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

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 Environmental Medicine/Applied Toxicology Branch
1600 Clifton Road NE
Mailstop F-62
Atlanta, Georgia 30333

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FOREWORD

This toxicological profile for perfluoroalkyls was prepared consistent with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA) for the preparation of toxicological profiles. The original guidelines were published in the *Federal Register* on April 17, 1987. While Perfluoroalkyls are not found on the ATSDR list of Priority Hazardous Substances, ATSDR has determined that a profile for these substances was necessary because data indicate that some perfluoroalkyls are found in the blood of the U.S. general population and in the environment. The agency also determined that it was important to characterize the current available information regarding the health effects from exposure in order to support and inform public health responses and activities by ATSDR and others. This profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous 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 hazardous 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.

Comments should be sent to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
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Background Information

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99 499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepare 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. The availability of the revised priority list of 275 hazardous substances was announced in the Federal Register on December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17,1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999(64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff 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 was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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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:

Section 1.6	**How Can (Chemical X) Affect Children?**
Section 1.7	**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)	***Fax:***	(770) 488-4178
E-mail:	cdcinfo@cdc.gov	***Internet***:	http://www.atsdr.cdc.gov

The following additional material can be ordered through the ATSDR Information Center:

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

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 incFidents 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, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

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.

Referrals

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 Applied 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. 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

This public health statement tells you about perfluoroalkyls and the effects of exposure to them.

Thirteen perfluoroalkyls 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), perfluorooctanesulfonamide (PFOSA), 2-(N-methyl-perfluorooctane sulfonamide) acetic acid (Me-PFOSA-AcOH), and 2-(N-ethyl-perfluorooctane sulfonamido) acetic acid (Et-PFOSA-AcOH). Seven of these substances are perfluoroalkyl carboxylic acids (PFOA, PFDoA, PFDeA, PFBA, PFHpA, PFNA, and PFUA), three are perfluoroalkyl sulphonic acids (PFOS, PFHxS, and PFBuS), and three are perfluoroalkyl sulfonamides (PFOSA, Me-PFOSA-AcOH, and Et-PFOSA-AcOH).

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact. Most human exposures to perfluoroalkyls are to PFOA and PFOS. Most human exposures to perfluoroalkyls are expected to be through contaminated food and drinking water.

If you are exposed to perfluoroalkyls, many factors will determine whether you will be harmed. These factors include the dose (how much), the duration (how long), and pathway (how you contact the perfluoroalkyls). Other important factors are any other chemicals you are exposed to, your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT ARE PERFLUOROALKYLS?

Description	Perfluoroalkyls are stable chemicals made of a carbon chain surrounded by fluorine atoms and an acid or amide group located at the end of the carbon chain. These substances are unique because they repel oil, grease, and water.
Uses **• Manufacturing**	Perfluoroalkyls have been made in large amounts in the United States. PFOA and PFOS are the two perfluoroalkyl compounds made in the largest amounts. PFOS and PFOA each had a reported produced volume between 15,000 and 500,000 pounds during 2002. Over the past several years, facilities either have stopped production or have begun changing manufacturing practices to reduce releases and the amounts of these chemicals in their products. Perfluoroalkyls have been used in surface protection products such as carpet and clothing treatments and coatings for paper and cardboard packaging.
• Consumer products	Perfluoroalkyls have been used in fire-fighting foams. Some facilities have announced that they will begin replacing many of the perfluoroalkyls that have been used in the above applications with other substances.

1.2 WHAT HAPPENS TO PERFLUOROALKYLS WHEN THEY ENTER THE ENVIRONMENT?

Releases to the environment	Perfluoroalkyls are not found naturally in the environment, but are there because of the action of humans. Perfluoroalkyls can be released into the environment when facilities and people use products that contain them. Perfluoroalkyls have been released into the environment near facilities that made or used these substances, and in many cases, contaminated the groundwater. These types of releases appear to be decreasing based on reports provided by these facilities. Perfluoroalkyls may be formed in the environment when other related chemicals degrade.

Break down **• Air**	Perfluoroalkyls break down very slowly in air, but are expected to fall out of the air to the ground within days to weeks.
• Water	Perfluoroalkyls are very stable in water and are not known to break down in water. These chemicals may be carried over great distances by ocean currents.
• Soil	Perfluoroalkyls are not known to break down in soil. These substances may be carried through soil by groundwater.

1.3 HOW MIGHT I BE EXPOSED TO PERFLUOROALKYLS?

Perfluoroalkyls have been widely found in human blood, indicating that human exposure to these substances is common.

Air	Perfluoroalkyls have been found in both air and dust. You may be exposed to perfluoroalkyls by breathing air containing these substances. Ingestion of dust may also be a source of exposure.
Water and soil	Perfluoroalkyls have been found in surface water, groundwater, soil, and sediment, especially near facilities that have made or used these substances. They have also been found at remote locations such as the Arctic and the open ocean. Drinking water contaminated with PFOA released from a nearby fluorochemical facility was found to be a major source of exposure to that substance. Perfluoroalkyls have also been detected in bird eggs, fish, polar bears, etc.
Food and human breast milk	In addition to drinking water, food is expected to be an important source of exposure to perfluoroalkyls based on the amounts found in food samples. Human breast milk may contribute to the exposure of infants to perfluoroalkyls since these substances have been detected in human breast milk.
Consumer products	Perfluoroalkyls have been widely used in many consumer products (see Section 1.1). The presence of these substances in carpet treatments could be an important source of exposure to perfluoroalkyls, especially for children.

Workplace	People who work where perfluoroalkyls are made or used may be exposed to these substances. 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 may also occur for people with jobs that require frequent handling or use of perfluoroalkyls.

1.4 HOW CAN PERFLUOROALKYLS ENTER AND LEAVE MY BODY?

Enter your body **• Inhalation**	When you breathe air containing perfluoroalkyl compounds, some will enter your body through your lungs, but there is limited information on how fast, how much, or what specific perfluoroalkyl may preferentially enter the body.
• Ingestion	Perfluoroalkyl compounds in food or water may enter your body through the digestive tract.
• Dermal contact	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.
Leave your body	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. PFOA, PFOS, PFHxS, and PFNA are measureable in the serum of most U.S. citizens.

1.5 HOW CAN PERFLUOROALKYLS AFFECT MY HEALTH?

Workers	Inhalation/dermal—Long-term exposure to perfluoroalkyls at work has not been associated with significant adverse health effects, but two studies in workers found changes in sex hormones and cholesterol associated with the levels of PFOA in blood.
General population	Little research has been done on the general population to answer the question of whether perfluoroalkyls may be associated with adverse health effects. Ingestion—A single study of people whose drinking water contained perfluoroalkyls did not find problems in a number of clinical measures tested. The study did not, however, examine developmental risks for children or cancer. The 326-person study was too small to address these issues.

Laboratory animals	One way to learn about the effects of perfluoroalkyls is to see how they affect test animals. Inhalation—Short-term exposure of rats to very high levels of PFOA has caused irritation of the eyes and the nose. Short-term exposure of rats to lower levels of PFOA caused damage to the liver and weight loss. Ingestion—Feeding food or capsules containing perfluoroalkyls to animals mainly produced alterations in the liver of the animals. It also reduced their growth, possibly because these chemicals affect the way the body processes food the animals eat. Dermal—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.
Cancer	The information available does not prove that perfluoroalkyls cause cancer in humans, but the evidence is not conclusive. Some increases in prostate and bladder cancer have been seen, but the cause is not certain. 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.

1.6 HOW CAN PERFLUOROALKYLS AFFECT CHILDREN?

This section discusses potential health effects in humans from exposures during the period from conception to maturity at 18 years of age.

Effects in children	A study of people, including children, in an area of southeastern Ohio, whose drinking water was contaminated with PFOA found no short-term adverse health effects associated with PFOA. However, the study found the highest levels of PFOA in the blood of young children and older adults. The study did not look for cancer or delays in childhood development. The levels of PFOA in the blood from these people were much higher than those found in the general population of the United States. Three studies of pregnant women found that as the levels of PFOA in the mother's blood increased there was a tendency for the newborn babies to have slightly lower birth weight. However, another study that looked at exposure to PFOA in drinking water did not find such an association. Based on both animal and human study reports, developmental effects are the greatest concern in regards to potential adverse effects from PFOA exposure.
Laboratory animals	One way to learn about the effects of perfluoroalkyls is to see how they affect test animals. Birth defects were seen in mice born to females exposed to relatively high amounts of PFOS during pregnancy. Exposure to PFOA and PFOS has resulted in increased early death and delayed development of mice and rat pups, but this did not occur in animals exposed to PFBA or PFHxS.
Human breast milk	Perfluoroalkyl compounds have been found in the breast milk of women, but there are no studies that looked at whether the health of the babies was affected by drinking this milk. Levels of perfluoroalkyls in breast milk are much lower than in the mother's blood indicating that these substances are not concentrated during the production of mother's milk.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PERFLUOROALKYLS?

Consumer products	Families may choose to use products that do not contain perfluoroalkyls.
Drinking water	Families whose tap or well water that contains perfluoroalkyls may choose to drink or cook with bottled water or to install activated carbon water filters.

1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PERFLUOROALKYLS?

Detecting exposure	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 from a representative sample of the U.S. general population; mean serum PFOA and PFOS concentrations were reported to be 3.9 and 20.7 µg/L, respectively. Elevated serum PFOA levels were reported in Little Hocking, Ohio, community residents who had environmental exposure to PFOA from a nearby industrial facility through contaminated drinking water; the median serum PFOA concentration was 354 µg/L. Higher serum perfluoroalkyl concentrations have been reported in fluorochemical product workers. Mean serum PFOA and PFOS levels for 263 employees in a Decatur, Alabama, 3M facility were 1,780 and 1,320 µg/L, respectively.
Measuring exposure	The presence of perfluoroalkyl compounds in your blood may indicate that you have been exposed to and absorbed perfluoroalkyls into your body. The presence of perfluoroalkyl compounds in your blood does not necessarily mean that you will suffer adverse health effects. Additional studies are needed to help determine the health effects associated with exposure to perfluoroalkyls. There are a number of studies underway that should help to answer questions about the health effects of perfluoroalkyls.

1.9 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. The EPA, the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA) are some federal agencies that develop regulations for toxic substances. Recommendations provide valuable guidelines to protect public health, but *cannot* be enforced by law. The Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH) are two federal organizations that develop recommendations for toxic substances.

Regulations and recommendations can be expressed as doses, intakes, or amounts in air, water, and food that are expected to be safe, usually based on levels that affect animals. Sometimes these not-to-exceed

levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

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 provides it. The U.S. EPA (2009) provisional drinking water advisory for PFOA and PFOS are 0.4 and 0.2 ppb, respectively.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more 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 tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses that result from exposure to hazardous substances.

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
Division of Toxicology and Environmental Medicine
1600 Clifton Road NE
Mailstop F-62
Atlanta, GA 30333
Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
5285 Port Royal Road
Springfield, VA 22161
Phone: 1-800-553-6847 or 1-703-605-6000
Web site: http://www.ntis.gov/

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. Large amounts of perfluoroalkyls, especially PFOS and PFOA, have been released to the 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, perfluoroalkyls can also be formed from environmental degradation of precursor compounds and releases 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. 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 of these substances is taking place.

Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (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. Background concentrations of perfluoroalkyls in groundwater, drinking water, soil, and sediment have not been established. 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 fluorochemical industrial facilities.

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. In living organisms, perfluoroalkyls bind to protein albumin in blood, liver, and eggs and do not accumulate in fat tissue. However, some perfluoroalkyls such as PFOA, PFOS, and PFHxS have a very low rate of elimination from serum. Elimination half-lives of several years have been estimated. A much faster elimination half-life of about 75 days was estimated for PFBA.

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) are 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 were 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. 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 larger. 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. These estimated intakes are significantly lower than the doses administered to laboratory animals.

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, respectively. Other perfluoroalkyls have been detected less frequently, with maximum concentrations <2.6 ng/mL.

Estimated onsite intake of PFOA by individuals working at a fluorochemical facility ranged from $3.2x10^{-6}$ to 2.4 ng/kg/day. This amount reflects combined inhalation, oral, and dermal exposure. 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 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. Drinking water was expected to be the major exposure pathway for individuals living near one fluorochemical facility. The estimated offsite intake of PFOA by local residents living near a fluorochemical production facility to PFOA from contaminated environmental media ranged from 0.011 to 260 ng/kg/day.

2.2 SUMMARY OF HEALTH EFFECTS

Information regarding the effects of exposure to perfluoroalkyl compounds in humans is derived mainly from health evaluations of subjects exposed in occupational settings, epidemiologic studies of relatively highly exposed communities, and from much more limited data regarding exposures of the general population. Measurements of the concentrations of several perfluoroalkyl compounds in human blood can be compared with levels measured in studies with experimental animals. For the most part, no significant adverse effects have been identified in these populations, but some potentially adverse changes in clinical tests associated with serum levels of perfluoroalkyl compounds have been reported. Most of the health evaluations have focused on detecting possible hepatic and endocrine effects and alterations in lipid metabolism based on the extensive data available from studies in animals.

A study of 371 subjects from the general population who experienced significant environmental exposure to PFOA via the water supply found no significant deviations in hematology parameters, liver and kidney

function tests, or thyroid stimulating hormone (TSH) levels among the study subjects. Approximately 50% of the subjects were female and there were 43 children under the age of 18. The results were the same when the analysis included all of the individuals as a group and when separate analyses were done for adults and children. The population median serum PFOA concentration was 354 ng/mL (ppb) and the interquartile range was 184–571 ng/mL. The study did not evaluate reproductive or cancer outcomes in the group, but neonates born to women from this cohort were evaluated for birth weight and gestational age.

In a study of 115 workers with a mean serum concentration of PFOA of 3,300 ng/mL (range <1,000–26,000 ng/mL [ppb]), tests of liver function and serum lipid profiles were within normal limits. Similar finding have been reported in other cross-sectional studies that measured serum levels of PFOS and in a longitudinal analysis that also included women. In the latter study, mean serum concentrations of PFOS and PFOA were 1,320 and 1,780 ng/mL, respectively. In a larger study of 506 workers from three chemical plants, serum PFOA was negatively associated with serum high-density lipoproteins (HDL) for the three facilities combined, possibly as a consequence of uncontrolled residual confounding due to different demographic profiles at these sites, but not in the individual plants. Serum PFOA levels in this study ranged from 7 to 92,030 ng/mL (arithmetic mean 2,210 ng/mL). In a longitudinal study of 454 workers with multiple PFOA measurements, in which an average of 10.8 years elapsed between the first (mean 1,040 ng/mL) and last (mean 1,160 ng/mL) serum PFOA measurement, serum PFOA was positively associated with total serum cholesterol, with an increase of 1.06 mg/dL of cholesterol per 1,000 ng/mL increase in PFOA. In addition, PFOA was negatively associated with total bilirubin and positively with serum aspartate aminotransferase (AST) activity, but not with alanine aminotransferase (ALT) or γ-glutamyltransferase (GGT) activity. A cross-sectional study of 1,025 active workers at the same plant found a modest but statistically significant association between PFOA and total cholesterol, low-density lipoproteins (LDL), very low density lipoprotein (VLDL), and GGT activity. A positive relationship between PFOA and total cholesterol was also observed in Italian workers. These and other occupational studies also evaluated other health outcomes such as pulmonary function, electrocardiograms, hematological parameters, renal function, and thyroid hormone levels and found no consistent deviations from normal ranges. Two studies independently reported a significant increase in serum estradiol associated with increasing PFOA levels in male workers. A study found that workers with the highest PFOA levels had mean estradiol levels 10% higher than the other groups. The investigators could not rule out that high body mass index (BMI, kg body weight/height in meters^2) values in these workers were confounding the results. Another study found a significant association between increased serum estradiol and testosterone with increasing PFOA in a study of 1,025 men

occupationally exposed to PFOA. A retrospective cohort mortality analysis of 6,027 workers exposed to PFOA at a polymer production facility found a statistically significant increase in mortality due to diabetes mellitus among male workers. However, the lack of agreement with other studies of PFOA workers and the lack of any animal toxicology findings to support this association suggest that the findings may have been due to chance, but follow-up of these results is warranted. That study also found no significant association between exposure to PFOA and mortality due to ischemic heart disease. A health evaluation of workers exposed to PFNA found no significant associations between exposure to PFNA and liver parameters. Exposure was categorized based on work histories; serum PFNA levels were not available.

Limited information regarding developmental effects of perfluoroalkyl compounds in humans is available. A study of self-reported health outcomes in relation to occupational exposures to PFOS at a PFOS-based fluorochemical manufacturing facility that included 263 women reported that birth weight of singleton births, adjusted for maternal age at birth, gravidity, and smoking status, did not vary between exposure groups; however, the most important determinant of birth weight that was not accounted for in the study was length of gestation. PFOS serum concentrations ranged from 110 to 1,970 ng/mL. In a recent study of the general population in the United States, both PFOA and PFOS in cord blood (respective medians were 1.6 and 5 ng/mL) were negatively associated with birth weight, ponderal index (ratio of birth weight in grams to length in centimeters cubed, multiplied by 100), and head circumference. No significant associations were observed between either PFOS or PFOA concentrations and newborn length or gestational age. A study of 1,400 Danish women reported that birth weight was inversely associated with plasma levels of PFOA collected during the first trimester (mean 35.3 ng/mL). Neither PFOA nor PFOS was statistically associated with length of gestation. Neither head circumference nor ponderal index was evaluated. In a follow-up evaluation of the same cohort, maternal PFOA levels were associated with smaller abdominal circumference and birth length. A study of 428 Japanese women and their infants reported a negative correlation between birth weight and maternal PFOS, but not PFOA, serum levels; neither PFOS or PFOA was associated with birth size (length and head and chest circumference). The blood levels of PFOA and PFOS in the studies of the general population are significantly lower than those reported in the worker and animal studies (see below). Further research will be needed to determine the significance of the findings with respect to human health. However, in yet a more recent follow-up of the Danish cohort, the investigators found little evidence that the prenatal levels of PFOA and PFOS reported influence motor or mental developmental milestones in early childhood. Other much smaller studies of Japanese and Chinese women did not find correlations between PFOS in maternal blood and TSH and T4 in cord blood or between PFOA and PFOS

in breast milk and infant weight, but their small sample size limits the conclusions that can drawn from them. A study of women exposed to high levels of PFOA in the drinking water (6.78 µg/L) found that neonatal birth weight and gestational age were not significantly different than those from neonates born to women who consumed water with significantly lower levels of PFOA. These results indicate that the negative associations between birth weight and PFOA in some of the studies mentioned above may be non-causal.

There is no conclusive evidence that exposure to perfluoroalkyl compounds produces cancer in humans based on a limited number of studies. In a retrospective cohort mortality study of 2,788 male and 749 workers at a plant that produced PFOA, male workers categorized as being exposed for at least 10 years had a 3.3-fold increase (95% confidence interval [CI] 1.02–10.6) in prostate cancer mortality compared to those with no employment in PFOA production. Due to the small number of cases involved, the investigators cautioned that the results should not be over-interpreted. In another retrospective mortality study of 2,083 workers exposed to PFOS, the most significant finding was an increased risk of death from bladder cancer for the entire cohort; three cases were observed and 0.62 were expected (standardized mortality ratio [SMR] 4.81, 95% CI 0.99–14.05) and all of them worked in a high-exposure group. All three cases occurred among 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. The geometric mean serum PFOS levels were 900 ng/mL for workers in the high-exposure group and 100 ng/mL for those assigned to a low-exposure group. A reanalysis of this cohort identified a total of 11 cases of bladder cancer, 6 from surveys and 5 from death certificates. 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. However, compared with those in the lowest cumulative exposure category, the high-exposure workers had a 1.5–2.0-fold increased risk. While the results did indicate an excess risk of bladder cancer among the highest exposed workers, study limitations such as uncertainty in case ascertainment and the size of the cohort did not allow for a conclusive exposure response analysis. A retrospective cohort mortality study of workers (n=6,027) at a polymer production plant did not find significantly increased mortality rates due to cancer among the workers. Specific sites evaluated included the liver and biliary passages, pancreas, kidney and urinary tract, bronchus, trachea or lungs, and prostate. However, comparisons using the population of DuPont workers residing in West Virginia (DuPont Region 1) and seven neighboring states reference rates (but not the general population of the United States or the West Virginia general population reference rates) showed a statistically non-significant increase in SMR for kidney cancer mortality in males (12 cases in males and no cases in females) (SMR=195 [95% CI 95–323; $p>0.05$]).

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. 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 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 half-life of PFOA and PFOS is approximately 4 years 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.

Regardless of the route of exposure, the liver is a main target for perfluoroalkyl compounds in animals (the effects of perfluoroalkyl compounds in laboratory animals do not appear to be route-specific). Liver 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. 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. 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. 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.

The liver was the most sensitive target for perfluoroalkyl compounds in the very limited inhalation database, which consists of a few studies with PFOA dusts and one study with PFNA dusts. 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.

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 include hepatomegaly, due to hypertrophy rather than hyperplasia and proliferation of smooth endoplasmic reticulum and predominantly of peroxisomes vs. mitochondria, confirmed by increased activity of biochemical markers and light and electron microscopy. Reductions in serum cholesterol and triacylglycerols are commonly seen most likely due to reduced synthesis and esterification of cholesterol together with enhanced oxidation of fatty acids in the liver. 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 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 recovery tends to parallel the decline in blood levels of PFOA. Studies in mice have provided similar results. However, studies in PPARα-null mice suggested that hepatomegaly induced by PFOA is not a PPARα-dependent process in mice since PFOA induced hepatomegaly to the same extent in wild mice and PPARα-null mice, but failed to increase acyl-CoA oxidase activity in PPARα-null mice. PFOA increased absolute liver weight in monkeys treated with ≥3 mg/kg/day for 26 weeks, an effect that was associated with significant mitochondrial proliferation, but not peroxisome proliferation.

PFOS increased liver weight and induced hepatocyte hypertrophy and vacuolation in a 14-week study in rats and in a 2-year study in rats. However, the hepatic effects did not seem to be related to peroxisome proliferation, since no significant increases in hepatic peroxisomal enzyme activity were reported compared with acute-duration studies. Some have postulated the existence of an exposure threshold, which was not achieved rapidly enough to produce an increase in palmitoyl-CoA oxidase, and suggested that a mechanism may exist *in vivo* for an adaptive down-regulation of the hepatic peroxisome proliferation response to PFOS treatment. 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 perfluorodecanoic acid (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.

PFOA and PFOS have induced developmental effects in rodents, but no consistent teratogenicity has been reported. 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, and delays in mammary gland differentiation, eye opening, vaginal opening, and first estrus. These effects occurred generally in the absence of 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 study that exposed mice at various times during pregnancy showed that developmental effects were progressively more severe as the exposure began earlier, but it could not be determined whether this was due to a higher cumulative dose or to a developmentally sensitive period. Cross-fostering experiments showed that gestational exposure was sufficient to induce postnatal deficits in body weight and developmental delays. 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. No fetal toxicity or teratogenicity was reported in offspring from 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.

Studies conducted with wild 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. However, treatment of pregnant mice with PFOA induced a substantial delay in maternal mammary gland differentiation on PND 10 and 20 and alterations in milk protein gene expression, which could explain, at least in part, the delayed growth development in the exposed offspring. 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.

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 $\geq$70,000 ng/mL. Dosing rats late during gestation (gds 17–20) causes significantly more lethality than dosing early (gds 2–5). Since pups had difficulty breathing within minutes of birth and their lungs resembled prenatal lungs, the possibility that early death was due to immature lungs was examined. However, experiments with agents known to enhance terminal lung maturation and accelerate surfactant production failed to reverse the delaying effects of PFOS, suggesting that neonatal mortality was not due to lung immaturity. Mean serum PFOS levels in rat pups and dams on PND 21 associated with neonatal mortality were approximately 89,000 ng/mL in a study in which dams were exposed to PFOS before and during gestation. Delays in eye opening have been reported in developmental studies in rats and mice. Neurological evaluations of pups from mice exposed to 6 mg/kg/day PFOS on gds 12–18 showed no significant or consistent alterations compared with controls, but administration of a single gavage dose of PFOS to 10-day-old male mice induced alterations in spontaneous activity when tested at the age of 2 or 4 months. Serum PFOS levels were not available in these studies. Evaluation of immunological parameters in 8-week-old pups from mice exposed to PFOS during gestation showed reduced natural killer cell activity, suppressed IgM response to immunization, and alterations in splenic and thymic lymphocyte subpopulations.

In contrast to results obtained with PFOA and PFOS, PFBA exhibited much reduced developmental toxicity in mice, whereas PFHxS was not a developmental toxicant in rats exposed to up to 10 mg/kg/day

PFHxS for a period that included premating, gestation, and lactation. Administration of PFBA (35–350 mg/kg/day) to pregnant mice on gds 1–17 had no significant effect on a comprehensive number of developmental parameters evaluated including neonate weight gain and viability. On gd 18, maternal serum PFBA was 2,000–4,000 ng/mL with no apparent dose-response relationship. In pups, serum PFBA was 400–600 ng/mL on PND 1 and 110–150 ng/mL on PND 10. The milder response compared to PFOA was attributed by the investigators to faster elimination of PFBA as well as to lower biochemical potency. Serum levels of PFHxS were not available in a study.

PFOA induced immunological alterations in adult mice characterized by thymus and spleen atrophy and alterations in thymocytes and splenocytes. Since no alterations in thymocytes and splenocytes could be seen in studies *in vitro*, the investigators suggested that the thymic and splenic atrophy induced by PFOA may involve an indirect pathway, possibly via alteration of fatty acid transport and/or metabolism. Experiments in PPARα-null mice indicated that the effects of PFOA on the spleen were PPARα-dependent, whereas those in the thymus were only partially dependent. The effects reported occurred with PFOA doses in the range of 10–30 mg/kg/day. The results from a more recent study suggest that suppression of parameters of humoral immunity can occur at doses as low as 3.75 mg/kg/day administered for 15 days; this dosing level resulted in a mean PFOA serum level of 75,000 ng/mL. 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.

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 perfluorododecanoic acid (PFDoA).

Oral exposure to PFOA and PFOS has induced alterations in serum thyroid hormone levels in animals. Most of these studies reported reductions in total serum thyroxine (TT4) without significant alterations in serum TSH levels and no alterations in thyroid gland histology. Thus, there has been no suggestion of a hypothyroid response due to exposure to perfluoroalkyl. Results from a recent study suggest that the reduction in TT4 can be explained by a perfluoroalkyl-induced displacement of thyroxine (T4) from serum binding proteins. This, in turn, could lead to an increased tissue uptake and turnover of T4, which would result in a lowering of serum TT4 while rebalancing the equilibrium between bound and free T4. Reduced serum TT4 was also reported in rats treated with PFDeA by intraperitoneal injection. Hypertrophy/hyperplasia of the thyroid follicular cells was reported in intermediate-duration studies in rats dosed with PFBA and PFHxS. According to the investigators, this is probably a compensatory response of the thyroid to hepatocellular hypertrophy, leading in turn to an increase plasma turnover of thyroxine and associated stimulation of TSH.

PFOA, as many other PPARα agonists, induced hepatocellular adenomas, Leydig cell adenomas, and pancreatic acinar cell adenomas in rats. The issue, which has been extensively reviewed, is whether the mode(s) of action is relevant for risk assessment in humans. A 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 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 PPRAα-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 consequence 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, such that PFOA may pose a carcinogenic risk for humans, even though an intermediate-duration study in Cynomolgus monkeys did not find treatment-related alterations in serum estradiol or testosterone, suggesting that PFOA is unlikely to induce

Leydig cell tumors in humans because humans are less sensitive than rats to LH stimulation. 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 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, the animal tumor responses are presumed to be relevant to humans. The EPA has encouraged a cancer risk assessment for each of the PFOA-induced tumors where data permit.

PFOS did not induce malignant tumors in a bioassay conducted in rats, but it increased the incidence of liver hepatocellular adenoma and thyroid follicular cell adenoma. A mode of action for PFOS-induced tumors has not been proposed.

2.3 MINIMAL RISK LEVELS (MRLs)

No MRLs were derived for perfluoroalkyl compounds for the reasons detailed below.

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 (Olsen and Zobel 2007; Olsen et al. 1998, 1999, 2003a) and of members of the general population known to have been environmentally exposed to these compounds primarily via drinking water (Emmett et al. 2006b). A small number of studies that examined developmental outcomes in relation to perfluoroalkyl body burdens in the general population are also available (Apelberg et al. 2007b; Fei et al. 2007, 2008a, 2008b; Washino et al. 2009). Direct exposure data are not available for the occupational exposures. In the cohort studied by Emmett et al. (2006b), the average concentration of PFOA in water that the subjects may have consumed over a period of 3 years before the health assessment was conducted was 3.5 µg/L. Median serum PFOA levels in residents were 105 times the level in their residential drinking water. Blood levels of perfluoroalkyl compounds have been measured both in

workers and in members of the general population. As indicated in the preceding section, no significant health effects have been associated with specific serum levels of perfluoroalkyl compounds, although minor alterations in serum lipids and in serum estradiol levels in male workers have been reported (Costa 2004; Olsen et al. 1998; Sakr et al. 2007b).

It could be proposed that measured serum levels of perfluoroalkyls in the populations for whom health data are available be considered body burdens corresponding to no-observed-adverse-effect levels (NOAELs) or perhaps lowest-observed-adverse-effect levels (LOAELs) if the alterations reported in workers are considered adverse. The health evaluations of workers have mainly focused on liver effects and serum lipids profiles. However, there are concerns that other end points, such as immunological and neurological effects, have not been adequately evaluated in exposed human populations. Therefore, there is significant uncertainty in relying on these existing workers studies as the basis for a risk assessment. The same concern applies to the population studied by Emmett et al. (2006b) since only a limited number of end points were examined in that study. Defining NOAELs or LOAELs associated with specific perfluoroalkyl body burdens from the developmental studies is also problematic. In one study, levels of PFOA and PFOS in cord blood were negatively associated with birth weight (Apelberg et al. 2007b). In another study, PFOA in maternal blood collected in the first trimester was negatively associated with birth weight (Fei et al. 2007). In yet an additional study, PFOS, but not PFOA, in maternal blood collected in the second trimester of pregnancy was negatively associated with birth weight (Washino et al. 2009). None of these studies was sufficient to establish a cause-and-effect relationship between PFOA/PFOS serum levels and birth weight. In addition, there is some question as to whether the magnitude of the decrease in birth weight is actually considered to be an adverse effect. Moreover, a follow-up of the Fei et al. (2007) study found “no convincing associations between developmental milestones in early childhood and levels of PFOA or PFOS measured in maternal plasma early in pregnancy” (Fei et al. 2008b). Thus, it is difficult to define points of departure for MRL derivation with any degree of confidence based on the human data available at this time. Furthermore, even if a wide range of end points had been examined in the studies available and points of departure could have been defined, there is currently not enough information regarding the pharmacokinetics of this group of compounds in humans to facilitate estimations of exposure levels resulting in measurable body burdens of perfluoroalkyls.

A model has been created to estimate the total daily consumer exposure of PFOA and PFOS in North America and Europe occurring through various pathways (Trudel et al. 2008). Similar studies have been conducted by others (Fromme et al. 2008). Since blood levels of PFOA and PFOS (and other

perfluoroalkyl) in the U.S. population have been measured (e.g., Calafat et al. 2007b), efforts to examine combined exposure and body burden information may be useful.

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, at this time, derivation of MRLs for PFOA or PFOS based on animal studies would be highly uncertain, 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, non-human primates, and in 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), animal species (i.e., slower in humans compared to non-human primates and rodents), and show pronounced gender differences within certain species (i.e., 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 non-human primates, or humans and rats (Andersen et al. 2006; Tan et al. 2008). Important characteristics of the toxicokinetics of perfluoroalkyls that would contribute to uncertainty in extrapolation of dose-response relationships across species include those discussed below.

Inter-species Variation in Elimination Rate. The elimination rate for PFOA in female rats (half-life [$t_{1/2}$]≈4 hours at low doses) is approximately 40 times faster than in male rats ($t_{1/2}$≈160 hours), 120 times faster than in Cynomolgus monkeys ($t_{1/2}$≈20 days), and approximately 6,000 times faster than in humans ($t_{1/2}$≈1,000 days). Elimination of PFOS in male rats ($t_{1/2}$≈180 hours) is approximately 20 times faster than in Cynomolgus monkeys ($t_{1/2}$≈150 days), and approximately 240 times faster than in humans ($t_{1/2}$≈1,800 days) (Hundley et al. 2006). There are two important implications of these large differences in elimination rates. First, 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. For example, steady-state serum concentrations achieved in humans may be approximately 6,000 times greater than in female rats, at the same external dosages. Second, exposure durations required to achieve steady state would be expected to be much longer in humans than in monkeys or rats. Assuming an elimination $t_{1/2}$ of 1,000 days for PFOA in humans, a constant rate of intake for 12 years would be required to achieve 95% of steady state.

Steady state (i.e., 95%) would be achieved in approximately 90 days in monkeys, 30 days in male rats ($t_{1/2}$≈160 hours), and 1 day in female rats ($t_{1/2}$≈4 hours). As a result of these large differences in kinetics, the extrapolation of internal doses (i.e., serum concentrations of PFOA) achieved during intermediate-duration exposures in rats or monkeys could only be appropriate for human populations where the exposure was of sufficient duration to reach steady-state serum concentrations. Given uncertainties in knowing the duration of exposure in any human population, there are significant limitations in directly extrapolating across species for the purpose of deriving MRLs. For PFBA, interspecies variability of elimination rate exceeded that expected for allometric scaling of body weight (Chang et al. 2008a). The monkey:rodent ratio for half-time was approximately 14 for female mice and 20–40 for female rats. Based on body weight alone, one would predict ratios of approximately 4.5 and 2.5, respectively.

Dose- and Sex-dependences of Elimination. In addition to faster elimination rate of PFOA and PFOS in female rats compared to male rats, elimination rate and renal clearance of PFOA in female rats appear to be dependent on dose (Kemper 2003). Dose- and gender-dependence of elimination of PFOA have been attributed, in part, to capacity-limited tubular secretion of PFOA, which may be hormonally regulated by androgens and estrogens (Kudo et al. 2002; Vanden Heuvel et al. 1992a). Dose-dependence of elimination rates in humans have not been studied and all reported estimates of elimination rates of PFOA (or PFOS) in humans are based on subjects whose serum perfluoroalkyl concentrations were substantially lower (i.e., >100 times lower) than those observed in rat studies. Therefore, extrapolation of external dose dependences or serum concentration dependences of elimination rates of PFOA or PFOS observed in rats to humans would be highly uncertain (as would the assumption that clearance is completely independent of dose or serum concentration in humans). Dose- and gender-dependence of elimination also exist for PFBA (Chang et al. 2008a). In male mice, half-times decreased as the dose increased in the range 10–100 mg/kg/day. The male:female ratio for half-time elimination was approximately 2–5 for mice, 5–6 for rats, and 1 for monkeys.

Maternal-fetal Transfer. Although some information is available on fetal transfer (i.e., tissue levels; (Hinderliter et al. 2005) of PFOA in rats, information on humans is limited to a few studies of maternal:infant serum ratios of PFOA and PFOS (Inoue et al. 2004b; Midasch et al. 2007). This information does not provide a basis for a reliable extrapolation of fetal doses that would occur in developmental studies conducted in rats (or mice) to equivalent fetal doses in humans.

Structure Specificity of Elimination Rate. A trend for decreasing elimination rate with increasing perfluoroalkyl chain length is evident from comparison of the elimination rates in rats (Chang et al.

2008a; Ohmori et al. 2003). The elimination rate of PFDeA in male rats was estimated to be approximately 7 times slower than PFOA in male rats and approximately 150 times slower than PFOA in female rats. Structure-activity relationships for elimination rates in humans have not been explored, making extrapolations of the relationships observed in rats to humans highly uncertain. Therefore, extrapolation of dose-response relationships for PFOA or PFOS to other perfluoroalkyls would be highly uncertain.

Physiologically-based Pharmacokinetic (PBPK) Models. Modeling of the toxicokinetics of PFOA and PFOS is currently in the research phase, and is currently focused on developing modeling approaches to simulate dose-dependencies and gender differences in kinetics that have been observed in monkeys and rats. Human PBPK models have not been reported. Features of the PBPK models of monkeys and rats that have been explored to simulate the complex kinetics observed in these animals include: (1) time-dependent variation in protein binding and volume of distribution of PFOA in monkeys; and (2) capacity limited renal tubular reabsorption of PFOA with gender-specific and species-specific values for the V_{max} and K_m in rats. Although the models have been successfully calibrated to observations, they do not fully capture dose-dependencies that have been observed in either species. Furthermore, the time- and dose-dependent features of the models have not been extrapolated to humans or other species (Andersen et al. 2006; Tan et al. 2008). Therefore, in their current state of development, these models cannot be reliably extrapolated to simulating external-internal dose relationships in humans.

Although MRL derivation is not recommended for perfluoroalkyls at this time based on the information summarized above, relevant information from animal studies that could have been considered for MRL derivation (i.e., studies with the LOAELs) for perfluoroalkyls with at least a minimal size database is summarized below.

Perfluorobutyric Acid (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 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) oral 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 (van Otterdiijk 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-day 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 (van Otterdiijk 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 single study of PFHxS was available for review. The study evaluated the reproductive and developmental effects of this perfluoroalkyl compound in male and female rats exposed from premating until PND 21 (females) (Hoberman and York 2003). Doses of 0, 0.3, 1, 3, or 10 mg/kg/day were administered by oral gavage. PFHxS did not significantly affect any reproductive or developmental parameter nor did it induce maternal toxicity assessed by clinical chemistry and hematology tests and organ histopathology. PFHxS did induce hematological alterations in male rats at ≥0.3 mg/kg/day and liver and thyroid effects at ≥3 mg/kg/day. The thyroid effects were thought to be a compensatory response to liver hypertrophy.

PFBuS. A 28-day gavage study in rats was available for review for this chemical (3M 2001). The study evaluated a wide variety of end points including hematology, clinical chemistry, and histopathology of all major organs and tissues. In addition, the rats were subjected to neurobehavioral testing during week 4 of the study; the tests assessed sensory reactivity to stimuli, grip strength, and motor activity. The administered doses were 0, 100, 300, or 900 mg/kg/day PFBuS. Following the treatment period, rats from the control and high-dose groups were allowed to recover for approximately 14 days. Significant increases in absolute and relative liver weight were reported in high-dose males and in absolute and relative kidney weight in high-dose females. There were no chemical-related histopathological alterations

in the organs and tissues examined. The only notable neurobehavioral effect was a significant decrease in tail flick latency to a thermal stimulus in males from all treated groups 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 alteration.

