TOXICOLOGICAL PROFILE FOR DEET (N,N-DIETHYL-*META*-TOLUAMIDE)

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

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DISCLAIMER

Use of trade names is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services.

UPDATE STATEMENT

A Toxicological Profile for DEET, Draft for Public Comment was released in September 2015. This edition supersedes any previously released draft or final profile.

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

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FOREWORD

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

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

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

Each profile includes the following:

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

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

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staffs of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and 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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*Legislative Background

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

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 may 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 (e.g., death, systemic, immunologic, reproductive), by route of exposure, and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

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

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

Other Sections of Interest:

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

ATSDR Information Center

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

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

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 (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

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 • Web Page: https://www.cdc.gov/nceh/.

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

Clinical Resources (Publicly Available Information)

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 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard,

Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

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

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PEER REVIEW

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

1. Dr. Mohamed B. Abou-Donia, Professor of Pharmacology and Cancer Biology and of Neurobiology, Duke University Medical Center, Durham, North Carolina;

2. Dr. Thomas G. Osimitz, Diplomat, American Board of Toxicology, European Registered Toxicologist, Science Strategies, LLC, Charlottesville, Virginia; and

3. Dr. Andrey I. Nikiforov, President, Principal, Charlottesville, Virginia.

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

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

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

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1. PUBLIC HEALTH STATEMENT FOR DEET

This Public Health Statement summarizes the Agency for Toxic Substances and Disease Registry's (ATSDR) findings on DEET, including chemical characteristics, exposure risks, possible health effects from exposure, and ways to limit exposure.

The U.S. Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. U.S. EPA has found DEET in at least 2 of the 1,832 current or former NPL sites.

The total number of NPL sites evaluated for DEET is not known. But the possibility remains that as more sites are evaluated, the sites at which DEET is found may increase. This information is important because these future sites may be sources of exposure, and exposure to DEET may be harmful.

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

WHAT IS DEET?

DEET is the chemical N,N-diethyl-*meta*-toluamide. Technical DEET is a nearly colorless liquid with a faint characteristic odor. DEET is the active ingredient in some common repellents widely used to repel biting pests such as mosquitos and ticks. A significant benefit of DEET is protection against mosquito or tick borne illnesses. Examples of tick-borne illnesses include Lyme disease and Rocky Mountain Spotted Fever. Mosquito-borne illnesses may include those caused by West Nile Virus and Zika Virus.

DEET is the common name for an insect and acarid repellent used to repel, but not kill, biting insects, mites, and ticks. DEET formulations are typically used as sprays or mists, lotions and wipes. DEET formulations can be applied directly onto human skin or onto clothing. DEET has been formulated with sunscreen lotions for direct application to skin. DEET has also been infused into various products such as wrist bands, intended to be worn by the consumer while outdoors.

DEET has been previously and is currently sold as an ingredient in several common repellent products, including Skeeter Skat®, as well as various Off!®, Repel®, and Old Time Woodsman® brand products and various Cutter brand products, such as Cutter All Family®, Cutter Dry®, and Cutter Backwoods®.

WHAT HAPPENS TO DEET WHEN IT ENTERS THE ENVIRONMENT?

DEET can enter the air during spray applications. Approximately 9.6% of the DEET applied to human skin evaporates in 1 hour. DEET has occasionally been detected in air samples at low concentrations. If released to the atmosphere, DEET will exist solely as a vapor. Half of the amount of DEET in air will disappear in approximately 5 hours. DEET is not expected to persist or be transported long distances in the environment.

DEET can be released from common showering and laundering practices and eventually may enter waste water treatment facilities. DEET can also enter surface water from recreational activities such as swimming. DEET has been detected at low levels in streams, surface water, and groundwater systems, and sewage treatment plant effluents throughout the United States. If released to water, bioaccumulation of DEET in aquatic organisms is not expected. Volatilization from water surfaces is not expected. DEET may be biodegraded in water or undergo direct photolysis in sunlit waters; therefore, persistence in water systems is not expected.

Although DEET is registered by the EPA Office of Pesticides, it only acts as a repellent, not a pesticide. Therefore, applications to crops or agricultural products do not typically occur. DEET may enter soils as the result of overspray, disposal in landfills, or irrigation of soils with reclaimed water containing DEET. No data were located on the environmental concentrations of DEET in sediment or soil. If released to soils, volatilization is not expected and DEET will have moderate mobility. Data suggest that DEET would be biodegradable in soils under aerobic conditions and would biodegrade slowly under anaerobic conditions.

HOW MIGHT I BE EXPOSED TO DEET?

The most important route of exposure to the general population is through dermal contact from intentional application to human skin and clothing of consumer products containing DEET. It might also get into your eyes if sprayed improperly. DEET can be released into the air, water, and soil at places where it is produced or used. DEET is most often released into surface waters following its incomplete removal at waste water treatment facilities, and to a lesser extent released into the air when applying DEET-

containing repellents. You will be exposed to DEET if you use water containing DEET for drinking or bathing. However, the levels of DEET detected in water and air are generally low.

HOW CAN DEET ENTER AND LEAVE MY BODY?

Scientists have not yet studied whether DEET in the air can be absorbed into your lungs after inhalation. It is absorbed through the skin and digestive tract, so it is likely that DEET can also be absorbed through the lungs and into the blood. DEET in the lungs can be coughed up and swallowed, if it is not absorbed first. DEET in water or food can be absorbed from the digestive tract; studies in animals suggest that most of the ingested DEET will be absorbed. Small quantities of DEET (less than 10–20% of the applied DEET) can be absorbed through your skin. In addition, if your skin contacts water with DEET in it, you may absorb some DEET through your skin.

Although rarely found in soil, if you accidentally eat soil contaminated with DEET, some of the DEET will enter your body through the digestive tract. In addition, if you touch soil contaminated with DEET, some of the DEET may enter your body through the skin.

In your body, most of the DEET is broken down into other substances (metabolites) in the liver, and both DEET and the metabolites distribute widely throughout your body. Studies have detected DEET or its metabolites in many organs of exposed animals, including the brain, liver, kidneys, lungs, spleen, fat, tears, and inside the nose. DEET does not appear to accumulate in any particular organ in the body.

Most of the DEET that is absorbed into your body is excreted quickly through your urine either unchanged or as a metabolite. A small proportion of the DEET that is taken in is excreted in the feces.

HOW CAN DEET AFFECT MY HEALTH?

The health effects of DEET depend on several factors including how much of this substance you are exposed, the route and length of that exposure, and how often you are exposed. Environmental monitoring data suggest that any DEET levels that the public might encounter in the environment are much lower than levels causing effects in animal studies, and at much lower levels than people are exposed to when using insect or acarid repellents. Considering the intentional extensive consumer use of products containing DEET on the skin, the risk of health effects due to exposure to DEET appears to be quite low.

There have been sporadic reports over the last several decades of an association between excessive use of repellents containing DEET and adverse neurological effects including seizures, uncoordinated movements, agitation, aggressive behavior, low blood pressure, and skin irritation.

In a study of more than 9,000 exposures to DEET-containing repellents reported to Poison Control Centers between 1985 and 1989, most exposures (88%) did not produce symptoms that required treatment in a health care facility. In a similar study of more than 20,764 exposures to DEET-containing repellents reported to Poison Control Centers between 1993 and 1997, nearly 89% of the occurrences were managed at the exposure site; 11% of the cases were evaluated in a health care facility (80% of these subjects were treated and released). About half of the subjects were reported or judged to suffer no ill effects due to DEET exposure. A similar percentage was reported or judged to have a minor effect that were not bothersome, did not last long, and did not require treatment. Some of these included drowsiness, skin irritation, or temporary cough. Four percent experienced a moderate or greater effect or a potentially toxic exposure such as corneal abrasion, high fever, disorientation, or isolated brief seizures, and required treatment. In both reports, nearly 50% of cases were a result of DEET ingestion.

Workers at a national park who used insect repellents or lotions containing DEET repeatedly during the summer season complained more often of chest pain or wheezing, muscle cramping, skin rashes and blisters, dizziness, disorientation, and difficulty concentrating than workers who used the products less often or did not use them at all. Because exposure was inferred only from survey responses, these findings should be interpreted with caution.

A study of workers in Sweden found that those who used insect repellents for 115 days or longer had an increased risk of developing testicular cancer. However, because of deficiencies in the study, the results were not conclusive.

