92	0.78	1.23	77.06	ND	ND
Polynomial (2-degree)[e]	0.001	0.38	0.23	-0.74	0.38	1.34	75.04	76.61	46.79
Polynomial (3-degree)[f]	0.001	0.38	0.36	-0.52	0.10	1.29	74.18	86.98	62.33
Power[d]	0.001	0.38	0.20	-0.36	0.00	1.23	75.81	127.78	48.45
Female monkeys									
Constant variance									
Linear[e]	0.005	0.07	0.72	-0.39	0.07	0.63	93.04	ND	ND
Nonconstant variance									
Linear[e]	0.006	0.05	<0.0001	-1.86E+3	4.66E+3	4.66E+3	6	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model.
[f]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = BMDL computation failed; ND = not determined, model does not provide adequate fit to the data; PFOS = perfluorooctane sulfonic acid; SD = standard deviation

Table A-14. Absolute Liver Weights of Male and Female Cynomolgus Monkeys Exposed to PFOS for 6 Months (Seacat et al. 2002)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{2SD} (µg/mL)	$BMDL_{2SD}$ (µg/mL)
Male monkeys									
Constant variance									
Linear[e]	0.001	0.002	0.38	-1.01	0.37	-1.01	84.90	ND	ND
Nonconstant variance									
Exponential (model 2)[d,e]	**0.001**	**0.38**	**0.10**	**-0.98**	**0.68**	**1.26**	**76.83**	**105.76**	**44.60**
Exponential (model 3)[d]	0.001	0.38	0.20	-0.36	0.00	1.23	75.81	134.19	74.61
Exponential (model 4)[d]	0.001	0.38	0.03	-0.91	0.78	1.23	79.06	ND	ND
Exponential (model 5)[d]	0.001	0.38	NA	-0.36	0.00	1.23	77.81	ND	ND
Hill[d]	0.001	0.38	NA	-0.36	0.00	1.23	77.81	ND	ND
Linear[f]	0.001	0.38	0.09	-0.92	0.78	1.23	77.06	ND	ND
Polynomial (2-degree)[e]	0.001	0.38	0.23	-0.74	0.38	1.34	75.04	108.34	66.17
Polynomial (3-degree)[f]	0.001	0.38	0.36	-0.52	0.10	1.29	74.18	109.58	78.53
Power[d]	0.001	0.38	0.20	-0.36	0.00	1.23	75.81	133.32	73.41
Female monkeys									
Constant variance									
Linear[e]	0.005	0.07	0.72	-0.39	0.07	0.63	93.04	ND	ND
Nonconstant variance									
Linear[e]	0.006	0.05	<0.0001	NA	-1.86E+3	4.66E+3	6	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model.
[f]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); ND = not determined, model does not provide adequate fit to the data; PFOS = perfluorooctane sulfonic acid; SD = standard deviation

Table A-15. Absolute Liver Weights of Male and Female Cynomolgus Monkeys Exposed to PFOS for 6 Months (Seacat et al. 2002)

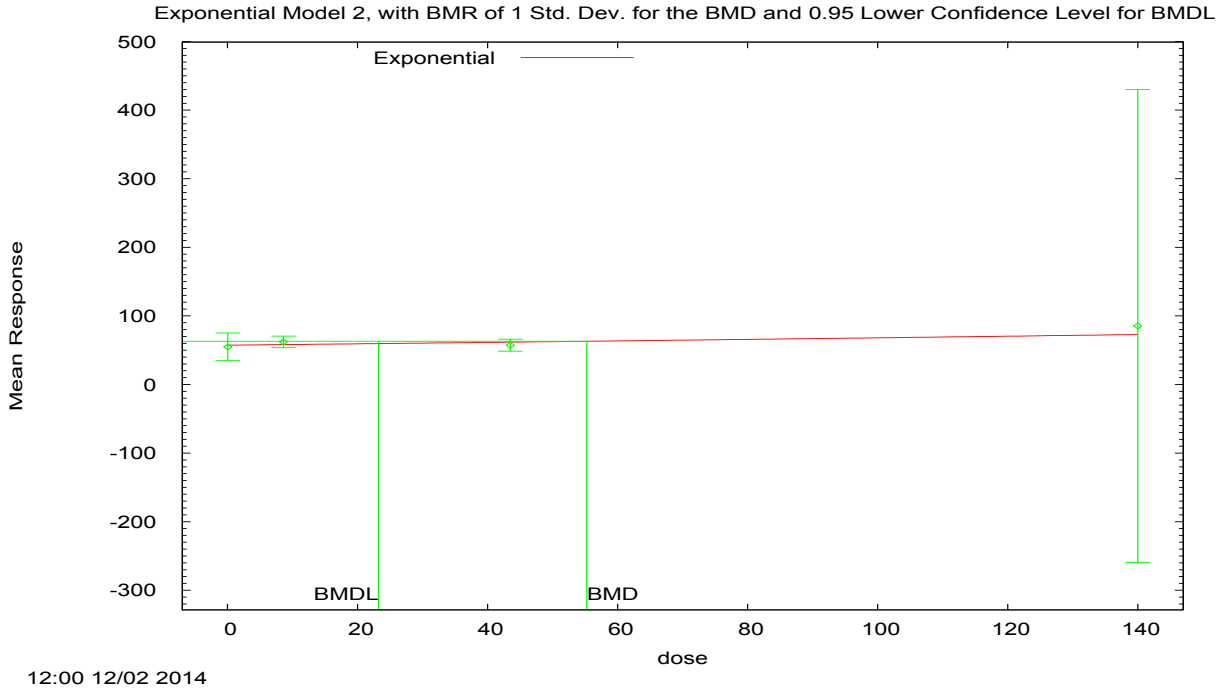
Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	$BMD_{RD10\%}$ (µg/mL)	$BMDL_{RD10\%}$ (µg/mL)
Male monkeys									
Constant variance									
Linear[e]	0.001	0.002	0.38	0.80	-1.01	-1.01	84.90	ND	ND
Nonconstant variance									
Exponential (model 2)[d,e]	**0.001**	**0.38**	**0.10**	**-0.98**	**0.68**	**1.26**	**76.83**	**55.67**	**23.28**
Exponential (model 3)[d]	0.001	0.38	0.20	-0.36	0.00	1.23	75.81	128.77	46.13
Exponential (model 4)[d]	0.001	0.38	0.03	-0.91	0.78	1.23	79.06	ND	ND
Exponential (model 5)[d]	0.001	0.38	NA	-0.36	0.00	1.23	77.81	ND	ND
Hill[d]	0.001	0.38	NA	-0.36	0.00	1.23	77.81	158.14	83.86
Linear[f]	0.001	0.38	0.09	-0.92	0.78	1.23	77.06	ND	ND
Polynomial (2-degree)[e]	0.001	0.38	0.23	-0.74	0.38	1.34	75.04	75.17	46.08
Polynomial (3-degree)[f]	0.001	0.38	0.36	-0.52	0.10	1.26	74.18	85.88	62.30
Power[d]	0.001	0.38	0.20	-0.36	0.00	1.23	75.81	127.50	47.13
Female monkeys									
Constant variance									
Linear[e]	0.005	0.07	0.72	0.63	-0.39	0.63	93.04	ND	ND
Nonconstant variance									
Linear[e]	0.006	0.05	<0.0001	4.66 E+3	-3.03 E+3	4.66E+3	6	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model.
[f]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); ND = not determined, model does not provide adequate fit to the data; PFOS = perfluorooctane sulfonic acid; RD = relative deviation