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). The limited database would have been insufficient for MRL derivation, especially due to the lack of information on postnatal viability in offspring from rodents, which was significantly reduced at relatively low maternal doses in studies with PFOA and PFOS. Data on serum levels of PFDeA were not available in any of the studies reviewed.

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 were available in rats and mice and provided information on systemic, immuno/lymphoreticular, 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 (Yang et al. 2001). This was accompanied by a significant increase in peroxisome proliferation, as measured by increases in acyl-CoA oxidase activity. That dose was the lowest dose tested in the study. In subsequent studies, Yang et al. (2002b) reported that exposure of PPARα-null mice to PFOA induced hepatomegaly to the same extent than in wild mice, but failed to increase acyl-CoA oxidase activity, suggesting that, at least in mice, hepatomegaly induced by PFOA is not a PPARα-dependent process. Blood levels of PFOA were not monitored in these studies. A LOAEL of 2 mg/kg/day and 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 serious LOAEL of 5 mg/kg/day was identified for reduced body weight (35–43%) at weaning in pups from mice exposed to PFOA on gds 7–17 (Wolf et al. 2007). Exposure to PFOA did not significantly affect maternal weight or weight gain during pregnancy. The 5 mg/kg/day dose level was the lowest dose level tested. At weaning, the mean PFOA levels were 37,000 ng/mL in dams' blood and 25,000 ng/mL in pups. An additional study from the same group of investigators showed that neonatal viability, including postnatal pup weight gain, was a PPARα-dependent effect (Abbott et al. 2007). A relative low 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 a main target. 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. In a 13-week dietary study in male rats, the lowest LOAEL was 0.64 mg/kg/day for minimal to moderate hepatocellular hypertrophy; the NOAEL was 0.06 mg/kg/day (Perkins et al. 2004). Hepatic palmitoyl CoA-oxidase, a marker of

peroxisome proliferation, was significantly increased only on week 4 of the study in the 0.64 mg/kg/day dose group. Mean serum PFOA levels in this group were 55,000, 46,000, and 41,000 ng/mL on weeks 4, 7, and 13 of the study, respectively. A relatively low serious LOAEL of 0.6 mg/kg/day for reduced pup survival from birth to weaning was identified in a developmental study in mice; the NOAEL was 0.3 mg/kg/day (Abbott et al. 2007). At weaning, the mean level of PFOA in serum from dams in the 0.6 mg/kg/day was 5,200 ng/mL; the corresponding serum level of PFOA in the pups was 3,800 ng/mL. As indicated above, experiments conducted with PPARα-null mice showed that the expression of PPARα was required for induction of postnatal lethality by PFOA and that one functional copy of the gene was sufficient to significantly increase postnatal lethality (Abbott et al. 2007). In a 26-week study with Cynomolgus monkeys, the study LOAEL was 3 mg/kg/day (the lowest dose tested) for a 36% increase in absolute liver weight attributed to significant mitochondrial proliferation (Butenhoff et al. 2002). No significant hepatic peroxisomal proliferation was detected. Serum PFOA levels appeared to reach a steady state by week 6 of the study, and in the 3 mg/kg/day dose group, this concentration of PFOA was approximately 77,000 ng/mL.

The chronic oral animal database for PFOA is limited to two studies, both dietary studies in rats (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 used only one dose level in addition to controls. Treatment with PFOA induced a significant increase in relative liver weight at all time points except at 24 months relative to both controls. Hepatic beta-oxidation activity was significantly elevated at all times, but cell proliferation was not increased in the liver. Pancreatic acinar cell proliferation was increased at 15, 18, and 21 months. Serum estradiol was increased during the first year of the study, serum LH at 6 and 18 months, and serum follicle-stimulating hormone (FSH) at 6 months; changes in serum testosterone did not show any consistent pattern. Treatment with PFOA increased the incidence of hepatocellular adenomas, but there were no hepatocellular carcinomas in the treated group. PFOA also increased the incidence of Leydig cell adenomas and the incidence of pancreatic acinar cell adenomas. Due to the limited scope of the study and the use of only one dose level, a preferential target cannot be defined. 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. Significant effects attributed to the low dose included significantly increased serum transaminases and inflammation of the salivary glands, both in males. Liver lesions occurred in the high-dose group, principally in males. PFOA at the high-dose level increased the incidence of fibroadenoma of the female mammary gland and of Leydig cell adenomas.

The serious LOAEL of 0.6 mg/kg/day for developmental effects in mice in the intermediate-duration study of Abbott et al. (2007) would have likely precluded using the 2-year 3M (1983) study as basis for derivation of a chronic-duration oral MRL for PFOA since the lowest dose in the 2-year study was 1.5 mg/kg/day.

PFOS. No inhalation data were available for PFOS. The oral database for PFOS is less extensive than that for PFOA. Acute-duration oral studies with PFOS have described effects on body weight, liver weight, serum and liver lipid profiles, and developmental effects in rodents. The lowest LOAEL 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. No significant developmental effects were reported in the fetuses of does dosed with 1 mg/kg/day PFOS and sacrificed on gd 29. The closest LOAEL was 2.5 mg/kg/day for a 10% reduction in weight in rabbit fetuses in the Case et al. (2001) study. This may have been due, at least in part, to the significant reduction in maternal weight gain during treatment (47%) and posttreatment (33%) in does from this dose group. Serum levels of PFOS were not available in this study.

The intermediate-duration oral database for PFOS consists essentially of a 4-week capsule study in monkeys (Thomford 2002a), a 26-week capsule study in monkeys (Seacat et al. 2002), a 4- and a 14-week dietary study in rats (Seacat et al. 2003), two 2-generation reproductive studies (gavage) in rats (Luebker et al. 2005a, 2005b), and developmental studies in rats and mice (Keil et al. 2008; Lau et al. 2003; Thibodeaux et al. 2003); the 2-generation studies also provided information on developmental effects. Several data sets could have been evaluated as possible basis for an intermediate-duration oral MRL for PFOS. 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. Similar results were reported in rats (Seacat et al. 2003). A LOAEL of 1.33 mg/kg/day, the highest dose tested, was established for increased liver weight, increased serum ALT, and hepatocyte hypertrophy and vacuolation; the NOAEL was 0.34 mg/kg/day. The mean serum PFOS level corresponding to the LOAEL in males was 148,000 ng/mL. A developmental study in rats reported a steep dose-response for postnatal survival of the pups, a serious LOAEL (Lau et al. 2003). Maternal doses of 2 mg/kg/day on gds 2–21 decreased

survival at weaning by approximately 60% compared with approximately 80% in controls (estimated from a figure in the paper). Maternal doses of 1 mg/kg/day appeared not to affect survival significantly. The concentrations of PFOS in serum of pups on PND 5 corresponding to the 1 and 2 mg/kg/day maternal doses were approximately 30,000 and 60,000 ng/mL. Maternal serum levels of PFOS were not available. Significant decreased pup survival was also reported in a 2-generation study in rats (Luebker et al. 2005b). The viability index on PND 5 in pups from dams dosed with 1.6 mg/kg/day PFOS (premating and during gestation) was 49.3% compared with 97.3, 97.6, 93.1, 88.8, and 81.7% in groups dosed with 0, 0.4, 0.8, and 1.2 mg/kg/day PFOS, respectively. Serum PFOS levels on PND 5 were not available for the group with 49.3% viability index, but the mean concentrations in groups dosed with 1.2 and 2 mg/kg/day were 147,000 and 138,000 ng/mL, respectively.

A 2-year bioassay for PFOS also identified the liver as a main target (Thomford 2002b). In that study, rats were fed a diet that provided approximately 0, 0.03, 0.1, 0.4, or 1.5 mg/kg/day PFOS. A significant increase in the incidence of cystic hepatocellular degeneration was reported in males dosed with ≥0.1 mg/kg/day PFOS, and this dose level constitutes the study LOAEL; the NOAEL was 0.03 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.

2. RELEVANCE TO PUBLIC HEALTH

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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 National Health and Nutrition Examination Survey (NHANES) 2003–2004 (Calafat et al. 2007b). These compounds include: perfluorobutane sulfonic acid (PFBuS), perfluorohexane sulfonic acid (PFHxS), perfluoroheptanoic acid (PFHpA), perfluorooctanoic acid (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDeA), perfluoroundecanoic acid (PFUA), perfluorododecanoic acid (PFDoA), perfluorooctane sulfonic acid (PFOS), perfluorooctane sulfonamide (PFOSA), 2-(N-methyl-perfluorooctane sulfonamide) acetic acid (Me-PFOSA-AcOH), and 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid (Et-PFOSA-AcOH). Also included in this document is perfluorobutyric acid (PFBA).

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. 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.

Information on the health effects of humans exposed to perfluoroalkyl compounds is available mainly from workplace exposure to these compounds and from a relatively few studies conducted on the general 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 can be found in Section 3.2.2, Oral Exposure based on reports of predominant exposure via drinking water and food items. It should be made clear, however, that based principally on results from studies in animals that indicate that the health effects of these substances are independent of the route of exposure, conclusions can be drawn across exposure routes.

3.2.1 Inhalation Exposure

Several studies have been conducted of workers exposed to perfluoroalkyl compounds. These types of studies have inherent limitations that can bias the results both towards finding nonexistent effects and failing to detect a true effect. Some of these limitations include: (1) low participations rates, (2) lack of inclusion of workers who were employed for a short period of time, workers who retired, or workers who died, (3) comparing rates of mortality or morbidity between workers, supposedly healthy enough to work, and members of the general population who may be too infirm to work (the "healthy worker effect"), (4) use of unreliable measures of health outcome such as self reports of health conditions, (5) potential exposure to more than one chemical, (6) studies where the comparison group (control) is also exposed and is therefore not a true control, (7) poor measures of exposure, and (8) small study size that have inadequate statistical power to detect relationships between exposures and adverse outcomes. Most of the occupational studies summarized below suffer from one or several of these limitations, yet ATSDR believes that, collectively, they provide useful information that future studies will help refute or confirm.

3.2.1.1 Death

There are no reports of human deaths from accidental or intentional acute exposure to high concentrations of PFOA or PFOS, but several studies have examined potential associations between mortality and long-term exposure in occupational settings. For example, Gilliland and Mandel (1993) conducted a retrospective cohort mortality evaluation of 2,788 male and 749 female workers employed 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. The SMR for all causes of death in women was 0.75 (95% CI 0.56–0.99). There was no association with duration of employment or latency for deaths from all causes, cancer, and cardiovascular diseases. The SMR for all causes of death in men was 0.77 (95% CI 0.69–0.86) using Minnesota rates for comparison; similar results were obtained when the expected number of male deaths was based on U.S. mortality rates. Among men, there was no association between any cause of death and duration of employment. The SMR for prostate cancer was 2.03 (95% CI 0.55–4.59) in the Chemical Division group and 0.58 (95% CI 0.07–2.09) in the non-Chemical Division men. Ten years of employment in the Chemical Division was associated with a 3.3-fold increase (95% CI 1.02–10.6) in prostate cancer mortality compared to no employment in PFOA production. The investigators concluded that since the findings in the study are based on a small number

of cases and could have resulted from chance or unrecognized confounding from exposure to other factors, the association between PFOA and prostate cancer should not be overinterpreted.

Alexander et al. (2003) conducted a retrospective mortality study of a cohort of employees at a perfluorooctanesulphonyl fluoride (PFOSF) based fluorochemical production facility in Decatur, Alabama, who had at least 1 year of cumulative employment at the facility. This criterion was met by 2,083 workers. The geometric mean serum PFOS level for workers in the chemical plant in the facility was 900 ng/mL and that for those in the film plant in the facility was 100 ng/mL. 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 non-exposed (n=812). Male workers made 83% of the cohort and 84% of the high-exposure group. The mortality experience of the cohort was compared to that of the state of Alabama. Age-, gender-, and calendar-period-adjusted SMRs were computed for all causes and specific causes of death using the Alabama reference data. The all-cause and cause-specific mortality rates for the entire cohort were lower than expected compared to the general population of Alabama, 145 observed and 230 expected (SMR 0.63, 95% CI 0.53–0.74). A similar pattern was observed for all deaths from cancer (gastrointestinal tract, respiratory system, breast, malignant melanoma, and lymphatic and hematopoietic cancers) and non-malignant causes (cerebrovascular disease, all heart disease, respiratory disease, and cirrhosis of the liver). There were two deaths from liver cancer in the entire cohort and 1.24 were expected (SMR 1.61, 95% CI 0.20–5.82). The most significant finding was an increased risk of death from bladder cancer for the entire cohort, 3 observed and 0.62 expected (SMR 4.81, 95% CI 0.99–14.05). All three cases occurred among 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 this cohort that included all current, retired, and former employees (total=1,895) was subsequently conducted by Alexander and Olsen (2007). Included in the study was also information from 188 deceased workers. 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). Eleven cases of bladder cancer were identified from surveys (n=6) and death certificates (n=5). The 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. However, compared with those in the lowest cumulative exposure category, the high-exposure workers had a 1.5–2.0-fold increased risk. While the results did indicate an excess risk of bladder cancer among the highest exposed workers, study limitations such as uncertainty in case ascertainment and the size of the cohort, acknowledged by the investigators, need to be considered in the interpretation of the results.

A study was conducted of DuPont employees at the Washington Works, West Virginia, polymer-manufacturing facility (Leonard 2006). The study's objective was to determine whether workplace exposure to PFOA was related to increased mortality risk for any cause. The study was part of an overall project that also comprised a cross-sectional surveillance that analyzed several types of clinical data and serum PFOA (as biomarker of exposure) for potential relationships (see Sakr et al. [2007b] under *Hepatic Effects*). Approximately one-half of the employees at the site had been assigned to ammonium perfluorooctanoate (APFO) areas at some time in their careers. The study also utilized job history information as well as serum PFOA data to classify each member of the historical cohort by level of potential occupational exposure for a more detailed analysis of ischemic heart disease. The cohort 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. The cohort (n=6,027; 4,872 males) was ascertained primarily through the DuPont Epidemiology Registries and additional members were identified from plant-based work history records. 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. SMRs were calculated for all causes of death, death from all cancers combined, and disease-specific causes of death by comparing the cohort rates for three reference populations: the general population of the United States, the West Virginia general population, and the population of DuPont workers residing in West Virginia (DuPont Region 1) and seven neighboring states in the region. Cox proportional hazards models (CPHM) provided an internal comparison based on exposure categories of serum PFOA for mortality due to ischemic heart disease. These categories were based on the cumulative exposure calculated for each member of the cohort based on the categorization of jobs. In turn, cumulative exposure was used to derive the average exposure intensity for each cohort member based on the job history data. Mortality rate ratios (MMRs) for ischemic heart disease were estimated using lagged exposure (5, 10, 15, and 20 years) to reduce any bias introduced by the healthy worker survivor effect. Three job-exposure categories were formed based on job-specific PFOA serum level information: category 1 consisted of all no APFO-use division jobs and APFO-use jobs within the same serum PFOA level range as those employees who had never had a job assignment in any APFO-use division (median serum PFOA <250 ng/mL; mean 210 ng/mL); category 2 consisted of APFO-use jobs with a median serum PFOA between 250 and 750 ng/mL (mean, 430 ng/mL); and category 3 consisted of all APFO-use jobs with median serum PFOA >750 ng/mL (mean, 1,690 ng/mL). Mean serum levels served as intensity factors for the three job-exposure categories. Validation of the exposure classification was done in a longitudinal study dataset (Sakr et al. 2007a).

Almost all SMRs comparing Washington Works mortality rates for defined causes to the United States and West Virginia population mortality rates were below 100, indicating no differences in the mortality rates between the compared populations. The SMRs for all causes based on comparison to DuPont Region 1 population was 94 (95% CI 87–100) for males and 147 (95% CI 101–207) for females. Comparisons using DuPont region 1 reference rates showed a statistically nonsignificant increase in SMR for kidney cancer mortality in males (12 cases in males and no cases in females) (SMR=195; [95% CI 95–323; $p>0.05$) and a statistically significant increase in diabetes mortality (SMR=197; 95% CI 123–298; $p<0.05$) in males and females combined (20 cases in males and 2 cases in females). Leonard (2006) pointed out that while few kidney cancer cases had been employed in APFO areas, the data from the study were inadequate for examining in appropriate detail rare outcomes such kidney cancer. Regarding diabetes mortality, the investigator noted that the lack of agreement with other studies of PFOA workers and the lack of any animal toxicology findings to support the association suggested that the finding may have been due to chance; however, future surveillance should follow-up on these results. Proportional hazards analyses of ischemic heart disease mortality showed an increase in the model based on equal distribution of cases across cumulative exposure categories in one lagged analysis (the 10-year lag period). Other exposure 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. A limitation of the study acknowledged by the investigator (Leonard 2006) included the potential loss to follow-up of decedents prior to 1979, a period where exposures may have been less well-controlled, causing potential bias towards the null due to the healthy worker survivor effect. Also, a major limitation was likely to be the lack of accounting for confounding by other occupational and non-occupational risk factors such as information about the major risk factors for cardiovascular disease (smoking, diet, and other life-style factors) and use of medications such as statins or anti-hypertensive medications.

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 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.

Unpublished information summarized by 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. Unspecified 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.

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 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).

Table 3-1 Levels of Significant Exposure to Perfluorooctanoate - 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 Perfluorooctanoate - 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 Perfluorooctanoate - 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
Immuno/ Lymphoret								
7	Rat (CD)	2 wk 6 hr/d 5 d/wk		84 M			Kennedy et al. 1986 Ammonium perfluorooctanoate	NOAEL is for histopathology of the spleen and thymus.
Neurological								
8	Rat (albino)	1 hr (NS)			18600 (excessive salivation)		Griffith and Long 1980 Ammonium perfluorooctanoate	
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 brain.
Reproductive								
10	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								
11	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 Perfluorooctanoate - Inhalation

Acute (≤14 days)

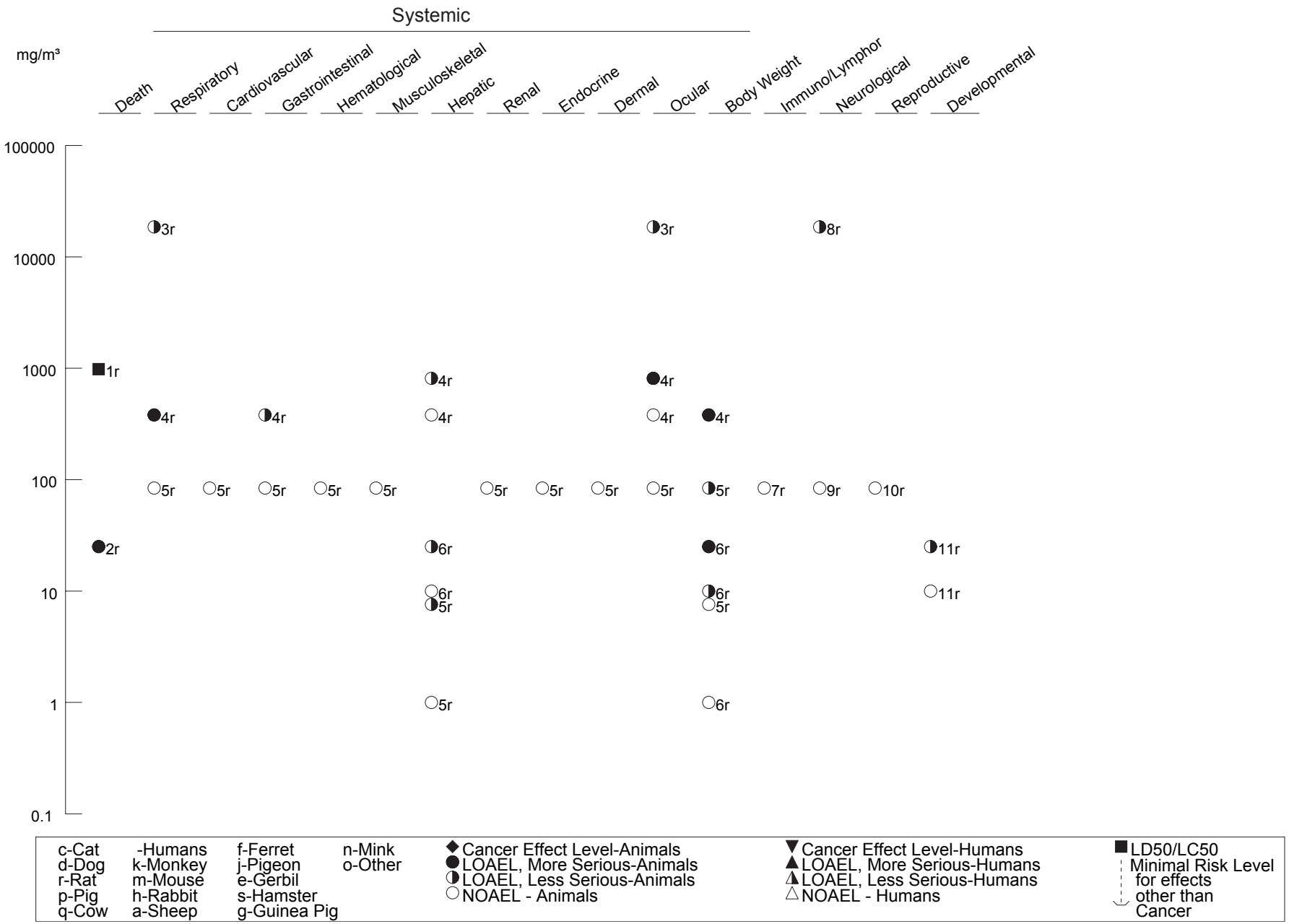


Table 3-2 Levels of Significant Exposure to Perfluorononanoic Acid - Inhalation

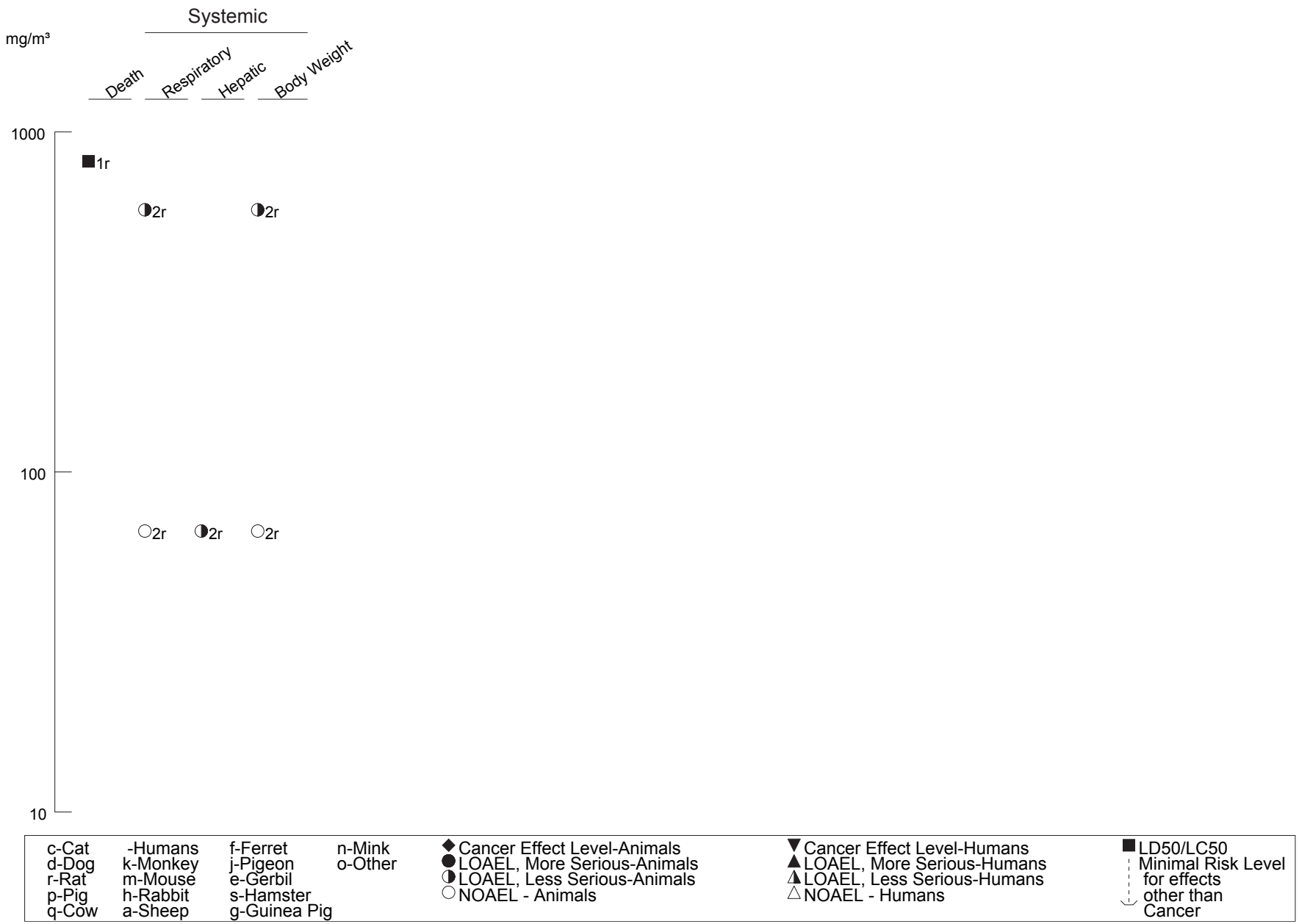
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/m³)	LOAEL Less Serious (mg/m³)	LOAEL Serious (mg/m³)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Rat (CD)	4 hr				820 M (14-day LC50)	Kinney et al. 1989	Exposure was nose-only.
Systemic								
2	Rat (CD)	4 hr	Resp	67 M	590 M (lung noise; labored breathing during and after exposure)		Kinney et al. 1989	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 Perfluorononanoic Acid - Inhalation

Acute (≤14 days)



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).

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. Information regarding cardiovascular effects of exposure to PFOS or PFOA in humans is limited to the observation of no alterations in the electrocardiograms (EKG) in a cross-sectional study of 1,025 workers potentially exposed to PFOA (Sakr et al. 2007b). Serum PFOA levels ranged from 5 to 9,550 ng/mL. It is likely that other occupational studies also conducted EKG assessments among workers, but no specific information was reported, as the main interest of most studies had been the evaluation of effects on the liver and on lipids. It should also be mentioned that a retrospective cohort mortality analysis of workers in the same plant studied by Sakr et al. (2007b) found no convincing evidence of increased mortality due to heart disease in general or ischemic heart disease specifically (Leonard 2006).

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. A study is available that evaluated self-reported health outcomes in relation to occupational exposures to PFOS at a PFOS-based fluorochemical manufacturing facility in Decatur, Alabama (Grice et al. 2007). The study cohort consisted of 1,400 employees (263 women) and included all current, retired, and former employees with a cumulative employment of at least 1 year. Based on PFOS serum concentrations, the workers were classified as having had no direct workplace exposure to PFOS-based fluorochemicals (0.11–0.29 mg/L), low-potential workplace exposure (0.39–0.89 mg/L), and high-potential workplace exposure (1.30–1.97 mg/L). The study found no association between self-reported incidence of gastric ulcer and having worked in a job with either low or high exposure to PFOS.

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). 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. Unspecified hematological parameters monitored in 115 male employees at two PFOS manufacturing plants in Decatur, Alabama and Antwerp, Belgium were not associated with serum PFOS levels (Olsen et al. 1999). 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 women and a 6-year longitudinal assessment of hematological parameters in relation to PFOS and PFOA values reported no substantial changes associated with the levels of these compounds measured in the study (<2 µg/mL) (Olsen et al. 2003a). 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.

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. The only information in animals is that examination of the sternebrae from male rats exposed head-only to up to 84 mg/m^3 APFO dusts for up to 2 weeks was unremarkable (Kennedy et al. 1986).

Hepatic Effects. Several reports have evaluated liver function and lipid profiles 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 clinical toxicity at the serum PFOA levels measured (<1,000–26,000 ng/mL, mean 3,300 ng/mL) (Gilliland and Mandel 1996). The investigators measured serum cholesterol, LDL, HDL and activities of AST, ALT, and GGT. It should be noted, however, 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). In addition to cholesterol, HDL, VLDL, and serum hepatic enzymes, the authors conducted other clinical chemistry tests. 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, BMI, and self-reported alcohol use, the authors conducted combined analyses as well as separate analyses by plant location. The results of the clinical chemistry tests were unremarkable. In addition, there were no substantial changes in serum hepatic enzymes, cholesterol, or lipoproteins at PFOS levels <6,000 ng/mL. 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). Some methodological issues that, according to the investigators, should be considered in evaluating the results included the cross-sectional design of the study, a less-than-ideal rate of voluntary participation among eligible fluorochemical production workers, the fact that serum PFOS may not reflect body burden since, in laboratory animals, it accumulates primarily in the liver, and the fact that the two cross-sectional analyses could not be viewed as independent studies because 61 workers were studied in both years. 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 lipid or hepatic parameters consistent with the known toxicological effects of PFOA or PFOS in laboratory animals (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 levels with total cholesterol or LDL (Olsen and Zobel 2007). PFOA was negatively associated with HDL for the three facilities combined, but not in individual sites. This was attributed to lower HDL values in two of the three locations and to markedly different demographic factors (i.e., BMI). 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). Serum triglycerides were significantly positively associated with PFOA, but not consistently by locations. Although the investigators stated that a biological association cannot be ruled out, they discuss several issues that could have contributed to the finding, including non-adherence to fasting requirements by some shift production workers and/or the effect of postprandial metabolic responses in shift workers. Olsen and Zobel (2007)

noted that there is evidence that postprandial serum triglyceride levels are higher among night shift workers than day workers. The study also found no statistically significant associations between PFOA and hepatic enzymes 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.

Two additional studies of workers at a facility that manufactures fluoropolymers in West Virginia are available. Sakr et al. (2007a) examined the relationship between serum PFOA and lipids and liver enzymes in a longitudinal study of 454 workers using a linear mixed effects model. The cohort comprised 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, the analyses showed serum PFOA positively associated with total cholesterol, with an increase of 1.06 mg/dL of cholesterol per 1,000 ng/mL increase in PFOA ($p=0.001$). Serum PFOA was not associated with changes in triglycerides or other lipoproteins. In addition, PFOA was negatively associated with total bilirubin and positively with serum AST activity, but not ALT or GGT. Limitations of the study discussed by the investigators included lack of information regarding lipid-lowering medications and alcohol intake, the fact that the studied workers represented only 16% of all workers who ever worked in the PFOA area, and exposure and outcome were not always measured on the same date. 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 total cholesterol, LDL, VLDL, and GGT activity. No associations were found for HDL, bilirubin, or ALT and AST activities. Strengths of the study included a large sample size that included female workers, same-day measurement of health outcome and marker of exposure, and control for cholesterol-lowering medications. Among the limitations are no information on baseline lipid levels and dietary intake, and the cross-sectional design of the study.

A small study of Italian perfluoroalkyl workers (n=35) studied over a period of 4 years also reported a positive association between serum levels of PFOA and increased total cholesterol ($p=0.03$), which appeared to have been due to an increase in non-HDL cholesterol (Costa 2004). No significant association was found between serum PFOA and HDL cholesterol, LDL cholesterol, non-HDL/LDL

cholesterol, or total triglycerides. The study also found no significant association between PFOA and protein metabolism or liver function.

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. Complete work histories, which were available for all employees, provided the basis for categorizing the employees into high-, low-, or no-exposure groups. Records were abstracted for height, weight, date of exam, and 32 clinical chemistry variables (lipid profile and hepatic enzymes among them). A limited number of blood samples obtained before the start of the study were used to validate the exposure categories, but were insufficient for use in any analysis (actual values were not provided). Annual cross-sectional analyses and longitudinal analyses that accounted for multiple measurements per person were conducted separately for men and women by exposure group. 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. Seven variables (total cholesterol, GGT, AST, ALT, alkaline phosphatase [AP], bilirubin, and triglycerides) that were examined in separate longitudinal models showed no significant increase or decrease by unit increase in exposure intensity score.

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 high-exposure 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 expect for AP that was significantly increased in the mid- and high-exposure groups immediately after exposure on day 10 and remained elevated in the high-exposure group on day 14 of recovery. Histopathological changes were restricted to the mid- and high-exposure groups and consisted of panlobular and centrilobular hepatocellular hypertrophy and necrosis. Panlobular hepatocellular hypertrophy was seen only after the 10^{th} 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 $\leq$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.

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. Kidney function, assessed by levels of blood urea nitrogen (BUN) and serum creatinine, were not associated with exposure to PFOS and/or PFOA in the epidemiological assessment conducted by Olsen et al. (2003a) or with exposure to PFNA in the study conducted by Mundt et al. (2007).

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

Endocrine Effects. The possible association between serum PFOA levels and hormone levels was investigated in two cross-sectional studies of male workers at a PFOA production plant (Olsen et al. 1998). The studies were conducted in 1993 (n=11) and 1995 (n=80). Eleven hormones were assayed: cortisol, dehydroepiandrosterone sulfate, estradiol, FSH, 17α-hydroxyprogesterone, free testosterone, total testosterone, LH, prolactin, 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. Taken together, the results showed no significant hormonal changes at the levels of PFOA measured. 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, in men, serum estradiol and testosterone were significantly positively associated with serum PFOA in linear regression models. The investigators could not find an explanation for this finding, but it confirmed the finding of elevated estradiol reported by Olsen et al. (1998).

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 (FT4), 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 THS 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, 95% CI 1,660–2,770 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.

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. 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.

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. Male rats that survived a 4-hour exposure to 380 mg/m^3 APFO dusts lost weight for 1–2 days after exposure for 4 hours, 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.

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.

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).

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

3.2.1.4 Neurological Effects

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

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

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. (1998) 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. 1998). 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. In the cross-sectional study of workers conducted by Sakr et al. (2007b), serum estradiol and testosterone were significantly associated with serum PFOA in linear regression models. The investigators could not find an explanation for this finding.

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

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 pregnant 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. An important determinant of birth weight that was not accounted for in the study was length of gestation.

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 1, but the difference over controls was no longer significant on postnatal day 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

In the study by Grice et al. (2007) of self-reported health conditions mentioned earlier, the risk of colon cancer, melanoma, and prostate cancer was not associated with any of the PFOS-exposure categories for analyses that included all self-reported or only validated cancers.

Studies that found increased risk of death due to prostate and bladder cancers in perfluororalkyl workers are summarized in Section 3.2.1.1. It should also be mentioned that a retrospective cohort mortality analysis of workers with measurable exposure to PFOA at a polymer production facility in West Virginia found no convincing evidence of increased deaths due to malignant neoplasms at sites that included the liver and biliary passages, pancreas, kidney and urinary tract, bronchus, trachea or lungs, and prostate (Leonard 2006; see Section 3.2.1.1).

No studies were located regarding cancer in animals following inhalation exposure to perfluoroalkyl compounds.

3.2.2 Oral Exposure

3.2.2.1 Death

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

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 4th 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.

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.

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 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}s 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 respiratory, cardiovascular, gastrointestinal, musculoskeletal, 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. 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). However, 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 ($p<0.05$).

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).

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 1.5 mg PFOS/kg/day in the diet for 104 weeks did not induce significant gross or microscopic alterations in the lungs and trachea (Thomford 2002b).

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 respiratory tract (3M 2007a; van Otterdiijk 2007a, 2007b). 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-

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 (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				
7	Rat (Sprague-Dawley)	14 d ad lib (F)	Hepatic		20 M (45% increase in relative liver weight)		Ikeda et al. 1985 Perfluorooctanoic acid	
8	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				
9	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				
10	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)			

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 (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)			
12	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	
13	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	
14	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)		

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
15	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)		
16	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				
17	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)			
18	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)			

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
19	Mouse (C57BL/6)	10 d ad lib (F)	Hepatic		1 M (35% increase in absolute liver weight)		Yang et al. 2001 Perfluorooctanoic acid	
20	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								
21	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.
22	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	
23	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
24	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	
25	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.
Reproductive								
26	Rat (CD)	14 d 1 x/d (GW)			25 M (184% increase in serum estradiol)		Biegel et al. 1995 Ammonium perfluorooctanoate	
27	Rat (CD)	14 d 1 x/d (GW)		1 M	10 M (63% increase in serum estradiol)		Cook et al. 1992 Ammonium perfluorooctanoate	
28	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	
Developmental								
29	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		100			Staples et al. 1984 Ammonium perfluorooctanoate	NOAEL is for fetal weight and teratology.

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 (CD-1)	once (G)			0.58 M (decreased motor activity)		Johansson et al. 2008 Ammonium perfluorooctanoate	
31	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	
32	Mouse (CD-1)	Gd 7-17 1 x/d (GW)				5 (reduced pup body weight at weaning, 43% in males and 35% in females)	Wolf et al. 2007 Ammonium perfluorooctanoate	
33	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.
INTERMEDIATE EXPOSURE								
Death								
34	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	

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	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	
Systemic								
36	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 (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
37	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)		
38	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
39	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)			
40	Rat (Sprague-Dawley)	70-90 d 1 x/d (GW)	Hepatic		3 M (increased absolute and relative liver weight)		Butenhoff et al. 2004 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)			

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	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 110 F		100 M (33% reduction in final mean body weight)		
42	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)		

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
43	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				
44	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				
45	Mouse (C57BL/6N)	15 d ad lib (W)	Bd Wt	7.5 F		15 F (weight loss)	Dewitt et al. 2008 Ammonium perfluorooctanoate	
46	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)		

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
47	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	
48	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)		
49	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)		
50	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				

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
Immuno/ Lymphoret								
51	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.
52	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	
53	Rat (albino)	90 d ad lib (F)		110 F			Griffith and Long 1980 Ammonium perfluorooctanoate	NOAEL is for histopathology of spleen and lymph nodes.
54	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	
Neurological								
55	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.
56	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
57	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.
58	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								
59	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.
60	Monkey (Rhesus)	90 d 1 x/d (G)		100			Griffith and Long 1980 Ammonium perfluorooctanoate	NOAEL is for histopahology of testes and ovaries.
61	Monkey (Cynomolgus)	30 d 1x/d (C)		20 M			Thomford 2001 Ammonium perfluorooctanoate	NOAEL is for serum estradiol, estriol and histopathology of the testes.
62	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.