Long-term studies in which dogs, rats, and mice were given DEET orally or in which liquid DEET was applied to the skin of mice and rabbits did not find an increase in tumors in the animals.

The U.S. Department of Health and Human Services (DHHS) has not classified DEET as to its carcinogenicity. The U.S. EPA's Office of Pesticide Programs (OPP) has classified DEET as a Group D chemical, not classifiable as a human carcinogen. The International Agency for Research on Cancer (IARC) has not classified DEET as to its carcinogenicity.

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

HOW CAN DEET AFFECT CHILDREN?

This section discusses potential health effects of DEET exposure in humans from when they're first conceived to 18 years of age.

Some children exposed to insect repellents or lotions containing DEET have experienced the same type of neurological effects observed in adults (i.e., agitation, hypertonia, seizures, ataxia, restlessness, and uncontrolled limb movements). In the specific case of seizures, it should be noted that because a relatively high percentage (23–29%) of children are exposed to DEET in the United States and because seizure disorders occur in approximately 3–5% of children from any cause, it might be possible, just by chance alone, to erroneously find an association.

A study of more than 9,000 human exposures involving insect repellents containing DEET reported to Poison Control Centers did not find evidence that children are more likely to develop adverse health effects than adults if exposed to DEET. As mentioned earlier, considering the extensive use of products containing DEET and limited reports of significant health effects, the risk of serious health effects from exposure to DEET may be quite low.

Two studies of women who used insect repellents containing DEET during pregnancy did not find abnormalities in the babies at birth that were attributable to exposure to DEET.

Studies in rats and rabbits administered DEET in their food during pregnancy did not find birth defects or other abnormalities in the offspring.

HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO DEET?

If your doctor finds that you have been exposed to significant amounts of DEET, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate. You may also contact the state or local health department with health concerns.

It is possible to transfer DEET from your hands onto food. Encourage good hygiene practices (e.g., hand-washing) to minimize this possible route of exposure and be careful not to overspray and contaminate foods, utensils, etc. when applying DEET-containing products from aerosol dispensers. The American Association of Pediatrics (AAP) recommends that products containing DEET should not be applied to

young children's hands or around the mouth, or to infants below the age of 2 months. The Centers for Disease Control and Prevention (CDC) supports these restrictions. Children under 10 years of age should not apply DEET by themselves. Do not re-use DEET product containers, especially for storing food and water.

Many consumer repellents contain DEET as an active ingredient. Check the label of these products and follow the instructions listed below regarding the proper use, disposal, and application of DEET. In general, do not apply DEET near your mouth or eyes and do not apply over cuts or irritated skin. Do not apply it under clothing, and wash clothing that has been sprayed with DEET before wearing it again. When applying DEET to the facial area, first apply to your hands, then rub the product onto your face, and then wash your hands. Avoid direct spraying to the face as this could cause the product to get into your eyes, mouth, or lungs. To avoid overexposure, be sure to remove DEET containing products from your body before going to bed (shower or use a wash cloth to remove from skin).

The U.S. EPA requires the following statements on all DEET product labels:

1. Read and follow all directions and precautions on this product label.
2. Do not apply over cuts, wounds, or irritated skin.
3. Do not apply near eyes and mouth. Apply sparingly around ears.
4. Do not apply to children's hands.
5. Do not allow children to handle this product.
6. When using on children, apply to your own hands and then put it on the child.
7. Use just enough repellent to cover exposed skin and/or clothing.
8. Do not use under clothing.
9. Avoid over-application of this product.
10. After returning indoors, wash treated skin with soap and water.
11. Wash treated clothing before wearing it again.
12. Use of this product may cause skin reactions in rare cases.
13. If you suspect a reaction to this product, discontinue use, wash treated skin, and call your local poison control center.
14. If you go to a doctor, take this product with you.
15. ACTIVE INGREDIENTS: DEET…….XX.XX%
16. A toll-free telephone number for consumers to call for additional product information and to report incidents.

The EPA does not require an expiration date on the label of DEET products manufactured in the United States.

Animal research indicates that drinking less alcohol might reduce how much DEET passes into the body through the skin.

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

DEET and its breakdown products (metabolites) can be measured in blood and urine. However, the detection of DEET or its metabolites cannot predict whether or not health effects might develop from that exposure. Because DEET and its metabolites leave the body fairly rapidly, such tests need to be conducted within hours after exposure.

For more information on the different substances formed by DEET breakdown and on tests to detect these substances in the body, see Chapters 3 and 7.

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

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

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

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

In order to protect against vector-borne illnesses such as Lyme Disease or those caused, for example, by West Nile Virus or Zika Virus, the Centers for Disease Control and Prevention (CDC), the EPA, and the World Health Organization (WHO) all recommend and/or endorse the use of DEET-containing products.

CDC specifically recommends using products with at least 20% DEET on exposed skin to reduce biting by ticks or mosquitos that may spread disease. The concentration of DEET in a product can be selected to meet the type and duration of protection. The manufacturer's directions on the label should be followed for applying and reapplying the product; excessive reapplication is not useful and should be avoided.

The EPA has not recommended drinking water guidelines for DEET. OSHA has not set a legal limit for DEET in air. NIOSH has not set a recommended limit for DEET in air.

WHERE CAN I GET MORE INFORMATION?

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

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

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

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO DEET IN THE UNITED STATES

Technical DEET is a nearly colorless liquid with a faint characteristic odor. It is mainly used as a commercial insect or acarid repellent. In 1990, approximately 4 million pounds of the active ingredient DEET was used in commercial products and the average annual domestic use of DEET has been estimated as ranging from 5 to 7 million pounds based on product sales. Aquatic systems appear to be the main environmental sink for this chemical. DEET has been detected in sewage treatment plant effluents, streams, surface water, and groundwater systems. The largest contribution for DEET in water systems comes from sewage effluents containing this chemical. Concentrations of DEET in effluents result from washing skin and clothing where commercial products containing DEET have been applied. Albeit a minor contribution, human absorption of DEET after application and subsequent excretion of DEET, and its metabolites, also contributes to effluent concentrations. DEET-contaminated effluents may also enter surface water and groundwater systems after passing through waste water treatment plants (WWTPs) or domestic septic systems. Additionally, recreational activities such as swimming, via swimmers with DEET products on their skin or clothing washing off, can contribute to DEET in water systems.

Studies have shown that DEET is not expected to bioconcentrate in aquatic systems. DEET is expected to be hydrolytically stable under environmental conditions. Little degradation is expected under anaerobic conditions; however, DEET is considered readily biodegradable in aerobic conditions and should not persist in the environment.

See Chapter 6 for more detailed information regarding concentrations of DEET in environmental media and its environmental fate.

The general population is exposed to DEET as a result of its use as an insect and acarid repellent intended for direct human application. Insect repellent products containing DEET range in concentration from 4 to 100%. As of March 2017, there were 27 companies in the United States that manufactured approximately 119 consumer products containing DEET. According to the U.S. EPA, as of February 2014, there were 123 active registrations for DEET, including co-formulations with other chemicals, formulations with sunscreen, and one registration for use on horses. Dermal application of repellents is the major route of exposure. Inhalation may be a route of exposure when aerosol formulations are used, albeit a minor route of exposure. Children are expected to be exposed to DEET by the same routes that affect adults. No data

were located regarding DEET in breast milk; therefore, an adequate determination of the importance of this route of child exposure has not been made. DEET absorbed through the skin, however, can transfer through the placenta and expose the fetus.

Data from the National Health and Nutrition Examination Survey (NHANES) show that levels of DEET in 74% of the study population were below the detection limits of 0.449 µg/L (1999–2000) and 0.1 µg/L (2001–2002) in the urine of 4,512 members of the U.S. general population sampled during these two surveys. The respective 90th and 95th percentile values were 0.11–0.13 and 0.13–0.22 µg/L. The highest levels were found in people 12–19 years old and in non-Hispanic whites. Levels of DEET for the survey years 2007–2010 were also below the detection limit (0.089 µg/L). It should be noted, that human monitoring data measuring the parent compound DEET does not directly correlate to initial exposure concentrations due to the fact that the majority of absorbed DEET is metabolized. The main metabolites of DEET in humans are 3-(diethylcarbamoyl) benzoic acid (DCBA) and N,N-diethyl-3-(hydroxymethyl) benzamide (DHMB). Data from NHANES for the years 2007–2010 show levels of both DCBA and DHMB in urine higher than those reported for the parent compound, DEET, indicating the relevance of their evaluation when assessing exposures to DEET. Details of the results can be found in Section 6.5.