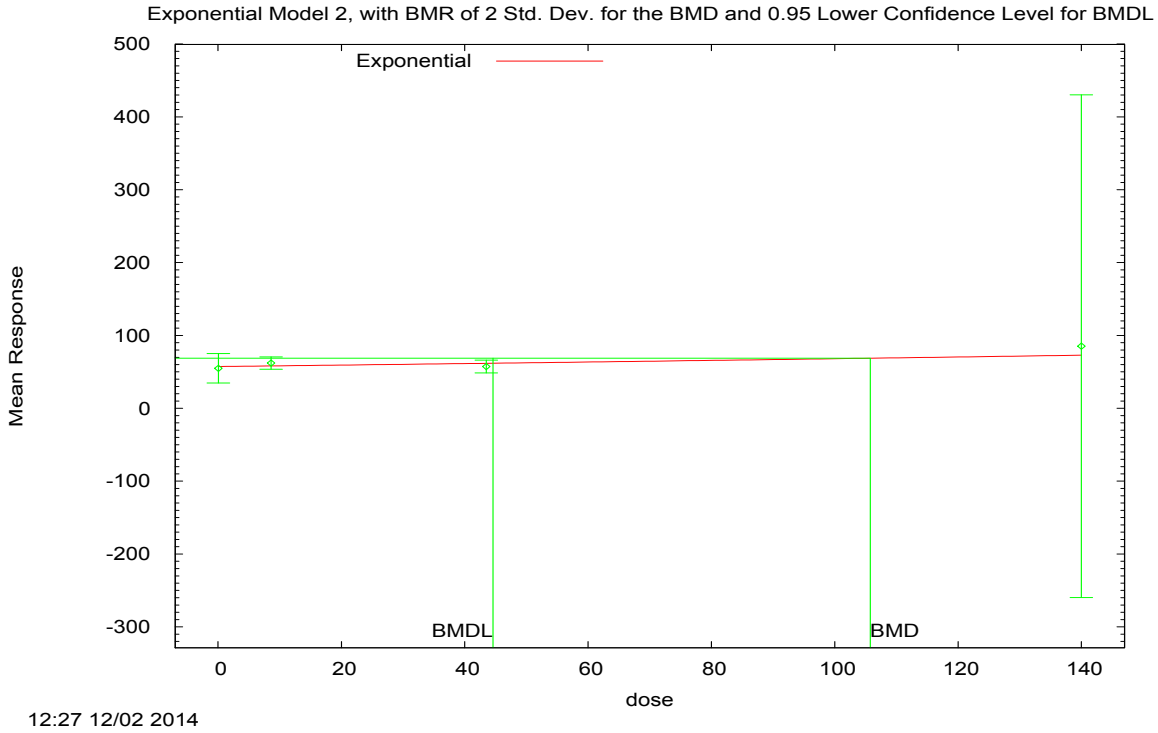
For the absolute liver weights in male monkeys (none of the models provided an adequate fit for the absolute liver weights in female monkeys), the differences between the BMDL values in BMD models with adequate fit were >3-fold and the model with the lowest BMDL was selected. The exponential model 2 plots are presented in Figures A-7, A-8, and A-9.

Figure A-7. Predicted (Exponential Model 2 with Nonconstant Variance, 1 Standard Deviation Benchmark Response) and Observed Absolute Liver Weights in Male Monkeys