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
63	Rat (Sprague-Dawley)	70-90 d 1 x/d (GW)		30			Butenhoff et al. 2004 Ammonium perfluorooctanoate	NOAEL is for reproductive performance of the P and F1 generations.
64	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.
65	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.
66	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	
Developmental								
67	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. 2004 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
68	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	Expression of PPARalpha was found to be required for induction of postnatal lethality.
69	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	
70	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	
71	Mouse (CD-1)	Gd 1-17 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								
72	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
73	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								
74	Rat (Sprague-Dawley)	2 yr ad lib (F)		15			3M 1983 Perfluorooctanoic acid	
Neurological								
75	Rat (Sprague-Dawley)	2 yr ad lib (F)		15			3M 1983 Perfluorooctanoic acid	
Reproductive								
76	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
77	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.

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 Perfluorooctanoate - Oral

Acute (≤14 days)

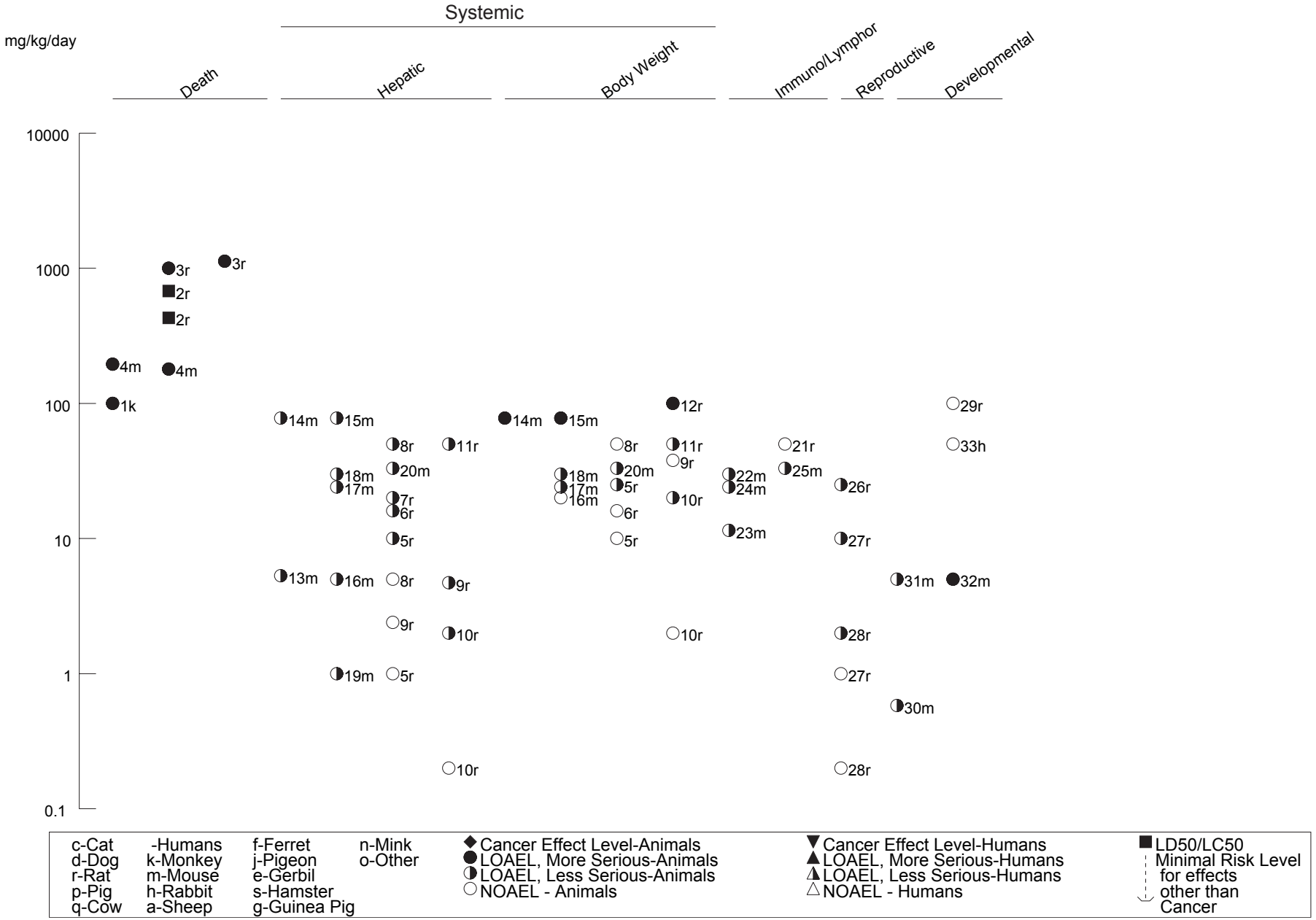


Figure 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral *(Continued)*

Intermediate (15-364 days)

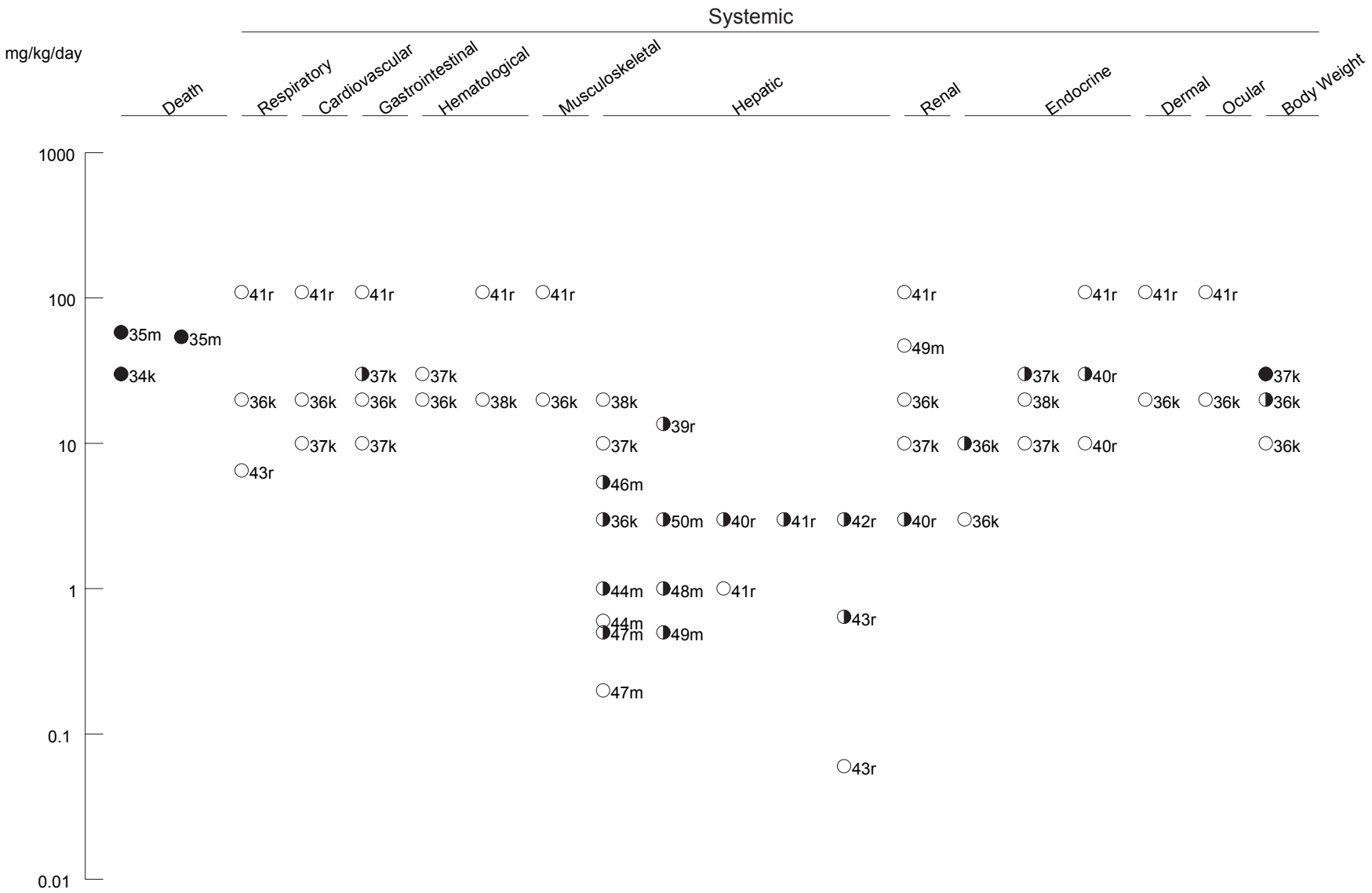


Figure 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral *(Continued)*

Intermediate (15-364 days)

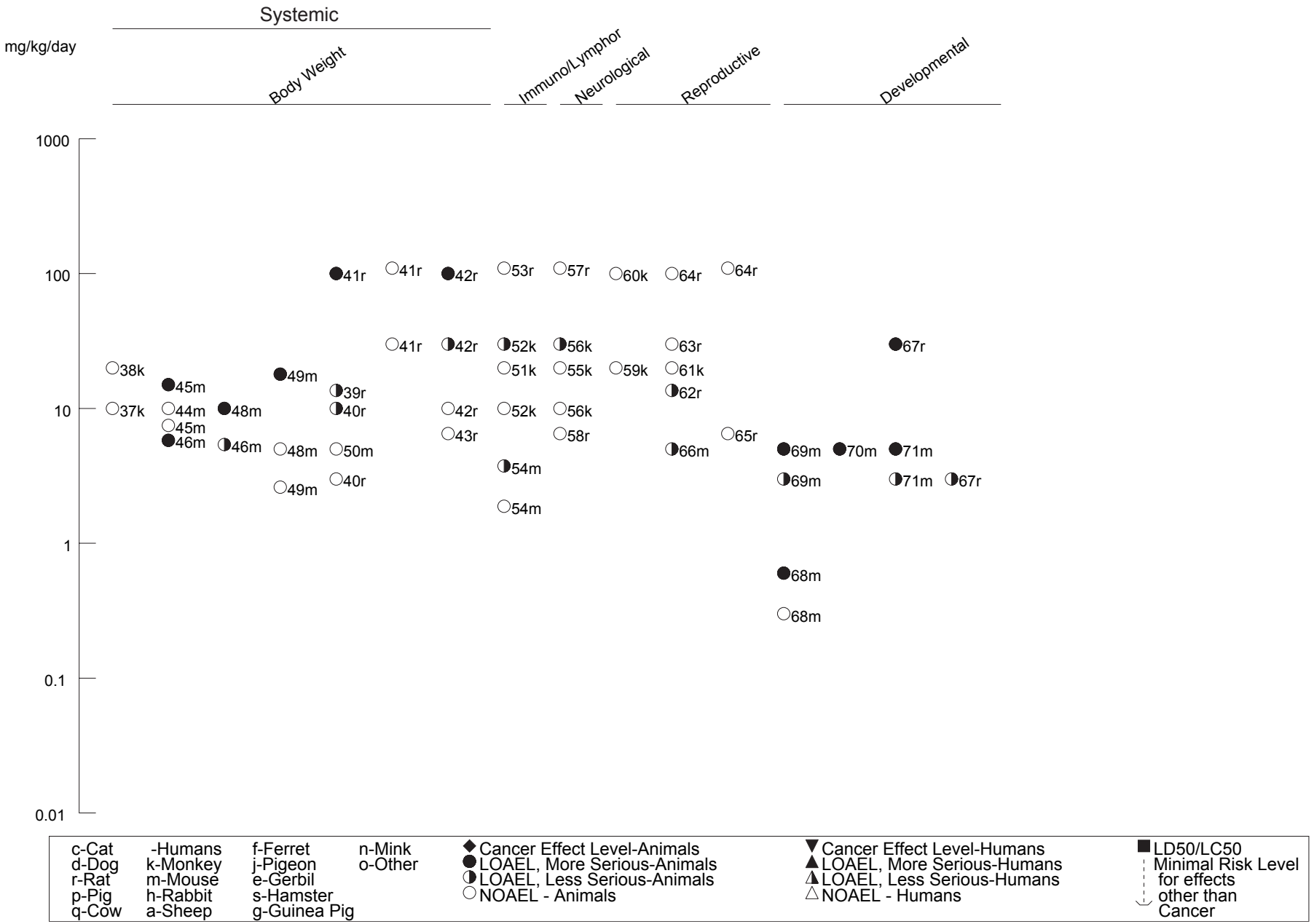


Figure 3-3 Levels of Significant Exposure to Perfluorooctanoate - Oral *(Continued)*

Chronic (≥365 days)

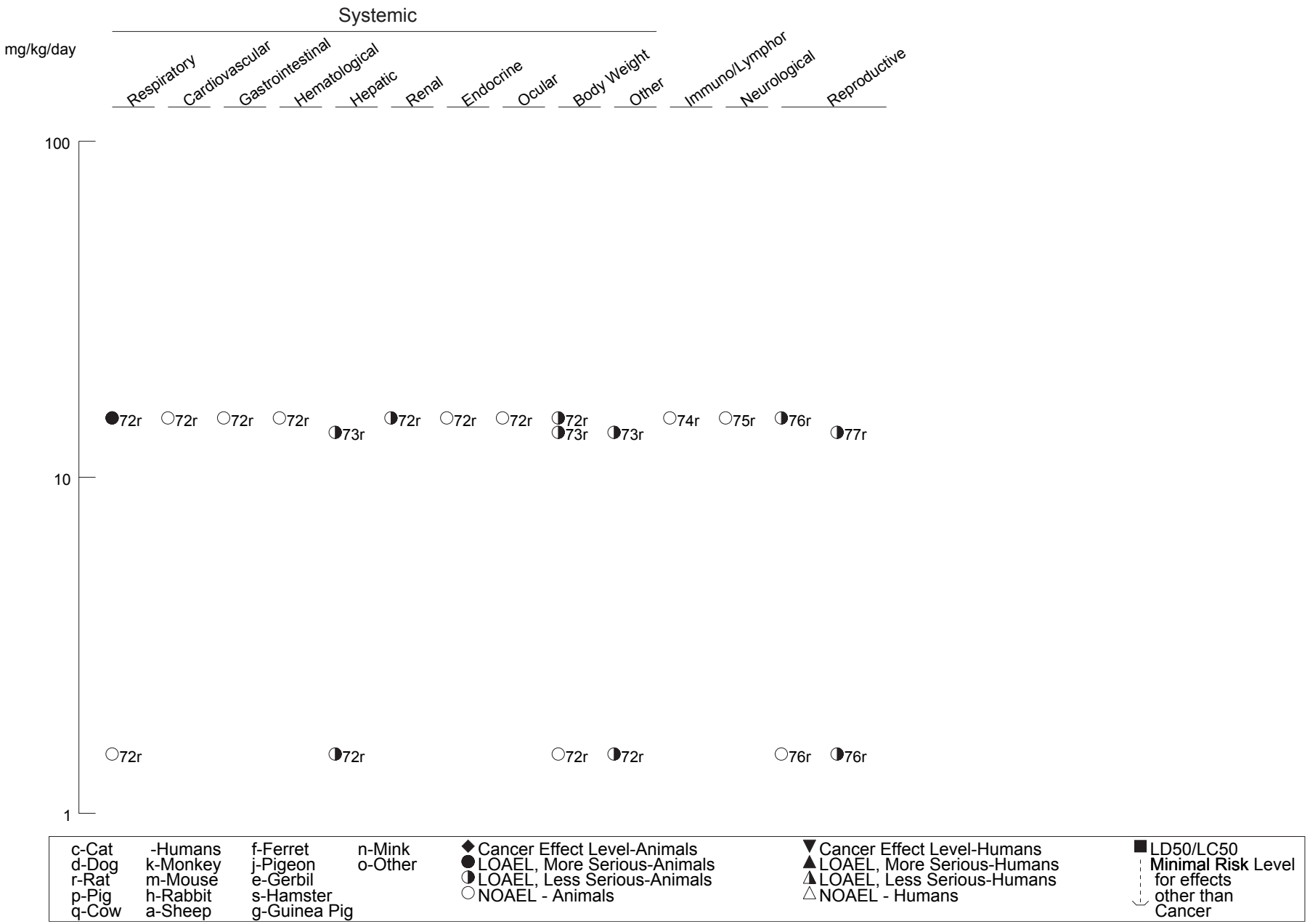


Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - Oral

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)	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	
3	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				
4	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				
5	Mouse (CD-1)	Gd 12-18 1 x/d (GW)	Bd Wt	6 F			Fuentes et al. 2007 Potassium perfluorooctane sulfonate	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - 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	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	
Reproductive								
7	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								
8	Rat (Sprague-Dawley)	2 d Gd 19-20 1 x/d (GW)				25 (decreased neonatal survival)	Grasty et al. 2003 Potassium perfluorooctane sulfonate	
9	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	
10	Rat (Sprague-Dawley)	Gd 19-20 1 x/d (G)				25 (increased neonatal mortality)	Grasty et al. 2005 Potassium perfluorooctane sulfonate	
11	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.

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - 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
12	Mouse (CD-1)	Gd 12-18 1 x/d (GW)			6 (reduced body weight of pups on postnatal days 4 and 8)		Fuentes et al. 2007 Potassium perfluorooctane sulfonate	
13	Mouse (CD-1)	once (G)			0.75 M (decreased motor activity)		Johansson et al. 2008 Potassium perfluorooctane sulfonate	
14	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	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - 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								
15	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	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 Sulfonate - 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	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				
17	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	
18	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%)		

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - 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
19	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				
20	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	0.4 F	1.56 F (significantly increased BUN)			
			Endocr	1.56 F				
			Ocular	1.56 F				
			Bd Wt	1.56 F				

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - 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	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)		
22	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 GD6)			
			Bd Wt	20 F				
Immuno/ Lymphoret								
23	Monkey (Cynomolgus)	26 wk 1 x/d (C)		0.75			Seacat et al. 2002 Potassium perfluorooctane sulfonate	NOAEL is for histopathology of lymphoreticular organs.
24	Monkey (Cynomolgus)	4 wk 1 x/d (C)		2			Thomford 2002a Potassium perfluorooctane sulfonate	NOAEL is for histopathology of the spleen and thymus.

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - 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	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.
26	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.
Neurological								
27	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.
28	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.
29	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.
Reproductive								
30	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.
31	Monkey (Cynomolgus)	4 wk 1 x/d (C)		2 M			Thomford 2002a Potassium perfluorooctane sulfonate	NOAEL is for histopathology of the testes.

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - 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
32	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.
33	Rat (Sprague-Dawley)	90 d 1 x/d (G)		2 F			Luebker et al. 2005b Potassium perfluorooctane sulfonate	NOAEL is for fertility.
34	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.
35	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.
Developmental								
36	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	
37	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.

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - 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
38	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	
39	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 postnatal day 5)	Luebker et al. 2005b Potassium perfluorooctane sulfonate	
40	Rat (Sprague-Dawley)	Gd 2-20 1 x/d (GW)			10 F	(increased incidences of cleft palate)			Thibodeaux et al. 2003 Potassium perfluorooctane sulfonate	
41	Mouse (B6C3F1)	Gd 1-17 1 x/d (GW)		0.1 M	1 M	(42.% suppressed NK cell activity in 8-week old mice)			Keil et al. 2008 Potassium perfluorooctane sulfonate	
42	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	
43	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	

Table 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - 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								
44	Rat (Sprague-Dawley)	104 wk ad lib (F)	Resp	1.5			Thomford 2002b Potassium perfluorooctane sulfonate	
			Cardio	1.5				
			Gastro	1.5				
			Hemato	1.5				
			Musc/skel	1.5				
			Hepatic	0.03 M	0.1 M (increased incidence of cystic hepatocellular degeneration)			
			Renal	1.5				
			Endocr	1.5				
			Dermal	1.5				
			Ocular	1.5				
			Bd Wt	0.4 F	1.5 F (14% reduction in final body weight)			
Immuno/ Lymphoret								
45	Rat (Sprague-Dawley)	104 wk ad lib (F)		1.5			Thomford 2002b Potassium perfluorooctane sulfonate	NOAEL is for histopathology of lymphoreticular organs.
Neurological								
46	Rat (Sprague-Dawley)	104 wk ad lib (F)		1.5			Thomford 2002b Potassium perfluorooctane sulfonate	NOAEL is for histopathology of central and peripheral nervous tissue.

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

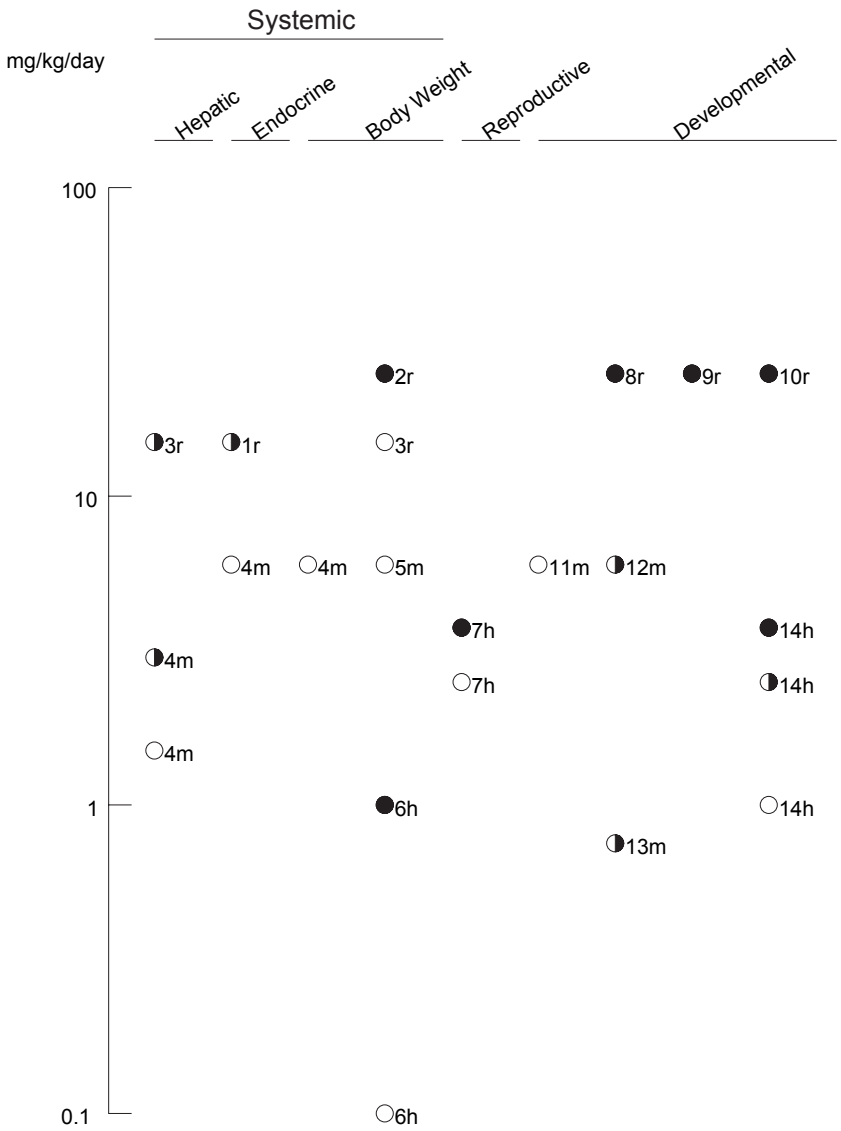
Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Reproductive								
47	Rat (Sprague-Dawley)	104 wk ad lib (F)		1.5			Thomford 2002b Potassium perfluorooctane sulfonate	NOAEL is for histopathology of sex organs.

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

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 Sulfonate - Oral

Acute (≤14 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

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

Intermediate (15-364 days)

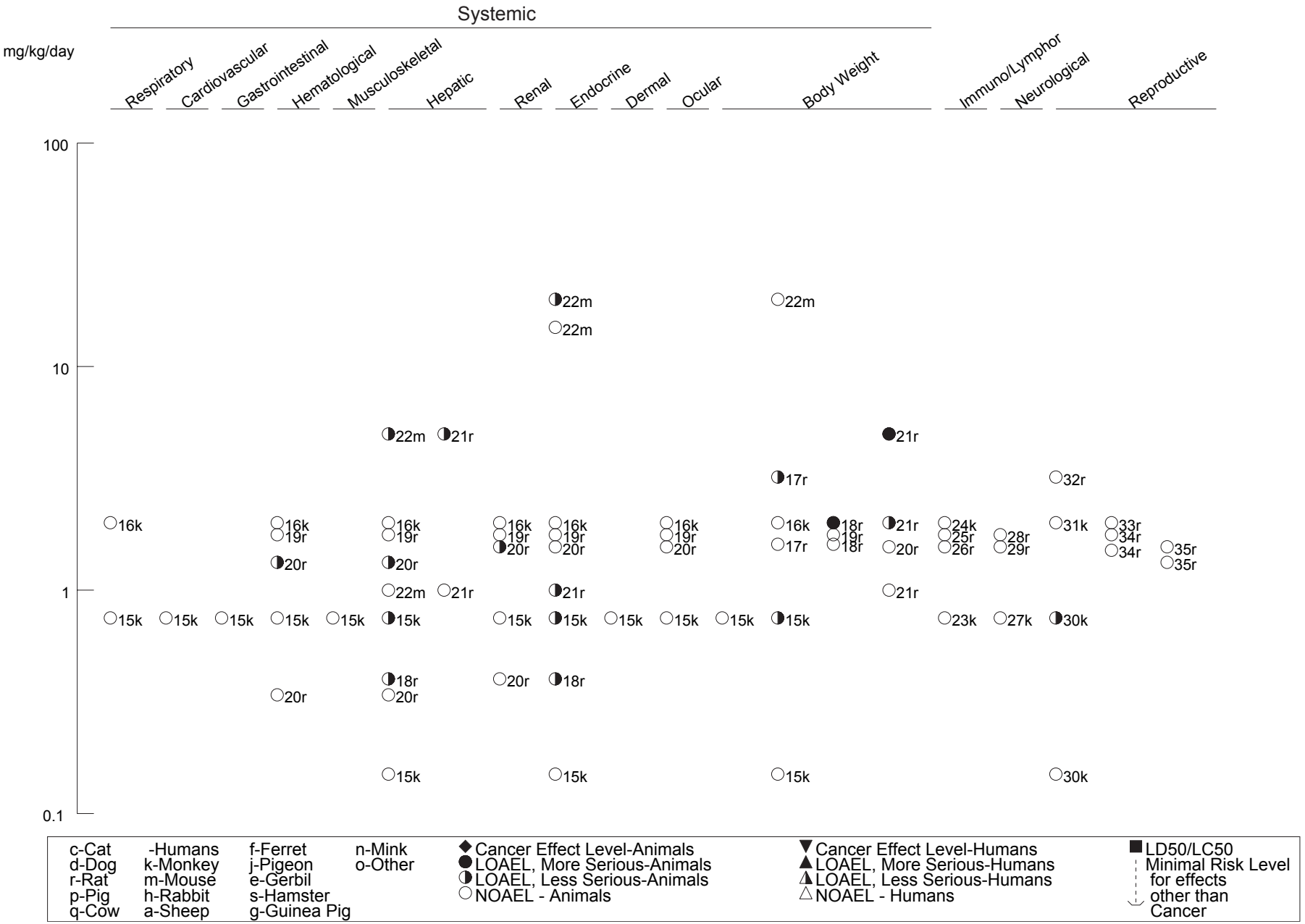


Figure 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - Oral *(Continued)*

Intermediate (15-364 days)

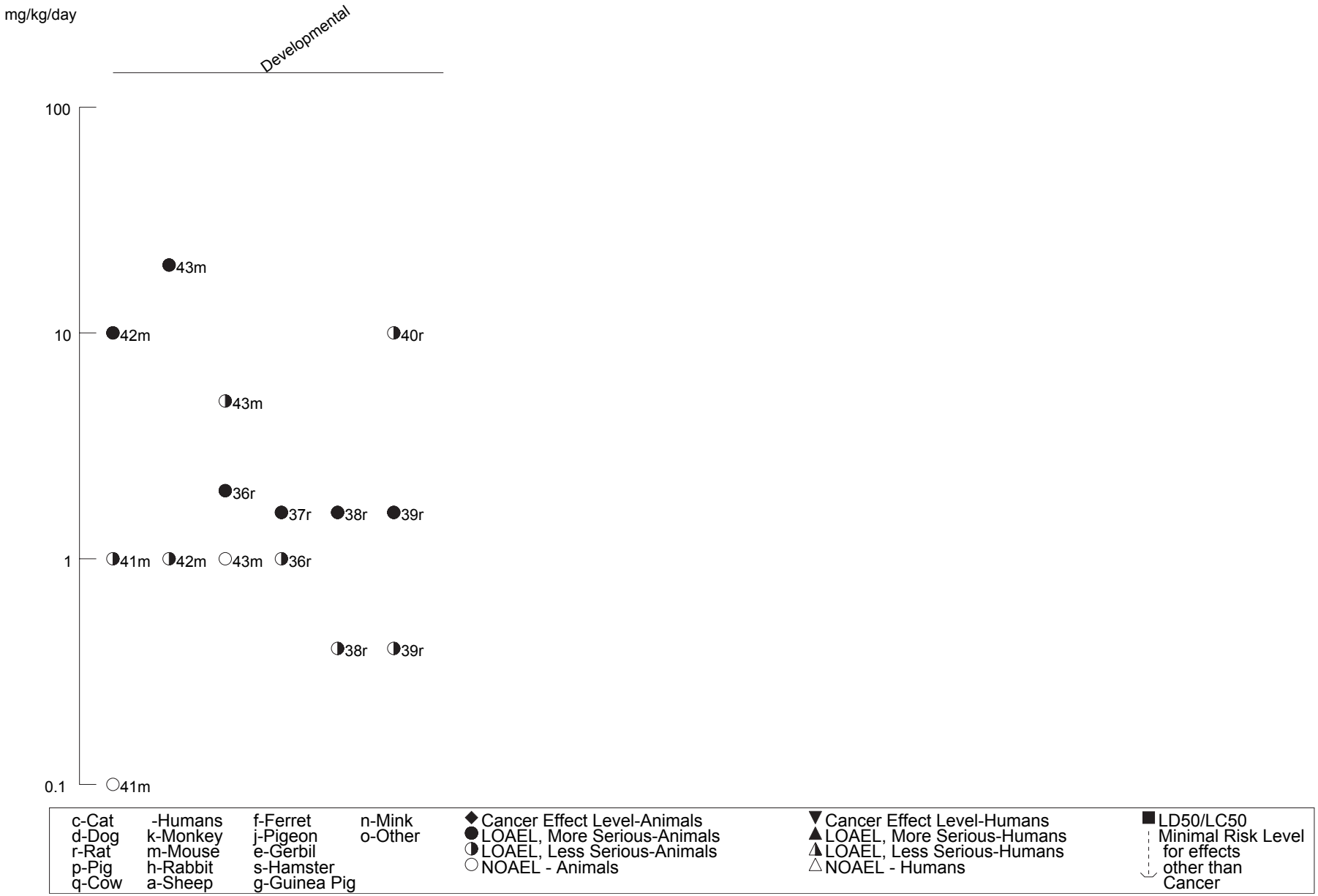


Figure 3-4 Levels of Significant Exposure to Perfluorooctane Sulfonate - Oral *(Continued)*

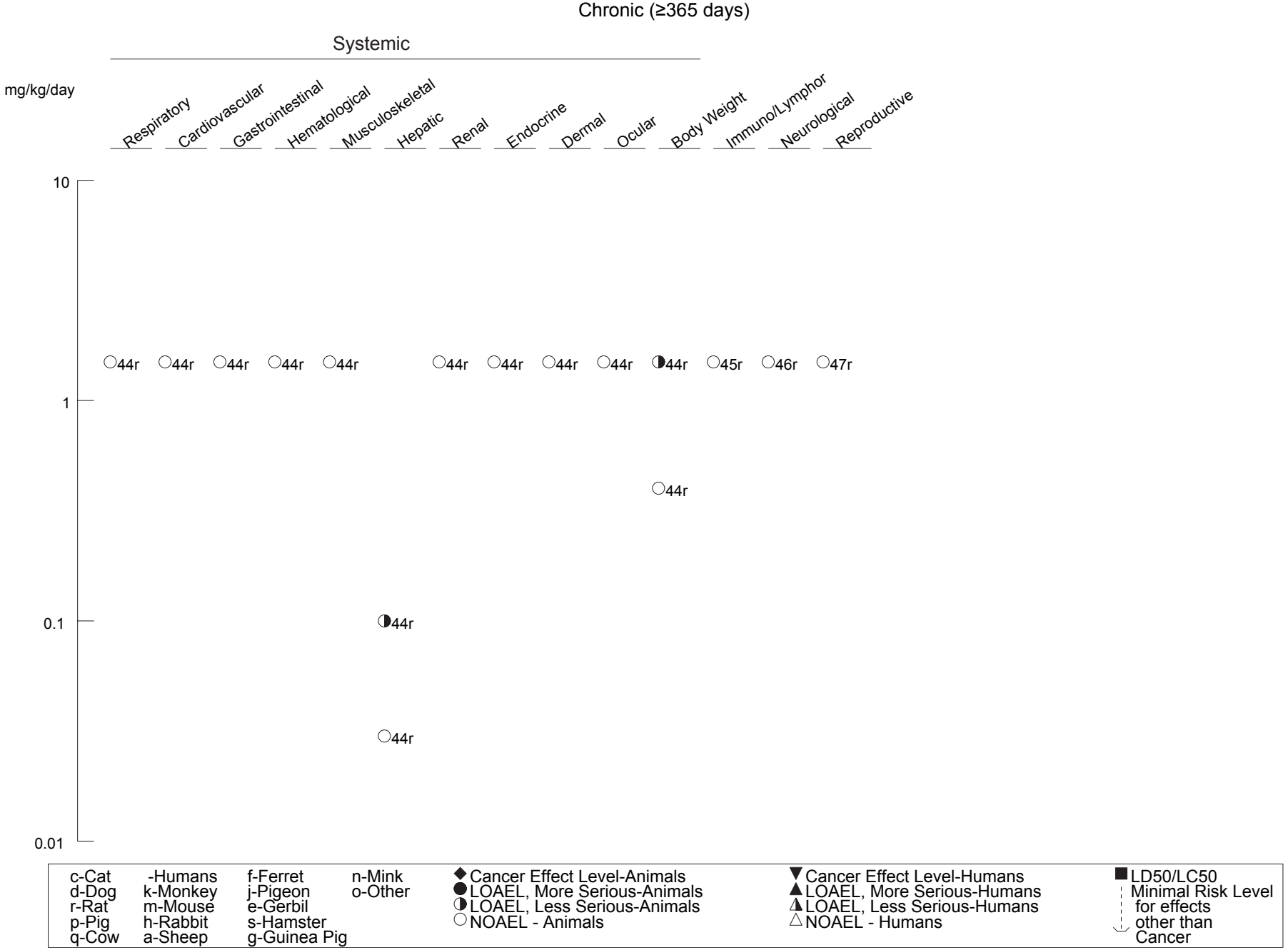


Table 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral

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	PFDeA
2	Mouse (CD-1)	14 d ad lib (F)				54 (all 10 mice died before day 14)	Kennedy 1987	PFNA
Systemic								
3	Rat (Sprague-Dawley)	5 d 1 x/d (GW)	Resp				3M 2007a	PFBA
			Cardio[184]	184				
			Gastro	184				
			Hemato	184				
			Musc/skel	184				
			Hepatic	184				
			Renal	184				
			Endocr	184				
			Bd Wt	184				
4	Rat (Sprague-Dawley)	14 d ad lib (F)	Hepatic		20 M (biochemical and ultrastructural evidence of peroxisome proliferation)		Ikeda et al. 1985	PFBA

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 (Wistar)	1 wk ad lib (F)	Hepatic	1.2 M	2.4 M (approximately 30% increase absolute liver weight)		Kawashima et al. 1995	PFDeA
			Bd Wt	4.7 M		9.5 M (approximately 32% weight loss)		
6	Rat (Sprague-Dawley)	once (GW)	Hepatic	5 M			Seacat and Luebker 2000	PFOSA Hepatic NOAEL is for absolute and relative organ weight.
			Bd Wt	5 M				
7	Rat (Sprague-Dawley)	14 d 1 x/d (GW)	Hepatic	5 M	10 M (35% increase in total serum cholesterol)		Shi et al. 2007	PFDoA
			Bd Wt	1 M		5 M (25% reduction in final body weight)		
8	Mouse (C57BL/6N)	once (GO)	Hepatic		40 F (69% increase in absolute liver weight in 2 days)		Brewster and Birnbaum 1989	PFDeA

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
9	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	PFDeA Weight gain was adjusted for weight of uterus and its contents.
10	Mouse (C57BL/6N)	once (GO)	Cardio	40 F	80 F (significant decrease in relative heart weight)		Harris et al. 1989	PFDeA
			Hepatic		20 F (85% increase in relative liver weight; peroxisome proliferation)			
			Renal	80 F				
			Bd Wt	40 F	80 F (12% reduction in final body weight)			
11	Mouse (CD-1)	14 d ad lib (F)	Hepatic		0.5 (50-70% increase in absolute liver weight)		Kennedy 1987	PFNA
12	Mouse (C57BL/6N)	10 d ad lib (F)	Hepatic		78 M (63% increase in absolute liver weight)		Permadi et al. 1992	PFBA
			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
13	Mouse (C57BL/6N)	10 d ad lib (F)	Hepatic		78 M (36% increase in absolute liver weight)		Permadi et al. 1992	PFDeA
			Bd Wt			78 M (33% weight loss)		
14	Mouse (C57BL/6N)	10 d ad lib (F)	Hepatic		78 M (63% increase in absolute liver weight)		Permadi et al. 1993	PFBA
			Bd Wt	78 M				
15	Mouse (C57BL/6N)	10 d ad lib (F)	Hepatic		78 M (36% increase in absolute liver weight)		Permadi et al. 1993	PFDeA
			Bd Wt			78 M (33% weight loss)		
Immuno/ Lymphoret								
16	Rat (Sprague-Dawley)	5 d 1 x/d (GW)		184			3M 2007a	PFBA NOAEL is for histopathology of the spleen and lymph nodes.
17	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	PFDeA

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
Neurological								
18	Rat (Sprague-Dawley)	5 d 1 x/d (GW)		184			3M 2007a	PFBA NOAEL is for histopathology of the brain and spinal cord.
Reproductive								
19	Rat (Sprague-Dawley)	5 d 1 x/d (GW)		184			3M 2007a	PFBA NOAEL is for histopathology of ovaries and testis.
20	Rat (Sprague-Dawley)	14 d 1 x/d (GW)		1 M	5 M (decreased serum testosterone and estradiol)		Shi et al. 2007	PFDoA
Developmental								
21	Mouse (C57BL/6N)	Gd 6-15 1 x/d (GO)		3		6.4 (33% decrease fetal weight per litter)	Harris and Birnbaum 1989	PFDeA
22	Mouse (CD-1)	once (G)		10.8 M			Johansson et al. 2008	PFDeA NOAEL is for spontaneous behavior tests.