2.2 SUMMARY OF HEALTH EFFECTS

Exposure of humans to DEET has been associated with a variety of health effects including neurological, respiratory, cardiovascular, gastrointestinal, dermal, and ocular. It should be noted, however, that considering the many millions of applications of DEET per year in the United States, there have been limited reports of serious health effects following DEET applications. A few deaths in humans have been associated with oral and dermal exposure to DEET, sometimes in combination with other drugs or chemicals. This also needs to be considered in studies reporting effects other than death since commercial DEET products usually contain additional ingredients. The most serious effects reported following oral and dermal exposure to products containing DEET have been neurological effects. Neurological signs and symptoms reported in children and adults include seizures, ataxia, restlessness, uncontrolled limb movements, agitation, aggressive behavior, combativeness, impaired cognitive functioning, and opisthotonos (a postural abnormality characterized by hyperextension of the back and neck muscles, with retraction of the head, and arching forward of the trunk). Because of the wide spectrum of neurological effects reported, some researchers have noted that it is unlikely that they were due to exposure to a single agent. In a study of 242 cases in the DEET Registry, a collection of self-reported cases spanning 6 years of DEET use in North America, there were 59 seizure cases. At the

1-year follow-up of 35 of these cases, medical tests showed evidence of an underlying neurological disorder in five of these cases, questioning the role of DEET as the sole cause of seizures in those cases. The issue of seizures in children following exposure to DEET needs to be evaluated with caution. In the specific case of seizures, it should be noted that because a relatively high percentage (23–29%) of children are exposed to DEET in the United States and because seizure disorders occur in approximately 3–5% of children from any cause, it might be possible, just by chance alone, to erroneously find an association. There is no reliable information regarding doses or exposure concentrations associated with effects. A survey of 143 employees of the Everglades National Park, Florida who used DEET regularly in their work, showed that more highly exposed workers (estimated >4.25 g DEET/week or about 8.7 mg DEET/kg/day assuming 70 kg of body weight) had a higher prevalence of dizziness, disorientation, difficulty concentrating, and skin rashes than non-users of DEET. Because exposure was inferred from only survey responses, a notable weakness, the findings from this report should be interpreted with caution. In a study of 9,086 exposures involving insect repellents containing DEET reported to Poison Control Centers from 1985 to 1989, it appeared that the concentration of DEET in the product used was not related to the severity of the symptoms following exposure. Those patients experiencing a major effect had used products containing 11–50% DEET. The same observations were made in a later study of 20,764 exposures involving insect repellents containing DEET that were reported to poison control centers from 1993 to 1997.

Exposure to DEET has produced skin irritation, desquamation of the skin, dermatitis, and erythema in humans. Cases of non-immunological and immunological contact urticaria have also been reported.

Neurological effects also have been reported in animals exposed to DEET primarily by the oral route or by application of DEET onto the skin. Results from high dose-studies in animals support the findings in humans exposed to high amounts of DEET. Tremors and seizures occurred at the highest oral doses tested: 400 mg DEET/kg/day in dogs and ≥2,000 mg DEET/kg in rats. In rats, but not in dogs, the higher doses also caused histological alterations in the brain. Tremors were also reported in rats exposed by inhalation to a high concentration of 4,100 mg/m^3 DEET aerosol. One study reported neurobehavioral alterations in rats acutely dosed by oral gavage with lower doses of DEET (500 mg/kg) but others have not. Dermal application of doses of 4 mg DEET/kg/day as 10 mg/mL DEET in 70% alcohol to a 2.5-cm^2 area for 60 days affected some sensory parameters in rats and doses ≥40 mg DEET/kg/day (which the authors considered equivalent to typical exposures of military personnel during wartime) induced histological alterations in various brain areas and affected cholinergic neurotransmitter systems. It should be mentioned, however, that some scientists have raised concerns about possible misinterpretation of the

histopathological findings because of artifacts resulting from inadequate handling and fixation of the brain tissue. The neurobehavioral alterations reported in some of these studies, however, were not observed in a more recent similar study in rats that also applied doses of 40 mg DEET/kg/day, as 100 mg/mL DEET in 70% alcohol, to a larger 4-cm^2 exposure area and shorter 30-day exposure time. The apparent inconsistent results between some studies need to be resolved considering the differences in route of exposure, exposure area and exposure duration.

DEET exhibited relatively little systemic toxicity in repeated inhalation, oral and dermal exposure studies in animals. Daily intermittent exposure of rats to up to 1,511 mg/m^3 aerosolized DEET (the highest concentration tested) for 13 weeks did not cause morphological alterations in organs and tissues or produce significant alterations in hematology or clinical chemistry tests. In general, alterations were seen only at the highest oral dose tested (≥400 mg DEET/kg/day). Oral studies reported reductions in body weight gain in rats, mice, hamsters, rabbits, and dogs. Oral exposure to DEET also caused alterations in serum electrolytes in hamsters, dogs, and rabbits. Other systemic effects induced by repeated oral exposure to DEET include slightly decreased hemoglobin and hematocrit, increased platelets, increased serum alkaline phosphatase, and decreased cholesterol in dogs, fatty changes in hepatocytes in rabbits, and increased cholesterol in rats. In the absence of histological alterations in organs and tissues, the toxicological significance of these findings is unclear. Following repeated dermal exposure, DEET was not a skin sensitizer in guinea pigs or rabbits, but induced erythema and acanthosis/hyperkeratosis in rats, skin desquamation, hyperkeratosis and acanthosis in micropigs and rats, and skin irritation in rabbits following repeated dermal exposure.

There are no studies of reproductive effects in humans exposed to DEET.

DEET did not affect fertility in male or female rats in a 2-generation continuous feeding study. DEET also did not induce gross or microscopic alterations in the reproductive organs of male rabbits, or male or female rats, mice, or dogs in intermediate- or chronic-duration oral studies, or in male rats in an intermediate-duration dermal study. DEET at ≥624 mg/kg/day, however, increased the incidence of tubular degeneration in the testes of hamsters in a 90-day study.

Exposure to DEET was not associated with developmental effects in two epidemiological studies. In one of them, pregnant women applied DEET onto themselves in the second and third trimester of pregnancy. The results did not show significant differences between exposed and control neonates regarding head and arm circumference or length or in a series of neurological tests in the neonates. The other

epidemiological study did not find significant associations between the presence of DEET in maternal blood or cord serum and birth weight, head circumference, abdominal circumference, or birth length in neonates. DEET did not induce embryotoxicity or teratogenicity in rats or rabbits at doses that caused a significant reduction in maternal body weight gain during gestation. Sacrifices were conducted the last day of gestation in these studies. In the 2-generation continuous feeding study in rats, DEET induced significant reductions in weight in both male and female F1 and F2 pups during lactation.

Limited information exists regarding exposure to DEET and cancer and occupational exposure. A case-control study of testicular cancer and occupational exposure in Sweden reported a significant association between exposure to insect repellents for more than 115 days and testicular cancer. No evidence, however, was provided that DEET was the causative agent. In addition, exposure was assessed by self-recollection, which is known to be unreliable. DEET was not carcinogenic following long-term oral assays in rats, mice, or dogs or following long-term skin application to mice or rabbits. The EPA's OPP classified DEET as a Group D substance, not classificable as a human carcinogen, based on no evidence of mutagenicity in multiple tests, or of carcinogenicity in long-term oral ingestion studies in adult rats or mice. DHHS and IARC have not classified DEET as to its carcinogenicity.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been established for DEET. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

No inhalation MRLs were derived for DEET due to insufficient data. Qualitative information regarding effects in humans following inhalation exposure to DEET was found in a study of 20,764 exposures involving insect repellents containing DEET that were reported to poison control centers from 1993 to 1997 (Bell et al. 2002). In 520 of these cases, inhalation was identified as the leading exposure route. Respiratory (coughing/choking, dyspnea, bronchospasm, respiratory depression, pneumonitis), cardiovascular (tachycardia, hypertension, hypotension), gastrointestinal (oral irritation, vomiting, nausea), and neurological (dizziness/vertigo, headache, drowsiness/lethargy) signs and symptoms were most commonly reported. About half of the subjects were reported or judged to suffer no ill effects due to DEET exposure. A similar percentage of subjects were reported or judged to have a minor effect. Four percent experienced a moderate or greater effect or a potentially toxic exposure. Similar qualitative data regarding 9,086 human exposures were published earlier by Veltri et al. (1994). In 2012, there were 4,075 single cases of exposure to insect repellents with DEET reported to the American Association of Poison Control Centers (AAPCC 2013). Two deaths were reported in this series of cases. Most of the other cases were in children ≤5 years of age (n=2,316, 57%) or adults ≥20 years of age (n=829, 20%), and the severity of health effects were primarily considered to be none (n=576, 14%) to minor (n=1,176, 29%). No information was provided regarding the remaining 57%. This qualitative information cannot be used for MRL derivation.