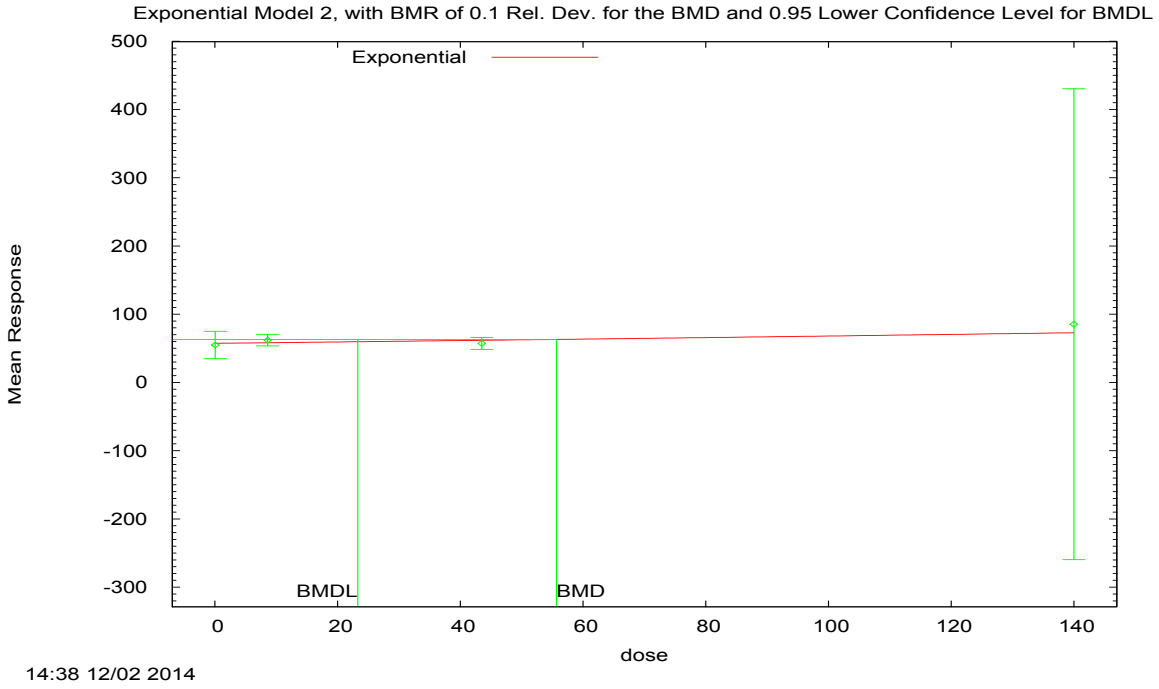
*The x-axis represents the serum PFOS level (µg/mL).

Figure A-8. Predicted (Exponential Model 2 with Nonconstant Variance, 2 Standard Deviation Benchmark Response) and Observed Absolute Liver Weights in Male Monkeys



*The x-axis represents the serum PFOS level (µg/mL).

Figure A-9. Predicted (Exponential Model 2 with Nonconstant Variance, 10% Relative Deviation Benchmark Response) and Observed Absolute Liver Weights in Male Monkeys



*The x-axis represents the serum PFOS level (µg/mL).

The results of the BMD modeling for relative liver weight are presented in Tables A-16, A-17, and A-18.

Table A-16. Relative Liver Weights of Male and Female Cynomolgus Monkeys Exposed to PFOS for 6 Months (Seacat et al. 2002)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Scaled residuals[c] Dose above BMD	Scaled residuals[c] Overall largest	AIC	BMD_{1SD} (µg/mL)	$BMDL_{1SD}$ (µg/mL)
Male monkeys									
Constant variance									
Exponential (model 2)[d,f]	**0.0004**	**0.23**	**0.63**	**0.56**	**-0.73**	**-0.73**	**-23.25**	**31.53**	**23.11**
Exponential (model 3)[d]	0.0004	0.23	0.56	-0.10	0.01	0.42	-21.82	48.06	23.83
Exponential (model 4)[d]	0.0004	0.23	0.18	0.58	-1.05	-1.05	-20.40	26.73	18.77
Exponential (model 5)[d]	0.0004	0.23	N/A	-0.08	0.01	0.43	-19.79	ND	ND
Hill[d]	0.0004	0.23	0.18	0.89	0.00	-0.93	-20.38	116.14	17.09
Linear[e]	0.0004	0.23	0.42	0.58	-1.05	-1.05	-22.40	26.73	18.77
Polynomial (2-degree)[e]	0.0004	0.23	0.58	-0.11	0.01	0.40	-21.86	47.12	20.79
Polynomial (3-degree)[e]	0.0004	0.23	0.63	-0.08	0.00	0.35	-21.92	47.62	20.91
Power[d]	0.0004	0.23	0.54	-0.08	0.01	0.43	-21.79	48.71	20.66
Female monkeys									
Constant variance									
Linear[e]	<0.0001	<0.0001	0.95	0.26	-0.15	0.26	-33.02	ND	ND
Nonconstant variance									
Linear[e]	<0.0001	<0.0001	<0.0001	0.33	-0.17	0.33	-33.73	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable; ND = not determined, model does not provide adequate fit to the data; PFOS = perfluorooctane sulfonic acid; SD = standard deviation

Table A-17. Relative Liver Weights of Male and Female Cynomolgus Monkeys Exposed to PFOS for 6 Months (Seacat et al. 2002)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c]			AIC	BMD_{2SD} (µg/mL)	$BMDL_{2SD}$ (µg/mL)
				Dose below BMD	Dose above BMD	Overall largest			
Male monkeys									
Constant variance									
Exponential (model 2)[d,f]	**0.0004**	**0.23**	**0.63**	**-0.73**	**0.19**	**-0.73**	**-23.25**	**59.78**	**44.26**
Exponential (model 3)[d]	0.0004	0.23	0.56	-0.10	0.01	0.42	-21.82	75.97	45.60
Exponential (model 4)[d]	0.0004	0.23	0.18	-1.05	0.41	-1.05	-20.40	53.46	37.54
Exponential (model 5)[d]	0.0004	0.23	NA	-0.08	0.01	0.43	-19.79	ND	ND
Hill[d]	0.0004	0.23	0.18	0.89	0.00	-0.93	-20.38	122.33	35.69
Linear[e]	0.0004	0.23	0.42	-1.05	0.41	-1.05	-22.40	53.46	37.54
Polynomial (2-degree)[e]	0.0004	0.23	0.58	-0.11	0.01	0.40	-21.86	75.01	41.59
Polynomial (3-degree)[e]	0.0004	0.23	0.63	-0.08	0.00	0.35	-21.92	79.10	41.83
Power[d]	0.0004	0.23	0.54	-0.08	0.01	0.43	-21.79	74.98	41.32
Female monkeys									
Constant variance									
Linear[e]	<0.0001	<0.0001	0.95	-0.15	0.03	0.26	-33.02	ND	ND
Nonconstant variance									
Linear[e]	<0.0001	<0.0001	<0.0001	0.33	-0.17	0.33	-33.73	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; NA = not applicable; ND = not determined, model does not provide adequate fit to the data; PFOS = perfluorooctane sulfonic acid; SD = standard deviation