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								
23	Rat (Sprague-Dawley)	28 d 1 x/d (GW)	Resp	900			3M 2001	PFBuS 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
24	Rat (Sprague-Dawley)	42-56 d 1 x/d (GW)	Resp	10			Hoberman and York 2003	PFHxS 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
25	Rat (Sprague-Dawley)	28 d 1 x/d (GW)	Resp	150			van Otterdiijk 2007a	PFBA 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
26	Rat (Sprague-Dawley)	90 d 1 x/d (GW)	Resp	30			van Otterdiijk 2007b	PFBA 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
27	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	PFBA
Immuno/ Lymphoret								
28	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		900			3M 2001	PFBuS NOAEL is for histopathology of lymphoreticular organs. histopathology.
29	Rat (Sprague-Dawley)	42-56 d 1 x/d (GW)		10			Hoberman and York 2003	PFHxS NOAEL is for histopathology of lymphoreticular organs.
30	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		150			van Otterdiijk 2007a	PFBA NOAEL is for histopathology of lymphoreticular organs.
31	Rat (Sprague-Dawley)	90 d 1 x/d (GW)		30			van Otterdiijk 2007b	PFBA NOAEL is for histopathology of lymphoreticular 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
Neurological								
32	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		900			3M 2001	PFBuS NOAEL is for histopathology of central and peripheral nervous tissue.
33	Rat (Sprague-Dawley)	42-56 d 1 x/d (GW)		10			Hoberman and York 2003	PFHxS NOAEL is for a functional observation battery and motor activity.
34	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		30 M	150 M (delayed pupillary reflex)		van Otterdiijk 2007a	PFBA
35	Rat (Sprague-Dawley)	90 d 1 x/d (GW)		30			van Otterdiijk 2007b	PFBA NOAEL is for histopathology or nervous tissues and observation battery.
Reproductive								
36	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		900			3M 2001	PFBuS NOAEL is for histopathology of sex 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
37	Rat (Sprague-Dawley)	42-56 d 1 x/d (GW)		10			Hoberman and York 2003	PFHxS NOAEL is for fertility parameters and sex organs histopathology.
38	Rat (Sprague-Dawley)	28 d 1 x/d (GW)		150			van Otterdiijk 2007a	PFBA NOAEL is for histopathology of reproductive organs.
39	Rat (Sprague-Dawley)	90 d 1 x/d (GW)		30			van Otterdiijk 2007b	PFBA NOAEL is for histopathology of reproductive organs.
Developmental								
40	Rat (Sprague-Dawley)	42-56 d 1 x/d (GW)		10 F			Hoberman and York 2003	PFHxS NOAEL is for a wide range of developmental parameters.
41	Mouse (CD-1)	18 d Gd 1-17 1 x/d (GW)			35 (eye opening delayed approximately 1 day)		Das et al. 2008	PFBA

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)

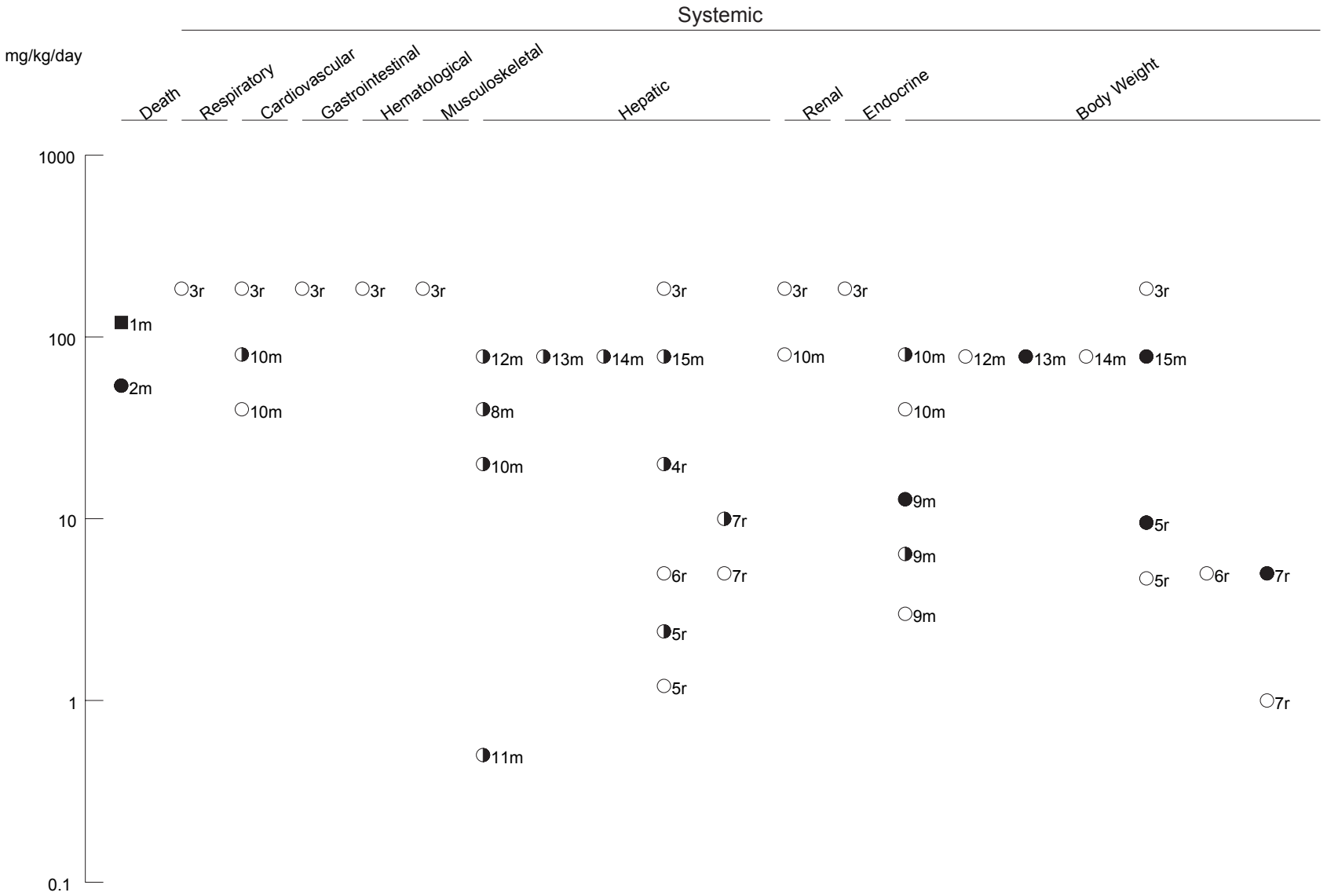


Figure 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral *(Continued)*

Acute (≤14 days)

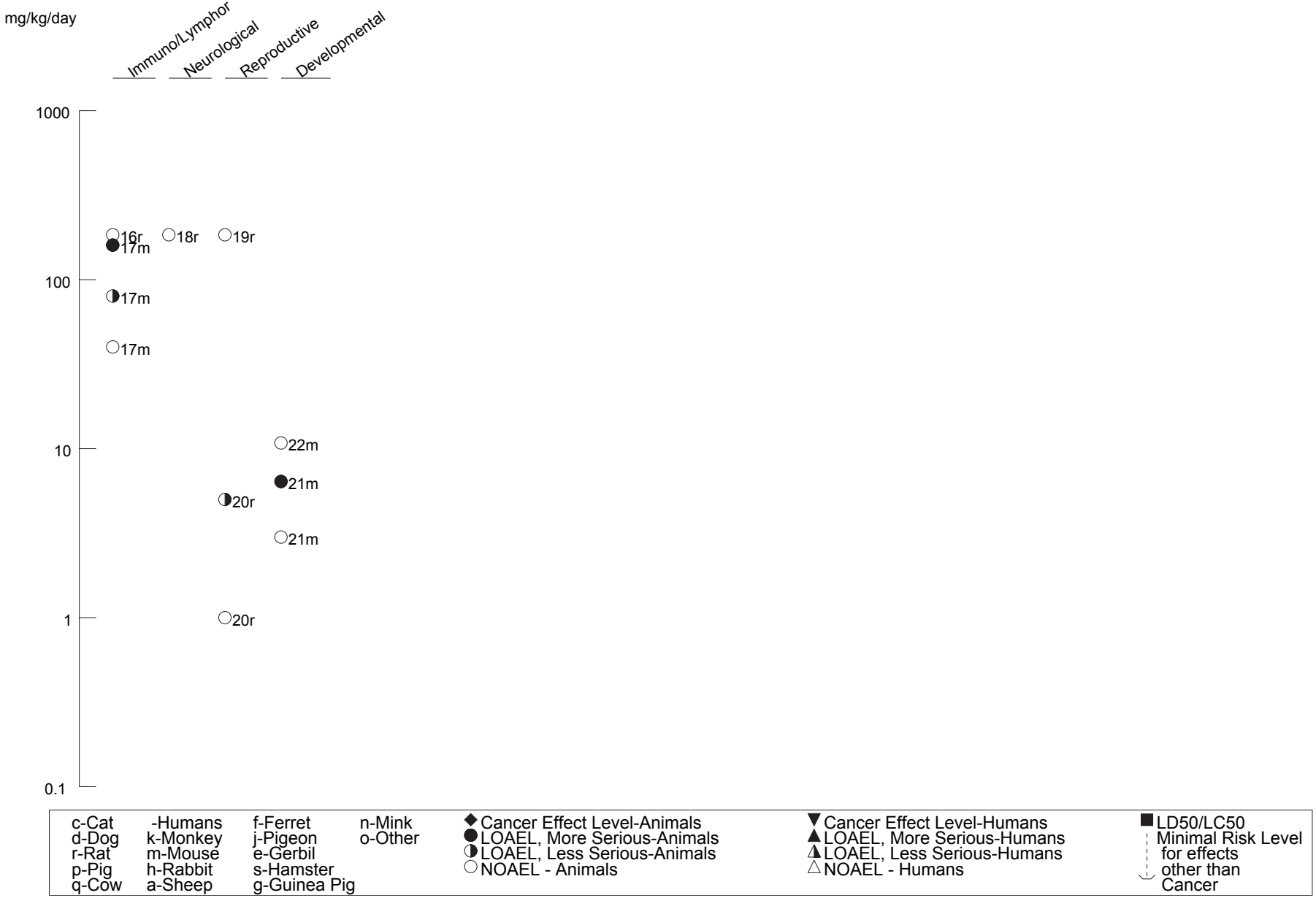
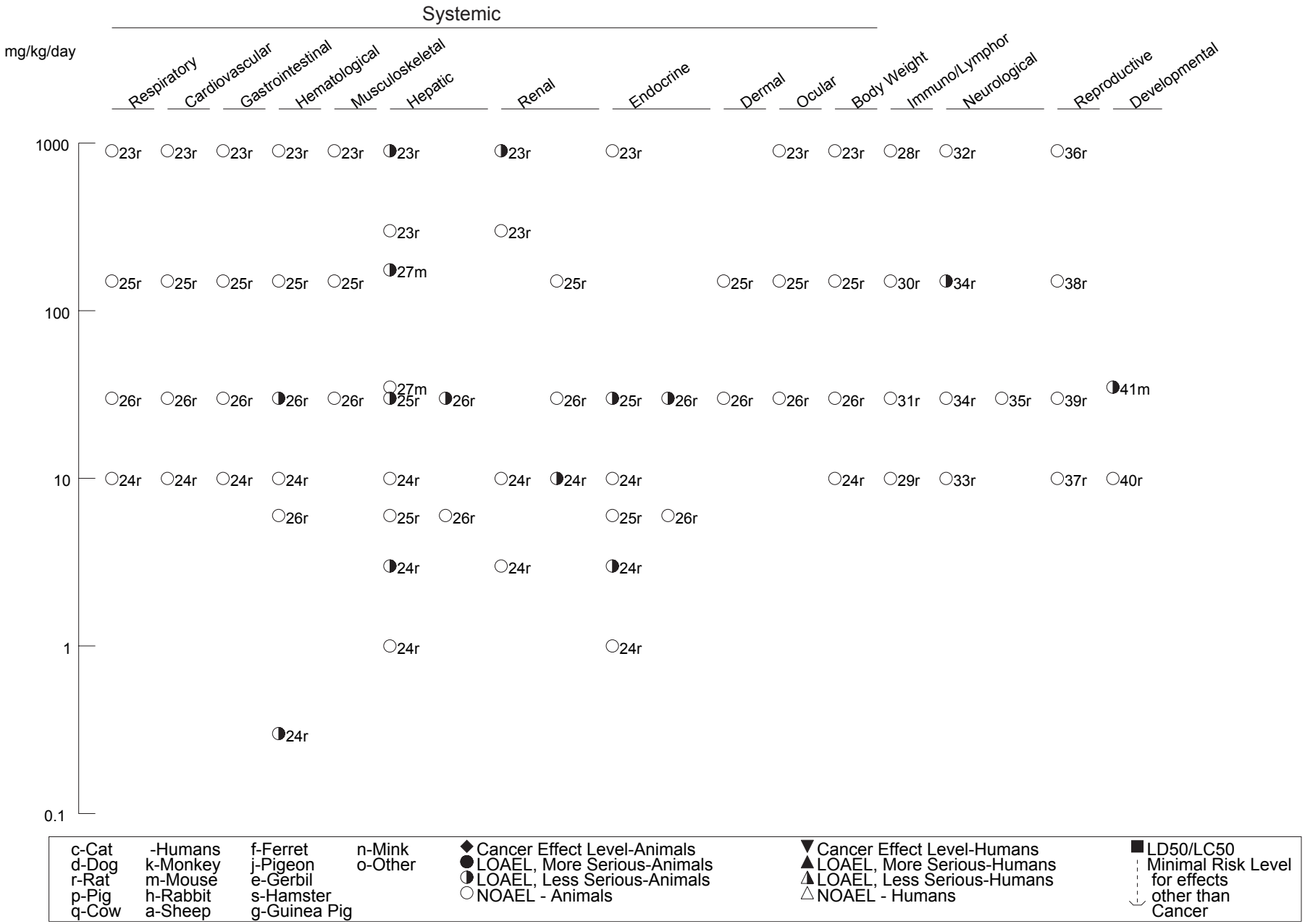


Figure 3-5 Levels of Significant Exposure to Other Perfluoroalkyls - Oral *(Continued)*

Intermediate (15-364 days)



related effects (Hoberman and York 2003). Dosing of rats with up to 900 mg/kg/day PFBuS by gavage for 28 days had no significant effect on the gross or microscopic morphology of the lungs and trachea (3M 2001).

Cardiovascular Effects. 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).

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 1.5 mg/kg/day of PFOS in the diet for 2 years had no significant gross or microscopic changes in the heart (Thomford 2002b).

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; van Otterdiijk 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 (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).

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. No significant gross or microscopic alterations of the gastrointestinal tract were observed in male and female rats exposed to up 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 up 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).

Treatment of rats with up to approximately 1.5 mg/kg/day PFOS via the diet for 2 years did not induce morphological alterations in the gastrointestinal tract (Thomford 2002b).

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; van Otterdiijk 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; Hoberman and York 2003).

Hematological Effects. Information 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. 2006a). 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. 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 (ppb) 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. Assuming that adults consume 2 L of water per day and have a mean body weight of 70 kg, the daily dose of PFOA via the drinking water would have been 0.1 µg/kg/day. This rough estimate does not include exposure via food or contact with consumer products.

No significant hematological alterations were reported in male and female rats dosed with up to 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 0, 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).

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). However, 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 high-dose 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 up to approximately 1.5 mg/kg/day PFOS in the diet (Thomford 2002b).

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; van Otterdiijk 2007a). However, 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 (van Otterdiijk 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 (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 (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).

Musculoskeletal Effects. No gross or microscopic alterations were reported in the sternum from rats following dietary dosing with approximately up to 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).

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 1.5 mg/kg/day PFOS in the diet for 2 years (Thomford 2002b).

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 (van Otterdiijk 2007a, 2007b). Treatment of rats with up to 900 mg/kg/day PFBuS by gavage for 28 days did not induce morphological alterations in skeletal muscle (3M 2001).

Hepatic Effects. No evidence of adverse liver function 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). The assessment included total serum cholesterol, serum transaminases, alkaline phosphatase, and serum bilirubin. 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.

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. Due to the high volume of information on this subject, representative examples are summarized below.

Administration of doses of 16 mg/kg/day PFOA to rats via the diet for 7 days resulted in a 66% increase in absolute liver weight (Haughom and Spydevold 1992). These investigators also reported a rapid reduction in serum cholesterol and triacylglycerols, possibly due to reduced activity of hydroxymethyl

glutaric acid Co-A reductase (HMG-CoA reductase), the rate-limiting enzyme in cholesterol synthesis and of acyl-CoA cholesterol acetyl transferase, the enzyme responsible for esterification of cholesterol. These findings suggested that the hypolipidemic effects of PFOA 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.

Administration of a range of doses between 0.2 and 40 mg/kg/day PFOA to male rats for 14 days induced a dose-related increase in absolute liver weight, which achieved statistical significance with a 2 mg/kg/day dose level (34% increase) (Liu et al. 1996). β-Oxidation activity was also significantly increased at this dose level, whereas hepatic microsomal concentration of total cytochrome P-450 was significantly increased at 20 mg/kg/day, suggesting different sensitivities for different end points. 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 total deoxyribonucleic acid (DNA) was not significantly changed, indicating that the hepatomegaly represented hypertrophy rather than hyperplasia (Pastoor et al. 1987). In this study, treatment with PFOA increased membrane-bound enzymes such as cytochrome P-450 content and the activity of benzphetamine N-demethylase, indicating proliferation of the smooth endoplasmic reticulum. However, soluble enzymes such as glutathione S-transferase and UPD-glucuronyltransferase were not affected. The activity of carnitine acetyltransferase was disproportionally increased relative to carnitine palmitoyltransferase, indicating predominant proliferation of peroxisomes vs. mitochondria. Light and electron microscopy confirmed the proliferation of the endoplasmic reticulum, mitochondria, and peroxisomes. Preferential proliferation of peroxisomes over mitochondria, as measured by specific markers, was also reported by Iwai and Yamashita (2006) in a similar study in rats.

In mice, administration of a relatively low dose of 1 mg/kg/day PFOA for 10 days resulted in a 35% increase in absolute liver weight, which correlated with a significant increase in peroxisome proliferation, as measured by increased acyl-CoA oxidase activity (Yang et al. 2001). However, in a subsequent study, the same group of investigators reported that exposure of PPARα-null mice to PFOA induced hepatomegaly to the same extent as in wild mice, but failed to increase acyl-CoA oxidase activity, suggesting that, at least in mice, hepatomegaly induced by PFOA is not a PPARα-dependent process (Yang et al. 2002b).

Intermediate-duration studies in male rats have reported liver effects at relatively low doses of PFOA. For example, in a 13-week dietary study, palmitoyl CoA oxidase activity was significantly increased in the 1.94 and 6.5 mg/kg/day groups on weeks 4, 7, and 13 and in the 0.64 mg/kg/day group on week 4

(Perkins et al. 2004). The maximum increase occurred on week 7. By recovery day 21, enzyme activity was comparable in all groups. There were no major incidences of gross lesions among the various groups. Liver weight relative to body weight was significantly increased at ≥0.64 mg/kg/day on week 4 and at ≥1.94 mg/kg/day on weeks 7 and 13. The level of PFOA in blood in the 0.64 mg/kg/day group on week 4 was 55,000 ng/mL. Liver to brain weight was also increased at 1.94 and 6.5 mg/kg/day on weeks 4 and 7. In rats allowed to recover after treatment ceased, relative liver weights were comparable among groups on recovery day 21. Absolute liver weight also increased at ≥0.64 mg/kg/day on weeks 4, 7, and 13. Microscopic changes in the liver occurred at ≥0.64 mg/kg/day and consisted of minimal-to-slight hepatocellular hypertrophy. By recovery day 21, the microscopic changes had disappeared. Serum levels of PFOA increased proportionally with dose, but there was no increase after week 4. A maximum concentration of PFOA of 159,000 ng/mL was detected in high-dose rats on week 4. By day 21 of recovery, levels of PFOA in serum were below or near the detection limit (700 ng/mL).

Treatment of male and female mice with approximately 5.3 mg/kg/day PFOA in the diet for 21 days induced a 39–41% increase in absolute liver weight (Kennedy 1987). The same dose of PFNA for 14 days increased absolute liver weight by 178–190% (Kennedy 1987). In mice dosed with approximately 5–6 mg/kg/day for 28 days, absolute liver weight of males and females was increased 2–3-fold (Griffith and Long 1980). All livers that were examined microscopically showed panlobular diffuse hypertrophy of hepatocytes accompanied by focal to multifocal cytoplasmic lipid vacuoles. In a developmental study, maternal absolute liver weight dams treated with 1 mg/kg/day on gds 1–17 increased by 38% by gd 18 relative to controls; the concentration of PFOA in serum on gd 18 was approximately 22,000 ng/mL (Lau et al. 2006). In another developmental study, absolute and relative weight of rats exposed to 1 mg/kg/day on gds 1–17 was significantly increased at weaning; in dams that had live pups at weaning, serum PFOA was 9,290 ng/mL, whereas in dams that had no pups surviving till weaning, serum PFOA was 26,300 ng/mL (Abbott et al. 2007). In a more recent study, administration of 0.5 mg/kg/day PFOA in the drinking water for 21 days induced a 27% increase in relative liver weight; doses of 47 mg/kg/day induced a 262% increase (Son et al. 2008). Serum ALT was significantly increased at 2.6 mg/kg/day (3-fold) and AST at 18 mg/kg/day (3-fold). Doses of 18 mg/kg/day induced disruption of the hepatic plate and marked hepatocytomegaly with acidophilic cytoplasm. Mice dosed with 47 mg/kg/day also showed diffuse hepatic damage characterized by multifocal coagulation and liquifaction necrosis. There was no inflammatory reaction. In a study of wild-type mice and PPARα-null mice exposed to PFOA during gds 1–17, absolute liver weight was significantly increased in wild mice at 1 mg/kg/day and in PPARα-null mice at 3 mg/kg/day (Abbott et al. 2007), in agreement with the findings of Yang et al. (2002b) that suggested that hepatomegaly is not a PPARα-dependent process in mice.

Rhesus monkeys appear to be far less sensitive to the liver effects of PFOA than rats and mice since daily gavage administration of up to 10 mg/kg/day for 90 days did not induce gross or microscopic alterations in the liver or alter the activity of serum transaminases (Griffith and Long 1980). In a preliminary study to a 26-week capsule study in Cynomolgus monkeys, administration of up to 20 mg/kg/day PFOA for 4 weeks did not affect gross or microscopic liver morphology and did not induce alterations in clinical tests used to assess liver function (Thomford 2001). In addition, cell proliferation was not increased in the liver. In the 26-week study, administration of 3, 10, or 20 mg/kg/day PFOA in a capsule caused no significant treatment-related effects on clinical chemistry 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 (Butenhoff et al. 2002). Dose-dependent 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% increase in the 3, 10, and 30 mg/kg/day groups, respectively). Relative liver weight was increased 19, 22, and 57% in the treated groups after 6 months of dosing. Except for the high-dose group, there were no significant changes in hepatic DNA content or enzymes that are specific markers of subcellular fractions. Mean PFOA serum concentrations at or after week 6 in the 3, 10, and 20 mg/kg/day dose groups were 77,000, 86,000, and 158,000 ng/mL, respectively.

A 2-year dietary study in male and female rats dosed with 1.5 or 15 mg/kg/day PFOA reported significant clinical alterations only in males consisting of increased serum ALT (low- and high-dose at 3, 6, 12, and 18 months), increased AST (low- and high-dose at 6 months, high-dose at 24 months), increased albumin (low- and high-dose at 3 and 6 months; high-dose at 12, 18, and 24 months), increased AP (low- and high-dose at 3 and 6 months; high-dose at 12, 18, and 24 months), and decreased creatine phosphokinase (low- and high-dose at 3 months) (3M 1983). At the 1-year interim sacrifices, high-dose males (low-dose rats were not evaluated) had statistically significantly elevated relative liver weight (20%). Histological evaluations at the 1-year time point (only control and high-dose rats were examined) revealed effects confined mostly to the liver of males consisting of diffuse hepatomegalocytosis, hepatocellular necrosis, portal mononuclear cell infiltration, and mild hepatocellular vacuolation (females). Significant histopathology after 2 years of treatment was restricted to rats in the high-dose group and included megalocytosis in the liver (males and females), cystoid degeneration in the liver (males), and portal mononuclear cell infiltration (males).

Studies in animals also suggest that the liver is the main target following oral exposure to PFOS. Rats dosed with 15 mg/kg/day PFOS for 7 days had a 40% increase in absolute liver weight (Haughom and

Spydevold 1992). As with PFOA, PFOS induced a significant and rapid reduction in cholesterol and triacylglycerols in serum. PFOS also increased markedly the concentration of triacyglycerols in the liver, suggesting that it inhibits excretion of these compounds from the liver; this effect was not seen with PFOA.

In a 4-week dietary study with PFOS in rats, relative liver weight in high-dose males (1.51 mg/kg/day) and females (1.77 mg/kg/day) was increased 22 and 8%, respectively (Seacat et al. 2003). Absolute liver weights were not significantly altered. Liver palmitoyl CoA oxidase, as an index of peroxisome proliferation, was not elevated when tested in one laboratory and was less than doubled in high-dose males when measured in a different laboratory, suggesting no significant peroxisome proliferation. Light microscopy of the liver did not show any abnormal findings; cell proliferation was not statistically increased. Extending the exposure to 14 weeks resulted in the following statistically significant changes in high-dose males (1.33 mg/kg/day): increased absolute liver weight (30%); increased relative liver weight (34%); decreased serum cholesterol (42%); and increased serum ALT activity (80%). High-dose females (1.56 mg/kg/day) only showed a significant increase in relative liver weight (30%). The concentration of PFOS in liver and serum increased proportionally with cumulative dose. Females had 31–42% higher serum PFOS than males; liver concentrations were comparable. After 14 weeks of treatment, the mean serum PFOS concentrations in high-dose males (1.33 mg/kg/day) and females (1.56 mg/kg/day) were 148,000 and 223,000 ng/mL, respectively. As a percentage of the cumulative dose, the amount of PFOS in serum remained relatively constant among groups and between sexes; however, in the liver, it varied widely with a range of 15–57%. Assays for palmitoyl CoA oxidase in the liver provided no evidence of peroxisome proliferation. There was also no evidence of cell proliferation. For the most part, morphological changes were restricted to the liver of high-dose rats and consisted of centrilobular hepatocyte hypertrophy and midzonal to centrilobular vacuolation.

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 longer-term study in Cynomolgus monkeys dosed with 0, 0.03, 0.15, or 0.75 mg/kg/day PFOS, absolute liver weight in high-dose males and females was increased 55 and 47%, respectively, relative to controls after 183 days of treatment (Seacat et al. 2002). Liver weight relative to body weight and brain weight was also significantly increased in high-dose males and females. 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 gender. The mean concentrations of PFOS in serum in high-dose males and females after 183 days of treatment were 173,000 and 171,000 ng/mL, respectively. Significant clinical chemistry changes consisted of a 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. The HDL concentration was significantly lower in low- and high-dose males on days 153 and 182 and in mid- and high-dose females on days 153 and 182. Serum bilirubin was significantly lower in high-dose males on days 91, 153, and 182. Liver peroxisome proliferation was significantly increased in high-dose females, but not enough to be considered biologically significant. Cell proliferation in liver 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. Observations conducted during a recovery period of up to 1 year showed that 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 pretreatment levels by day 36; HDL values returned to control levels within 61 days of cessation of treatment in the mid- and high-dose groups. Samples of liver collected after 7 months of recovery showed complete recovery of pathology by light and electron microscopy. The same observations were made after 1 year of recovery.

In a 2-year study of PFOS in rats, at termination, hepatotoxicity characterized by centrilobular hypertrophy, centrilobular eosinophilic hepatocytic granules, and centrilobular hepatocytic vacuolation was noted in rats that received doses of PFOS of approximately 0.4 and 1.5 mg/kg/day in the diet (Thomford 2002b). Also reported was a significant increase in the incidence of eosiniphillic clear cell altered foci and cystic hepatocellular degeneration in male rats dosed with ≥0.1 mg/kg/day PFOS. Observations made in a group of rats treated only for 52 weeks and allowed to continue in the study 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 with PFOS did not induce peroxisome proliferation or cell proliferation in the liver.

Considerable less information exists on liver effects in animals exposed orally to other perfluoroalkyl compounds.

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 Sprague-Dawley rats for 2 weeks did not significantly affect relative liver weight, but the same dose of PFOA induced a 45% increase (Ikeda et al. 1985). Catalase activity in liver homogenates was increased 42% by PFBA and by 56% by PFOA; both chemicals induced peroxisome proliferation. Dietary administration of doses of approximately 78 mg/kg/day PFBA to male C57BL/6 mice for 10 days induced a 63% increase in absolute weight, compared with 90 and 36% for PFOA and PFDeA, respectively (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 which were not as marked as those induced by PFOA. Doses of 78 mg/kg/day PFBA also had no significant effect on parameters of peroxisomal fatty acid β-oxidation (Permadi et al. 1993).

More recent intermediate-duration studies with PFBA that evaluated a wide range of end points suggest that the liver is a target for this perfluoroalkyl compound. 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 (van Otterdiijk 2007a). The 30 mg/kg/day also significantly decreased serum cholesterol. Doses 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, the highest dose tested, 30 mg/kg/day, increased absolute liver weight by 23%, increased serum alkaline phosphatase activity, and reduced total serum protein (van Otterdiijk 2007b). Microscopically, PFBA caused diffuse panlobular hepatocyte hypertrophy. None of these effects were observed after a 21-day recovery period; the NOAEL was 6 mg/kg/day.

An intermediate-duration study with PFHxS in rats reported that gavage doses ≥3 mg/kg/day induced a significant increase in absolute liver weight and in liver/body weight and liver/brain weight ratios in males (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, decreased serum triglycerides at 10 mg/kg/day, and increased serum albumin, alkaline phosphatase activity, and albumin/globulin ratio 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 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.

Administration of single gavage doses of ≥20 mg/kg PFDeA to female C57BL/6N mice resulted in significant and dose-related increases in relative liver weight, assessed 30 days after dosing (Harris et al. 1989). In mice treated with 20 mg/kg, the lowest dose tested, relative liver weight increased 85% relative to controls. 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. Ultrastructurally, the hepatocytes showed proliferation of peroxisomes, increases in smooth endoplasmic reticulum, and disruption of the rough endoplasmic reticulum. 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). That dose level also significantly increased hepatic acyl-CoA oxidase activity and hepatic lipids after 2 days of treatment. In both the Harris et al. (1989) and Brewster and Birnbaum (1989) studies, experiments conducted in congenic mice differing at the Ah locus showed that the hepatic morphological and biochemical effects of PFDeA are independent of the Ah receptor.

Kawashima et al. (1995) compared the effects of lower dietary doses of PFDeA (1.2–9.5 mg/kg/day) and PFOA (2.4–38 mg/kg/day) on hepatic effects in male rats in a 7-day dietary study. PFDeA was considerably more potent than PFOA in reducing body weight gain and food consumption, and 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. PFDeA lowered the activity of GSH-related enzymes in the same manner as PFOA. 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]).

Renal Effects. In the community health evaluation conducted by Emmett et al. (2006a) mentioned above, neither BUN nor serum creatinine levels were significantly associated with serum PFOA levels, so that there was no evidence for impaired kidney function.

Significantly elevated absolute and relative kidney weight was reported in male rats dosed daily 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 with daily doses of up to 20 mg/kg/day APFO in a capsule for 26 weeks (Butenhoff et al. 2002) or of 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).

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) for 4 weeks (Seacat et al. 2003). However, 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 0.4 or 1.5 mg/kg/day PFOS in the diet for 53 weeks in a 2-year study (Thomford 2002b). However, there were no significant gross or microscopic alterations in the kidneys at week 53 or at termination.

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, 150 mg/kg/day for 28 days, or 30 mg/kg/day by gavage for 90 days (3M 2007a; van Otterdijk 2007a, 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 (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 liver 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.

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. Serum level of TSH were not correlated with PFOA 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. 2006a). 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.

Effects on the levels of hormones related to reproductive function are discussed in Section 3.2.2.3, *Reproductive Effects*.

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, however, 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 thyroxine (FT4), total thyroxine (TT4), free triiodothyronine (FT3), total trioodothyronine (TT3), or TSH (Thomford 2001). Serum T4 and TT4 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 FT3, TT3, or TSH, and thyroid histology was unremarkable.

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/day by gavage in water (only dose level tested) reduced serum TT4 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 TT4. 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 TT4 in maternal serum on postpartum day 5 (Luebker et al. 2005b). FT4 and TSH were not significantly affected. Exposure of pregnant rats to ≥1 mg/kg/day PFOS on gds 2–20 induced significant reductions in TT4 and FT4 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 TT4 on gd 6 in mice dosed with 20 mg/kg/day PFOS on gds 1–17 (Thibodeaux et al. 2003). No alterations in TT4 were reported in mice dosed with 15 mg/kg/day. No information was provided regarding other thyroid hormones. 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 TT3 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 TT3 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 1.5 mg/kg/day PFOS in the diet for 2 years (Thomford 2002b).

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). However, 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 (van Otterdiijk 2007a, 2007b). These changes were not observed following a 3-week recovery period. Van Otterdiijk (2007a, 2007b) 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 Otterdiijk (2007b) were reported in male rats treated with ≥3 mg/kg/day PFHxS for at least 42 days (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). The toxicological significance of this finding was not discussed by the investigators.

Dermal Effects. The only information available in animals 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).

Administration of up to approximately 1.5 mg/kg/day PFOS to rats in the diet for 2 years did not induce morphological alterations in the skin (Thomford 2002b).

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 (van Otterdiijk 2007a, 2007b).

Ocular Effects. Examination of the eyes from rats fed a diet that provided up to 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).

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 1.5 mg/kg/day in the diet for 2 years (Thomford 2002b).

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 (van Otterdiijk 2007a, 2007b) (see also *Neurological Effects*). 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. 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 rather than a toxic effect (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).

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 1.5 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 (Thomford 2002b). No significant effect (<10% difference with controls) was seen in females dosed with ≤0.4 mg/kg/day PFOS.

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 (van Otterdiijk 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 (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.

3.2.2.3 Immunological and Lymphoreticular Effects

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

Limited information was located regarding immunological end points in rats exposed to perfluoroalkyl compounds. In an acute-duration study, male rats were exposed to up to 50 mg/kg/day PFOA by gavage for 14 days (Iwai and Yamashita 2006). This treatment 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. 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).

Dosing of Cynomolgus monkeys with up to 20 mg/kg/day PFOA in a capsule for 4 weeks did not affect the gross or microscopic morphology of the spleen (Thomford 2001). Similar results were reported in a 26-week study in Cynomolgus monkeys (Butenhoff et al. 2002). However, 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).

A series of studies in mice have been conducted by Yang and coworkers. Treatment of male mice with 30 mg/kg/day PFOA for 10 days induced severe thymus atrophy (Yang et al. 2000). Absolute and relative thymus weights were reduced 86 and 83%, respectively. Total and relative thymic DNA content

was significantly decreased. Absolute and relative spleen weights were reduced 30 and 23%, respectively, and total DNA in the spleen was reduced by half, but relative DNA content was unchanged. In a time course study, liver weight was significantly increased by day 2, but thymus and spleen weight were decreased by day 5. After 7 days of treatment with PFOA, the total number of thymocytes and splenocytes decreased significantly. Surface marker analysis showed that PFOA dramatically altered the phenotypic distribution of thymocytes. Analysis of isolated splenocytes showed decreases in the number of T cells (CD3) and in B cells (CD19). There were also decreases in both T-helper ($CD4^+$) and T-cytotoxic cells ($CD8^+$) in the splenocytes. Flow cytometry experiments showed that PFOA inhibited thymocyte proliferation, but in splenocytes, it only decreased the proportion of cells in the S phase. PFOA did not affect thymocytes or splenocytes *in vitro*, suggesting that thymic and splenic atrophy by PFOA may involve an indirect pathway, perhaps via altering fatty acid transport and/or metabolism (Yang et al. 2001). In a subsequent study, Yang et al. (2002a) reported that treatment of male mice with approximately 24 mg/kg/day PFOA significantly decreased both the numbers of splenocytes producing antibodies toward horse red blood cell (HRBC) and the titers of specific anti-HRBC antibodies in the sera, suggesting that PFOA also impairs splenocyte function. To determine the possible involvement of PPARα in the immunomodulation caused by PFOA, Yang et al. (2002b) conducted experiments in wild and PPARα-null mice (KO). In wild mice, PFOA induced significant reductions in spleen weight (40%) and thymus weight (79%), as well as in splenocytes and thymocytes. In KO mice, PFOA did not affect spleen weight or the number of splenocytes, but partially decreased thymus weight and the number of thymocytes, indicating that the effect on the spleen is PPARα-dependent, whereas the decrease in thymus weight is only partially dependent. Also attenuated in KO mice was the decrease in the size of the $CD4^+$ and $CD8^+$ population of cells in the thymus and in the number of thymocytes in the S and G2/M phases of the cell cycle. In addition, the response of splenocytes isolated from the spleen of null mice treated with PFOA was not reduced. Collectively, the data indicated that PPARα plays a major role in the immunomodulation caused by PFOA in mice.

Recently, Dewitt et al. (2008) conducted dose-response analysis studies of PFOA in female C57BL/6N mice and reported a LOAEL of 3.75 mg/kg/day PFOA, the lowest dose tested, for reduced sheep red blood cells (SRBC)-specific IgM antibody titers, suggesting that immunomodulation can occur at doses of PFOA lower than those tested by Yang and coworkers (Yang et al. 2002a). In the Dewitt et al. (2008) study, the mice were immunized with SRBC on day 11 of a 15-day dosing period via drinking water; analysis of SRBC-specific IgM antibodies was conducted in blood collected on day 16 of the study. The mean serum PFOA level in the mice dosed with 3.75 mg/kg/day was 75,000 ng/mL on day 16 and

decreased to 35,000 ng/mL 15 days later. In this study, delayed-type hypersensitivity (DTH) responses were not affected by dosing with up to 30 mg/kg/day PFOA for15 days.