The animal data are restricted to only a few studies, some with significant limitations. Acute-duration inhalation studies have been conducted in rats and mice. Head-only exposure of rats to an aerosol of 85% DEET for 2–6 hours induced minor changes in the lungs and trachea, but no further details were provided (Ambrose 1959). The actual exposure concentration that animals received was not provided in this study and there was no indication that a control group was used. An additional acute-duration study in rats reported that 4-hour exposures conducted at concentrations of ≥2,300 mg/m^3 DEET aerosol decreased performance in behavioral tests conducted within 50 minutes of termination of exposure (Army 1979). Gross necropsy following a 14-day observation period did not show treatment-related lesions. The limited scope of the study and the lack of histological examination of tissues, particularly the nervous system, made this study inadequate for MRL derivation. Furthermore, the lowest concentration tested was considerably higher than a 4-hour LC_{50} of 1,369 mg/m^3 reported in mice (Deb et al. 2010). In a study

in mice, head-only exposure to a target concentration of 135 mg/m^3 DEET aerosol for 4 hours increased respiratory frequency, but this effect was not observed at lower or higher exposure concentrations (Deb et al. 2010). Other respiratory parameters that were measured were not affected. Because the actual exposure concentrations were not specified and, according to the investigators, were 50–60% of the target concentrations, the results of this study are unreliable.

Only a few intermediate-duration inhalation studies were available for review. In an early study by Ambrose (1959), exposure of rats to air saturated with vaporized DEET (approximately 71 mg/m^3) 8 hour/day, 5 days/week for 7 weeks resulted in unspecified microscopic changes in the lungs and trachea. There was no indication that a control group was used in the study. Army (1980a) conducted 13-week intermittent exposure studies in Sprague-Dawley rats and Beagle dogs. In both studies, the animals were exposed whole-body to 252, 752, or 1,511 mg/m^3 aerosolized DEET. End points examined in rats included body weight, gross and microscopic appearance of all major tissues and organs, hematology and clinical chemistry parameters, and oxygen consumption. No significant alterations were reported other than the transient appearance of a red exudate around the eyes and nose of rats exposed to 1,511 mg DEET/m^3. The study in dogs tested only two animals per sex per exposure group and only evaluated hematology and clinical chemistry parameters as well as pulmonary function (compliance and resistance). No significant effects were reported. This information was inadequate for MRL derivation.

No chronic-duration inhalation studies in animals were located.

Oral MRLs

An acute-duration oral MRL for DEET was not derived. No reliable estimates of doses of DEET were available in the numerous cases of accidental or intentional ingestion of insect repellents containing DEET summarized in Chapter 3. The available acute-duration database in animals is limited. It should be noted that in all the acute-duration studies available for review, DEET was administered by gavage. Acute-duration studies provided information regarding lethal doses (Ambrose 1959; Carpenter et al. 1974; EPA 1998c; McCain et al. 1997; Verschoyle et al. 1992), developmental (Schoenig et al. 1994), and neurological (Schoenig et al. 1993, 1994; Verschoyle et al. 1992) effects in rats. In the developmental studies, the highest doses tested (750 mg/kg/day in rats and 325 mg/kg/day in rabbits) induced maternal toxicity in the form of significantly reduced body weight gain during the entire dosing period in rats (gestation days [GDs] 6–15) and during GDs 6–9 in rabbits and also induced adverse neurological signs in the rats (hypoactivity, ataxia, decreased muscle tone), although no incidence data

were provided (Schoenig et al. 1994). These signs were opposite to what has been reported in humans who ingested high amounts of DEET (i.e., hyperactivity, tremors, seizures, restlessness, uncontrolled limb movements, agitation, and aggressive behavior) (Petrucci and Sardini 2000; Tenenbein 1987; Zadikoff 1979). The reasons for this are uncertain. No significant fetotoxicity or teratogenicity was observed in either species in this study, other than a 6% reduction in fetal weight in the high-dose rats that may have been related in part to the 35% reduction in maternal weight gain during the treatment period. A neurological study in rats reported that a single dose of 500 mg DEET/kg (the highest dose tested) delayed the response to a thermal stimulus and decreased vertical activity 1 hour after treatment but not at 24 hours or 14 days post-treatment (Schoenig et al. 1993). These effects were characterized in the study as slight and questionable by the investigators (Schoenig et al. 1993). Another neurological study reported that single doses of ≥1,000 mg DEET/kg (approaching the lethal dose) induced clinical signs and histological alterations in the brain, but the exact dose level at which effects started to appear was not totally clear (Verschoyle et al. 1992). Although it would appear that studies such as the developmental study in rats and rabbits by Schoenig et al. (1994) or the neurotoxicity study by Schoenig et al. (1993) described above could be considered for MRL derivation, additional information suggests that it may not be appropriate to do so. Regarding the former, the Reregistration Eligibility Decision (RED) for DEET (EPA1998b) indicates that in an unpublished dose-range developmental toxicity study in rabbits administered DEET by gavage in doses ranging from 62.5 to 1,000 mg/kg/day on GDs 6–18, deaths occurred in groups dosed with ≥500 mg DEET/kg/day. Necropsy of the animals that died showed sloughing and/or ulceration of the stomach lining and suggested that the corrosive effects of DEET to the gastric lining may have been linked to the death of the rabbits. This effect was consistent with the report of significant reduction in maternal weight gain and food consumption during the dosing period in the developmental study in rabbits (Schoenig et al. 1994), as gastric irritation induced by DEET may have caused the animals to stop eating. This is also consistent with the results of a 15-day study in which rabbits dosed by gavage with 528 mg DEET/kg/day lost approximately 1/5 of their body weight during the study; no data regarding food consumption were provided in this study (Army 1980b). Also, in the 52-week study in dogs (Schoenig et al. 1999), tremors were observed in some dogs before administration of DEET in a capsule, and because of lack of temporal relationship, were not considered to be treatment-related. It is possible, however, that the dogs were able to associate feeding of a capsule with gastric discomfort, which may have caused the tremors. In the developmental study in rats (Schoenig et al. 1994), high-dose animals showed a significant reduction in weight gain and food consumption during dosing, although not as marked as the rabbits. In that study, two rats died on day 2 of treatment, but apparently no necropsy was conducted, so it is unknown whether gastric lesions occurred. Long-term dietary studies did not report gastrointestinal alterations in rats or mice administered doses of DEET

comparable to those given in gavage studies (400–860 mg/kg/day to rats, 1,000 mg/kg/day to mice) (Ambrose 1959; Schoenig et al. 1999) and no other significant toxic effects were reported. Taken together, this information suggests that DEET given as a bolus dose may induce stomach irritation, which in turn may cause the animals to stop eating and, therefore, lose weight or gain less weight than untreated animals. This effect also suggests that decreases in body weight observed in animals following gavage administration of DEET may be secondary to gastric irritation and reduced food consumption and may not be appropriate as a basis for MRL derivation. Additionally, exposure to DEET by people living near hazardous waste sites would likely be through drinking water rather than by ingestion of a DEET bolus, as occurs with gavage dosing.

Schoenig et al. (1993) reported that rats treated with a single gavage dose of 500 mg DEET/kg showed delayed response to a thermal stimulus and decrease vertical activity and vertical time when tested 1 hour post-dosing. The toxicological significance of these alterations is unknown. Furthermore, the investigators noted that: *"The effects of the high-dose on the thermal response was weak inasmuch as the statistically significant effect was found only in an analysis that included both males and females in a factorial ANOVA, but fell short of significance even for the most affected sex, the females ($p<0.06$) when the two sexes were analyzed separately."* Since only vertical activity and vertical time were affected by treatment with DEET out of multiple activity parameters measured (horizontal activity, vertical activity, total distance travel, movement time, rest time, number of movements, vertical time, number of vertical movements, stereotype time, number of stereotypic movements, clockwise revolutions, and counterclockwise revolutions), confidence in an MRL based on this endpoint would be minimal at best. In conclusion, the available acute-duration oral database does not support derivation of an acute-duration oral MRL for DEET.