Table A-18. Relative Liver Weights of Male and Female Cynomolgus Monkeys Exposed to PFOS for 6 Months (Seacat et al. 2002)

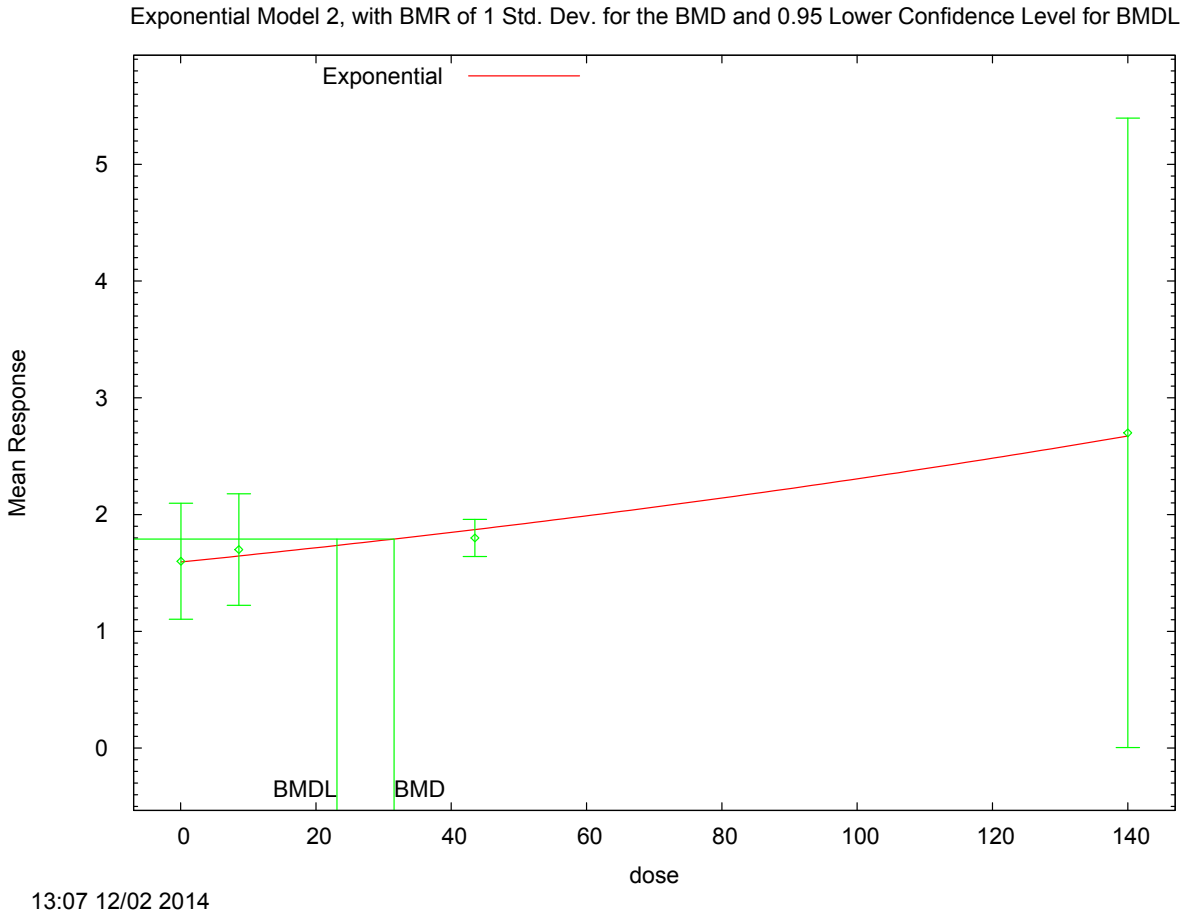
Model	Test for significant difference p-value[a]	Variance p-value[b]	Mean p-value[b]	Scaled residuals[c] Dose below BMD	Dose above BMD	Overall largest	AIC	$BMD_{RD10\%}$ (µg/mL)	$BMDL_{RD10\%}$ (µg/mL)
Male monkeys									
Constant variance									
Exponential (model 2)[d,f]	**0.0004**	**0.23**	**0.63**	**0.56**	**-0.73**	**-0.76**	**-23.25**	**25.80**	**20.87**
Exponential (model 3)[d]	0.0004	0.23	0.56	0.42	-0.10	0.42	-21.82	43.14	21.36
Exponential (model 4)[d]	0.0004	0.23	0.18	0.58	-1.05	-1.05	-20.40	20.70	15.32
Exponential (model 5)[d]	0.0004	0.23	NA	0.43	-0.08	0.43	-19.79	ND	ND
Hill[d]	0.0004	0.23	0.18	0.89	0.00	-0.93	-20.38	114.80	12.20
Linear[e]	0.0004	0.23	0.42	0.58	-1.05	-1.05	-22.40	20.70	15.32
Polynomial (2-degree)[e]	0.0004	0.23	0.58	0.40	-0.11	0.40	-21.86	42.10	16.88
Polynomial (3-degree)[e]	0.0004	0.23	0.63	0.35	-0.08	0.35	-21.92	41.71	16.97
Power[d]	0.0004	0.23	0.54	-0.08	0.01	0.43	-21.79	44.15	16.78
Female monkeys									
Constant variance									
Linear[e]	<0.0001	<0.0001	0.95	0.26	-0.15	0.26	-33.02	ND	ND
Nonconstant variance									
Linear[e]	<0.0001	<0.0001	<0.0001	0.33	-0.17	0.33	-33.73	ND	ND