Less information is available for PFOS. Rats treated with 1.77 mg/kg/day PFOS for 4 weeks, 1.56 mg/kg/day for 14 weeks, or 1.5 mg/kg/day for 2 years did not show significant morphological alterations in the spleen, thymus, and mesenteric lymph nodes (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 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; van Otterdiijk 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 (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.

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

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

The nervous system does not appear to be a sensitive target for perfluoroalkyl compounds, but comprehensive testing has not been conducted. 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).

Treatment of rats with up to 1.6–1.8 mg/kg/day PFOS for 4 or 14 weeks did not induce morphological alterations in the brain (Seacat et al. 2003). Administration of up to 1.5 mg/kg/day PFOS to rats in the diet for 2 years did not induce gross or microscopic alterations in the brain, spinal cord, or sciatic nerve (Thomford 2002b). Similarly, dosing Cynomolgus monkeys with up to 0.75 mg/kg/day PFOS for 26 weeks did not cause alterations in the brain, spinal cord, or sciatic nerve (Seacat et al. 2002).

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 (van Otterdiijk 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) (van Otterdiijk 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 toxicologically 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 (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.

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

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

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-hydroxy-progesterone 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).

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). This was suggested as a plausible mechanism to explain, at least in part, a delayed growth development in exposed offspring. The concentrations of PFOA in whole blood from dams and pups on PND 20 were 45,000 and 33,000 ng/mL, respectively.

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). However, 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 gds 22 and 28 (Case et al. 2001). Dietary exposure of rats to 1.3–1.8 mg/kg/day 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 1.5 mg/kg/day PFOS did not induce gross or microscopic alterations in the reproductive organs (Thomford 2002b).

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; van Otterdiijk 2007a, 2007b).

A reproductive study was conducted in rats dosed by gavage with 0, 0.3, 1, 3, or 10 mg/kg/day PFHxS (Hoberman and York 2003). Exposure of males began 14 days before cohabitation and continued until 1 day before sacrifice (a minimum of 42 days of exposure). Females were dosed starting 14 days before cohabitation and continued until 1 day before sacrifice on PND 21 or gd 25 (rats that did not deliver a litter). Treatment with PFHxS did not significantly alter sex organ weights, nor did it induce gross or microscopic lesions in the reproductive organs of males and females. 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. The reproductive NOAEL for PFHxS was 10 mg/kg/day. 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 mid- and high-dose 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 high-dose 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.

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

Recent studies are available that examined the relationship between levels of PFOA and PFOS in maternal and/or cord blood and developmental outcomes in the general population. For example, Apelberg et al. (2007b) conducted a hospital-based cross-sectional study of singleton deliveries in Baltimore, Maryland. Univariate and multivariate regression analyses were performed to examine the associations between PFOS and PFOA and gestational age, birth weight, head circumference, length, and ponderal index (ratio of birth weight in grams to length in centimeters cubed, times 100). Information on maternal (n=293) health conditions was obtained from the medical record; infant anthropometric measures were obtained from the infant medical record. The median concentration of PFOA and PFOS in cord blood serum samples were 1.6 ng/mL (range 0.3–7.1 ng/mL) and 5 ng/mL (range <0.2–34.8 ng/mL), respectively. After adjusting for potential confounders, both PFOA and PFOS were negatively associated with birth weight, ponderal index, and head circumference. In the fully-adjusted model, a natural logarithm-unit increase in cord concentration was associated with a decrease in mean birth weight of 69 g (95% CI 149–10) for PFOS and 104 g (95% CI 213–5) for PFOA; the corresponding changes in head circumference were 0.32 and 0.41 cm. No association was found between PFOS and PFOA concentrations and serum total cholesterol triglycerides, and total lipids. No significant associations were observed between either PFOS or PFOA concentrations and newborn length or gestational age. Limitations discussed by the investigators that could have influenced the results included issues related to the analytical method used to measure the chemicals, possible measurement errors in the anthropometric measurements, the use of medical records as the principal source for data on potential confounders, lack

of information regarding the diet of the subjects, and the fact that the study population represented a group of individuals with more risk factors for adverse birth outcomes than the United States as a whole. The investigators suggested cautious interpretation of the findings until the results can be replicated.

A similar study was conducted among a selected cohort of 1,400 Danish women (Fei et al. 2007). PFOS and PFOA were measured in blood samples collected twice during gestation, once in the first trimester and once in the second trimester; an umbilical cord blood sample was obtained shortly after birth. Analyses of the variance and linear regression were used to assess the relationship between birth weight and length of gestation and maternal plasma PFOA and PFOS levels. Mean PFOA and PFOS levels in maternal plasma collected in the first trimester were 35.3 and 5.6 ng/mL, respectively. The respective concentrations in the second trimester were 29.9 and 4.5 ng/mL. Umbilical cord levels of PFOA and PFOS were 11.0 and 3.7 ng/mL, respectively. Potential confounders adjusted for in the analyses included maternal age, parity, socio-economic status, pre-pregnancy BMI, smoking during pregnancy, infant sex, and gestational week at blood drawing. Also evaluated were alcohol use, fish intake, protein, fat, carbohydrate, and energy intake. After adjusting for potential confounders, birth weight was inversely associated with plasma levels of PFOA in the first blood sample; the regression coefficient was -10.63 (5% CI 20.79–0.47). Infants born to mothers with PFOA levels in the three highest quartiles had an adjusted average birth weight of 96, 98, and 105 g lower than infants born to mothers in the lowest quartile, respectively. The effects of PFOA on birth weight were more pronounced in preterm and post-term babies, but did not differ significantly by sex or parity. Neither PFOA nor PFOS was statistically associated with length of gestation. A potentially important covariate not included in the analyses was maternal weight gain.

In a follow-up report, Fei et al. (2008a) present data on placental weight, birth length, and head and abdominal circumferences in relation to maternal serum PFOA and PFOS levels. Covariates included gestational age, infant sex, maternal age, parity, socio-occupational status, prepregnancy body mass index, smoking during pregnancy, gestational week at blood drawing, alcohol drinking, nutritional factors, weight gain during pregnancy, hypertension and diabetes during pregnancy, and mode of delivery. The investigators categorized PFOA and PFOS levels into quartiles using the lowest quartile as the reference group and also analyzed exposure data as continuous variables. Maternal PFOS levels were not associated with any of the fetal growth indicators in the stratified analysis or with PFOS as a continuous variable. In the stratified analysis, after adjustment for confounders, only birth lengths in the second and fourth quartiles of PFOA exposure were statistically significantly lower than in the first quartile; the difference between the highest and lowest quartiles was 0.49 cm (95% CI 0.16–0.81). In the

analysis of PFOA as a continuous variable, after adjustments, only abdominal circumference and birth length were statistically negatively associated with maternal PFOA levels. For each ng/mL increase in maternal PFOA level, birth length decreased by 0.069 cm (95% CI 0.024–0.113) and abdominal circumference decreased by 0.059 cm (95% CI 0.012–0.106). A mechanism by which PFOA could impair fetal growth was not apparent.

In yet an additional study from the same group of investigators, Fei et al. (2008b) examined exposure to PFOS and PFOA and neurodevelopmental or musculoskeletal development using data on developmental milestones in early childhood from the Danish National Birth Cohort. The investigators randomly selected 1,400 pairs of pregnant women and their children among 43,045 women who met the sampling criteria. Blood samples were drawn from the mother twice during pregnancy and from the child (cord blood) shortly after birth. Only blood samples taken during the first trimester were used in the analysis. Subjects were divided *a priori* into four categories on the basis of quartiles of maternal PFOA and PFOS exposure during pregnancy. Midwives assessed Apgar score 5 minutes after birth following standardized procedures. Motor and mental development of infants was reported by the mothers using highly structured questionnaires when the infants were around 6 and 18 months of age. The motor domains assessed gross and fine motor functioning, whereas the mental domains assessed the child's attention and cognitive functions, language development, and social-personal development. Potential confounders that were considered in the models included maternal age, maternal occupational and educational status, parity, pre-pregnancy BMI, smoking and alcohol consumption during pregnancy, gestational week at blood drawing, child's sex, child's age at mother's interview, breast-feeding after the child turned 6 months of age, out-of-home day care, how many hours the mother spent with the child every day, and home density (total number of rooms divided by the total number of persons in the house). No significant association was found between levels of PFOA or PFOS and Apgar scores or time to achieve developmental milestones at the ages examined. However, children whose mothers had higher PFOS levels were more likely to start sitting without support at a later age (p for trend along quartiles = 0.041). PFOS was also associated with a later age to "use word-like sounds to tell what he/she wants." Potential limitations discussed included the risk of differential recall bias leading to misclassification and the fact that children can also be exposed through breast milk or by contact with products containing PFOA and PFOS making difficult to ascertain how these sources may have influenced the results. Fei et al. (2008b) concluded that the results provided little evidence to support influence of prenatal PFOA and PFOS, at the levels found in the general population, on motor or mental developmental milestones in early childhood.

Washino et al. (2009) examined the correlation between serum level of PFOA and PFOS and birth weight and birth size (length, chest circumference, and head circumference) in a group of 428 Japanese women and their infants. After the second trimester of pregnancy, the subjects completed a questionnaire that included information regarding dietary habits, smoking status, alcohol and caffeine intake, household income, and educational level. Information for exclusion criteria and potential confounders, which included pre-pregnancy BMI, pregnancy complications, gestational age, infant gender, parity, infant diseases, and birth weight and size, was obtained from medical records. Blood samples were collected after the second trimester of pregnancy. The geometric mean serum PFOS and PFOA levels were 4.9 and 1.2 ng/mL, respectively. Multiple regression analyses were performed to determine the correlations between PFOA and PFOS and birth weight and birth size. The mean birth weight was 3,058 g. In the fully-adjusted model, adjustments were made for maternal age, maternal educational level, smoking status during pregnancy, maternal BMI, parity, infant gender, gestational age, and blood sampling period. No correlation was found between serum levels of PFOA and birth weight or birth size whether the analyses were conducted in the total population or separately in male (n=198) and female (n=230) infants. For PFOS, there was a significant negative correlation between serum levels and birth weight in the fully-adjusted model. A $\log_{10}$-unit increase in PFOS level correlated with a decrease in mean birth weight of 148.8 g (95% CI, 297–0.5; p=0.049). In the separate analyses of male and female infants, the correlation remained significant only in females.

A small study of 15 Japanese women that analyzed PFOS, PFOA, and PFOSA in maternal and cord blood did not find any significant correlation between PFOS concentrations and age bracket, birth weight, or levels of TSH and free T4 in cord blood (Inoue et al. 2004b). Maternal blood was sampled between gestation weeks 38 and 41 and cord blood was sampled immediately after birth. PFOS concentrations in maternal and cord samples were 4.9–7.6 and 1.6–5.3 ng/mL, respectively. PFOSA was not detected in maternal or cord samples, whereas PFOA was detect only in 3 out of 15 maternal samples (<0.5–2.3 ng/mL). No correlation was found between TSH and free T4 in cord blood and PFOS in maternal blood, which according to the investigators, may have been due to a sample size too small to detect a relationship. Another small study of 19 women from China found no statistical significant correlation between concentrations of PFOS (0.045–0.36 ng/mL) and PFOS (0.047–0.21 ng/mL) in breast milk and infant weight (So et al. 2006b). Maximum concentrations of other perfluoroalkyl compounds in breast milk were 0.1 ng/mL for PFHxS, 0.062 ng/mL for PFNA, 0.015 ng/mL for PFDeA, and 0.056 ng/mL for PFUA. Limited conclusions can be drawn from these two studies due to their small sample size and thus, inadequate statistical power.

Recently, Nolan et al. (2009) published the results of a study of the relationship between high maternal exposure to PFOA via the drinking water and mean birth weights, incidence of low birth weight, incidence of preterm birth, and mean gestational age of single neonates born to mother residing within zip codes fully or partially serviced by Little Hocking Water Association (LHWA) in Washington County, Ohio (see above under *Hematological effects* for further details of the cohort). Women were assigned to one of three categories based on their water service: those serviced exclusively by LHWA only (mean water PFOA 6.78 µg/L), those serviced partially by LHWA, and those entirely outside the service area of the LHWA (mean water PFOA ≤0.007 µg/L). A total of 1,555 singleton neonates were studied: 168 from the LHWA area only, 212 from the area served partially by the LHWA, and 1,175 from the area not serviced by the LHWA. Univariate and multiple regression models were adjusted for maternal age, gestational age, sex, race, and population-level socioeconomic status. Mean birth weight for the entire cohort, regardless of water service category, was 3,264 g (±547 g). The results of the analysis showed that zip codes comprising services provided exclusively or partially by the LHWA were not associated with low birth weight, lowered mean birth weight, preterm birth, or reduced mean gestational age as compared to zip codes entirely outside the area serviced by the LHWA and national birth metrics. The study did find, however, that decreasing gestational age and maternal age 20–24 years were associated with an increased likelihood of low birth weight, while maternal age <24 years, female sex, and decreasing gestational age were associated with lowered mean birth weight. Potential study limitations discussed by the investigators include the lack of individual exposure levels that might have introduced exposure misclassification, socioeconomic status misclassification, lack of information regarding confounding known to influence birth weight and gestational age (i.e., parity, smoking status, asthma, hypertension, infection, and the mother's nutritional status prior to pregnancy), use of a data set with live neonates only, and reporting errors in the Ohio Department of Health database.

Developmental studies with PFOA have been conducted mostly in mice. Treatment of pregnant mice on gds 1–17, 8–17, or 12–17 with 5 mg/kg/day by gavage in water resulted in significant reductions in neonate body weight on PND 5, 10, and 20 ranging from 25 to 40% of control values (White et al. 2007). The doses tested did not significantly affect maternal weight or weight gain. Prenatal loss also was significantly increased in dams dosed on gds 1–17, 20% per live litter compared to 5.7–7.7% in groups dosed for shorter periods and controls. This study also reported that examination of the female pups on PND 10 or 20 showed significant delay in the development of the mammary gland among all treated groups. PFOA concentrations in whole blood from pups on PND 10 were higher than maternal levels (40,000–50,000 vs. 12,000–35,000 ng/mL). By PND 20, PFOA in the blood of pups had decreased nearly by half, whereas maternal levels remained almost unchanged. In a study that tested a range of

doses (1–40 mg/kg/day on gds 1–17), treatment with PFOA resulted in a drastic reduction in body weight gain in dams dosed with ≥10 mg/kg/day (Lau et al. 2006). All pregnancies were lost at 40 mg/kg/day. Maternal serum concentrations of PFOA on gd 18 ranged from approximately 22,000 ng/mL in mice dosed with 1 mg/kg/day PFOA to approximately 270,000 ng/mL in mice dosed with 40 mg/kg/day PFOA. The incidences of full litter resorptions (and percentages) in the 0, 1, 3, and 5 mg/kg/day groups were 3/45 (6.7%), 2/17 (11.8%), 1/17 (5.9%), and 7/27 (25.9%), respectively. Pair-wise comparison of the incidence in the control and 5 mg/kg/day groups by the Fisher's exact test gave a p-value <0.05. Among litters with viable fetuses at term, prenatal loss was observed only at 20 mg/kg/day and fetal body weight was reduced only at 20 mg/kg/day. Reduced ossification of the sternebrae occurred at ≥10 mg/kg/day and enlarged fontanel at ≥1 mg/kg/day, but with no clear dose-response relationship. Tail and limb defects occurred at ≥5 mg/kg/day and microcardia at ≥10 mg/kg/day. Most neonates in the 10 and 20 mg/kg/day group did not survive the first day of life. Survival at 5 mg/kg/day on postnatal day 23 was about 70% vs. approximately 80% in controls. On PND day 23, body weight of pups in the 3 mg/kg/day group was about 20% lower than in controls, but recovered subsequently. Significant delays in eye opening were reported at 5 mg/kg/day, in vaginal opening at 20 mg/kg/day, and in first estrus at 5 mg/kg/day; male pups in the 1 mg/kg/day group showed accelerated preputial separation.

Wolf et al. (2007) conducted a study in which pregnant mice were exposed to 0 or 5 mg/kg/day PFOA on gds 7–17, 10–17, 13–17, or 15–17. Exposure to PFOA did not affect maternal weight or weight gain during pregnancy. Eye opening was significantly delayed at 5 mg/kg/day in the groups exposed on gds 7–17 and 10–17 compared to controls. The delay was progressively more severe as the exposure began earlier, but it could not be determined whether this was due to a higher total dose or to a developmentally sensitive period. Pup body weights on PND 22 were reduced in all exposed groups. In males, a maximum reduction of approximately 43% occurred in the group exposed on gds 7–17; in females, the reduction was approximately 35%. Mean PFOA levels were 37,000 ng/mL in dam's blood from this group at weaning and 25,000 ng/mL in pups. After weaning, male pups in the gds 7–17 and 10–17 groups continued to exhibit delayed growth. Wolf et al. (2007) also conducted a cross-foster study to determine the relative contributions of gestational versus lactational exposures to the developmental toxicity of PFOA. The results showed that gestational exposure was sufficient to produce postnatal body deficits and developmental delays in the pups.

A study was conducted with wild 129S1/SvlmJ wild-type mice (WT) and PPARα knockout mice (KO) to determine if PPARα mediates PFOA-induced developmental toxicity (Abbott et al. 2007). Doses ranged between 0.1 and 20 mg/kg/day and were administered on gds 1–17. Maternal body weight and weight

gain were not affected by PFOA. The percent litter loss was significantly increased in WT pups at ≥0.6 mg/kg/day and in KO pups at ≥5 mg/kg/day. Birth weight of pups was not significantly affected in either mouse type. Relative liver weight at weaning was significantly increased at ≥0.1 mg/kg/day in WT pups and at 3 mg/kg/day in KO pups. Survival of pups from birth to weaning was significantly reduced at ≥0.6 mg/kg/day in WT pups, but was not affected in KO pups. Studies of heterozygous pups born to WT and KO dams showed that the expression of PPARα was required for induction of postnatal lethality by PFOA and that one functional copy of the gene was sufficient to significantly increase postnatal lethality. Eye opening was significantly delayed in WT pups at ≥1 mg/kg/day, but was not delayed in KO pups. The weight of pups at weaning was reduced by 18 and 14% in males and females, respectively, at 1 mg/kg/day in WT mice and was not significantly affected in KO mice. At weaning, mean levels of PFOA in serum from dams in the 0.6 mg/kg/day were 5,200 ng/mL; the corresponding serum level of PFOA in the pups was 3,800 ng/mL. There was no effect of strain or PPARα expression on serum PFOA levels.

Treatment of 10-day-old male mice with a single dose of 0.58 or 8.70 mg/kg PFOA by gavage resulted in significant decreases in locomotion and total activity relative to controls when tested at the age of 2 and 4 months (Johansson et al. 2008). Mice exposed to 8.70 mg/kg/day PFOA also showed decreased habituation capability and decreased activity in response to an injection of nicotine.

Exposure of artificially-inseminated New Zealand rabbits to up to 50 mg/kg/day PFOA by gavage on gds 6–18 did not cause embryotoxicity or teratogenicity (Gortner et al. 1982). Maternal toxicity manifested as reduced weight gain on gds 6–9 was reported in does treated with 50 mg/kg/day; no significant effects were observed in does treated with 5 mg/kg/day PFOA.

The developmental effects of PFOS have been studied in rats, mice, and rabbits. In pregnant rats treated on gds 2–21 with doses ranging from 1 to 10 mg/kg/day PFOS, pup survival decreased in a dose-related fashion (Lau et al. 2003). Over 95% of the pups in the 5 and 10 mg/kg/day groups did not survive the first day of life; PFOS levels in serum from these pups was >100 µg/mL. On PND 21, survival in controls was approximately 80 vs. 60% in the 2 mg/kg/day group. Cross-fostering exposed pups with unexposed dams failed to improve survival. Unexposed pups nursed by exposed dams survived a 3-day postnatal observation period. PFOS in serum from 5-day-old pups was slightly lower than at parturition (approximately 30,000, 60,000, and 85,000 ng/mL in pups from rats dosed with 1, 2, or 3 mg/kg/day, respectively). PFOS was also found in the liver of pups at parturition at levels similar to those found in blood. The body weight of pups at birth was significantly reduced at ≥2 mg/kg/day and remained reduced

until day 35 in the 5 mg/kg/day group. Pups had significantly lower total and free T4 as early as PND 2 (all groups). Free T4 remained lower up to PND day 35. There were no significant changes in T3 or TSH. Eye opening was significantly delayed (1 day) at ≥2 mg/kg/day, but neither vaginal opening nor preputial separation was affected by PFOS. The activity of choline acetyltransferase was significantly depressed in the prefrontal cortex on PND 35 at ≥3 mg/kg/day but not in the hippocampus. Learning in a T-maze was not affected.

Studies in rats have also shown that the later the dosing is during gestation the lower the survival rate (Grasty et al. 2003). The same group of investigators studied whether neonatal death might be due to lung immaturity of pups since newborns had trouble breathing within minutes of birth and the lungs taken shortly after birth resembled lungs of prenatal animals. However, experiments conducted with therapeutic agents known to enhance terminal lung maturation and accelerate surfactant production failed to reverse the delaying effects of PFOS, suggesting that neonatal mortality was not due to lung immaturity (Grasty et al. 2005).

Studies in which female rats were exposed to PFOS by gavage for some period before mating and exposure continued during gestation showed significantly reduced weight and decreased viability during PND 1–21 at maternal doses ≥1.6 mg/kg/day PFOS (Luebker et al. 2005a). Examination of dead pups did not reveal a cause of death; no labored breathing was noted in pups at birth. Developmental delays were noted at 1.6 mg/kg/day (pinna unfolding, surface righting, and air righting) and 0.4 mg/kg/day (eye opening). Sexual maturation was not affected in F1 males or females and no effects were noted in the neurobehavioral tests conducted on PND 24 and 70. Reproductive performance of F1 rats was not affected. Cross-foster experiments showed that neonatal mortality was greatest in the group exposed both *in utero* and during lactation suggesting that pre- and postnatal exposure to PFOS was additive. In a similar study, the following significant effects were reported in dams allowed to deliver naturally: decreased gestation length (≥0.8 mg/kg/day), increased number of dams with all pups dying on PND 1–5 (≥2 mg/kg/day), decreased pups birth weight (≥0.4 mg/kg/day), decreased pup's weight per litter on PND 5 (≥0.4 mg/kg/day), and decreased mean pup survival per litter (≥1.6 mg/kg/day) (Luebker et al. 2005b). Mean maternal serum PFOS levels in the 0.4, 0.8, 1, and 1.2 mg/kg/day groups were 27,000, 43,000, 52,000, and 86,000 ng/mL, respectively. The corresponding mean PFOS levels in the blood of pups were 36,000, 53,000, 84,000, and 147,000 ng/mL.

A study in mice showed that treatment with 10 mg/kg/day PFOS on gds 1–17 decreased postnatal survival at weaning by almost 50% (Lau et al. 2003), no significant effect was reported at 5 mg/kg/day.

Most pups from dams treated with 15 and 20 mg/kg/day did not survive for 24 hours after birth. The investigators estimated an LD_{50} of 10 mg/kg for the pups. Eye opening was significantly delayed (about 1 day) at 1, 5, and 10 mg/kg/day. A similar study in mice also dosed on gds 1–17 reported a significant decrease in percent live fetuses at 20 mg/kg/day, increased absolute (18%) and relative (27%) liver weight at 20 mg/kg/day, increased cleft palate at 15 mg/kg/day, sternal defects at 5 mg/kg/day, enlarged right atrium at 10 mg/kg/day, and ventricular septal defects at 20 mg/kg/day (Thibodeaux et al. 2003). Levels of PFOS in maternal serum at term in the 10, 15, and 20 mg/kg/day groups were approximately 175,000, 230,000, and 250,000 ng/mL, respectively.

Evaluation of neurological end points in pups from mice exposed to 6 mg/kg/day PFOS on gds 12–18 showed no significant alterations compared with controls (Fuentes et al. 2007a, 2007b). Evaluation of motor and reflex maturation showed isolated differences between treated and control pups. Postnatal resistance to backward pull was reduced on PND 10 and 11, but not PND 12. Postnatal time to climb a vertical screen was altered on PND 11, but not PND 10 or 12. Forelimb grip strength was reduced on PND 11, but not PND 9, 13, or 15. Evaluation of the 22-day-old pup's brain showed no effect on myelination pattern. Open field activity tests showed no significant difference between treated and control animals. In the rotarod test, there were also no significant differences in performance between treated and control mice. In male NMRI mice, treatment with a single gavage dose of 0.75 or 11.3 mg/kg PFOS at the age of 10 days resulted in alterations in spontaneous motor activity and habituation capability, and in an altered motor response to an injection of nicotine when tested at the ages of 2 or 4 months old (Johansson et al. 2008).

A recent study also examined immunological end points in 4- and 8-week-old pups from mice dosed with 0.1, 1, or 5 mg/kg/day PFOS on gds 1–17 (Keil et al. 2008). Spleen and thymus cellularity were not affected. No immunological deficits were evident on week 4. On week 8, NK cell activity was reduced by 42.5 and 32.1% in the 1 and 5 mg/kg/day males, respectively, and by 35.1% in the 5 mg/kg/day females. The primary IgM response to SRBC was only measured at 8 weeks of age and was suppressed by 53% in high-dose males, but it was not affected in females. Evaluation of splenic and thymic lymphocyte subpopulations showed a 21% reduction in splenic $B220^+$ cells in 4-week high-dose females and a 25% decrease in thymic $CD3^+$ and 28% decrease in thymic $CD4^+$ in 8-week high-dose males. Nitrate production by peritoneal macrophages was not significantly altered in any group.

In a study in rabbits dosed with up to 3.75 mg/kg/day PFOS on gds 6–20, the only significant developmental effects were a reduction in fetal body weight by approximately 10% at 2.5 mg/kg/day and

24% at 3.75 mg/kg/day (Case et al. 2001). There were no significant effects on numbers of corpora lutea, implantations, resorptions, or fetuses alive and dead. Skeletal examination revealed some reversible delays in ossification (sternebrae, hyoid, metacarpal, and pubic bones) at 2.5 and 3.75 mg/kg/day. Maternal body weight gain was significantly reduced during gds 7–21 (13, 21, and 47% in the 0.1, 1, and 2.5 mg/kg/day groups, respectively). During gds 21–29, maternal body weight gain was significantly reduced at 1 and 2.5 mg/kg/day. In the group dose with 2.5 mg/kg/day, food consumption was reduced about 8% during gds 7–21 and 13% during gds 21–29.

A recent study examined the developmental effects of PFBA in mice (Das et al. 2008). In that study, pregnant mice were administered 0, 35, 175, or 350 mg/kg/day PFBA by gavage on gds 1–17. A significant increase in full litter resorptions was reported in mice dosed with 350 mg/kg/day. However, there were no significant effects on number of implants, number of live fetuses, or fetal weight. PFBA did not affect newborn survival or weight gain on PND 1–21 or 22–291. In the pups, both absolute and relative liver weights were increased at 175 mg/kg/day on PND 1, but not on PND 10. Significant delays were seen in eye opening (approximately 1 day) at maternal doses of 35 mg/kg/day, in vaginal opening at 175 mg/kg/day (2 days), and in preputial separation at 350 mg/kg/day (2 days). PFBA did not significantly affect gene expression in fetal liver. Maternal serum/liver ratios of PFBA ranged between 35 and 55%; slightly higher ratios were seen in pups livers. On gd 18, maternal serum PFBA was 2,000–4,000 ng/mL with no apparent dose-response relationship. In pups, serum PFBA was 400–600 ng/mL on PND 1 and 110–150 ng/mL on PND 10. The milder response compared with PFOA was attributed by the investigators to faster elimination of PFBA as well as to lower biochemical potency.

Exposure of female rats to PFHxS by gavage to up to 10 mg/kg/day PFHxS for a period that included premating, gestation, and lactation did not significantly affect any developmental parameter evaluated, including gestation length, number of dams delivering litters, averages for implantation sites per delivered litter, number of dams with stillborn pups, number of dams with no live pups, dams with all pups dying, number of pups surviving per litter, sex ratios, litter size, and pups weight. Also, necropsy of the pups showed no significant effects on pups' liver weight (Hoberman and York 2003). The developmental NOAEL for PFHxS was 10 mg/kg/day.

Limited information regarding PFDeA is available from a study by Harris et al. (1989). Pregnant C57BL/6N mice were administered 0, 0.03, 0.1, 0.3, 1, 3, 6.4, or 12.8 mg/k/g/day PFDeA by gavage in corn oil on gds 6–15 and were sacrificed on gd 18. Net maternal body weight gain for the period gds 6–18 was severely depressed in the 6.4 and 12.8 groups; food consumption data were not provided. The

number of live fetuses per litter was significantly decreased in the 12.8 mg/kg/day group (4.6 vs. 7.2 in controls). Fetal body weight per litter was decreased at maternal doses ≥0.1 mg/kg/day, but only at 6.4 mg/kg/day was the difference with controls >10% (33% at 6.4 mg/kg/day and 50% at 12.8 mg/kg/day). Treatment with PFDeA did not induce soft tissue or skeletal malformations. Variations in ossification of the braincase were found in all fetuses examined from the 12.8 mg/kg/day dose group. Treatment of male mice with a single dose of 0.72 or 10.8 mg/kg by gavage at the age of 10 days did not induce significant alterations in spontaneous motor activity tests or in habituation capability when tested at the ages of 2 or 4 months old (Johansson et al. 2008).

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

There are no studies of cancer in humans exposed orally to perfluoroalkyl compounds.

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 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 did not consider PFOA carcinogenic in the rat under the conditions of the study. In the second study, male and female 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). In a feeding study in rainbow trout, PFOA was a promoter of liver tumors by a mechanism involving estrogenic signaling, independent of peroxisome proliferation (Tilton et al. 2008).

A 2-year bioassay for PFOS in Sprague-Dawley rats was conducted (Thomford 2002b); male and female rats were administered approximately 0, 0.03, 0.1, 0.4, or 1.5 mg/kg/day PFOS in the diet. An additional group was treated with 1.5 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 liver 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). Only one case of hepatocellular carcinoma was observed in the study and occurred in a high-dose female. 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.

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 3-6.

3.2.3.2 Systemic Effects

No information was located regarding systemic effects in humans following dermal exposure 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 Table 3-6.

Respiratory Effects. 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. No morphological alterations were seen in the heart from male rats in the study conducted by Kennedy (1985).

Gastrointestinal Effects. 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).

Table 3-6 Levels of Significant Exposure to Perfluorooctanoate - 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 3-6 Levels of Significant Exposure to Perfluorooctanoate - 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 3-6 Levels of Significant Exposure to Perfluorooctanoate - 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 3-6 Levels of Significant Exposure to Perfluorooctanoate - 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)

Hematological Effects. 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. 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. 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. 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. Application of as single dose of 5,000 mg/kg of an aqueous paste of APFO to a clipped are 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. 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. 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.

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 3-6.

3.2.3.4 Neurological Effects

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

No gross or microscopic alterations were reported in the brain from rats 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.

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 is presented as a NOAEL for reproductive effects in Table 3-6.

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

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. However, 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.

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 both cases in a dose-related manner (Yao and Zhong

2005). These effects were accompanied by a significant increase in reactive oxygen species, which the investigators suggested caused the DNA damage.

The results of various mutagenicity studies with PFOA in microorganisms were summarized by Griffith and Long (1980). The tests used *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, as well as *Saccharomyces cerevisiae* with or without metabolic activation. All tests yielded negative results. 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).

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. It 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 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).

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. However, serum concentrations of perfluoroalkyls in workers in fluorochemical production industry have been reported (see Table 6-13). 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 6-11) 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 1 and 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. However, 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 a study of residents in the Little Hocking water district in southeastern Ohio (Emmett et al. 2006a) and in two studies of children and adults in Germany (Hölzer et al. 2008; Wilhelm et al. 2008a). Emmett et al. (2006a) reported that the number of glasses of tap water ingested per day was a statistically significant factor in the best-fit model for PFOA exposure. Hölzer et al. (2008) reported that consumption of tap water at home was a significant predictor of PFOA blood concentrations.

Greater than 95% of an oral dose of ammonium [^{14}C]PFOA was absorbed in rats that received a single oral 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 an oral gavage dose of 10 mg ammonium PFOA/kg, were 2–3 times when administered to fasted rats, compared to fed rats (Hinderliter et al. 2006b). The estimated absorption fractions of ingested [^{14}C]PFOA or [^{14}C]PFOS (administered as a 4.2. mg/kg oral dose) were >93 and >95% in rats, respectively (Johnson and Ober 1979, 1999a). 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).

The highest observed concentrations of ^{14}C in plasma occurred in male rats at approximately 10 hours (range 7.5–15 hours) following a 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 half-time (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=0.35 $hour^{-1}$) can be calculated from these observations (Equations 1 and 2):

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

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

Absorption rate appears to be greater in female rats compared to male rats (t_{max} = time of maximum concentration of ^{14}C; k = elimination constant). The time to peak concentrations of ^{14}C in plasma occurred at approximately 1.1 hour (range 0.6–1.5 hours) 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 1 and 2, was approximately 0.25 hours (range 0.12–0.38 hours).

3.4.1.3 Dermal Exposure

Dermal exposures of rats to ammonium PFOA has been shown to produce systemic (e.g., liver) toxicity (see Section 3.3.3). Estimates of the amount or rates of dermal absorption in humans or animals have not been reported; however, dermal penetration of PFOA has been studied in preparations of isolated rat and human epidermis (Fasano et al. 2005). These studies indicate that the rat skin may be more permeable to PFOA than human skin and that PFOA is not well absorbed across human skin. Approximately 0.048% of a dose of PFOA (150 μL/cm^2 of a 20% aqueous solution of ammonium PFOA; approximately 30 mg ammonium PFOA/cm^2) applied to isolated human epidermis was absorbed in 48 hours. 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 6-13). 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 difference between plasma and serum and whole blood corresponded to volume displacement by red blood cells, suggesting that these perfluoroalkyls do not enter cellular components of blood or become attached to them. 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 (Johnson and Ober 1999a). RBC:plasma (or serum) ratios of 0.2–0.3 have also been observed in rats following intravenous injection of PFOA (Johnson and Ober 1999b; Kudo et al. 2007).

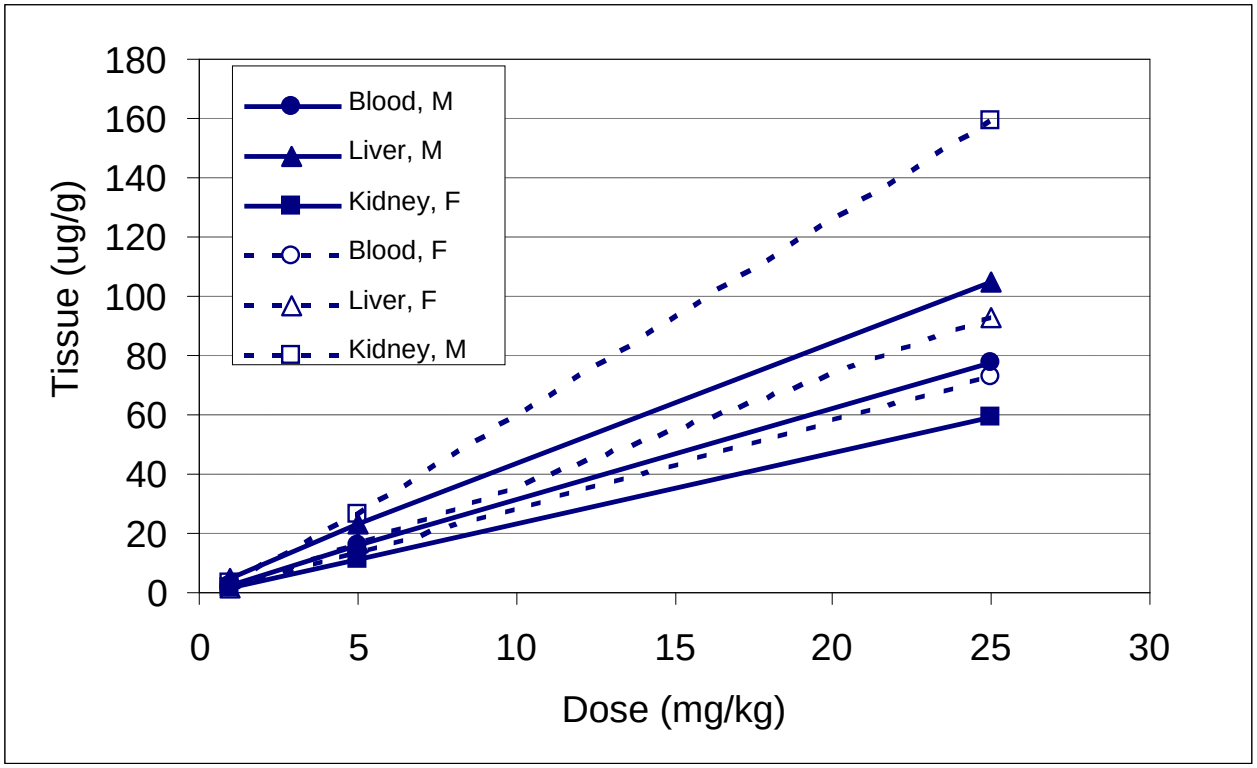
Perfluoroalkyls in plasma bind to serum albumin. The dissociation constant for binding of PFOA to serum albumin is approximately 0.4 mM (0.38 mM, ±0.04 standard deviation [sd] for human serum albumin; 0.36 nM, ±0.08 sd for rat serum albumin) and involves 6–9 biding sites (Han et al. 2003). A component of the binding of PFOA and PFDeA to serum albumin appears to be covalent, and may involve the sulfhydryl moiety of albumin (Vanden Heuvel et al. 1992b). 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 an oral 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). Perfluoroalkyls also bind to 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, exhibit profound species and gender 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 gender 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 relative to 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. 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 oral 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 gender 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

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



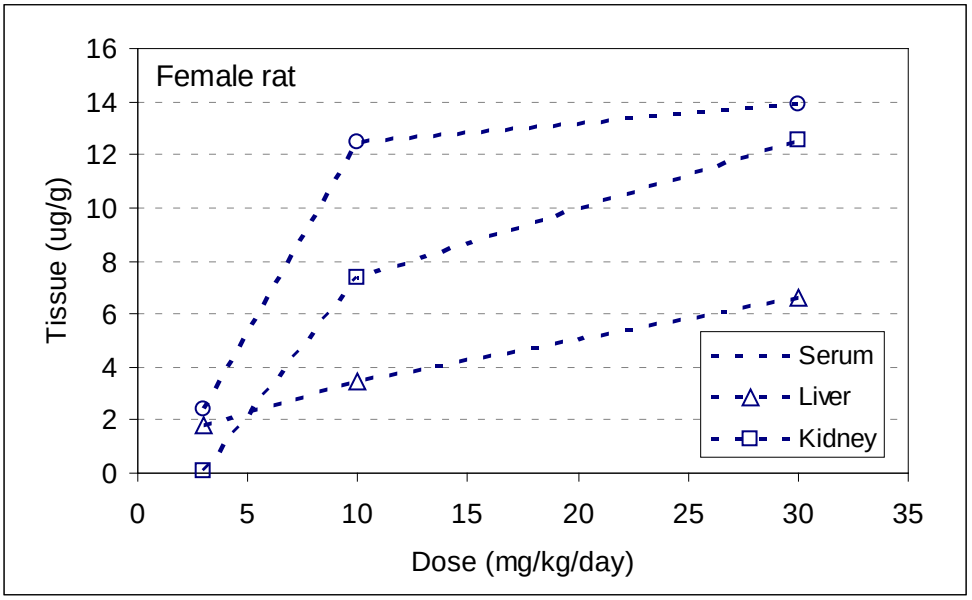
Source: Kemper 2003

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 gender 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. Gender differences in tissue distribution of PFOA in rats are not explained by gender 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 gender differences (Hundley et al. 2006; Table 3-7). 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 following the dose. 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; whereas, 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; however, ^{14}C levels in all tissues combined were lower in females compared to males. The opposite pattern was evident in 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, one day following the dose (Seacat and Luebker 2000).