- An MRL of 1.0 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to DEET.

No relevant human data were located. Intermediate-duration oral studies provide information regarding systemic, neurological, reproductive, and developmental effects in various animal species, but failed to identify a sensitive target for DEET toxicity. The lowest lowest-observed-adverse-effect level (LOAEL) in any study was 25 mg DEET/kg/day for hyaline nephropathy in F1 males in a 2-generation continuous feeding study (EPA 1989). This hydrocarbon-induced nephropathy has only been demonstrated in adult male rats and has been associated to a specific protein, $\alpha_{2\mu}$-globulin, which is produced under hormonal control by the liver (Alden 1986; Swenberg 1993). However, the $\alpha_{2\mu}$-globulin is unique to male rats and is not present in human kidneys. Hence, this particular nephropathy has no significance for humans and

would therefore be inappropriate to use for MRL derivation. Significantly higher LOAELs were reported in other intermediate-duration oral studies. A 200-day feeding study in rats reported a no-observed-adverse-effect level (NOAEL) of 863 mg DEET/kg/day (the highest dose tested) for organ histopathology and a LOAEL of 863 mg/kg/day for a statistically significant reduction (11.1%) in final body weight in female rats; food consumption was not significantly affected in this study and no clinical signs were observed (Ambrose 1959). A 90-day feeding study in hamsters reported NOAELs of 940 mg DEET/kg/day (which was also the highest dose tested) for organ histopathology (EPA 1990b). That study also identified a LOAEL of 624 mg DEET/kg/day for approximately 13% reduction in final body weight in male hamsters and for histopathology of the testes, and a LOAEL of 940 mg DEET/kg/day for a 10–16% increase in serum potassium in both male and female hamsters. Feeding dogs with DEET through a capsule for 52 weeks resulted in LOAELs of 400 mg DEET/kg/day for statistically significant hematology changes in females (reduced hemoglobin at 6 months, reduced hematocrit at 12 months, increased platelets at 6 and 12 months) and clinical chemistry changes in males (decreased serum alkaline phosphatase at 6 months, reduced cholesterol at 6 and 12 months, increased serum potassium at 6 months) (Schoenig et al. 1999); histological examination of tissues and organs was unremarkable. The toxicological significance of these effects is unknown, particularly since they were observed in one sex or the other. Terminal body weight was also reduced in dogs fed 400 mg DEET/kg/day. Although the extent cannot be read from a graph in the paper, the investigators noted that body weight decreased at several time points during the study for both males and females. Dogs in these groups consumed less food during the initial weeks of the study, which may have caused these animals growth to lag behind for the rest of the study. The authors stated that the absolute weight differences were generally small, within a few grams, and considered that 1,000 mg/kg/day was the only dose at which body weight and food consumption differences were toxicologically relevant. Treatment-related tremors and ataxia were also reported in one out of eight dogs several times after dosing with 400 mg DEET/kg/day. A 15-day gavage study in male rabbits reported LOAELs of 528 mg DEET/kg/day (highest dose tested) for a 14% decrease in serum calcium and 22% body weight loss (starting weight approximately 3,500 g, terminal weight approximately 2,750 g) (Army 1980b). No information was provided regarding food consumption. Histological examination of organs and tissues showed fatty changes in hepatocytes, but no significant alterations in other organs or tissues. The possible role that the considerable weight loss in high-dose rabbits in a short period of time could have had in the other effects reported was not discussed in the study. A study that conducted neurological examinations of F2 rats that were exposed to DEET during gestation, lactation, and then directly for approximately 9 months reported a transient increase in motor activity at 500 mg DEET/kg/day during the first 5–15 minutes of testing. No such increase was seen during the remaining 40 minutes of the test session (Schoenig et al. 1993). The investigators considered

this effect of minor or questionable significance based on the small magnitude of the changes and the transient nature (Schoenig et al. 1993). This study also reported a reduction of approximately 14% in final body weight in high-dose males, but no data on food consumption were provided. The lowest LOAEL in the database other than the 25 mg DEET/kg/day for hyaline nephropathy mentioned above, was 250 mg DEET/kg/day (highest dose tested) for significantly ($p<0.01$) reduced (11–13.3%) body weight in F1 and F2 male and female rat pups on lactation days 14 and 21 in the 2-generation continuous feeding study (EPA 1989). The NOAEL in the study was 100 mg DEET/kg/day. Because the effects showed dose-response relationships, occurred in both male and female pups, were observed in two generations, and may have resulted in important developmental delays, the 2-generation continuous feeding study in rats was selected for derivation of an intermediate-duration oral MRL for DEET. A detailed summary of the EPA study (1989) is presented in Appendix A.

Data for body weight in F1 and F2 male and female rat pups on day 21 of lactation in the EPA study (1989) could not be analyzed using the benchmark dose (BMD) approach for the following reason. While the total number of F1 and F2 pups alive on lactation day 21 is provided in the EPA study (1989), the sex distribution is not; however, the table that shows the body weight of the F1 and F2 pups presents the body weight broken down by sex. Without knowing the number of animals examined (n), the BMD approach could not be used. Therefore, the NOAEL/LOAEL approach was used for MRL derivation. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the NOAEL of 100 mg DEET/kg/day results in an intermediate-duration oral MRL of 1 mg/kg/day for DEET.

A chronic-duration oral MRL was not derived for DEET. No relevant human data were located. Well-conducted chronic dietary studies in rats and mice found virtually no DEET toxicity at the highest doses tested: 400 mg DEET/kg/day for 104 weeks in rats and 1,000 mg DEET/kg/day for 78 weeks in mice (Schoenig et al. 1999). This study conducted gross and microscopic examination of all major organs and tissues and hematological tests; in addition, ophthalmologic and clinical chemistry tests were conducted in rats. There were no treatment-related clinical signs during the studies. The only significant effects reported were an increase in serum cholesterol and reduced body weight in high-dose female rats and in high-dose mice. The reductions in body weight appeared to be associated with reduced food consumption, but no data were shown. The toxicological significance of the increase in serum cholesterol in female rats was unknown; in the same study, male dogs were dosed with 400 mg DEET/kg/day in a capsule for 52 weeks experienced a decrease in serum cholesterol. The available chronic-duration oral database does not support derivation of a chronic-duration oral MRL for DEET. Long-term exposure,

however, does not lead to more toxic effects than those reported for intermediate-duration exposure. The intermediate-duration oral MRL of 1 mg/kg/day for DEET, therefore, is considered protective for chronic-duration exposure.

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 DEET. 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.

Although normal use of products containing DEET involves predominantly dermal exposure, some inhalation and oral exposure may occur. It is also important to note that although most human exposures are to DEET and to other chemicals in the specific formulations, exposure to DEET is the common factor between the studies.

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 (e.g., death, systemic, immunological, neurological, reproductive, developmental, 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 and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

No reports of deaths in humans following inhalation exposure to DEET were located in the literature.

Without providing additional information, Army (1979) reported 4-hour LC_{50} values for aerosolized DEET in male and female Sprague-Dawley rats of 6,000 and 5,860 mg/m^3, respectively. Army (1980a) reported that the LC_{50} for aerosolized DEET in Sprague-Dawley rats was 5,950 mg/m^3. Rats were exposed whole-body for 4 hours and were observed for 14 days. No gross lesions were reported following the 14-day observation period. In male Swiss albino mice exposed head-only for 4 hours to target aerosol concentrations between 35 and 2,000 mg/m^3, the LC_{50} was 1,369 mg/m^3 (Deb et al. 2010). All mice exposed to 2,000 mg/m^3 (n=4) died after approximately 2 hours; there were no deaths at lower concentrations. The investigators noted that the actual exposure concentrations were 50–60% of the theoretical concentrations with large variations. Because they did not provide the actual exposure concentrations, the actual LC_{50} might be more than twice the reported value and is unreliable.

3.2.1.2 Systemic Effects

No studies were located regarding hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, or body weight effects in humans following inhalation exposure to DEET.