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Coefficients restricted to be positive.
[f]Selected model.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; NA = not applicable; ND = not determined, model does not provide adequate fit to the data; PFOS = perfluorooctane sulfonic acid; RD = relative deviation

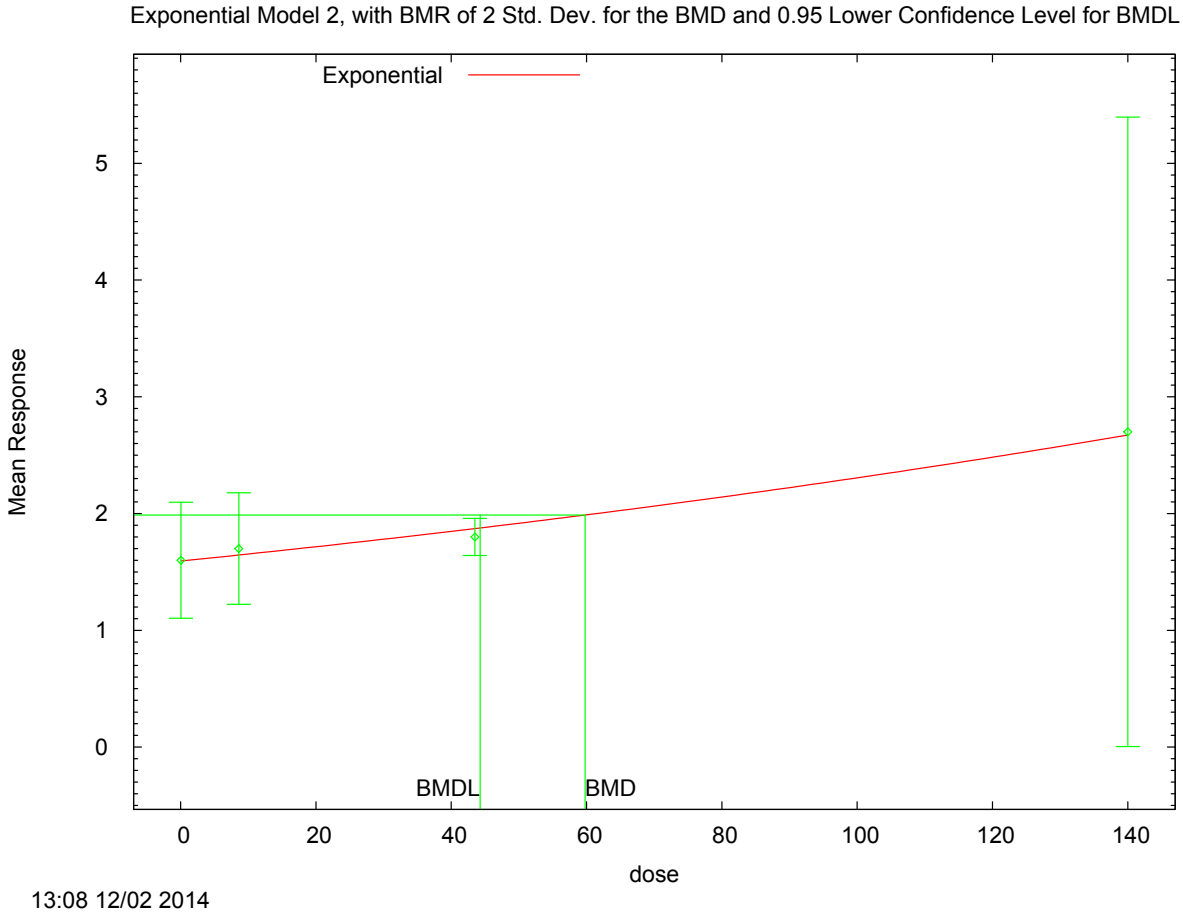
For the relative liver weights in male monkeys (none of the models provided an adequate fit for the absolute liver weights in female monkeys), the BMD models with adequate fit had similar BMDL values and the model with the lowest AIC was selected. The exponential model 2 plots are presented in Figures A-10, A-11, and A-12.

Figure A-10. Predicted (Exponential Model 2 with Constant Variance, 1 Standard Deviation Benchmark Response) and Observed Relative Liver Weights in Male Monkeys