Gender differences in elimination that give rise to gender 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

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 3-7. 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

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 PFOSA (0, 0.03, 0.15, or 0.75 mg PFOSA/kg/day) for 26 weeks, liver concentrations of PFOSA 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, gender 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; however, 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. A study of mother-infant pairs in Japan found a relatively high correlation (r^2=0.88) between concentrations of PFOS in cord serum at birth (from umbilical vein), and maternal serum measured between gestation week 38 and 41 (Inoue et al. 2004b). Cord serum concentrations of PFOS ranged from 1.6 to 5.3 ng/mL (n=15), whereas maternal serum concentrations ranged from 4.9 to 17.6 ng/mL (n=15). This same study attempted to measure maternal and cord serum concentrations of PFOA and PFOSA; however, levels were below the limit of detection in most maternal samples and in all cord samples (PFOS and PFOA detection limit <0.5 ng/mL; PFOSA <1.0 ng/mL). A study of 11 mother-infant pairs in Germany also found significant a correlation between concentrations of PFOS in maternal plasma, measured within 1–2 hours of birth, and cord plasma measured at birth (r=0.72), but not for PFOA (r=0.42; Midasch et al. 2007). Cord plasma PFOS concentrations were approximately 0.60 (range: 0.41–80, n=11) of maternal serum concentrations (range 7.8–16.4 ng/mL). Cord plasma PFOA concentrations were approximately 1.26 (range 0.91–1.95, n=11) of maternal serum concentrations (range 1.5–4.0 ng/mL).

Maternal-fetal transfer of PFOA has also been studied in rats (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 gd 4). Fetal plasma concentrations of PFOA measured on gestation day 21 were approximately 0.4 of maternal plasma concentration.

Maternal-infant Transfer. Perfluoroalkyls can be transferred to nursing infants. Measurements of perfluoroalkyl concentrations in paired samples of serum and human milk collected from Swedish women (n=12) found mean milk:serum concentration ratios of 0.01 for PFOS, 0.12 for PFOA (only one milk sample was above the limit of detection of 0.01 ng/mL), 0.02 for PFHxS, and 0.07 for PFOSA (Kärrman et al. 2007a). Mean maternal serum concentrations were 20.7 ng/mL (range 8.2–48) for PFOS, 3.8 ng/mL (range 2.4–5.3) for PFOA, 4.7 ng/mL (range 1.8–11.8) for PFHxS, and 0.24 ng/mL (range <0.10–0.49) for PFOSA. Annual composite samples collected from 25–90 Swedish women during the period 1996–2004 had perfluoroalkyl concentration ranges of 0.1–0.26 ng/mL for PFOS and 0.016–0.051 ng/L for PFHxS (most milk concentrations for PFOA and PFOSA were below the limits of detection). Concentration ranges for perfluoroalkyls in breast milk collected from women (n=19) in China were 45–360 ng/L for PFOS, 47–210 ng/L for PFOA, and 1.1–14 for PFHxs (So et al. 2006b). No data were located regarding concentrations of perfluoroalkyls in human milk in the U.S. population.

Studies conducted in rats provide further support for maternal-infant transfer of PFOA through breast milk (Hinderliter et al. 2005). 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 were approximately 0.1 of maternal plasma concentration.

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).

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 gender 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 days 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 PFOA and PFOS 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.

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 (Butenhoff et al. 2004c; Hanhijarvi et al. 1982, 1987; Hundley et al. 2006; Johnson and Ober 1979, 1980, 1999a, 1999b; Kemper 2003; Kudo et al. 2001; Vanden Heuvel et al. 1991b, 1991c). Perfluoroalkyls are secreted in bile and undergo extensive reabsorption from the gastrointestinal tract (Kudo et al. 2001; Vanden Heuvel et al. 1991a, 1991b). 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, 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 gender 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 gender differences and age-dependencies within certain species. Table 3-8 summarizes estimates of the elimination half-times ($t_{1/2}$) for perfluoroalkyls in humans and experimental animals. The elimination $t_{1/2}$ of PFOA has been estimated in humans, nonhuman primates, and rats. Estimates in humans are based on measurements of the decline in serum PFOA concentrations in retired fluorochemical production workers in the United States (Olsen et al. 2007a) or measurements of renal 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 3-8 as follows (Equations 3 and 4):

$$k_e = \frac{Cl}{V} \qquad \text{Eq. (3)}$$

$$t_{1/2} = \frac{\ln(2)}{k_e} \qquad \text{Eq. (4)}$$

where k_e is the elimination rate (e.g., day^{-1}), Cl is the renal clearance (e.g., mL/day), and *V* is the volume of distribution (L/kg). Estimated $t_{1/2}$ values for PFOA in humans range from 841–1,292 days and are not appreciably different in males and females. When interpreting these numbers, it must be kept in mind that they are based on evaluations of populations of limited size in relatively few studies. The Olsen et al. (2007a) study provided estimates of $t_{1/2}$ values of 1,221 and 1,223 days in two females; the group mean (22 males, 2 females) was 1,272 days (95% CI 1,083–1,495). Serum concentrations of PFOA in these subjects ranged from 17 to 5,100 ng/mL. Estimates of $t_{1/2}$ values were similar, 841–1,292 days, in the Harada et al. (2005a) study, in subjects whose serum PFOA concentrations ranged from 3 to 21 ng/mL. Elimination of PFOA in Cynomolgus monkeys and rats is considerably faster than in humans. Following cessation of 6 months of oral dosing with PFOA at 10 mg/kg/day, the $t_{1/2}$ was estimated to be approximately 20.1 days in male monkeys (Butenhoff et al. 2004c). Estimates made in Cynomolgus monkeys that received an intravenous dose of 10 mg/kg PFOA were 20.9 (±12.5 sd) days in males and 32.6 (±8.0 sd) in females (Butenhoff et al. 2004c). In rats, elimination of PFOA exhibits pronounced gender differences, with faster elimination in females than in males. Estimates of $t_{1/2}$ values in male rats ranged from 115 to 202 hours, for oral dosing, and from 105 to 216 hours for parenteral dosing (i.e., intraperitoneal or intravenous). By contrast, estimates for female rats ranged from 3.2 to 16.2 hours for oral dosing, and from 1.9 to 24 hours for parenteral dosing. Pronounced dose dependence appears in the $t_{1/2}$ estimates in female rats. Following an oral dose of PFOA of 0.1, 1, 5, or 25 mg/kg, the $t_{1/2}$ 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). The divergence in elimination kinetics between male and female rats appears to be age-dependent, with faster elimination becoming evident in female rats after

Table 3-8. Summary Elimination Half-times for Perfluoroalkyls Estimated in Humans and Experimental Animals

Species, age, and gender	Route	Dose	Exposure duration	Elimination half-time	Reference
PFOA—Human					
Human (n=26), adult, M (24) F (2)	NA	NA	NA	1,273 days (95% CI: 1,083–1,495)	Olsen et al. 2007a
Human (n=5), 22±0.9, M	NA	NA	NA	841 days	Harada et al. 2005a
Human (n=5), 68±5, M	NA	NA	NA	953 days	Harada et al. 2005a
Human (n=5), 23±3, F	NA	NA	NA	1,292 days	Harada et al. 2005a
Human (n=5), 69±5, F	NA	NA	NA	1,053 days	Harada et al. 2005a
PFOS—Human					
Human (n=26), adult, M (24) F (2)	NA	NA	NA	1,751 days (95% CI: 1,461–2,099)	Olsen et al. 2007a
Human (n=5), 22±0.9, M	NA	NA	NA	2,701 days	Harada et al. 2005a
Human (n=5), 68±5, M	NA	NA	NA	1,053 days	Harada et al. 2005a
Human (n=5), 23±3, F	NA	NA	NA	1,632 days	Harada et al. 2005a
Human (n=5), 69±5, F	NA	NA	NA	1,669 days	Harada et al. 2005a
PFHxS—Human					
Human (n=26), adult, M (24) F (2)	NA	NA	NA	2,662 days (95% CI: 2,112–3,355)	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
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

Table 3-8. Summary Elimination Half-times for Perfluoroalkyls Estimated in Humans and Experimental Animals

Species, age, and gender	Route	Dose	Exposure duration	Elimination half-time	Reference
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, M	IV	2 mg/kg	1 day	132 days (SD 13)	Noker and Gorman 2003
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, F	IV	2 mg/kg	1 day	110 days (SD 26)	Noker and Gorman 2003
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
PFOA—Rat					
Rat (CR), adult, M	Oral	11.4 mg/kg	1 day	115 hours	Johnson and Ober 1980a
Rat (SD), adult, M	Oral	0.1 mg/kg	1 day	202 hours (SD 38)	Kemper 2003
Rat (SD), adult, M	Oral	1 mg/kg	1 day	138 hours (SD 32)	Kemper 2003
Rat (SD), adult, M	Oral	5 mg/kg	1 day	174 hours (SD 29)	Kemper 2003
Rat (SD), adult, M	Oral	25 mg/kg	1 day	157 hours (SD 38)	Kemper 2003
Rat (SD), adult, M	IV	1 mg/kg	1 day	185 hours (SD 19)	Kemper 2003
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 (SD), 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 (SD), adult, F	Oral	0.1 mg/kg	1 day	3.2 hours (SD 0.9)	Kemper 2003
Rat (SD), adult, F	Oral	1 mg/kg	1 day	3.5 hours (SD 1.1)	Kemper 2003
Rat (SD), adult, F	Oral	5 mg/kg	1 day	4.6 hours (SD 0.6)	Kemper 2003
Rat (SD), adult, F	Oral	25 mg/kg	1 day	16.2 hours (SD 9.9)	Kemper 2003
Rat (SD), 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

Table 3-8. Summary Elimination Half-times for Perfluoroalkyls Estimated in Humans and Experimental Animals

Species, age, and gender	Route	Dose	Exposure duration	Elimination half-time	Reference
Rat (Wistar), adult, F	IV	20.1 mg/kg	1 day	1.9 hours (SD 0.7)	Ohmori et al. 2003
Rat (SD), 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
PFOS—Rat					
Rat, adult, M	Oral	4.2 mg/kg	1 day	179 hours	Johnson and Ober 1979
PFOSA—Rat					
Rat (SD), adult, M	Oral	5.0 mg/kg	1 day	125 hours	Seacat and Luebker 2000
PFDeA—Rat					
Rat (SD), 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 (SD), adult, F	IP	4.8 mg/kg	1 day	552 hours	Vanden Heuvel et al. 1991b
PFNA—Rat					
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
PFBA—Rat					
Rat (SD), adult, M	Oral	30 mg/kg	1 day	9.22 hours (SE 0.75)	Chang et al. 2008b
Rat (SD), adult, F	Oral	30 mg/kg	1 day	1.76 hours (SE 0.26)	Chang et al. 2008b
Rat (SD), adult, M	IV	30 mg/kg	1 day	6.38 hours (SE 0.53)	Chang et al. 2008b
Rat (SD), adult, F	IV	30 mg/kg	1 day	1.03 hours (SE 0.03)	Chang et al. 2008b

Table 3-8. Summary Elimination Half-times for Perfluoroalkyls Estimated in Humans and Experimental Animals

Species, age, and gender	Route	Dose	Exposure duration	Elimination half-time	Reference
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

CI = confidence interval; F = female; 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

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). Collectively, these studies show that elimination rates of PFOA vary substantially across species. The elimination rate in female rats ($t_{1/2}$≈4 hours at low doses) is approximately 40 times faster than in male rats ($t_{1/2}$≈160 hours), 120 times faster than in Cynomolgus monkeys ($t_{1/2}$≈20 days), and approximately 6,000 times faster than in humans ($t_{1/2}$≈1,000 days). Furthermore, in addition to faster elimination rate in female rats compared to male rats, elimination rate and renal clearance of PFOA appeared to decrease as dose increased. This dose dependence has been attributed to a capacity-limited renal tubular secretion of PFOA in female rats (see Section 3.5.1). Gender differences in elimination of PFOA have also been observed in hamsters; however, unlike the rat, male hamsters excreted absorbed PFOA more rapidly than female hamsters. Following a single oral gavage dose of 10 mg/kg as ammonium [^{14}C]PFOA, cumulative excretion of ^{14}C in urine at 24 hours postdosing was 96.4% of the dose in female rats and 8.7% in male rats; 25.% 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).

Elimination $t_{1/2}$ values for PFOS in humans, nonhuman primates, and rats are summarized in Table 3-8. In general, PFOS $t_{1/2}$ values are higher than those for PFOA (i.e., elimination of PFOS is slower than PFOA); however, as with PFOA, substantial interspecies variability is evident in the $t_{1/2}$ values for PFOS. Analysis of kinetics of serum PFOS concentrations in retired U.S. fluorochemical production workers (24 males, 2 females) yielded an estimate of 1,751 days (95% CI 1,461–2,099) 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 1,792 and 2,474 days. Estimates based on renal clearance of PFOS from serum in subjects from the general population of Japan ranged from 1,053 to 2,701 days; these subjects had serum PFOS concentrations that ranged from 4 to 49 ng/mL. Estimates in males (2,701, 1,053 days) were similar to females (1,632, 1,699 days). Estimates of the elimination $t_{1/2}$ in Cynomolgus monkeys were similar across studies, doses and routes (oral, intravenous) and ranged from 110 to 170 days (Noker and Gorman 2003; Seacat et al. 2002). Estimates for male and female Cynomolgus monkeys were similar; $t_{1/2}$=170 days, in monkeys that received 0.15 or 0.75 mg PFOS/kg/day for 6 months (Seacat et al. 2002). Plasma PFOS kinetics in male rats that received a single oral gavage dose of 4.2 mg/kg PFOS yielded an estimate of 179 hours for the elimination $t_{1/2}$ (Johnson and Ober 1979). Comparisons of the elimination kinetics of PFOS in male and female rats have not been reported. Collectively, these estimates indicate that elimination of PFOS in male rats ($t_{1/2}$≈180 hours) occurs approximately 20 times faster than in Cynomolgus monkeys ($t_{1/2}$≈150 days), and approximately

240 times faster than in humans ($t_{1/2}$≈1,800 days). In each of these species, elimination of PFOS was slower than PFOA.

Estimates of elimination rates for PFHxS and PFBA in humans are also available (Table 3-8). Analysis of kinetics of serum PFHxS concentrations in retired U.S. fluorochemical production workers (24 males, 2 females) yielded an estimate of 2,662 days (95% CI 2,112–3,355) 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 4,458 and 4,885 days.

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 days (±41 sd). In a larger study of nine workers (seven males, two females), the mean $t_{1/2}$ was 72 days (±38 sd). Estimates for the two female subjects were 56 and 118 days. The combined mean value for the 12 estimates was 75 days (±38 sd). Based on these observations, the PFBA is eliminated substantially faster in humans than perfluoroalkyls having longer carbon chain lengths (e.g., PFHxS, PFOA, PFOS). Studies conducted in Cynomolgus monkeys and rats provide further evidence for more rapid elimination of PFBA compared to PFOA or PFOS. Elimination $t_{1/2}$ values for male and female Cynomolgus monkeys that received an intravenous dose of 10 mg/kg PFBA were 40.3 hours (±2.4 sd) and 41.0 hours (±4.7 sd), respectively (Chang et al. 2008a). Elimination rates in rats following an oral gavage dose of 30 mg PFBA/kg were approximately 4 times faster in female rats ($t_{1/2}$=1.8 hours±0.3, standard error [SE]) compared to male rats ($t_{1/2}$=9.2 hours ±0.8, SE; Chang et al. 2008a). Elimination rates in female mice were 2–4 times faster than in male mice. In mice that received an oral dose of 30 mg PFBA/kg, the $t_{1/2}$ in female mice was 3.1 hours (±0.3, SE) compared to 16.3 (±7.2 hours, SE) in male mice (Chang et al. 2008a). Elimination rates in male mice appeared to be dose-dependent, based on lower mean values for $t_{1/2}$ in mice that received an oral dose of 100 mg PFBA/kg ($t_{1/2}$=5.2 hours ±2.3, SE) compared to mice that received 10 mg/kg ($t_{1/2}$=13.3 hours ±4.6, SE) or 30 mg/kg ($t_{1/2}$=16.3 hours ±7.2, SE); however, these estimates were based on three animals per dose group, and the means are not significantly different ($p>0.05$; Fisher's least significant difference).

A trend for decreasing elimination rate with increasing perfluoroalkyl chain length is also evident from comparison of the elimination rates in male and female rats that received an equimolar intravenous dose of PFHpA (17.7 mg/kg), PFOA (20.1 mg/kg), PFNA (22.6 mg/kg), or PFDeA (25.0 mg/kg). In both male and female rats, $t_{1/2}$ values increased with increasing chain length; in males, $t_{1/2}$ values for the series

(PFHpA to PFDeA) were 2.4, 135, 710, and 958 hours in males and 1.2, 1.9, 59, and 1,406 hours, in females (Ohmori et al. 2003). Eliminations rates of PFHpA, PFOA, and PFNA were faster in females than in males, whereas rates for PFDeA were faster in males.

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 3-8. 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.

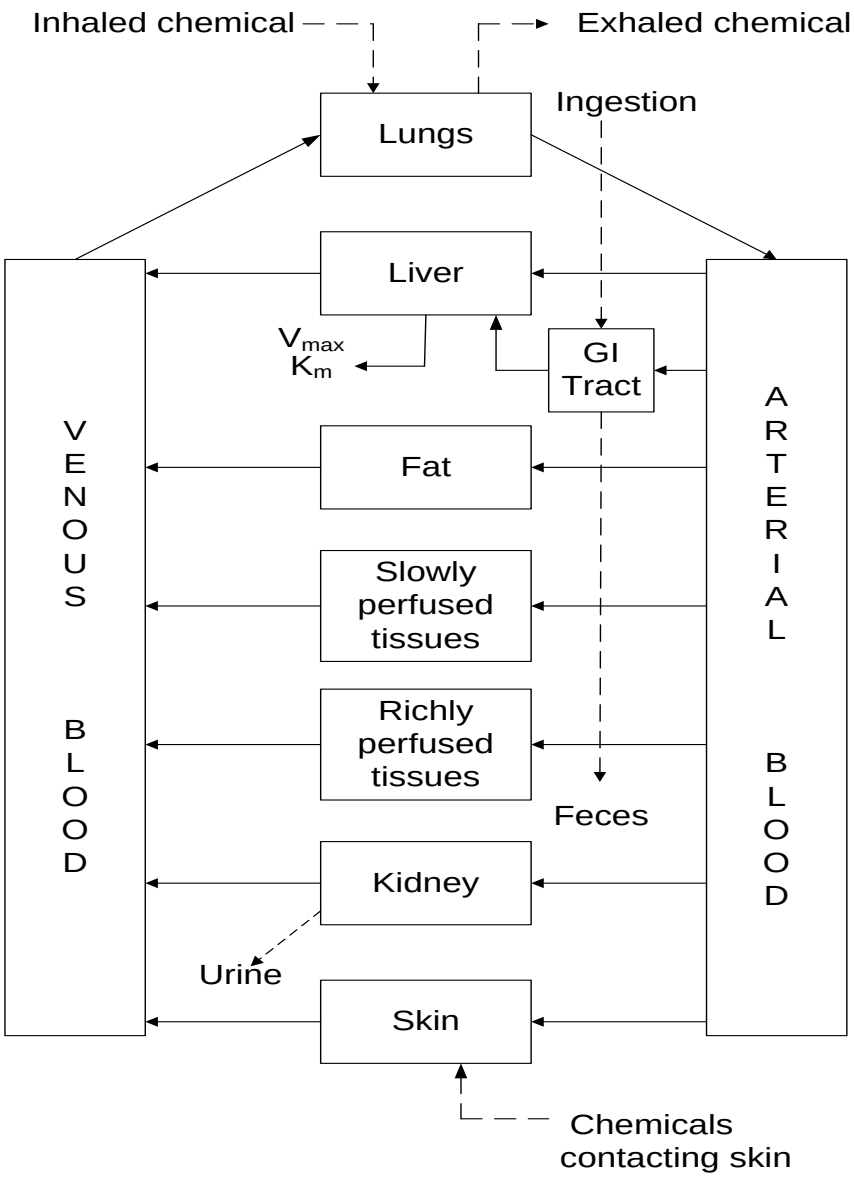
The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically 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

PBPK models for perfluoroalkyls are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations. PBPK models for PFOA and PFOS in rats and monkeys have been reported (Tan et al. 2008).

3.4.5.1 Tan et al. (2008) Models

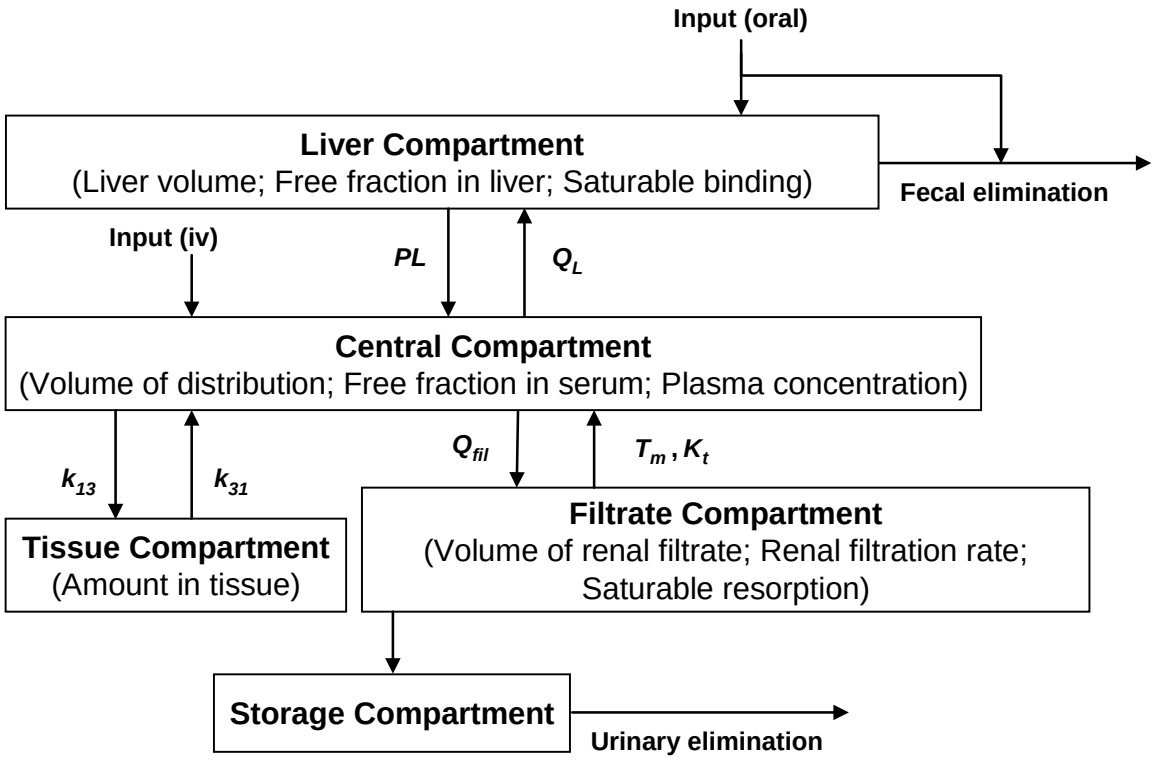
Tan et al. (2008; Andersen et al. 2006) developed a model for simulating the kinetics of plasma and urinary PFOA in male and female rats, PFOS in male rats, and PFOS in male and female monkeys. The general structure of the Tan et al. (2008) model is depicted in Figure 3-9. Values for parameters for the rat and monkey models are presented in Tables 3-9 and 3-10. The model includes compartments representing a central compartment (which includes plasma), liver, other tissues, renal glomerular filtrate, and a kidney storage compartment (for simulating the time delay between glomerular filtration and urinary excretion). Absorption from the gastrointestinal tract is simulated as a first-order process constrained by absorption fractions of 0.94 and 0.98 for PFOA in male and female rats; and 0.96 for PFOS in male rats (values for monkeys were not reported). Absorbed PFOA and PFOS are assumed to be delivered to the liver where saturable binding to liver proteins occurs. Exchanges between unbound (free) PFOA or PFOS in liver with the free pool in the central compartment are assumed to be flow-limited (governed by liver blood flow) with equilibrium determined by the liver:blood partition coefficient. Exchanges between the lumped compartment representing other tissues and the free pool in the central compartment are represented as first order processes with plasma-to-tissue and tissue-to-plasma rate constants.

A time dependence in the volume of distribution in the central compartment was introduced into the models for PFOA and PFOS in the male rat (but not in the female rat or monkey models) to achieve agreement between model predictions and observed kinetics of PFOA and PFOS in plasma. The time-dependence is simulated with a Michaelis-Menten function (Equation a):

$$V_d = V_{dc} + \frac{V_{d\max} \cdot t}{k_0 + t} \qquad \text{Eq. (a)}$$

where V_d is the volume of distribution the central compartment (L/kg body weight) at time, t; V_{dc} is the volume (L/kg) at t=0; and k_0 is the time (hour) at which the changing fraction of the volume is half of maximum. The time dependence results in the volume of distribution of PFOA in the central compartment increasing from initial values of 0.06–0.41, with 188 hours for the time at which half of

Figure 3-9. Structure of PBPK Model of PFOA and PFOS in the Rat and Monkey



Source: Tan et al. 2008

Table 3-9. Parameters Used in the Male and Female Rat Model for Exposure to PFOS and PFOA

		Values		
		PFOS	PFOA	
Parameters	Unit	Male	Male	Female
Body weight (BW)	kg	0.285	0.197–0.27	0.175–0.2
Cardiac output (Q_{cc}), $Q_c = Q_{cc}BW^{0.74}$	L/hour/kg	14	14	14
Liver volume as percent BW (V_{LC})	L/kg	0.034	0.034	0.034
Blood flow to liver as percent cardiac output (Q_{LC})		0.183	0.183	0.183
Volume of distribution at time 0 (V_{dc0})	L/kg	0.05	0.06	0.11
Maximum increase in volume of distribution (V_{dmax})	L/kg	0.01	0.35	0
Volume adjustment constant (k_0)	hour	0.11	188	Not applicable
Oral absorption rate (k_{abs})	$hour^{-1}$	25.1	11.5	31.3
Free fraction of PFOS in blood at time zero ($Free_0$)		0.087	0.006	0.045
Free fraction adjustment factor (δ)		0.94	0.35	0
Free fraction adjustment factor (k_{free})		7.34	1.1	Not applicable
Liver:blood partition coefficient (PL)		6.51	1.56	1.9
Maximum association rate constant (k_{on_max})	µg/hour	1.19	17.1	3.43
Binding affinity constant (KB)	µg/L	0.0036	100	6.06
Disassociation constant (k_{off})	$hour^{-1}$	0.015	1.02	0
Transport maximum as percent BW (T_{mc})	µg/kg/hour	125.3	516	9.35
Transport affinity constant (K_T)	µg/L	16.7	209	50
Rate constant to urine (k_u)	$hour^{-1}$	96.2	15.9	0.32
Renal plasma filtration rate as fraction of cardiac output (Q_{filc})		0.028	0.028	0.028
Volume of renal filtrate (V_{fil})	L	0.01 L	0.01	0.01
Rate constant from liver to feces (k_{feces})	$hour^{-1}$	0.3	0.49	$1.6x10^{-6}$
Fraction of dose that goes directly to feces ($F_{unabsorbed}$)		0.041	0.062	0.024
Transfer rate constant from intake to fecal elimination (k_f)	$hour^{-1}$	0.0054 $hour^{-1}$	0.001	0.037
Rate constant from central to tissue (k_{13})	$hour^{-1}$	1.91 $hour^{-1}$	1.84	0.65
Rate constant from tissue to central (k_{31})	$hour^{-1}$	0.001 $hour^{-1}$	0.37	0.007

Source: Tan et al. 2008

Table 3-10. Parameters Used in the Male and Female Monkey Model for Exposure to PFOS

Parameters	Unit	Male	Female
Body weight (BW)	kg	6.5	3.9
Cardiac output (Q_{cc}), $Q_c = Q_{cc}BW^{0.74}$	L/hour/kg	15	15
Liver volume as percent BW (V_{LC})	L/kg	0.05	0.05
Blood flow to liver as percent cardiac output (Q_{LC})		0.2	0.2
Volume of distribution at time 0 (V_{dc0})	L/kg	0.11	0.17
Maximum increase in volume of distribution (V_{dmax})		0	0
Volume adjustment constant (k_0)		Not applicable	Not applicable
Free fraction of PFOS in blood at time zero ($Free_0$)		0.017	0.015
Free fraction adjustment factor (δ)		0.74	0.74
Free fraction adjustment factor (k_{free})		0.009	0.009
Liver:blood partition coefficient (PL)		1	1
Maximum association rate constant (k_{on_max})		0	0
Binding affinity constant (KB)		Not applicable	Not applicable
Disassociation constant (k_{off})		0	0
Transport maximum as percent BW (T_{mc})	mg/kg/hour	182.8	104.2
Transport affinity constant (K_T)	mg/L	2.66	2.34
Rate constant to urine (k_u)	$hour^{-1}$	0.005	0.004
Renal plasma filtration rate as fraction of cardiac output (Q_{filc})		0.034	0.034
Volume of renal filtrate (V_{fil})	L	0.01	0.01
Rate constant from liver to feces (k_{feces})	$hour^{-1}$	0.18	0.32
Rate constant from central to tissue (k_{13})	$hour^{-1}$	3.60	1.61
Rate constant from tissue to central (k_{31})	$hour^{-1}$	0.05	0.04

Source: Tan et al. 2008

maximum increase occurs. For PFOS, the initial value of 0.05 increases to 0.061 and achieves half of the maximum change in 0.11 hours.

Time dependence was also introduced into the binding parameters for PFOA in the central compartment of male rats, and for PFOS in male rats and in male and female monkeys (Equation b):

$$Free = Free_0 \cdot (1 - \delta \cdot (1 - e^{-k_{free} \cdot t})) \qquad \text{Eq. (b)}$$

where *Free* is the free fraction in the central compartment at time, *t*; $Free_0$ is the free fraction at t=0, δ is an adjustment factor, and k_{free} is the rate constant for the change in free fraction ($hour^{-1}$). The time dependence results in a decrease in the free fraction for PFOA in the male rat from an initial value of 0.006–0.004 L/kg, with a half-time for the change of approximately 0.6 hours. Corresponding changes for PFOS in the male rat are 0.087–0.052 L/kg with a half-time of approximately 0.094 hours. Corresponding changes for PFOS in monkeys are 0.0017–0.0044 L/kg in males and 0.0015–0.0039 L/kg in females; with a half-time of approximately 77 hours in both males and females. Mechanistic explanations for these species- and gender-specific time-dependences have not been elucidated.

Transfer of PFOA and PFOS 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 net rate resulting from glomerular filtration of the free fraction in plasma and renal tubular reabsorption, which removes PFOA and PFOS from the glomerular filtrate. Renal tubular reabsorption is simulated as a capacity-limited process with a Michaelis-Menten function (Equation c):

$$T = \frac{T_m \cdot C_{gf}}{K_T + C_{gf}} \qquad \text{Eq. (c)}$$

where *T* is the rate of reabsorptive transport (µg/hour/kg body weight), T_m is the maximum rate of transport (µg/hour/kg body weight), C_{gf} is the concentration of PFOA or PFOS in the glomerular filtrate (µg/L), and K_T is the concentration in the glomerular filtrate (µg/L) at which reabsorptive transport rate is half of maximum. A "storage" compartment in kidney simulates the time delay between entrance of PFOA or PFOS into the glomerular filtrate and its appearance in urine. Transfer from the storage compartment to urine is first-order. Parameter values for renal tubular reabsorption of PFOA in rats result in lower reabsorptive clearances from the glomerular filtrate (T_m/K_T=0.19) in male rats compared to

female rats (T_m/K_T=7.5) and urinary clearances from plasma that are approximately 10-fold higher in male rats.

Validation of the model. Description of the optimization of parameter values and evaluation of the rat and monkey models model are described in Tan et al. (2008). Initial PFOS parameter values for the male rat model were established based on data reported in single intravenous and oral dosing studies (Johnson and Ober 1979, 1980). All PFOS parameters were fit to achieve agreement with the time course for PFOS in plasma and cumulative excretion of PFOS in urine and feces. The predicted plasma elimination $t_{1/2}$ was approximately 300 hours (based on Figure 6 of Tan et al. 2008) compared to 179 hours reported in Johnson and Ober (1979). The predicted liver PFOS concentrations 89 days after a simulated dose of 4.2 mg PFOS/kg was 21.55 µg/g, compared to the reported value of 20.56 µg/g (Johnson and Ober 1980).

Parameter values for PFOA for the male and female rat models were established based on single oral dosing studies (Kemper 2003). This study found substantially faster elimination kinetics of PFOA in female rats compared to male rats and a dose-dependent decrease in elimination in female rats. Following a single oral dose of ≤5 mg/kg, the observed elimination half-time in the female rat was approximately 10–50 times that in males (see Section 3.4.4.2). The rat PFOA models reproduced the gender differences in the elimination rates of PFOA from plasma. However, better agreement was achieved with observed plasma and excretory kinetics in male rats than in females. Contributing to this outcome may have been failure to correctly capture in the model pharmacokinetics processes underlying the dose-dependence in elimination kinetics observed in female rats; in particular, renal tubular mechanisms which may involve both reabsorption and secretion in rats (see Section 3.5.1). Also unexplained are the pharmacokinetics bases for the time-dependence in volume of distribution and plasma binding of PFOA, which improved model fits to observations on male rats, but did not improve model fits to the observations on female rats.

Parameter values for PFOS in monkeys were initially established based on single intravenous dosing studies conducted on Cynomolgus monkeys (Noker and Gorman 2003). This study found similar elimination half-time values for PFOS in male ($t_{1/2}$=132±13 hours) and female ($t_{1/2}$=110±25 hours) monkeys; these observations were reproduced in the models. Introducing time-dependency of plasma binding of PFOS (i.e., decreasing free fraction with increasing time after dose) improved fits to observed plasma and urine PFOS kinetics following a single intravenous dose of 2 mg PFOS/kg administered to male or female monkeys. The models, with parameters optimized to the observations from the intravenous study, were implemented to simulate plasma PFOS kinetics in Cynomolgus monkeys,

observed during and following repeated oral doses of 0.03, 0.15, or 0.75 mg PFOS/kg/day for 26 weeks (Butenhoff et al. 2002). Predicted plasma kinetics before and after cessation of dosing reproduced observations for the two lower doses; however, predictions were less satisfactory for the 0.75 mg/kg/day dose. Improved fit to the 0.75 mg/kg/day observations were achieved by introducing a time-dependency in the volume of distribution of the central compartment (increasing volume with increasing time after dose). The mechanistic underpinnings to this adjustment have not been elucidated.

Risk assessment. The rat and monkey models reported in Tan et al. (2008) have not been applied to risk assessments and several characteristics of the models, in their current form, limit their use in risk assessment (e.g., intra- or interspecies extrapolation). The models use species- and gender-specific time dependent parameter values that alter the volume of distribution and free fraction of PFOA or PFOS in plasma. Given the absence of an understanding of mechanisms for these time-dependencies, scaling of parameter values across species (i.e., to humans) would be highly uncertain. The rat model did not capture observed dose-dependencies of elimination kinetics in female rats. This may have resulted from an inadequate parameterization of gender- and dose-dependent clearance mechanisms, which would introduce additional uncertainty into intra- or inter-species extrapolations. Renal clearance mechanisms for PFOA and PFOS appear to be modulated by sex hormones, which may give rise to age dependence and other sources of variability in elimination kinetics related to sex hormone status, in addition to gender differences. The influence of sex hormones on elimination of PFOA and PFOS are not simulated in current models.

Target tissues. The rat and monkey models include parameters for predicting levels of PFOA or PFOS in plasma, liver (a toxicity target), urine, and feces.

Species extrapolation. Evaluation of the robustness of extrapolation of the rat or monkey models to other species has not been reported. It should be noted that the extreme differences in pharmacokinetics among species, particularly with humans, create an unusual degree of difficulty in making extrapolations to humans from animal models.

Interroute extrapolation. The rat and monkey models include parameters for simulating gastrointestinal absorption of PFOA or PFOS. Evaluations of the robustness of the models for predicting kinetics following exposures to other routes have not been reported.

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 (Han et al. 2003, 2005; Ohmori et al. 2003; Kerstner-Wood et al. 2003; Vanden Heuvel et al. 1992b; Ylinen and Auriola 1990). 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 biding sites (Han et al. 2003). A component of the binding of PFOA and PFDeA to serum albumin appears to be covalent, and may involve the sulfhydryl moiety of albumin (Vanden Heuvel et al. 1992b).

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 gender- 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; however, protein complexes formed have not been fully characterized. A component of intracellular binding appears to be covalent (Vanden Heuvel et al. 1992b). PFOA exhibits a low affinity for binding to rat kidney and urine α2μ-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).