Respiratory Effects. In a study of 20,764 human exposures involving insect repellents containing DEET that were reported to poison control centers from 1993 to 1997, 520 were identified as being exposed predominantly by inhalation (Bell et al. 2002). Of these, 70 exhibited respiratory effects that included coughing/choking, dyspnea, bronchospasm, respiratory depression, and pneumonitis. Two of those (a male infant and a male adult) experienced a major respiratory outcome.

Head-only exposure of albino rats to an aerosol of 85% DEET for single periods of 2–6 hours did not induce gross alterations in the lungs or trachea, but did induce unspecified minor microscopic changes in both tissues (Ambrose 1959). There was no indication that a control group was used in this study and the actual exposure concentrations were not provided. Head-only exposure of male Swiss albino mice to target concentrations of DEET aerosol between 35 and 950 mg/m^3 for 4 hours resulted in an increase in respiratory frequency at 135 mg/m^3 but not at lower or higher exposure concentrations (Deb et al. 2010). Other respiratory parameters that were measured including tidal volume (Vt), air flow at 0.5 Vt, time of inspiration, and time of expiration were not affected. Because the actual exposure concentrations were not specified and were 50–60% of the target concentrations, according to the investigators, the findings from this study are unreliable.

In an intermediate-duration study, exposure of albino rats to air saturated with DEET vapor (approximately 71 mg/m^3; 1 mL of DEET was carried over 14,000 L of air) 8 hour/day, 5 days/week for 7 weeks resulted in unspecified microscopic changes in the lungs and trachea (Ambrose 1959). There was no indication that a control group was used in the study. Whole-body intermittent exposure of male and female Sprague-Dawley rats to up to 1,511 mg/m^3 (the highest concentration tested) aerosolized DEET for 13 weeks did not cause gross or microscopic alterations in the respiratory tract, including nares and nasal passages (Army 1980a). In the same study, there were no differences in measurements of pulmonary compliance and resistance between control and exposed Beagle dogs, but there were only two dogs per exposure group, so the study is limited.

Cardiovascular Effects. Only 12 of the 520 human cases of exposure to DEET by inhalation and 6 cases by multiple routes studied by Bell et al. (2002) exhibited cardiovascular effects; these included tachycardia, hypertension, and hypotension.

In the Army (1980a) 13-week, intermittent exposure study in Sprague-Dawley rats mentioned above, examination of the heart and aorta did not show exposure-related gross or microscopic alterations.

Gastrointestinal Effects. In the study of Bell et al. (2002) mentioned above of the 520 human cases reported to the AAPCC, those involving gastrointestinal effects included 130 exposed by inhalation and 225 by multiple routes. The gastrointestinal effects included oral irritation, vomiting, and nausea.

Exposure of Sprague-Dawley rats to up to 1,511 mg/m^3 aerosolized DEET for 13 weeks had no significant effect on the gross or microscopic morphology of the gastrointestinal tract (Army 1980a).

Hematological Effects. Hematology tests conducted in Sprague-Dawley rats and Beagle dogs exposed to up to 1,511 mg/m^3 DEET aerosol intermittently for 13 weeks were within normal limits (Army 1980a). Because only two dogs per sex per group were tested, the results in this species are unreliable. No further information was located.

Musculoskeletal Effects. Exposure of Sprague-Dawley rats to up to 1,511 mg/m^3 aerosolized DEET for 13 weeks had no significant effect on the gross or microscopic morphology of skeletal muscle, femur, or sternum (Army 1980a).

Hepatic Effects. Intermediate-duration exposure of Sprague-Dawley rats to 253, 752, or 1,511 mg/m^3 aerosolized DEET induced a significant trend for increased relative liver weight in females after 7 weeks of exposure and in males and females after 13 weeks of exposure (Army 1980a). In the absence of morphological alterations in the liver, the increase in relative liver weight probably represents an adaptive effect.

Renal Effects. Exposure of Sprague-Dawley rats to 253, 752, or 1,511 mg/m^3 aerosolized DEET for 13 weeks resulted in a significant trend for increased relative kidneys weight in males (Army 1980a). Microscopic examination of the kidneys from exposed rats, however, did not reveal exposure-related alterations.

Endocrine Effects. Exposure of Sprague-Dawley rats to up to 1,511 mg/m^3 aerosolized DEET for 13 weeks had no significant effect on the gross or microscopic morphology of the adrenal, pituitary, or thyroid glands (Army 1980a).

Dermal Effects. Exposure of Sprague-Dawley rats to up to 1,511 mg/m^3 DEET aerosol for 13 weeks had no significant effect on gross or microscopic appearance of the skin (Army 1980a).

Ocular Effects. Exposure of Sprague-Dawley rats to up to 1,511 mg/m^3 DEET aerosol for 13 weeks had no significant effect on gross or microscopic appearance of the eye (Army 1980a).

Body Weight Effects. Exposure of male and female Sprague-Dawley rats to concentrations of up to 4,100 mg/m^3 DEET aerosol for 4 hours did not significantly affect body weight during a 14-day observation period (Army 1979). Head-only exposure of male Swiss albino mice to target concentrations of up to 950 mg/m^3 for 4 hours did not significantly affect body weight over a 14-day observation period (Deb et al. 2010). Exposure to Sprague-Dawley rats to up to 1,511 mg/m^3 DEET aerosol for 13 weeks had no significant effect on body weight (Army 1980a). No further relevant information was located.

Metabolic Effects. Values for serum electrolytes and glucose were within normal ranges in male and female Sprague-Dawley rats following intermittent exposure to up to 1,511 mg/m^3 aerosolized DEET for 13 weeks (Army 1980a).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans following inhalation exposure to DEET.

The only information in animals is that exposure of Sprague-Dawley rats to up to 1,511 mg/m^3 aerosolized DEET for 13 weeks had no significant effect on the gross or microscopic morphology of the spleen or thymus (Army 1980a).

The NOAEL values for immunological and lymphoreticular effects from the Army (1980a) study is presented in Table 3-1 and plotted in Figure 3-1.

Table 3-1 Levels of Significant Exposure to DEET - 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 (Sprague-Dawley)	4 hr				5950 (LC50)	Army 1980a	
INTERMEDIATE EXPOSURE								
Systemic								
2	Rat (albino)	7 wk d/wk 8 hr/d	Resp		71 (unspecified alterations in lungs and trachea)		Ambrose 1959	
3	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d	Resp	1511			Army 1980a	
			Cardio	1511				
			Gastro	1511				
			Hemato	1511				
			Musc/skel	1511				
			Hepatic	1511				
			Renal	1511				
			Endocr	1511				
			Dermal	1511				
			Ocular	1511				
			Bd Wt	1511				
			Metab	1511				
Immuno/ Lymphoret								
4	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		1511			Army 1980a	NOAEL is for histopathology of spleen and thymus.

Table 3-1 Levels of Significant Exposure to DEET - 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
Neurological								
5	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		1511			Army 1980a	NOAEL is for histopathology of the brain and spinal cord.
Reproductive								
6	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		1511			Army 1980a	NOAEL is for histopathology of the sex organs.

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

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; Gastro = gastrointestinal; Hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LC50 = lethal concentration, 50% kill; LOAEL = lowest-observed-adverse-effect level; Metab = metabolic; Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

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Figure 3-1 Levels of Significant Exposure to DEET - Inhalation

Acute (≤14 days)