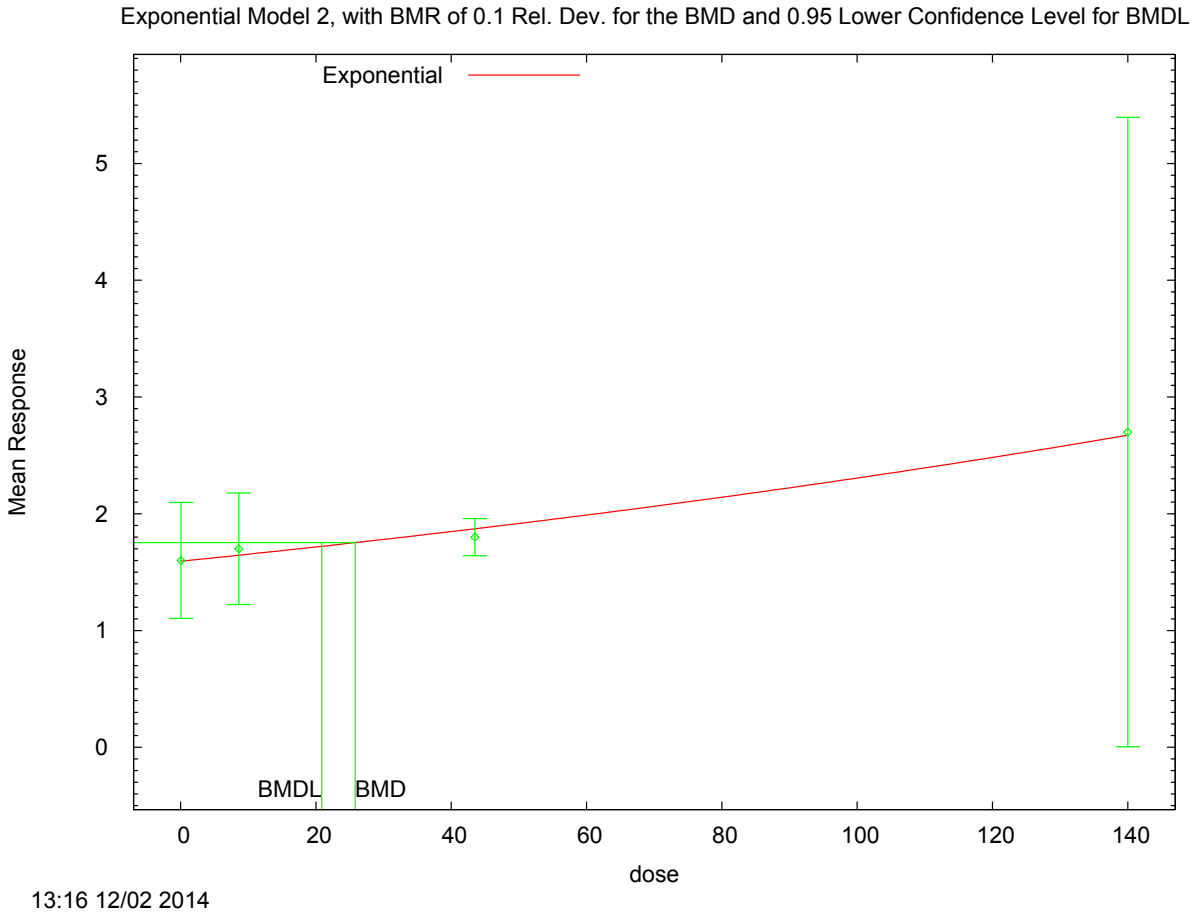
*The x-axis represents the serum PFOS level (µg/mL).

Figure A-11. Predicted (Exponential Model 2 with Constant Variance, 2 Standard Deviation Benchmark Response) and Observed Relative Liver Weights in Male Monkeys



*The x-axis represents the serum PFOS level (µg/mL).

Figure A-12. Predicted (Exponential Model 2 with Constant Variance, 10% Relative Deviation Benchmark Response) and Observed Relative Liver Weights in Male Monkeys



*The x-axis represents the serum PFOS level (µg/mL).

The BMDL serum concentrations can be converted to an equivalent dose in humans, defined as the continuous ingestion dose (mg/kg/day) that would result in steady-state serum concentrations of PFOS equal to the serum concentration (µg/mL) selected as the POD.

The relationship between PFOS external dosage (mg/kg/day) and steady-state serum concentration in humans can be estimated assuming a single-compartment first-order model in which elimination kinetics are adequately represented by observed serum elimination half-time for PFOS (≈2,000 days) in retired workers (e.g., Olsen et al. 2007a) and an assumed apparent volume of distribution (e.g., 0.2 L/kg, Butenhoff et al. 2004c; Chang et al. 2012; Harada et al. 2005a) and gastrointestinal absorption fraction (e.g., 1.0; based on studies in rodents and non-human primates). In the first-order single-compartment model, continuous exposure will result in a steady-state body burden (BB_{SS}, mg/kg) for PFOS, which will be distributed in a single volume of distribution (V_d, L/kg) to yield a steady-state serum concentration (CC_{SS}, mg/L, Equation A-6):

$$C_{SS} = \frac{BB_{SS}}{V_d} \quad \text{Eq. (A-6)}$$

At steady state, the rate of first-order elimination rate (a constant fraction of the body burden, k_e per day) will equal the absorbed dosage (mg/kg/day, Equation A-7):

$$D_{SS} \cdot AF = BB_{SS} \cdot k_e \quad \text{Eq. (A-7)}$$

Rearrangement of Equation 2 allows calculation of the steady-state body burden corresponding to a given external dosage (Equation A-8):

$$BB_{SS} = \frac{D_{SS} \cdot AF}{k_e} \quad \text{Eq. (A-8)}$$

The relationship between the elimination rate constant (k_e, day^{-1}) and the elimination half-time ($t_{1/2}$, day), is given in Equation A-9:

$$k_e = \frac{\ln(2)}{t_{1/2}} \quad \text{Eq. (A-9)}$$

Combining Equations A-6 and A-7, yields an expression relating the external steady-state dosage and steady state serum concentration (Equation A-10)

$$D_{SS} = \frac{C_{SS} \cdot k_e \cdot V_d}{AF} \quad \text{Eq. (A-10)}$$

Equation A-10 can be used to calculate an external dosage (mg/kg/day) that would be equivalent to any given steady-state serum concentration (mg/L).

The above estimates of C_{SS}/D_{SS} are sensitive to the input parameters, $t_{1/2}$, AF, and V_d. Estimates of the half-time ($t_{1/2}$) based on Olsen et al. (2007a) were derived from longitudinal measurements of serum concentrations of PFOS in a group of fluorochemical production workers (24 males, 2 females) observed from a 5-year period; the estimated half-time was 5.4 years (1,956 days). The range of initial serum concentrations was 145–3490 ng/mL (mean of 626 ng/mL) and the final concentrations ranged from 37 to 1,740 ng/mL (mean of 295 ng/mL). Estimates of the $t_{1/2}$ for PFOS are most applicable to serum concentrations within the above ranges and would be less certain if applied to serum concentrations substantially below or above these range.

Estimates of volume of distribution (V_d) are based on non-compartmental modeling of serum concentration kinetics in monkeys and are assumed to be applicable to humans at the above serum concentrations (see Table A-19).