Excretion. Urinary excretion of PFOA in rats appears to involve glomerular filtration, reabsorption of PFOA from tubular fluid, and secretion of PFOA into tubular fluid (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). 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. Evidence in support of this includes the following:

(1) 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).

(2) Urinary excretion and renal clearance of PFOA are decreased by treatment with probenecid, a competitive inhibitor of organic anion secretion in the kidney (Kudo et al. 2002; Vanden Heuvel et al. 1992a).

(3) Urinary elimination rate and renal clearance in adult rats increase following castration and the increase is attenuated with testosterone replacement (Kudo et al. 2002; Vanden Heuvel et al. 1992a).

(4) Gender differences and hormone-mediated changes in renal clearance in adult rats correlate with differences and changes in expression of genes for organic anion transporters in the basolateral membrane (OAT1, OAT2) and luminal membrane (oatp1) of kidney (Kudo et al. 2002).

(5) Gender differences in elimination kinetics in rats develop at approximately the same time of sexual maturation (Hinderliter et al. 2006b).

Perfluoroalkyls (PFOA, PFDeA) are secreted in bile and undergo extensive reabsorption from the gastrointestinal tract (Kudo et al. 2001; Vanden Heuvel et al. 1991a, 1991b). 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 gender influence on biliary secretion (compared to the gender influence on renal clearance) may reflect a relative gender 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 Cattley et al. (1998), Maloney and Waxman (1999), Corton et al. (2000), and Klaunig et al. (2003).

The liver is a main target for perfluoroalkyl compounds in animals. Liver 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; 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.

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. 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 reporter 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. 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).

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 effects on peroxisome fatty acid β-oxidation did not seem to be receptor-mediated since PPARα mRNA expression was not affected. The study by Hu et al. (2005) also showed that PFOS may not be a typical peroxisome proliferator as it 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 mechanism of action including being a substrate for fatty acid metabolism, alteration of peroxisomal membrane permeability, or uncoupling of mitochondrial membrane potential (Hu et al. 2002a; 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. However, 7 genes were unchanged and 4 could not be found in the PFOA study. Of the 19 genes that were suppressed by PFOS, only 1 was found to be suppressed and all others but 1 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 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).

Overall, the *in vivo* 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, however, 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: (1) large interspecies differences in the toxicokinetics of perfluoroalkyls, (2) general lack of adverse health effects reported by limited research done to date in populations exposed chronically to elevated amounts of perfluoroalkyls, and (3) some mechanisms of toxicity in animals may not be operant in humans. These issues are strongly interrelated.

Toxicokinetics Differences. The elimination rate for PFOA in female rats is approximately 40 times faster than in male rats, 120 times faster than in Cynomolgus monkeys, and approximately 6,000 times faster than in humans. Elimination of PFOS in male rats is approximately 20 times faster than in Cynomolgus monkeys, and approximately 240 times faster than in humans (Hundley et al. 2006). 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 an elimination half-life of 1,000 days for PFOA in humans, a constant rate of intake for 12 years would be required to achieve 95% of steady state. Steady state (i.e., 95%) would be achieved in approximately 90 days in monkeys, 30 days in male rats, and in 1 day in female rats. As a result of these large differences in kinetics, internal doses (i.e., serum concentrations of PFOA) achieved during intermediate-duration exposures in rats or monkeys would not represent steady-state internal doses that might be achieved in humans over longer exposure durations.

Lack of Reported Effects in Humans. Health evaluations of humans exposed occupationally or environmentally to elevated amounts of perfluoroalkyl compounds for long periods of time have not provided evidence of significant adverse effects have, although sporadic deviations in clinical tests associate with serum levels of perfluoroalkyl compounds have been reported (Emmett et al. 2006b; Gilliland and Mandel 1996; Mundt et al. 2007; Olsen and Zobel 2007; Olsen et al. 1998, 1999, 2003a; Sakr et al. 2007a, 2007b). Thus, the lack of reported health effects at the reported body burdens precludes identifying the animal model that would be most appropriate for human risk assessment based on similar toxic effects.

Mode(s) of Action. As previously mentioned, 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). However, 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 evidence that perfluoroalkyl compounds are endocrine disruptors in humans is inconclusive based on a limited number of studies. A study on male workers at a PFOS production plant found no significant association between PFOA exposure and the levels of 11 hormones (cortisol, dehydroepiandrosterone sulfate, estradiol, FHS, 17α-hydroxyprogesterone, free testosterone, total testosterone, LH, prolactin, TSH, and sex hormone-binding globulin) in serum (Olsen et al. 1998). Workers who had PFOA serum 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 were significantly associated with serum PFOA in linear regression models. Other assessments of workers exposed to perfluoroalkyls did

not find associations between serum levels of PFOS and PFOA and thyroid hormones (Olsen and Zobel 2007; Olsen et al. 2003a; Sakr et al. 2007b). Mean levels of PFOA and PFOS in these studies were ≤2.5 µg/mL. An additional occupational study did not find alterations in thyroid hormones levels in workers exposed to PFNA (Mundt et al. 2007); serum levels of PFNA were not available in this study. A study of a population environmentally exposed to PFOA reported no association between serum PFOA and serum levels of TSH; the median serum PFOA concentration in the study subjects was 354 ng/mL (Emmett et al. 2006b). While mostly negative results are reported in these studies, it is worth pointing out that, in general, they did not account for factors that are known to affect hormonal levels such as time of day, seasonal variation, stress, and in the case of women, menopausal status.

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 TT4 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 TT4 (Chang et al. 2008b). Reduced serum TT4 were also reported in rats treated with PFDeA by intraperitoneal injection (Gutshall et al. 1988, 1989; Van Rafelghem et al. 1987a).

In general, studies with PFBA, PFBuS, PFOA, PFOS, and PFHxS have not reported morphological alterations in endocrine glands or in reproductive organs of experimental animals (3M 2001; Butenhoff et al. 2002; Griffith and Long 1980; Hoberman and York 2003; Perkins et al. 2004; Seacat et al. 2002, 2003; van Otterdiijk 2007a, 2007b). However, a single intraperitoneal dose of 50 mg/kg PFDeA induced signs of atrophy and degeneration of the seminiferous tubules in the testes from rats (George and Andersen 1986). These signs were first seen 16 days after dosing and were still evident 30 days after dosing.

In multi-generation studies, neither PFOA nor PFOS have altered fertility parameters (Butenhoff et al. 2004b; Luebker et al. 2005a, 2005b) and the same was observed in a reproductive study with PFHxS (Hoberman and York 2003). However, alterations in estrous cycling was reported in a study in rats treated with 1 or 10 mg/kg/day PFOS intraperitoneally for 2 weeks (Austin et al. 2003). Serum PFOS levels in these rats at termination were 10,500 and 45,500 ng/mL, respectively. This finding is in disagreement with the results of Luebker et al. (2005a) who did not observe alterations in estrous cycling in rats dosed by gavage with up to 3.2 mg/kg/day before mating and continuing during gestation, and that

achieved mean serum levels of PFOS of 82,000 ng/mL. No explanation could be found for these apparently conflicting results.

While there have not been significant effects on fertility in animals exposed to PFOA, PFOS, or PFHxS, several studies have reported alterations in sex hormone levels. Studies in male rats reported that oral dosing with PFOA reduced serum and testicular testosterone while significantly increasing serum estradiol (Cook et al. 1992). The decrease in serum testosterone was thought to be due to a decrease in the conversion of 17α-hydroxyprogesterone to androstenedione, which could be attributed to the elevated serum levels of estradiol since elevated serum estradiol are known to depress steroidogenesis at the Leydig cell level by negative feed-back influences on the hypothalamus and adenohypophysis. Treatment with PFOA was also reported to increase the activity of aromatase in the liver, but not in other sites, including the testes, and suggested that this was probably the mechanism by which PFOA increased serum estradiol (Biegel et al. 1995). PFOA also was shown to increase testicular interstitial fluid transforming growth factor α, which was consistent with the hypothesis that estradiol may modulate growth factor expression within the testis. These events beginning with the increase in serum estradiol have been thought to be responsible for the induction of Leydig cell tumors in rats treated with PFOA (Biegel et al. 2001).

Treatment of male rats with PFDoA by gavage (5–10 mg/kg/day) for 14 days significantly decreased serum LH, testosterone, and estradiol (Shi et al. 2007). 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. The results suggested that the decrease in testosterone synthesis probably resulted from decreased steroidogenesis gene expression.

A study with PFDeA administered by intraperitoneal injection to male rats reported decreased serum testosterone and 5α-dihydrotestosterone and decreases in the weights of accessory sex organs (Bookstaff et al. 1990). Experiments in castrated rats implanted with testosterone-containing capsules showed that the androgenic deficiency caused by PFDeA was the result of decreased secretion of testosterone from the testis rather than increased clearance from blood. Since LH levels in blood were unaffected, the decreased secretion of testosterone from the testis appeared to be due to decreased testicular responsiveness to LH stimulation. Bookstaff et al. (1990) suggested that PFDeA disrupts the normal feedback relationships that exists between plasma androgen and LH concentrations.

Studies *in vitro* of PFOA, PFOA, 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).

While the available data in experimental animals indicate that some perfluoroalkyl compounds can alter the levels of some hormones in blood, it does not appear that these compounds can mimic or block the action of natural hormones by binding to their receptors, but additional studies are needed before more definite conclusions can be drawn.

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 infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). 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).

There are no studies that specifically address the health effects of exposure to perfluoroalkyl compounds in children; therefore, it is unknown whether children differ from adults in their susceptibility to health effects from these compounds. It is known, however, that children can absorb these compounds, that perfluoroalkyl compounds can cross the placenta (i.e., Midasch et al. 2007), and that can be transferred to newborn babies via maternal milk (i.e., Kärrman et al. 2007a).

A health evaluation was conducted of 371 residents, including 43 children under the age of 18, in the Little Hocking water district in southeastern Ohio where significant environmental exposure to PFOA via the water occurred (Emmett et al. 2006b). The population median serum PFOA was 354 ng/mL and the interquartile range was 184–571 ng/mL. The study found no significant associations between serum PFOA levels and hematology parameters, total cholesterol and liver enzymes, indices of kidney function, and serum TSH levels whether the analysis included all the individuals as a group or separate analyses

were done for adults or children. In a study of self-reported health outcomes in relation to occupational exposures to PFOS at a PFOS-based fluorochemical manufacturing facility that included 263 women, birth weight of singleton births, adjusted for maternal age at birth, gravidity, and smoking status, did not vary between exposure groups (Grice et al. 2007). PFOS serum concentrations ranged from 110 to 1,970 ng/mL). Information regarding gestational length, the most important predictor of birth weight, was not available.

In a study of children born in Baltimore, both PFOA and PFOS in cord blood (respective medians were 1.6 and 5 ng/mL) were negatively associated with birth weight, ponderal index, and head circumference (Apelberg et al. 2007b). No significant associations were observed between either PFOS or PFOA concentrations and newborn length or gestational age. Similar studies of Danish women reported that birth weight, birth weight, and abdominal circumference were inversely associated with plasma levels of PFOA collected during the first trimester (mean 35.3 ng/mL) (Fei et al. 2007, 2008a). Neither PFOA nor PFOS was statistically associated with length of gestation. An additional study by Fei et al. (2008b) found no convincing associations between developmental milestones in early childhood and levels of PFOA and PFOS measured in maternal blood early during pregnancy. A study of 428 Japanese women and their infants reported a marginally significant negative correlation between birth weight and maternal blood PFOS, but not PFOA levels (Washino et al. 2009). It is worth noting that the blood levels of PFOA and PFOS in these studies of the general population are significantly lower than those reported in the workers studied by Grice et al. (2007) and in animal studies. Other, much smaller studies of Japanese and Chinese women did not find correlations between PFOS in maternal blood and TSH and T4 in cord blood (Inoue et al. 2004b) or between PFOA and PFOS in breast milk and infant weight (So et al. 2006b), but their small sample size severely limits the conclusions that can be drawn from them. In contrast with the findings of some of the studies mentioned above, Nolan et al. (2009) found that mean birth weights, incidence of low birth weight, incidence of preterm birth, and mean gestational age of singleton neonates born to mother residing in an area with high levels of PFOA in the drinking water did not differ significantly from those born to mothers living in areas with significantly lower PFOA levels in the water. Mean serum PFOA levels from a random sample of individuals residing in the high PFOA area was 354 ng/mL.

Exposure of rodents to PFOA and PFOS during gestation has produced developmental toxicity. Studies with PFOA reported prenatal loss, reduced neonate weight and viability, and delays in mammary gland differentiation, eye opening, vaginal opening, and first estrus (Abbott et al. 2007; Lau et al. 2006; White et al. 2007; Wolf et al. 2007). These effects occurred generally in the absence of maternal toxicity. These

studies also showed that gestational exposure was sufficient to induce postnatal deficits in body weight and developmental delays and that PPARα was required for PFOA-induced postnatal lethality. Exposure to PFOS also increased neonatal mortality (Lau et al. 2003) and dosing rats late during gestation (gds 17–20) caused significantly more lethality than dosing early (gds 2–5) (Grasty et al. 2003). In contrast to PFOA and PFOS, PFBA exhibited considerably less developmental toxicity, possibly due to a much faster elimination rate and lower biochemical potency (Das et al. 2008). PFHxS in doses of up to 10 mg/kg/day was not a developmental toxicant in rats exposed from premating until PND 21 (Hoberman and York 2003).

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

Both PFOA and PFOS are biomarkers of exposure to themselves, but based on studies in animals, 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 or of subjects environmentally exposed via their drinking water have not provided evidence of adverse health effects in the groups studied (Emmett et al. 2006a; Mundt et al. 2007; Olsen and Zobel 2007; Olsen et al. 1999, 2003a; Sakr et al. 2007a, 2007b). Based on the existing information regarding the effects of perfluoroalkyl compounds in animals, it is difficult to envision a health condition that could be attributed solely to exposure to perfluoroalkyls. Even if one had been identified in animal studies, extrapolation to what might occur in humans is problematic based on the fact that studies in animals have used doses that resulted in serum levels of perfluoroalkyl considerably higher than those found in humans and on the differences in toxicokinetics between animals and humans.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No studies were 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.

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.

A specific target for perfluoroalkyl compounds toxicity in humans exposed to the substances has not been identified, but it is reasonable to assume that the liver could be a main target, based on studies in animals and the therapeutic use of hypolipidemic substances (i.e., clofibrate, gemfibrozil) with similar mechanisms of action. Therefore, individuals with compromised liver function may represent a

susceptible population. Obese people also may represent a susceptible population based on limited data from a study of occupationally exposed men (Gilliland and Mandel 1996). In that study, in obese subjects only, serum ALT and AST activities increased with increasing PFOA concentrations, which according to the investigators, has biological plausibility because obesity has been associated with elevation of transaminases through fatty infiltration.

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. However, Emmett et al. (2006a) described two interventions that resulted in reduced PFOA in residents with a contaminated public water source. One intervention was the use of a residential carbon filter, which resulted in a statistically significant reduction in serum PFOA in a best-fit model. The other intervention was the substitution of bottled water for public water, which resulted in a much greater serum PFOA reduction.

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. This is largely because health evaluations of workers exposed to perfluoroalkyl compounds (i.e., Olsen and Zobel 2007; Olsen et al. 1999, 2003a; Sakr et al. 2007a, 2007b) and of members of the general population exposed to elevated amounts of PFOA via the drinking water (Emmett et al. 2006b) have not shown associations between surrogates of exposure, such as blood levels of perfluoroalkyl compounds, and adverse health conditions.

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

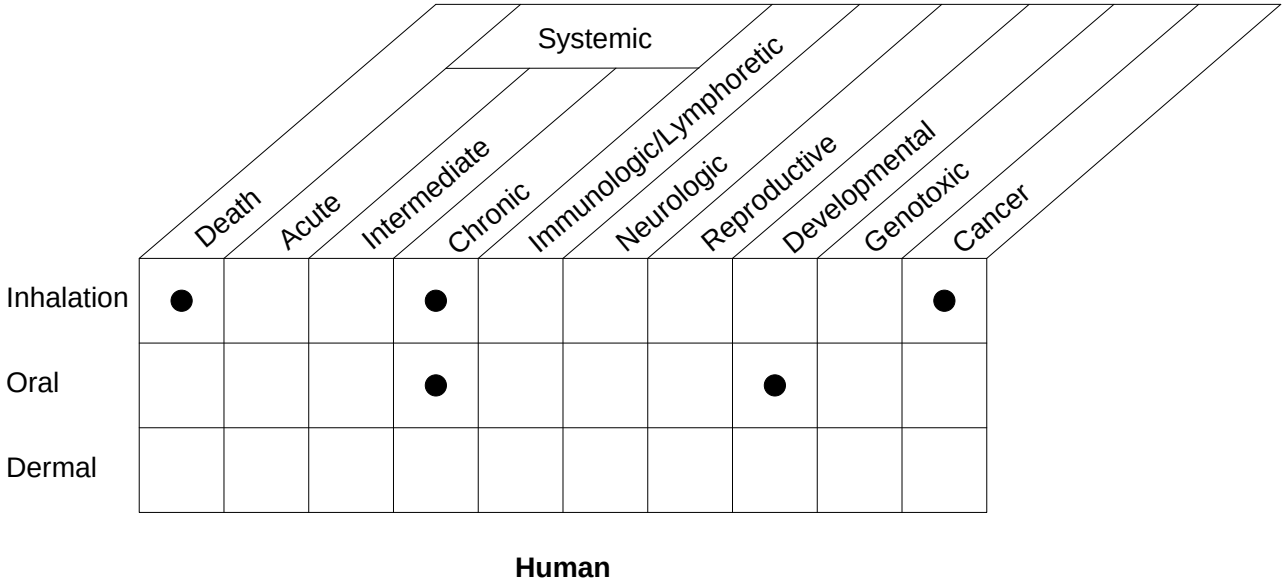
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of perfluoroalkyls is available. Where adequate information is 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.

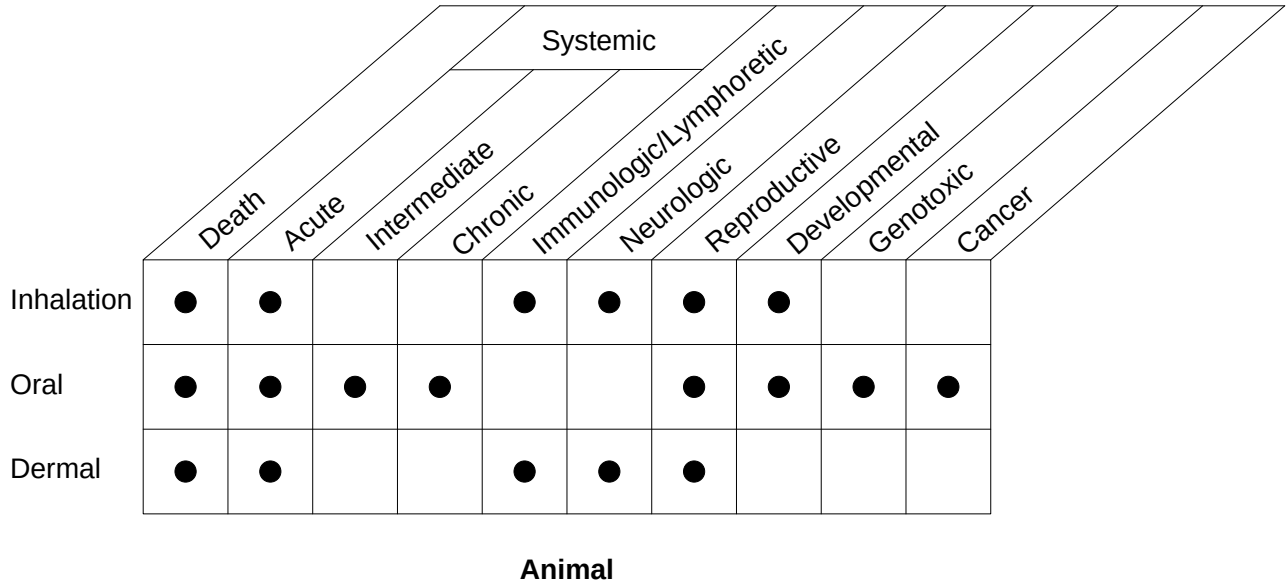
3.12.1 Existing Information on Health Effects of Perfluoroalkyls

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to PFOA and PFOS are summarized in Figures 3-10 and 3-11. Figures for the remaining perfluoroalkyls discussed in this profile are not presented due to the paucity of data for these chemicals, especially data in

Figure 3-10. Existing Information on Health Effects of PFOA



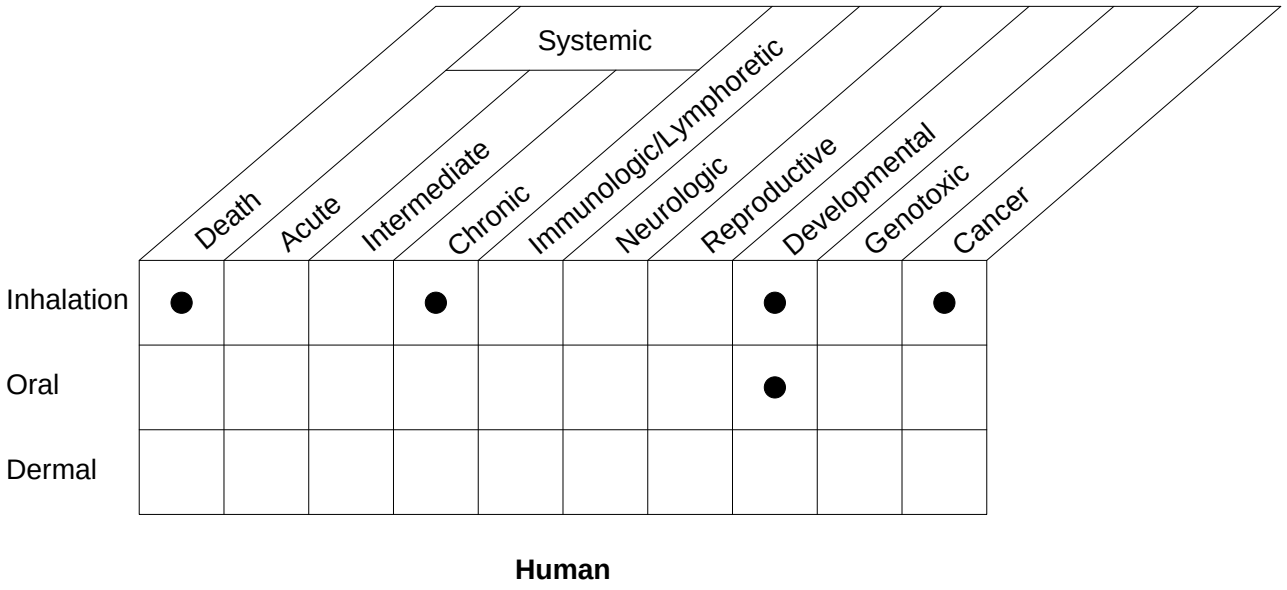
Human



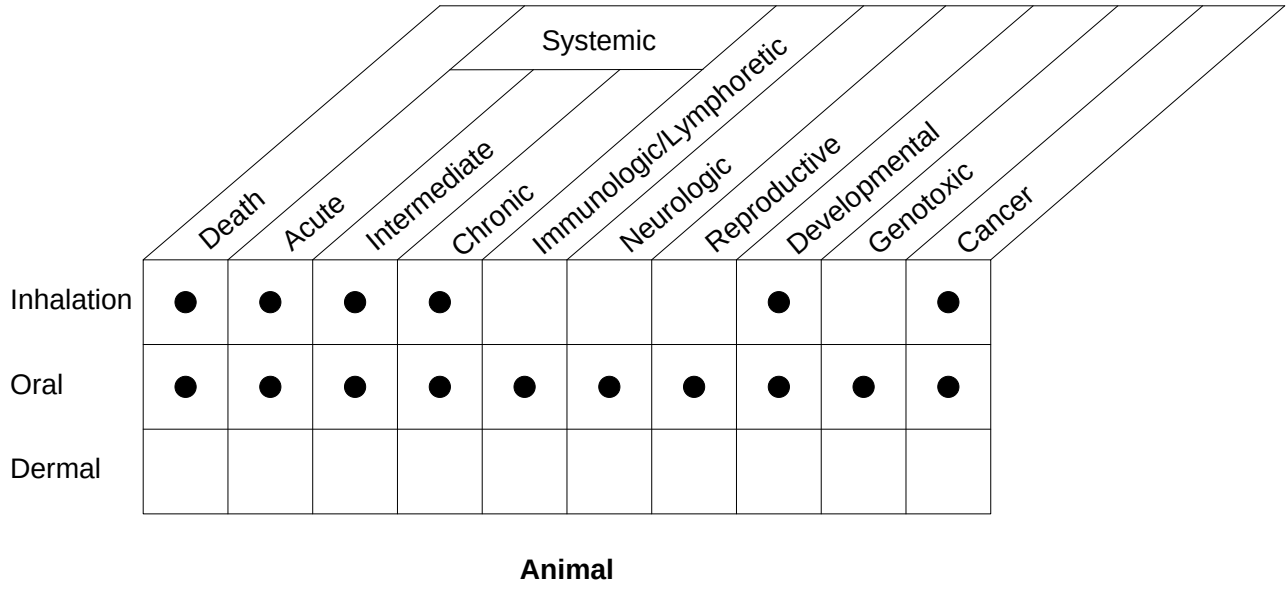
Animal

● Existing Studies

Figure 3-11. Existing Information on Health Effects of PFOS



Human



Animal

● Existing Studies

humans. The purpose of Figures 3-10 and 3-11 is to illustrate the existing information concerning the health effects of perfluoroalkyls. Each dot in the figure indicates that one or more studies provide 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 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 health evaluations have focused on detecting possible hepatic effects and alterations in lipid metabolism based on the extensive data available from studies in animals.

Most of the information regarding the effects of perfluoroalkyl compounds in animals is 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

MRLs were not derived for perfluoroalkyl compounds due to the fact that human studies to date are insufficient to determine with a sufficient degree of certainty that the effects are either exposure-related or adverse. In addition, there are large interspecies differences in the toxicokinetics of perfluoroalkyls for which mechanisms are not completely understood. Thus, extrapolation of external dose-response relationships from animals to humans would be highly uncertain (see Section 2.3 for a detailed explanation; see also the toxicokinetics sections below).

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; however, much fewer studies are available of PFBA, PFDeA and other perfluoroalkyls. The available studies indicate that the liver is main target (i.e., Fuentes et al. 2006; Haughom and Spydevold 1992; Kennedy 1987; Liu et al. 1996; Yang et al. 2001) and also that developmental effects can occur in mice at relatively low PFOA doses (i.e., 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.

Intermediate-Duration Exposure. Intermediate-duration oral studies have been conducted with PFOA, PFOS, PFBuS, and PFBA. The liver was a main target (3M 2001; Butenhoff et al. 2002; Kennedy 1987; Perkins et al. 2004; Seacat et al. 2002, 2003; Son et al. 2008; Thomford 2001, 2002a; van Otterdiijk 2007a, 2007b). Pup survival was also established as a sensitive end point in intermediate-duration oral studies with PFOA (Abbott et al. 2007) and PFOS (Lau et al. 2003; Luebker et al. 2005b). 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. However, 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 (Gilliland and Mandel 1996; Leonard 2006; Mundt et al. 2007; Olsen and Zobel 2007; Olsen et al. 1998, 1999, 2003a; Sakr et al. 2007a, 2007b) and from subjects exposed environmentally (Emmett et al. 2006b). 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. For the most part, no significant adverse effects have been identified in these populations, but sporadic deviations in clinical tests associate with serum levels of perfluoroalkyl compounds have been reported. Most of the health evaluations have focused on detecting possible hepatic effects and alterations in lipid metabolism based on the extensive data available from studies in animals. 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 (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.

A few epidemiological studies have examined the potential association between cancer and perfluoroalkyl compounds. In a retrospective cohort mortality of workers at a plant that produced PFOA, among male workers categorized as exposed for at least 10 years there was a 3.3-fold increase in prostate cancer mortality compared to no employment in PFOA production (Gilliland and Mandel 1993). Due to the small number of cases involved, the investigators cautioned that the results should not be over interpreted. In another retrospective mortality study of workers exposed to PFOS, the most significant finding was an increased risk of death from bladder cancer for the entire cohort, three cases were observed and 0.62 were expected and all of them worked in a high-exposure group (Alexander et al. 2003). A reanalysis of this cohort identified a total of 11 cases of bladder cancer, 6 from surveys and 5 from death certificates (Alexander and Olsen 2007). Compared with those in the lowest cumulative exposure category, the high-exposure workers had a small 1.5–2.0-fold increased risk. While the results did indicate an excess risk of bladder cancer among the cohort studied, study limitations such as uncertainty in case ascertainment and the size of the cohort did not allow for a conclusive exposure response analysis. An additional retrospective cohort mortality study of workers at a polymer production plant did not find increased mortality rates due to cancer among the workers (Leonard 2006). Follow-up assessments of perfluoroalkyl workers and of groups of the general population exposed to higher than background levels of perfluoroalkyls seems logical. 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). However, 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) and of mammary gland adenocarcinomas (mid-dose only). It has been

suggested that an independent, appropriately designed histopathology reanalysis of the male rat livers and the female mammary glands be conducted (EPA 2006c). In a 2-year dietary bioassay of PFOS in rats, there was an increased incidence of liver hepatocellular adenoma and thyroid follicular cell adenoma (Thomford 2002b). No cancer studies were located for the remaining perfluoroalky 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. 1998). Further studies of workers and of 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; 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. Limited information is available regarding developmental effects in humans exposed to perfluoroalkyl compounds. A study of children in Baltimore reported negative associations between both PFOA and PFOS in cord blood and birth weight, ponderal index, and head circumference (Apelberg et al. 2007b). Similar studies of Danish women reported that plasma levels of PFOA during the first trimester of pregnancy were inversely associated with birth weight, birth length, and abdominal circumference (Fei et al. 2007, 2008a), but had no significant influence on the achievement of developmental milestones in early childhood (Fei et al. 2008b). A study of Japanese women found a negative correlation between birth weight and serum PFOS levels in maternal blood collected during the second trimester of pregnancy (Washino et al. 2009). An additional study of Japanese women did not find correlations between PFOS in maternal blood and TST and T4 in cord blood (Inoue et al. 2004b) and a study of Chinese women found no association between PFOA and PFOS in breast milk and infant weight (So et al. 2006b), but the small sample size in these two studies severily limits their conclusions, and need to be repeated. Future studies of this type need to incorporate into the analysis all covariates known to influence fetal growth indicators. One of these factors is plasma volume, which expands with maternal weight gain during pregnancy and can affect the distribution of protein-bound PFOA and PFOS that are found primarily in extracellular space. A different type of study found that birth weight and gestational age of neonates born to women residing in an area in with high levels of PFOA in the drinking water were not significantly different than those from neonates born to women who resided in areas with significantly lower levels of PFOA in the water (Nolan et al. 2009).

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 (as in Nolan et al. [2009], mentioned above) 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. 2007a; 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, but a study with PFHxS is also available. Recently, a study with PFBA also became available. Standard gestational exposure studies with other perfluoroalkyl compounds would be valuable. Specific effects reported in studies with PFOA and PFOS include prenatal loss, reduced neonate weight and viability, 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; Lau et al. 2006; Luebker et al. 2005a; White et al. 2007; Wolf et al. 2007). PFHxS had no significant effects on a wide range of developmental parameters evaluated in rats (Hoberman and York 2003). In the study with PFBA, the chemical had no significant effect on neonatal weight gain or viability (Das et al. 2008). A recent study reported that gestational exposure of mice to PFOS resulted in alterations in some immune parameters in the offspring (Keil et al. 2008). Further studies on immunological effects in animals exposed *in utero* would be valuable. Studies are also available that examined periods of special susceptibility during gestation. 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 lung immaturity could be the cause of early pup death following maternal exposure to PFOS (Grasty et al. 2003, 2005). Other research suggested that delayed maternal mammary gland differentiation could, in part, explain the growth retardation seen mice offspring following maternal exposure to PFOA (White et al. 2007). This study also reported alterations in milk protein gene expression. Recently, 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.

The effects of perinatal exposure on neurological end points have also been studied. Fuentes et al. (2007a, 2007b) reported no significant alterations in neurobehavioral tests in offspring from mice exposed to PFOS *in utero* and tested during the first weeks of life. In contrast, Johansson et al. (2008) reported that administration of a single, relatively low, gavage dose of PFOS or PFOA, but not PFDeA, at the age of 10 days resulted in altered spontaneous behavior when tested at the age of 2 or 4 months old. Replication of these studies by other research groups would be useful.

Immunotoxicity. No studies were located that examined immunological effects in humans exposed to perfluoroalkyl compounds. 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. 1998, 1999, 2003a; Sakr et al. 2007a, 2007b) or of subjects environmentally exposed to elevated amounts of PFOA through their drinking water (Emmett et al. 2006b). However, it is reasonable to assume that no frank clinical signs were detected in the groups examined. Studies in

animals have not provided evidence that the nervous system is a sensitive target for perfluoroalkyl compounds based on observations of demeanor 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 (Hoberman and York 2003) and one with PFBuS, also in rats, that reported a decrease in tail flick latency test in males of unknown toxicological significance (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 (Gilliland and Mandel 1996; Leonard 2006; Mundt et al. 2007; Olsen and Zobel 2007; Olsen et al. 1998, 1999, 2003a; Sakr et al. 2007a, 2007b) and from subjects exposed environmentally (Emmett et al. 2006b). No significant health conditions have been associated with the serum levels of perfluoroalkyls measured in these studies, but the main focus has been the liver. Evaluations of other end points seem warranted. Two studies have provided suggestive evidence of effects on sex hormones and lipids (Olsen et al. 1998; Sakr et al. 2007b) and there are also reports of increased risk of death from prostate and bladder cancer (Alexander and Olsen 2007; Alexander et al. 2003; Gilliland and Mandel 1993). Clarification of the details, significance, and dose-response relationships of the observed changes is needed. 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; Emmett et al. 2006a, 2006b; Olsen et al. 2003c, 2003b, 2004b, 2007b) and perfluoroalkyl workers (Gilliland and Mandel 1996; Olsen and Zobel 2007; Olsen et al. 1999, 2003b, 2003c; Sakr et al. 2007a, 2007b). 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 perfluroalkyl workers (Olsen et al. 1998; 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. Very limited information is available regarding toxicokinetics of perfluoroalkyl compounds in humans; therefore, studies on all aspects of toxicokinetics in humans are needed.

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). Toxicokinetics 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.

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. Toxicokinetics studies have provided information on the tissue distribution of PFOA and PFOS in rodents (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 species and gender 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 gender differences in elimination kinetics of absorbed perfluoroalkyls and dose dependence of elimination kinetics (see Section 3.4.2). Toxicokinetics studies have found gender- 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 is 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). However, 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 exhibit time-dependencies that may be gender- and species-specific (Andersen et al. 2006; Tan et al. 2008). Mechanisms underlying these time dependencies have not been elucidated.

Rates of elimination of perfluoroalkyls vary substantially across chemical species and animal species, and show gender 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 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 differences in elimination rate. The influence of gender on elimination rates of perfluoroalkyls in humans has not been thoroughly examined. Although the few studies that have estimated elimination half-times or renal clearances in male and female humans have not found significant gender 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 rodents and nonhuman primates (i.e., gender influence may vary with dose and/or plasma concentration).

Comparative Toxicokinetics. Toxicokinetics studies conducted in various rodent species (mice, rats, hamsters, rabbits) and in Cynomolgus monkeys have revealed profound species and gender 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 gender 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). Gender differences in elimination of PFOA have also been observed in hamsters; however, unlike the rat, male hamsters excreted absorbed PFOA more rapidly than female hamsters. Gender differences in

elimination of PFOA have not been observed in other rodent species, in Cynomolgus monkeys, or in limited observations made in humans. A mechanistic explanation for the species differences in gender-specificity of elimination kinetics of PFOA has not been established.

Methods for Reducing Toxic Effects. As previously mentioned, health evaluations of workers exposed to perfluoroalkyl compounds or of members of the general population exposed to elevated amounts of PFOA via the drinking water have not shown, with few exceptions, consistent associations between exposure and adverse health effects. Therefore, it is difficult to design studies or methods for reducing toxic effects if no significant health effects have been reported to date. However, studies that examine the issue of how to reduce body burden by increasing the lengthy 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 to the effects of exposure to perfluoroalkyl compounds because there are no studies that specifically addressed this question. The only health evaluation done in children exposed to perfluoroalkyls is that conducted by Emmett et al. (2006b) of residents in the Little Hocking water district in southeastern Ohio that included 43 children under the age of 18. The cohort was exposed to elevated levels of PFOA via the drinking water. The study did not find significant associations between serum PFOA levels and hematology parameters, total cholesterol and liver enzymes, indices of kidney function, and serum TSH levels whether the analysis included all the individuals as a group or separate analyses were done for adults or children. Similar evaluations should be made in any group identified as having high exposure to perfluoroalkyls and should include children of all ages. Toxicokinetics information in children is needed. Half-life studies have been conducted in elderly retired workers; there is the need to understand if these are applicable to children. The significance to children, if any, of the endocrine disturbances reported in some studies of perfluoroalkyl workers needs to be better understood. 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 FEDRIP (2008) database.

Dr. M. Peden-Adams, at the Medical University of South Carolina, Charleston, South Carolina, is conducting research to determine the role of PPARα in the suppression of T-dependent antibody production by PFOS by assessing antibody responses in wild (control) type mice and PPARα-null mice. She also aims to elucidate the mode of action of PFOS on T-dependent antibody production. The research is sponsored by the National Institute of Environmental Health Sciences.

Drs. F. Rubio, W. Shelver, and associates, at ABBRAXIS LLC, Warminster, Pennsylvania, intend to produce polyclonal antibodies and hybridoma cell lines that provide monoclonal antibodies suitable for a commercial PFOA immunoassay, and to document the production method. The research is sponsored by the Department of Agriculture.

The C8 Science Panel (2008) lists the following proposed research to be conducted on the roughly 70,000 participants in the C8 Health Project:

Cardiovascular Risk Factors Measured in the Blood. Researchers will look at the data already collected from approximately 55,000 participants in the C8 Health Project over age 20 to determine whether the results of some tests related to heart disease, such as total cholesterol, triglycerides, uric acid, red blood cell counts, glucose, and others, are associated with C8 blood level. Kyle Steenland is listed as investigator.