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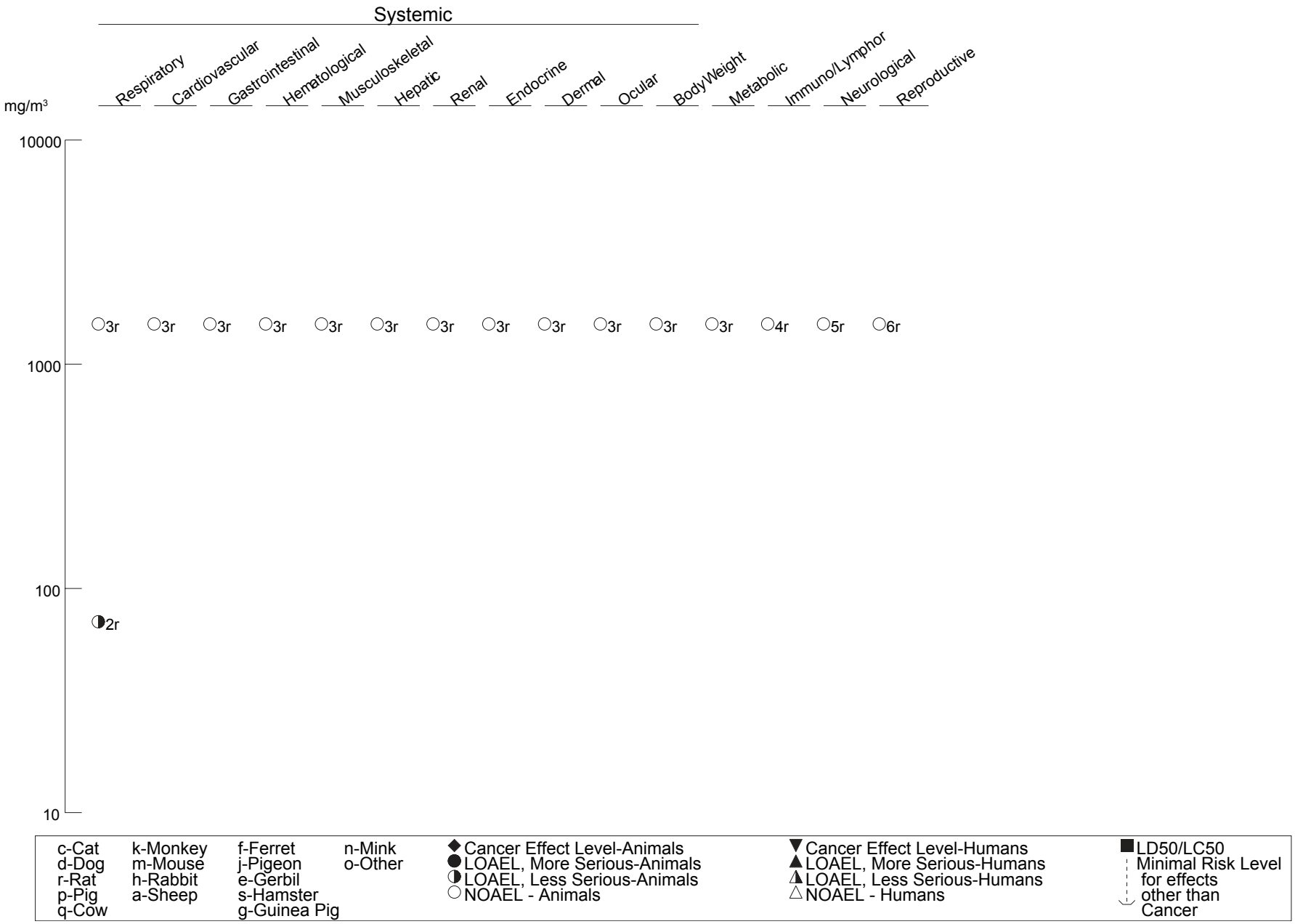
Figure 3-1 Levels of Significant Exposure to DEET - Inhalation *(Continued)*

Intermediate (15-364 days)



3.2.1.4 Neurological Effects

Fifty-seven of the 520 human cases in which inhalation was the leading route of exposure in the study by Bell et al. (2002) showed neurological effects. The most common symptoms were dizziness/vertigo, headache, and drowsiness/lethargy.

The only information available in animal studies is that from an acute-duration study in Sprague-Dawley rats (Army 1979). After a 4-hour exposure to 0, 2,300, 2,900, or 4,100 mg/m^3 DEET aerosol, the rats were examined for 15 common toxic neurological signs. In addition, seven behavioral tests were conducted within 50 minutes of termination of exposure. Toxic signs were restricted to the high-exposure group and consisted of shaking, prostration, and loss of balance in females and shaking in males. In general, performance in the various tests decreased as the exposure concentration increased. The test that seemed to show the clearest dose-response relationship and was affected at the lowest exposure concentration tested was the performance on a balance beam. Gross necropsy at the end of a 14-day observation period did not show treatment-related lesions. In an intermediate-duration study, exposure of Sprague-Dawley rats to up to 1,511 mg/m^3 aerosolized DEET for 13 weeks did not induce gross or microscopic alterations in the brain or spinal cord (Army 1980a).

The NOAEL values for neurological effects from the Army (1980a) study is presented in Table 3-1 and plotted in Figure 3-1.

3.2.1.5 Reproductive Effects

The only relevant information available is that from a 13-week inhalation study in which whole-body exposure of male and female Sprague-Dawley rats to up to 1,511 mg/m^3 aerosolized DEET for 13 weeks did not induce gross or microscopic alterations in the reproductive organs (Army 1980a).

The NOAEL values for reproductive effects from the Army (1980a) study is presented in Table 3-1 and plotted in Figure 3-1.

3.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to DEET.

3.2.1.7 Cancer

No studies were located regarding cancer effects in humans or animals after inhalation exposure to DEET.

3.2.2 Oral Exposure

3.2.2.1 Death

Ingestion of DEET by humans has resulted in death; however, in two out of four cases other substances were ingested at the same time, so deaths could not be attributed solely to DEET in these two cases. Tenenbein (1987) reported two cases. The first case was a 33-year-old woman who intentionally ingested up to 50 mL of an insect repellent containing 95% DEET and 5% related toluamides along with presumably excessive amounts of prescription chlorpromazine hydrochloride and hydralazine hydrochloride. She was discovered approximately 1 hour after the ingestion and taken to a hospital where she was comatose with a pulse of 80 beats per minute and blood pressure of 80/55 mm Hg. After gastric lavage and treatment with activated charcoal, she was transferred to a tertiary care facility, arrived comatose and pulseless, was resuscitated and received aggressive care in the intensive care unit. During the first 24 hours, she experienced generalized seizure activity and died the second day of a massive generalized bowel infarction. DEET was measured prior to death in blood (16.8 mg/dL) and postmortally in blood and liver (11.2 and 17.7 mg/dL, respectively). The second case was a 26-year-old man who was found dead after ingesting up to 50 mL of an insect repellent containing 95% DEET and 5% related toluamides following a bout of drinking. DEET levels measured in blood, vitreous, and urine were 24, 15, and 10 mg/dL, respectively. Blood alcohol was 130 mg/dL and cannabinoids were present in the urine. The authors estimated that consumption of 50 mL of 100% DEET by an 8-year old child is potentially lethal, if the 2.0 g/kg median lethal dose for rats reported by Ambrose (1959) is applicable to humans (50 mL weighs approximately 50 g based on a specific gravity of almost 1 for DEET; therefore, 50 g/25 kg body weight for an 8-year-old boy yields a lethal dose of 2 g/kg). In their study of 9,086 exposures involving insect repellents containing DEET reported to Poison Control Centers from 1985 to 1989, Veltri et al. (1994) reported that one 33-year-old adult male died 9 days after intentionally ingesting 8 ounces of an insect repellent containing between 11–50% DEET. Clinical signs included transitory cardiorespiratory arrest shortly after poisoning followed by hyperglycemia on day 2, status epilepticus and disseminated intravascular coagulopathy, and ultimately cerebral edema. Recently, Wiles et al. (2014) described the case of a 37-year-old male who died 3 days after ingesting 6 ounces of an insect repellent containing 40% DEET (approximately 748 mg DEET/kg). Within minutes of ingesting the solution, the man suffered a seizure and was transported to a community emergency department and

later to a healthcare facility. On arrival to the latter, the patient was unresponsive, had metabolic acidosis, tachycardia and hypotension, and hypothermia. Physical examination showed the patient to be unresponsive, areflexic with unreactive dilated pupils, and having an altered electrocardiogram (ECG). Blood samples collected <1 hour after poisoning showed DEET concentrations ranging from 8.7 to 10.2 mg/dL; urine samples contained an average of 0.64 mg DEET/dL. Over the next 3 days, the patient remained unresponsive. On the 3rd day, tests revealed no cerebral blood flow, little brain electrical activity, cerebral edema, and transtentorial and tonsillar herniations, and the patient was declared brain dead.