Table A-19. Apparent Volume of Distribution for Perfluorooctane Sulfonic Acid (PFOS)

PFOS V_d (L/kg)	Source
NA NA	Butenhoff et al. (2004c)
0.20 (male) 0.27 (female)	Chang et al. (2012)
0.3	Harada et al. (2005a)

Numerous studies conducted in various animal models provide evidence for approximately complete absorption of oral doses of PFOS (i.e., AF≈1, see Section 3.4.1).

The first-order one-compartment model input parameters ($t_{1/2}$, V_d, and AF) are given in Table A-20.

Table A-20. PFOS Model Parameters for Humans

Parameter		Unit	PFOS
Serum elimination half-time[a]	$t_{1/2}$	day	2,000
Serum elimination rate constant[b]	k_e	day^{-1}	3.47×10^{-4}
Gastrointestinal absorption fraction[c]	AF	--	1
Apparent volume of distribution[d]	V_d	L/kg	0.2

[a]Estimates from Olsen et al. (2007a).
[b]Calculated using Equation A-9.
[c]Based on studies in rodents and nonhuman primates.
[d]Estimates based on studies in nonhuman primates (Butenhoff et al. 2004c; Chang et al. 2012; Harada et al. 2005a).

PFOS = perfluorooctane sulfonic acid

HEDs were calculated for each POD for the absolute and relative liver weights. The HEDs, presented in Table A-21, were calculated using Equation A-10 and the model parameters in Table A-20. Because decreases in body weight were observed, the increased absolute liver weight was selected as the critical effect. The HEDs calculated for the increased absolute liver weight ranged from 1.61×10^{-3} to 3.09×10^{-3} mg/kg/day. The lowest HED was 1.61×10^{-3} estimated from the BMDL predicted using a benchmark response of 10% relative deviation in absolute liver weight in male monkeys; however, this value is lower than the empirical NOAELs identified in male monkeys (9.07×10^{-3} mg/kg/day estimated from a serum concentration of 140 μg/mL) and in female monkeys (2.52×10^{-3} mg/kg/day estimated from a serum concentration of 36.4 μg/mL) and was not selected as the POD for the MRL. Rather, the NOAEL identified in female monkeys for increased absolute liver weight was selected as the POD for the MRL.

Table A-21. Human Equivalent Doses for PFOS

	POD (µg/mL)	HED (mg/kg/day)
Absolute liver weight in males, $BMDL_{1SD}$; exponential model 2 with nonconstant variance	23.21	$1.61x10^{-3}$
Absolute liver weight in males, $BMDL_{2SD}$; exponential model 2 with nonconstant variance	44.60	$3.09x10^{-3}$
Absolute liver weight in males, $BMDL_{RD10\%}$; exponential model 2 with nonconstant variance	23.28	$1.61x10^{-3}$
Absolute liver weight in females, NOAEL	36.4	$2.52x10^{-3}$
Relative liver weight in males, $BMDL_{1SD}$; exponential model 2 with constant variance	23.11	$1.30x10^{-3}$
Relative liver weight in males, $BMDL_{2SD}$; exponential model 2 with constant variance	44.26	$2.60x10^{-3}$
Relative liver weight in males, $BMDL_{RD10\%}$; exponential model 2 with constant variance	20.87	$1.06x10^{-3}$
Relative liver weight in females, NOAEL	36.4	$2.52x10^{-3}$

BMDL = lower confidence limit on the benchmark dose; HED = human equivalent dose; NOAEL = no-observed-adverse-effect level; PFOS = perfluorooctane sulfonic acid; POD = point of departure; RD= relative deviation; SD = standard deviation

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 3 for extrapolation from animals to humans with dosimetric adjustment
[X] 10 for human variability
[X] 3 for database deficiencies particularly studies examining developmental and immunological end points in monkeys.

Intermediate-duration studies in rats and mice have demonstrated that the developing organism and the immune system are also sensitive targets of PFOS toxicity. Impaired host resistance to a virus was observed in mice exposed to 0.025 mg/kg/day (Guruge et al. 2009); this is lower than the lowest LOAEL for liver effects observed in 28-day rat studies (0.14 mg/kg/day; Curran et al. 2008; Lefebvre et al. 2008). The lowest LOAEL for developmental effects in mice (0.4 mg/kg/day; Luebker et al. 2005a) was slightly higher than the lowest LOAEL for liver effects. A database uncertainty factor was used to account for the lack of studies examining the possible developmental and immune toxicity of PFOS in monkeys, which would allow for a more thorough evaluation of the most sensitive target of PFOS toxicity in humans.

Was a conversion factor used from ppm in food or water to mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: The identification of the liver as one of the critical targets of toxicity of intermediate-duration oral to PFOS is well supported by studies in rats and mice. Increases in liver weight, hepatocellular hypertrophy, and decreases in serum cholesterol levels have been observed following intermediate-duration exposure (Cui et al. 2009; Curran

et al. 2008; Elcombe et al. 2012a; Luebker et al. 2005b; Seacat et al. 2003; Thibodeaux et al. 2003). The lowest LOAEL for liver effects is 0.14 mg/kg/day for increased relative liver weight in female rats exposed for 28 days (Curran et al. 2008).

Other sensitive effects observed in rodents, but not adequately examined in monkeys, include immunotoxicity and developmental toxicity. No alterations in spleen or thymus morphology were observed in rats (Butenhoff et al. 2012b; Lefebvre et al. 2008). Exposure to very low concentrations of PFOS (0.00166, 0.025, or 0.083 mg/kg/day) can result in an impaired response to T-dependent antigen (Dong et al. 2009, 2011; Peden-Adams et al. 2008) or an impaired host resistance to one strain of influenza virus (Guruge et al. 2009). In monkeys, no morphological alterations were observed in the spleen after a 4-week exposure to 2 mg/kg/day (Thomford 2002a) or 0.75 mg/kg/day for 26 weeks (Seacat et al. 2002).