The Immune Function, Liver, Hormone Disorders, and Cancer Prevalence Study. This study will look in depth at this information. The participant also filled out a questionnaire, and researchers will look at the self-reported disease the participants listed in the questionnaire on cancers and diseases related to problems with the immune system, the liver, and the endocrine or hormone regulation system. Using this information, the investigators will look at the relationships between C8 blood levels and the above outcomes taking into consideration factors such as age, sex, smoking, and obesity for each participant. Tony Fletcher is listed as investigator.

The Community Follow-up Study. Investigators will look at new diseases occurring for such end points as cancer, heart disease, and diabetes, among adults who participated in the C8 Health Study. They will follow approximately 37,000 adults (a subset of the original 70,000 participants residing in the six water districts) for 4 years to see whether health effects develop overtime. Kyle Steenland is listed as investigator.

The Worker Follow-up Study. Investigators will follow-up a study of 6,000 Washington Works plant workers (who worked anytime between January 1, 1952 and December 31, 2001) for about 4 years to determine what diseases they have had, with special interest in cancer, heart disease, and diabetes. Kyle Steenland is listed as investigator.

The Study of Birth Outcomes in the Mid-Ohio Valley. This study will determine whether birth outcomes, including stillbirth, preterm birth (early delivery), and birth weight, are related to C8 exposure. David Savitz is listed as investigator.

The Study of Birth Outcomes Among the C8 Health Project Participants. In addition to the birth outcomes examined in the Mid-Ohio Valley Community Study (stillbirth, preterm birth, birth weight), in this study, the investigators propose to look at miscarriage, pregnancy complications like preeclampsia (high blood pressure during pregnancy), and birth defects among newborn babies. David Savitz is listed as investigator.

The Geographic Patterns of Cancer Study. Investigators will use state cancer registries, census tract and zip codes, water district records and other records in West Virginia and Ohio to study whether rates of cancer incidence and cancer deaths differ in relation to levels of exposure to C8. Rates in the affected water districts will be compared to unexposed counties nearby and within the exposed areas to assess how cancer rates vary depending on exposure to C8 in the different water districts. Tony Fletcher is listed as investigator.

Follow-up Study on Immune Function, Liver, and Hormone Disorders. A subset of 1,000 subjects from the 70,000 participants in the C8 Health Projects will be re-contacted to participate in this study. Researchers will conduct interviews and collect further blood samples to help better understand the relationships between C8 blood levels and outcomes with the immune, liver, and endocrine systems. Using the new blood samples, the researchers will do a much more complete set of tests of the immune system and relate these to C8 levels. Tony Fletcher is listed as investigator.

The Half-life Study. To better understand the relationship between past C8 exposures and current C8 blood levels, investigators will invite 200 adults from the C8 Health Project to participate in a longer study to determine the elimination half-life of C8 from the body. Participants will provide up to eight blood samples. Kyle Steenland and Barry Ryan are listed as investigators.

NTP (2008) has initiated a long-term carcinogenicity study of PFOA in Sprague-Dawley rats. Female rats will receive 0, 300, or 1,000 ppm PFOA in the diet, whereas males will receive 0, 150, or 300 ppm.

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.

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). Perfluoroalkanecarboxylic acids decompose when heated to temperatures >550 °C forming an olefin, HF, and CO_2 (Kissa 2001).

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 will exist as both the anion and the neutral species (SPARC 2008). Perfluoroalkyl salts, such as ammonium perfluorooctanoate (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

Table 4-1. Chemical Identity of Perfluoroalkyls

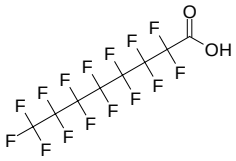
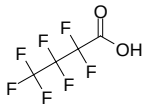
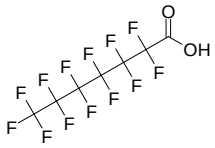
Characteristic	Information		
Chemical name	Perfluorooctanoic acid	Perfluorobutyric acid	Perfluoroheptanoic acid
Synonym(s)	PFOA; pentadecafluoro-1-octanoic acid; pentadecafluoro-n-octanoic acid; pentadecaflurooctanoic acid; perfluorocaprylic acid; perfluoroctanoic acid; perfluoroheptanecarboxylic acid; 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

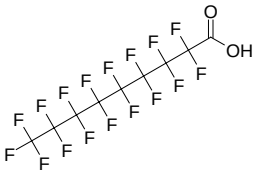
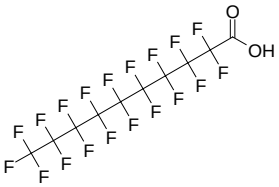
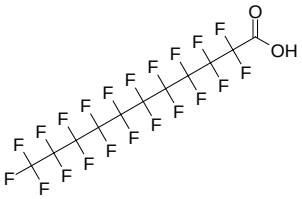
Characteristic	Information		
Chemical name	Perfluorononanoic acid	Perfluorodecanoic acid	Perfluoroundecanoic acid
Synonym(s)	PFNA; perfluoro-n-nonanoic acid; perfluorononan-1-oic acid; heptadecafluoro-nonanoic acid; nonanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluoro-	PFDA; PFDeA; Ndfda; nonadecafluoro-n-decanoic acid; nonadecafluoro-decanoic 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

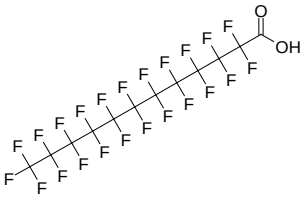
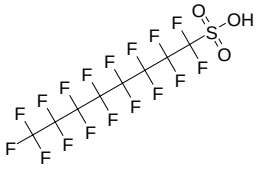
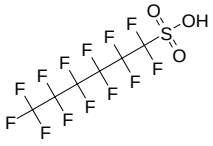
Characteristic	Information		
Chemical name	Perfluorododecanoic acid	Perfluorooctane sulfonic acid	Perfluorohexane sulfonic acid
Synonym(s)	PFDoA; tricosafluorododecanoic acid; dodecanoic acid, 2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,12-tricosafluoro-	PFOS; 1-perfluorooctanesulfonic acid; heptadecafluoro-1-octanesulfonic acid; heptadecafluorooctan-1-sulphonic acid; perfluorooctane sulfonate; perfluorooctylsulfonic 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

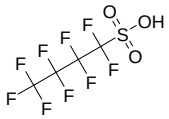
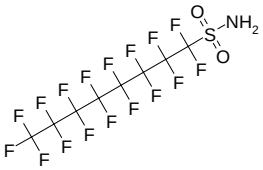
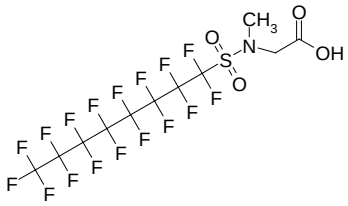
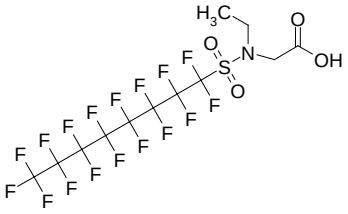
Characteristic	Information		
Chemical name	Perfluorobutane sulfonic acid	Perfluroroocatanesulfonamide	2-(N-methyl-perfluorooctane sulfonamido) acetic acid
Synonym(s)	PFBuS; 1-perfluorobutanesulfonic acid; nonafluoro-1-butanesulfonic acid; nonafluorobutanesulfonic acid; pentyl perfluorobutanoate; 1,1,2,2,3,3,4,4,4-nonafluoro-1-butanesulfonic acid; 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulphonic acid; 1-butanesulfonic acid, nonafluoro- (6Cl,7Cl,8Cl)	PFOSA; perfluoroctylsulfonamide; perfluorooctanesulfonic acid amide; heptadecafluorooctanesulphonamide; 1-octanesulfonamide, 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]	No data	No data
Boiling point	188 °C[a]	121 °C[a]	No data	No data
Density at 20 °C	1.8 g/cm^3 [d]	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[f]	Not applicable[f]	Not applicable[f]	Not applicable[f]
K_{oc}	17–230[g]	No data	No data	No data
pKa	2.8[h]	0.08 (estimated)[i]	-0.15 (estimated)[i]	-0.17 (estimated)[i]
Vapor pressure	0.017 mm Hg at 20 °C (extrapolated); 0.962 mm Hg at 59.25 °C (measured)[j]	No data	No data	No data
Henry's law constant	Not applicable[k]	Not applicable[k]	Not applicable[k]	Not applicable[k]
Autoignition temperature	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]
Flashpoint	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]
Flammability limits	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]
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 (calculated using molecular weight)	1 ppm= 15.14 mg/m^3; 1 mg/m^3= 0.07 ppm (calculated using molecular weight)	1 ppm= 19.29 mg/m^3; 1 mg/m^3= 0.05 ppm (calculated using molecular weight)
Explosive limits	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]

Table 4-2. Physical and Chemical Properties of Perfluoroalkyls

Property	PFDeA	PFUA	PFDoA	PFOS
Molecular weight	514.084[a]	564.085 (ChemID Plus 2008)	614.1[b]	500.03[b]
Color	No data	No data	No data	No data
Physical state	No data	No data	No data	No data
Melting point	No data	No data	No data	≥400 °C (potassium salt) (3M 2000)
Boiling point	219 °C	No data	No data	No data
Density at 20 °C	No data	No data	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	No data	No data	No data	570 mg/L (potassium salt in pure water) (3M 2000)
Organic solvents	No data	No data	No data	No data
Partition coefficients:				
Log K_{ow}	Not applicable[f]	Not applicable[f]	Not applicable[f]	Not applicable[f]
K_{oc}	No data	No data	No data	No data
pKa	-0.17 (estimated)[i]	-0.17 (estimated)[i]	-0.17 (estimated)[i]	0.14 (estimated)[i]
Vapor pressure	No data	No data	No data	2.48×10^{-6} mm Hg at 20 °C (potassium salt)[c]
Henry's law constant at 25 °C	Not applicable[k]	Not applicable[k]	Not applicable[k]	Not applicable[k]
Autoignition temperature	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]
Flashpoint	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]
Flammability limits	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]
Conversion factors	1 ppm= 21.37 mg/m^3; 1 mg/m^3= 0.05 ppm (calculated using molecular weight)	1 ppm= 23.45 mg/m^3; 1 mg/m^3= 0.04 ppm (calculated using molecular weight)	1 ppm= 25.53 mg/m^3; 1 mg/m^3 =0.04 ppm (calculated using molecular weight)	1 ppm= 20.79 mg/m^3; 1 mg/m^3 =0.05 ppm (calculated using molecular weight)
Explosive limits	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]

Table 4-2. Physical and Chemical Properties of Perfluoroalkyls

Property	PFHxS	PFBuS	PFOSA	Me-PFOSA-AcOH	Et-PFOSA-AcOH
Molecular weight	400.12[b]	300.1[b]	499.15[b]	571.21 (from structure)	585.24[b]
Color	No data	No data	No data	No data	No data
Physical state	No data	No data	No data	No data	No data
Melting point	No data	No data	No data	No data	No data
Boiling point	No data	No data	No data	No data	No data
Density at 20 °C	No data	No data	No data	No data	No data
Odor	No data	No data	No data	No data	No data
Odor threshold:					
Water	No data	No data	No data	No data	No data
Air	No data	No data	No data	No data	No data
Solubility:					
Water	No data	No data	No data	No data	No data
Organic solvents	No data	No data	No data	No data	No data
Partition coefficients:					
Log K_{ow}	Not applicable[f]	Not applicable[f]	Not applicable[f]	Not applicable[f]	Not applicable[f]
K_{oc}	No data	No data	No data	No data	No data
pKa	0.14 (estimated)[i]	0.14 (estimated)[i]	6.24 (estimated)[i]	3.92 (estimated)[i]	3.92 (estimated)[i]
Vapor pressure	No data	No data	No data	No data	No data
Henry's law constant	Not applicable[k]	Not applicable[k]	Not applicable[k]	Not applicable[k]	Not applicable[k]
Autoignition temperature	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]
Flashpoint	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]
Flammability limits	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]

Table 4-2. Physical and Chemical Properties of Perfluoroalkyls

Property	PFHxS	PFBuS	PFOSA	Me-PFOSA-AcOH	Et-PFOSA-AcOH
Conversion factors	1 ppm= 16.63 mg/m^3; 1 mg/m^3= 0.06 ppm (calculated using molecular weight)	1 ppm= 12.48 mg/m^3; 1 mg/m^3 =0.08 ppm (calculated using molecular weight)	1 ppm= 20.75 mg/m^3; 1 mg/m^3 =0.05 ppm (calculated using molecular weight)	1 ppm= 23.75 mg/m^3; 1 mg/m^3= 0.04 ppm (calculated using molecular weight)	1 ppm= 24.33 mg/m^3; 1 mg/m^3= 0.04 ppm (calculated using molecular weight)
Explosive limits	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]	Not applicable[l]

[a]Lide 2005
[b]EPA 2008h
[c]3M 2008c
[d]Kroschwitz and Howe-Grant 1994
[e]Kauck and Diesslin 1951
[f]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).
[g]Prevedouros et al. 2006)
[h]Kissa 2001
[i]SPARC 2008
[j]Washburn et al. 2005
[k]Henry's law constant is not applicable for these substance since they are dissociated in the environment.
[l]Perfluoroalkyls are nonflammable and chemically stable even at high temperatures (3M 1999; Kissa 2001; OECD 2007).

Et-PFOSA-AcOH = 2-(N-ethyl-perfluorooctane sulfonamide) acetic acid; Me-PFOSA-AcOH = 2-(M-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

for the perfluorooctanoate anion (PFO). Above these values, the solubility of PFO is expected to increase abruptly due to the formation of micelles.

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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 1998).

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 importing 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; 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.

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. 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.

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

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]
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

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).

Perfluoroalkyls have been manufactured industrially through two methods, the electrochemical fluorination (ECF) process and the telomerization process (Schultz et al. 2003). During the ECF process, an organic acyl or 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

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; PFBA = perfluorobutyric acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Source: EPA 2008g

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 telomerization 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 telomerization process produces linear perfluorocarboxylic acids of even carbon numbers. An example of telomerization is shown 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 perfluorooctanoate is currently manufactured in Japan through oxidation of a mixture of linear fluorotelomer olefins (Prevedouros et al. 2006). Fluorotelomer iodide carboxylation has also been described; however, it does not appear that this production method has been used commercially (Prevedouros et al. 2006).

5.2 IMPORT/EXPORT

Information regarding the import and export of perfluoroalkyl compounds were not located.

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

Recommended disposal methods specific to perfluoroalkyl compounds have not been located. DuPont (2008) stated that it had developed proprietary technologies for the safe disposal, recovery, and/or recycling of PFOA extracted during fluoropolymer production processes; however, this company has since committed to the phase-out of PFOA from their fluoropolymer production streams. The Fluoropolymers Division has outlined two preferred disposal options for fluoropolymer dispersions, which may contain <1% fluoropolymer polymerization aids such as PFOA. 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 while the liquid waste is discharged to a waste water treatment facility. The second method involves incineration at temperatures >800 °C using a scrubber to remove hydrogen fluoride. 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).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Perfluoroalkyls have not been reported at EPA National Priorities List (NPL) sites, however, it's unknown how many of the 1,467 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 are 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 migration from paper packaging and wrapping into food, general food and water ingestion, inhalation from impregnated clothes, and dust ingestion. Based on these proposed exposure pathways, adult uptake doses estimated for high exposure scenarios were approximately 30 and 47 ng/kg body weight/day for PFOS and PFOA, respectively (Trudel et al. 2008). The proposed PFOS and PFOA exposure pathways are expected to be similar for children except that exposure from hand-to-mouth transfer from treated carpets would be much larger.

PFOS and PFOA doses determined for children under the age of 12 under high exposure scenarios were 101–219 and 65.2–128 ng/kg body weight/day, respectively (Trudel et al. 2008). 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 (Kärrman et al. 2007a; 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.

Estimated on-site exposure of individuals to PFOA while working at a fluorochemical facility ranged from $3.2x10^{-6}$ to 2.4 ng/kg/day (3M 2008c). 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 suggest that drinking water is the major exposure pathway (Emmett et al. 2006a; Holzer et al. 2008; Wilhelm et al. 2008b). 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 1998).

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 fire fighting 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).

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. 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 2008).

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 1998).

Table 6-1. Reported Emissions of PFOA, PFOA Homologues, or PFOA Precursors in Products from the 2006 U.S. Operations of Fluoropolymer/Fluorotelomer Companies

				Percent reduction in emissions[a]
Company	Chemicals	Releases to all media from fluorotelomer and telomer manufacturing (kg)	Releases to all media from fluorotelomer and telomer manufacturing (kg of release/kg of product produced)	Percent reductions in total quantity of chemical(s) released from baseline year
Arkema, Inc.	PFOA and higher homologues	>1,000–10,000	For fluorotelomer production: >0.1–1 kg/100 kg	22%
	Precursors	Not applicable	Not applicable	Not applicable
Asahi Glass Company	PFOA, PFOA salts, and higher homologues	4,922	For fluorotelomer production: <1 kg/100 kg	6%
	Precursors	Not applicable	Not applicable	Not applicable
Ciba Specialty Chemicals Corporation	PFOA	0.05	0.05 kg	>99%
	Higher homologues	0.05	0.05 kg	>99%
	Precursors	0 kg	0	>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} kg/100 kg; for telomer production: 6.4×10^{-7} kg/100 kg	94% for FP production; 92% for telomer production
	Precursors and higher homologues	Confidential business information	For telomer production: 6.4×10^{-7} kg/100 kg	22% for telomere 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%

Table 6-1. Reported Emissions of PFOA, PFOA Homologues, or PFOA Precursors in Products from the 2006 U.S. Operations of Fluoropolymer/Fluorotelomer Companies

				Percent reduction in emissions[a]
Company	Chemicals	Releases to all media from fluorotelomer and telomer manufacturing (kg)	Releases to all media from fluorotelomer and telomer manufacturing (kg of release/kg of product produced)	Percent reductions in total quantity of chemical(s) released from baseline year
Solvay Solexis	PFOA and PFOA salts	Not applicable	Not applicable	Not applicable
	Higher homologues	>1,000–10,000	For fluorotelomer production: 0.161 kg/100 kg	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.

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 fire fighting 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 fire fighting foams; APFN = ammonium perfluorononanoate; APFO = ammonium perfluorooctanoate; PFCA = perfluorinated carboxylic acid; PFO = perfluorooctanoate; POSF = perfluorooctanesulfonyl fluoride

Source: Prevedouros et al. 2006

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). 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 1998).

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 wastewater 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.

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 1998).

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 is highly 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). Measurements of PFOA in soil and groundwater near a perfluoropolymer manufacturing facility indicate migration of air deposited ammonium perfluorooctanoate from surface soil to unsaturated subsurface soil to the aquifer (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).

One hypothesis is the long-range atmospheric transport of precursor compounds such as fluorotelomer alcohols and perfluoroalkyl sulfonamides followed by the atmospheric photooxidation of these substances

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			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			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			Verreault et al. 2005, 2007
Herring gull eggs	<91–652	21,400–42,200	
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

Location and organism	Concentration (ng/g) PFOA	PFOS	Reference
Nanavut, Canada			Butt et al. 2007a, 2007b
Thick-billed murres	<MDL[a]–0.16	<0.40–0.76	
Northern fulmars	<MDL[a]–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	263–3,770	
Greenland, 1999–2001			Smithwick et al. 2005b
Polar bears (n=29)	10	2,470	
Greenland, 1972–2002			Smithwick et al. 2006
Polar bears	1.6–4.4	120–1,400	

[a]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

to form perfluoroalkyl carboxylic acids and perfluoroalkyl sulfonic acids (Barber et al. 2007; D'eon et al. 2006; Dinglasan-Panlilio and Mabury 2006; Ellis et al. 2004; Martin et al. 2006; Simcik 2005; Wallington et al. 2006; Wania 2007). Proponents of this hypothesis state that fluorotelomer alcohols and perfluoroalkyl sulfonamides are volatile enough and have 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 hypothesis for the 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 hypothesis 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 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 perfluoroalkyls 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 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).

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 5.8×10^{-12} and 3.74×10^{-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.

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).

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.

Table 6-4. Concentrations of Perfluoroalkyl in Outdoor Air

Location	Mean (range) concentration (pg/m^3) PFOA	PFHpA	PFNA	Reference
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) PFDeA	PFUA	PFDoA	Reference
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

	Mean (range) concentration (pg/m^3)				
Location	PFOS	PFBuS	PFHxS	PFOSA	Reference
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

	Mean (range) concentration (pg/m^3)				
Location	PFOS	PFBuS	PFHxS	PFOSA	Reference
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

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). 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 PFUnA.

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, PFDA, 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.

Very few 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 PFUnA, and 1.2 ng/m^3 for PFDoA (Barber et al. 2007).

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.

Atmospheric monitoring data were not located for PFBA, Me-PFOSA-AcOH, and Et-PFOSA-AcOH.

Table 6-5. Concentrations of Perfluoroalkyl in Indoor Air

	Mean (range) concentration			
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 (median)[a]	—	—	Kubwabo et al. 2005
Japan (n=16)	380 (70–3,700); 165 (median)	—	—	Moriwaki et al. 2003
North Carolina and Ohio (n=112)	296 (<10.2–1960); 142 (median)[b]	109 (<12.5–1150); 50.2 (median)[b]	22.1 (<11.3–263); 7.99 (median)[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 (median)[b]	30.4 (<10.7–588); 7.57 (median)[b]	18.0 (<11.0–520); 7.78 (median)[b]	Strynar and Lindstrom 2008

Table 6-5. Concentrations of Perfluoroalkyl in Indoor Air

Location	Mean (range) concentration (pg/m^3) 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 (median)[a]	ND[a]	391.96 (<4.56–4,305); 23.1 (median)[a]	<1.38[a]	Kubwabo et al. 2005
Japan (n=16)	200 (11–2,500); 24.5 (median)	—	—	—	Moriwaki et al. 2003
North Carolina and Ohio (n=112)	761 (<8.93–12,100); 201 (median)[b]	41.7 (<12.5–1150); 9.11 (median)[b]	874 (<12.9–35,700); 45.5 (median)[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.

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

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 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 6-6 and 6-7. 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.

Levels of some perfluoroalkyl compounds measured in surface water and groundwater surrounding perfluorochemical industrial facilities are listed in Table 6-8. 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.

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 6-9. 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,

Table 6-6. 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 6-6. 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	

[a]Detection limit is 0.05 ng/L

ND = not detected; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Table 6-7. Concentrations of Other Perfluoroalkyls in Surface Water

Location (reference)[a]	Concentration (ng/L)								
	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	—	—
Percent not detected[b]	32.9	10.1	15.2	17.7	53.2	38.0	45.6	—	—

Table 6-7. Concentrations of Other Perfluoroalkyls in Surface Water

Location (reference)[a]	Concentration (ng/L)								
	PFHpA	PFNA	PFDeA	PFUA	PFDoA	PFBuS	PFHxS	PFOSA	Et-PFOSA-AcOH
Raisin and St. Clair Rivers, Michigan (Kannan et al. 2005)									
Raisin River	—	—	—	—	—	—	<1	<10	—
St. Clair River (n=3)	—	—	—	—	—	—	<1	<10	—

[a]See Table 6-5 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 6-8. Concentrations of Perfluoroalkyls in Surface Water and Groundwater at Fluorochemical Industrial Facilities

Location	Percent detection and concentration (µg/L)					Reference
	PFOA	PFBA	PFOS	PFHxS	PFBuS	
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 2007
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 2007
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 2007
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 2007
Percent detected	14%	12%	0%	0%	0%	
Maximum	0.0501	0.0530	ND	ND	ND	
3M Decatur Facility, Alabama						

Table 6-8. 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
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 6-9. 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

PFDeA, PFNA, PFHpA) were generally below detection in most samples, with the exceptions being in samples collected near Shanghai, the Philippines, and Indonesia. Maximum concentrations of these perfluoroalkyls ranged from 3.1 to 70.2 pg/L near Shanghai.

Little information is available regarding the concentrations of perfluoroalkyl compounds in drinking water. The widespread presence of PFOA and PFOS detected in surface water in the United States indicates that drinking water taken from these sources may contain perfluoroalkyls. 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). Emmett et al. (2006a) reported an average PFOA concentration of 3.55 ng/mL 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 <2 ng/L at these locations. 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.

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 6-10. 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.

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

Table 6-10. 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 2007
Percent detected	100%	—	95%	90%	60%	
Maximum	21,800	—	104,000	3,470	139	
Fire training area (n=8–11)						3M 2007
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 2007
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 2007
Percent detected	70%	44%	80%	28%	29%	
Maximum	341	124	79.0	11.5	29.4	
Mississippi River transect (n=38–40)						3M 2007
Percent detected	18%	0%	82%	0%	0%	
Maximum	1.09	ND	3.16	ND	ND	
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	—	—	—	—	

Table 6-10. Concentrations of Perfluoroalkyls in Soil and Sediment at Fluorochemical Industrial Facilities

	Percent detection and concentration (ng/g)					
Location	PFOA	PFBA	PFOS	PFHxS	PFBuS	Reference
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

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.

Limited monitoring data are available for the DuPont Washington Works Facility in West Virginia. Davis et al. (2007) reported that APFO was detected in 8 out of 22 boring samples collected at a site along the Ohio River opposite from the Washington Works Facility. Reported APFO concentrations ranged from <0.17 to 170 ng/g in these samples.

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 90^{th} 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 measurement 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). 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).

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 6-11 and 6-12 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, 14.7–55.8, and 1.5–

Table 6-11. 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			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		
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	

Table 6-11. Concentrations of PFOA and PFOS in Human Serum Collected in the United States

	Detection and concentration (ng/mL [ppb])[a]		
Location	PFOA	PFOS	Reference
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 (n=238)			Olsen et al. 2004c
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	

[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.

LLOQ = lower limit of quanitification; LOD = limit of detection; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Table 6-12. 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
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
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					

Table 6-12. 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
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
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-(M-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

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 were slightly lower in the 2003–2004 survey for PFOA, PFOS, and PFHxS while PFNA levels were slightly higher. A more dramatic difference 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.

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 et al. 2007b; Begley et al. 2005; Calafat et al. 2006b; Trudel et al. 2008; Washburn et al. 2005). 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. (2008) 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.

Limited information has been located regarding pathways of human exposure to PFBA, PFHpA, PFNA, PFUnA, 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 6-13. 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 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

Table 6-13. Concentrations of PFOA, PFOS, and PFHxS in Human Serum for Perfluoroalkyl Workers

	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, Parkersburg, West Virginia				
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

[a]Data include results from three retirees from the 3M plant in Cottage Grove, Minnesota.
[b]Reported as the interquartile range.

PFHxS = perfluorohexane sulfonic acid; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

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 6-14 and 6-15. 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 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 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.

Although mean serum concentrations of perfluoroalkyl compounds are reported to be similar for children 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).

Table 6-14. 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	
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	
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	

Table 6-14. 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
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	
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. 2007a
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	

Table 6-14. 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
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; PFOA = perfluorooctanoic acid; PFOS = perfluorooctane sulfonic acid

Table 6-15. 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
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%	—	—

Table 6-15. 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
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	—	—	—
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-(M-methyl-perfluorooctane sulfonamide) acetic acid; ND = no data; 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

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 PFBS 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. 2007a; 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. 2007a; 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; Emmett et al. 2006a; Holzer et al. 2008; Agency for Toxic Substances and Disease Registry 2008; Wilhelm et al. 2008b). 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).

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 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. 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.

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). Further study of the transport and fate of perfluoroalkyl compounds in the environment would be helpful in verifying these assumptions.

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).

Food Chain Bioaccumulation. 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. 2006a; Kannan et al. 2005; Smithwick et al. 2005a, 2005b, 2006). 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. Limited 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; 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.

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. Limited data are available regarding the levels of perfluoroalkyls in young children (Olsen et al. 2004b). 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 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. 2007a; 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 Federal Research in Progress (FEDRIP 2008) 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 6-16.

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 6-16. Ongoing Studies on Perfluoroalkyls

Investigator	Affiliation	Research description	Sponsor
Emmett EA	University of Pennsylvania	Assessment of exposure of residents in the Little Hocking Water Association district to perfluorooctanoate (C8). The area is near the DuPont Washington Works facility in Parkersburg, WV. The study will involve measurement of perfluorooctanoate in a sample of residents and identification of the relative importance of potential exposure sources.	National Institute of Environmental Health Sciences
Lee LS et al.	Purdue University, Agronomy	This study will include research on environmental degradation of fluorotelomer alcohols resulting in formation of perfluorocarboxylates.	U.S. Department of Agriculture, HATCH

Source: FEDRIP 2008

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). No methods approved by federal agencies and organizations were located for perfluoroalkyl compounds. 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).

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 extaction 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.

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.

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)

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 uM/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
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

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 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-(M-methyl-perfluorooctane sulfonamide) acetic acid; MS = 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

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.

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. 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

As part of PFOA stewardship program, EPA and member companies have agreed to develop analytical standards for measured the perfluoroalkyl chemicals included within the program by 2010. Lynne Petterson of the U.S. EPA is leading an ongoing study to develop analytical methods to investigate human exposures to compounds including some perfluoroalkyls, such as PFOS and PFOA (FEDRIP 2008). No other ongoing studies regarding analytical methods for measuring perfluoroalkyls in biological materials or environmental media were located.

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 did not derive MRLs for perfluoroalkyl compounds based on lack of adequate human data and uncertainties related to the appropriateness of using animal data for human risk assessment. The EPA has not derived a reference dose (RfD) or reference concentration (RfC) for perfluoroalkyl compounds and has not classified perfluoroalkyls as to their carcinogenicity (IRIS 2008).

Perfluoroalkyl compounds are included on the chemical imports and exports regulations (EPA 2008d) and significant new uses of chemical substances, whereas manufacturers are required to follow the regulations including: chemical substance and significant new uses subject to reporting; industrial, commercial, and consumer activities; protection in the workplace; hazard communication program; disposal; releases to water; and recordkeeping (EPA 2008d).

OSHA has not required employers of workers who are occupationally exposed to perfluoroalkyl compounds to institute engineering controls and work practices to maintain employee exposure to a minimum.

Perfluoroalkyl compounds are among the chemicals nominated to the National Toxicology Program (NTP) for in-depth toxicological evaluation for carcinogenesis testing in fiscal years 1988–2003 (NTP 2005).

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 2008
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	No data	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	No data	
EPA	AEGL-1, -2, and -3[a]	No data	EPA 2007a
	Hazardous air pollutant	No data	EPA 2007b
NIOSH	REL (10-hour TWA)	No data	
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2007 29 CFR 1910.1000, Table Z-1
b. Water			
EPA	Drinking water standards and health advisories (provisional)		
	Perfluorooctanoic acid	0.4 µg/L	EPA 2009
	Perfluorooctane sulfonate	0.2 µg/L	EPA 2009
	National primary and secondary drinking water standards	No data	EPA 2003
	National recommended water quality criteria	No data	EPA 2006b
c. Food			
FDA	Bottled drinking water	No data	FDA 2007 21 CFR 165.110
	EAFUS[b]	No data	FDA 2008
d. Other			
ACGIH	Carcinogenicity classification	No data	
EPA	Carcinogenicity classification	No data	
	RfC	No data	
	RfD	No data	
	Chemical imports and exports regulations	Yes	EPA 2008a 40 CFR 707
	Master Testing List[c]	No data	EPA 2008c
	Significant new uses of chemical substances	Yes[d]	EPA 2008d 40 CFR 721

Table 8-1. Regulations, Advisories, And Guidelines Applicable to Perfluoroalkyls

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	No data	EPA 2008b 40 CFR 302.4
EPA	Superfund, emergency planning, and community right-to-know		
	Effective date of toxic chemical release reporting	No data	EPA 2008e 40 CFR 372.65
NTP	Chemicals nominated to the NTP for in-depth toxicological evaluation for carcinogenesis testing in fiscal years 1988–2003		NTP 2005
	Perfluorobutane sulfonic acid	Yes	
	Pefluorodecanoic acid	Yes	
	Perfluorohexane sulfonic acid	Yes	
	Perfluorooctane sulfonic acid	Yes	
	Perfluorooctanoic acid	Yes	
STATE			
Minnesota	Groundwater regulations		Minnesota Department of Health 2007
	Health risk limits[e]		
	Perfluorooctanoic acid	0.3 µg/L	
	Perfluorooctane sulfonic acid	0.3 µg/L	
	Toxicologic end point[f]		
	Perfluorooctanoic acid	Liver, hematologic system, developmental effects, and immune system	
	Perfluorooctane sulfonic acid	Liver and thyroid	
New Jersey	Drinking-water guidance value		New Jersey Department of Environmental Protection 2007
	Perfluorooctanoic acid	0.04 ppb	

Table 8-1. Regulations, Advisories, And Guidelines Applicable to Perfluoroalkyls

Agency	Description	Information	Reference
STATE *(cont.)*			
Washington	Persistent Bioaccumulative Toxins rule		Washington State Department of Ecology 2006
	Perfluorooctane sulfonic acid	Yes	

[a]AEGLs are intended to describe the risk to humans resulting from once-in-a-lifetime, or rare, exposure to airborne chemicals (EPA 2007a).
[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.
[c]OPPT uses a "Master Testing List" (MTL) since 1990 to establish its TSCA Existing Chemical Testing Program agenda. The MTL presents a consolidated listing of OPPT's Existing Chemical Testing Program priorities. The main purposes of the MTL are to (1) identify chemical testing needs of the Federal Government (including EPA) and relevant international organizations (e.g., OECD); (2) focus limited EPA resources on the highest priority chemical testing needs; (3) publicize the testing priorities for industrial chemicals; (4) obtain broad public input on OPPT's TSCA Chemical Testing Program and its priorities; and (5) encourage voluntary initiatives by the U.S. chemical industry to fill the priority data needs that are identified on the MTL (EPA 2008c).
[d]Under Section 40 CFR 721, manufacturers are required to follow the regulations for chemical substances with significant new uses: Chemical substance and significant new uses subject to reporting; industrial, commercial, and consumer activities; protection in the workplace; hazard communication program; disposal; releases to water; and recordkeeping (EPA 2008d).
[e]A Health Risk Limit is an exposure value for a concentration of a groundwater contaminant, expressed in µg/L, that can be safely consumed daily for a lifetime.
[f]The Toxicologic End point indicates the organ or organ system that is most sensitive to the contaminant.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OECD = Organisation for Economic Co-operation and Development; OPPT = Office of Pollution Prevention and Toxics; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TWA = time-weighted average; 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 Environmental Medicine, 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 Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

For reasons discussed in Section 2.3, MRLs were not derived for perfluoroalkyls.

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 toxicologic, 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 judgement 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

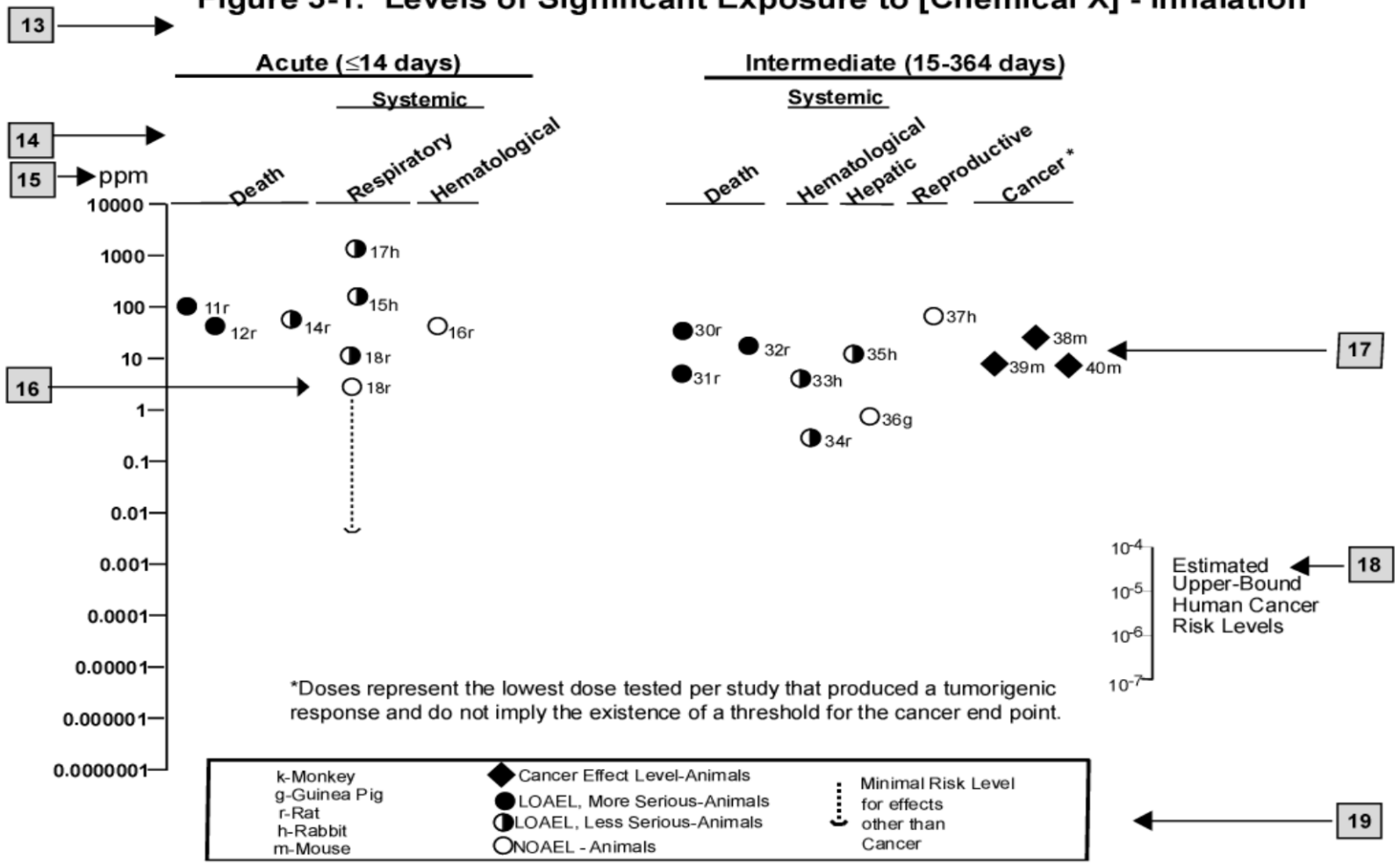
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	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

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APPENDIX D. INDEX