Developmental effects have been observed in rats and mice exposed to ≥0.3 mg/kg/day (Abbott et al. 2009; Case et al. 2001; Chen et al. 2012b; Era et al. 2009; Fuentes et al. 2006, 2007a, 2007b; Grasty et al. 2003, 2005; Lau et al. 2003; Luebker et al. 2005a, 2005b; Onishchenko et al. 2011; Thibodeaux et al. 2003; Xia et al. 2011; Yahia et a. 2008). The observed developmental effects include decreases in postnatal survival, decreases in pup body weight, decreased locomotor activity, sternal defects, or cleft palate.

Studies in humans provide suggestive evidence that chronic exposure to PFOA can result in increases in serum cholesterol levels in workers (Olsen et al. 1999, 2003a), residents living near a PFOA facility (Frisbee et al. 2010; Steenland et al. 2009b), and the general population (Château-Degat et al. 2010; Eriksen et al. 2013; Nelson et al. 2010). The mechanism involved in the increased cholesterol levels in humans is not known; it may be related to liver effects.

Agency Contact (Chemical Manager): Selene Chou

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public, especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicological, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal Risk Levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgment or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, MRLs to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(1) Route of Exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.

(2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 weeks. For a more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Nitschke et al. 1981).

(7) System. This column further defines the systemic effects. These systems include respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, one systemic effect (respiratory) was investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference. The complete reference citation is given in Chapter 9 of the profile.

(11) CEL. A CEL is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the acute and intermediate exposure periods are illustrated.

(14) Health Effect. These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL. Key number 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

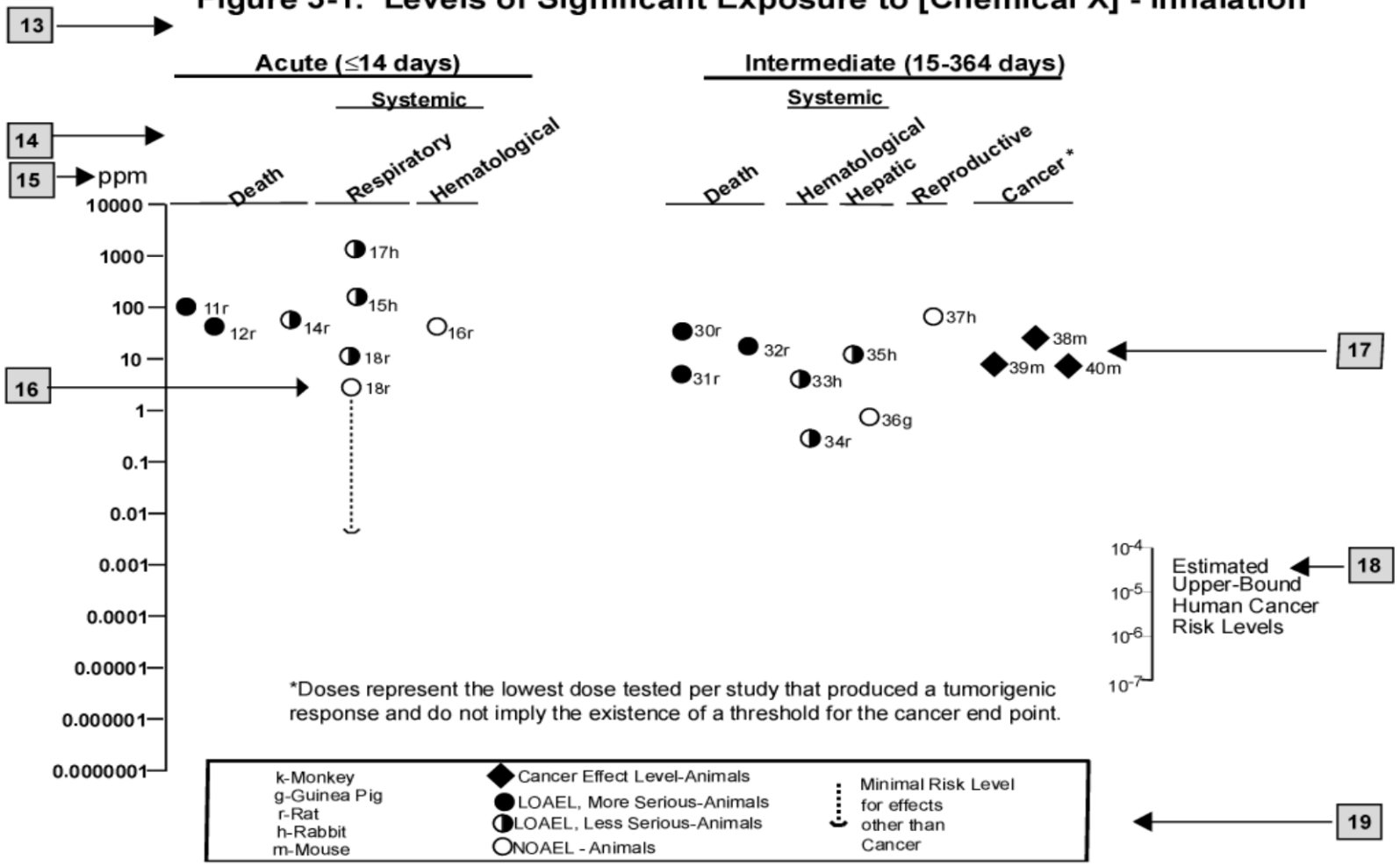
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	Serious (ppm)	Reference
2 →	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10
3 →	Systemic	↓	↓	↓	↓	↓		↓
4 →	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
	CHRONIC EXPOSURE							
	Cancer					11		
						↓		
	38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
	39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
	40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor

DOT	Department of Transportation
DOT/UN/ NA/IMDG	Department of Transportation/United Nations/ North America/Intergovernmental Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie

MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances

OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result