WHO identified an LD_{50} of 2,000 mg/kg for male rats (WHO 1987). An early study determined oral LD_{50} values of 1.8–2.7 and 1.75–1.8 mL/kg (1,793–2,689 and 1,743–1,793 mg/kg based on a specific gravity of 0.996 for DEET) with a central range of 1.83–2.19 mL/kg for 90% DEET in cottonseed oil in male and female albino rats, respectively; the observation period was 7 days (Ambrose 1959). Clinical signs included hyperemia at the base of the ears, lacrimation, chromodacryorrhea, depression, prostration, tremors, and asphyxial convulsions. Respiratory failure usually preceded cardiac failure. Gross examination showed questionable degrees of hyperemia of the gastrointestinal tract. An oral LD_{50} of 3,664 mg/kg was estimated in male Sprague-Dawley rats administered technical-grade DEET in propylene glycol (McCain et al. 1997). Seven out of 10 rats administered 5,010 mg/kg, the highest dose tested, died during the 14-day observation period, whereas only one rat died following administration of 2,000 mg/kg, the lowest dose tested (McCain et al. 1997). EPA (1998c) reported that the LD_{50} in rats (strain not specified) varied from 2,170 to 3,664 mg/kg. A study that examined the effect of age on the acute toxicity of DEET reported oral LD_{50} values of 3,564 and 3,429 mg/kg in adult male and female Wistar rats, respectively (Verschoyle et al. 1992); the respective LD_{50} values in 11-day-old rats were 891 and 667 mg/kg, indicating a 4–5-fold increased sensitivity in the young rats relative to the older rats.

The LC_{50} in rats from the Army (1980a) study is presented in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

No studies were located regarding respiratory, musculoskeletal, endocrine, dermal, ocular, or body weight effects in humans following oral exposure to DEET.

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 3-2 and plotted in Figure 3-2.

Table 3-2 Levels of Significant Exposure to DEET - 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	Rat (albino)	once (GO)				1793 M (LD50) 1743 F (LD50)	Ambrose 1959	
2	Rat (Wistar)	once (G)				2669 M (LD50)	Carpenter et al. 1974	
3	Rat (Sprague-Dawley)	once (G)				3664 M (LD50)	McCain et al. 1997	
4	Rat (Wistar)	once (GO)				3564 M (LD50 in adults) 891 M (LD50 in 11-day-old) 3429 F (LD50 in adults) 667 F (LD50 in 11-day-old)	Verschoyle et al. 1992	
Systemic								
5	Rat (CD)	once (G)	Bd Wt	500			Schoenig et al. 1993	
6	Rat (CD)	10 d Gd 6-15 1 x/d (G)	Bd Wt	250 F		750 F (35% reduced weight gain)	Schoenig et al. 1994	
7	Rabbit (New Zealand)	13 d Gd 6-18 1 x/d (G)	Bd Wt	100 F		325 F (69% reduced weight gain)	Schoenig et al. 1994	

Table 3-2 Levels of Significant Exposure to DEET - 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								
8	Rat (Sprague-Dawley)	once (G)		500			Hoy et al. 2000a	NOAEL is for locomotor activity.
9	Rat (Sprague-Dawley)	7 d 1 x/d (G)		200			Hoy et al. 2000b	NOAEL is for locomotor activity and thigmotaxis.
10	Rat (CD)	once (G)		500			Schoenig et al. 1993	NOAEL is for neurobehavioral effects.
11	Rat (CD)	10 d Gd 6-15 1 x/d (G)				750 F (hypoactivity, ataxia, decreased muscle tone)	Schoenig et al. 1994	Neurological signs occurred during dosing period.
12	Rat (Wistar)	once (GO)			1000 (vacuolization of myelin sheath in cerebellum)		Verschoyle et al. 1992	
Developmental								
13	Rat (CD)	10 d Gd 6-15 1 x/d (G)		250 F	750 F (6% reduced fetal weight)		Schoenig et al. 1994	Weight gain significantly reduced in dams.
14	Rabbit (New Zealand)	13 d Gd 6-18 1 x/d (G)		325 F			Schoenig et al. 1994	NOAEL is for fetotoxicity and teratogenicity.

Table 3-2 Levels of Significant Exposure to DEET - 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	Rat (albino)	200 d ad lib (F)	Resp	863 F			Ambrose 1959	NOAELs are for organ histopathology.
			Cardio	863 F				
			Gastro	863 F				
			Hepatic	863 F				
			Renal	863 F				
			Endocr	863 F				
			Bd Wt	397 F	863 F (11.1% reduced terminal body weight)			
16	Rat (Sprague-Dawley)	80 d ad lib (F)	Renal		25 M (hyaline nephropathy)		EPA 1989	
17	Rat (CD)	9 mo ad lib (F)	Bd Wt	200 M	500 M (14% reduced final body weight)		Schoenig et al. 1993	

Table 3-2 Levels of Significant Exposure to DEET - 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
18	Hamster (Golden Syrian)	90 d ad lib (F)	Resp	940			EPA 1990b	NOAELs are for organ histopathology.
			Cardio	940				
			Hemato	940				
			Hepatic	940				
			Renal	940				
			Endocr	940				
			Bd Wt	305	624 M (12.7% reduced terminal body weight)			
			Metab	624	940 (10-16% increased serum potassium)			

Table 3-2 Levels of Significant Exposure to DEET - 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	Dog (Beagle)	52 wk 2 x/d (C)	Resp	400			Schoenig et al. 1999	NOAELs are for organ and tissue histopathology.
			Cardio	400				
			Gastro	400				
			Hemato	100	400 F (decreased hemoglobin and hematocrit; increased platelets)			
			Musc/skel	400				
			Hepatic	100 M	400 M (decreased serum alkaline phosphatase; decreased cholesterol)			
			Renal	400				
			Endocr	400				
			Dermal	400				
			Ocular	400				
			Bd Wt	100	400 (>10% reduced terminal body weight)			
			Metab	100 M	400 M (23% increased serum potassium)			

Table 3-2 Levels of Significant Exposure to DEET - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
20	Rabbit (New Zealand)	15 d 1 x/d (G)	Resp	528 M			Army 1980b	
			Cardio	528 M				
			Gastro	528 M				
			Musc/skel	528 M				
			Hepatic	264 M	528 M (fatty change in hepatocytes)			
			Renal	528 M				
			Endocr	528 M				
			Dermal	528 M				
			Ocular	528 M				
			Bd Wt	264 M		528 M (22% body weight loss)		
			Metab	264 M	528 M (14% decrease in serum calcium)			
Immuno/ Lymphoret								
21	Rat (albino)	200 d ad lib (F)		863 F			Ambrose 1959	NOAEL is for spleen histopathology.
22	Hamster (Golden Syrian)	90 d ad lib (F)		940			EPA 1990b	NOAEL is for histopathology of lymphoreticular organs.

Table 3-2 Levels of Significant Exposure to DEET - 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
23	Dog (Beagle)	52 wk 2 x/d (C)		400			Schoenig et al. 1999	NOAEL is for histopathology of lymphoreticular organs.
24	Rabbit (New Zealand)	15 d 1 x/d (G)		528 M			Army 1980b	NOAEL is for histopathology of lymphoreticular organs.
Neurological								
25	Rat (albino)	200 d ad lib (F)		863 F			Ambrose 1959	NOAEL is for brain histopathology.
26	Rat (CD)	9 mo ad lib (F)		200	500 (transient increase in motor activity)		Schoenig et al. 1993	Effects were considered of questionable biological significance.
27	Hamster (Golden Syrian)	90 d ad lib (F)		940			EPA 1990b	NOAEL is for histopathology of the brain.
28	Dog (Beagle)	52 wk 2 x/d (C)		400			Schoenig et al. 1999	1 in 8 dogs showed DEET-related tremors during the study.
29	Rabbit (New Zealand)	15 d 1 x/d (G)		528 M			Army 1980b	NOAEL is for histopathology of the brain.

Table 3-2 Levels of Significant Exposure to DEET - 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								
30	Rat (albino)	200 d ad lib (F)		701 M 863 F			Ambrose 1959	NOAEL is for histopathology of reproductive organs.
31	Rat (Sprague-Dawley)	80 d ad lib (F)		250			EPA 1989	NOAEL is for fertility.
32	Hamster (Golden Syrian)	90 d ad lib (F)		305 M		624 M (tubular degeneration in testes)	EPA 1990b	Fertility was not tested.
33	Dog (Beagle)	52 wk 2 x/d (C)		400			Schoenig et al. 1999	NOAEL is for histopathology of the reproductive organs.
34	Rabbit (New Zealand)	15 d 1 x/d (G)		528 M			Army 1980b	NOAEL is for histopathology of the testes.
Developmental								
35	Rat (Sprague-Dawley)	80 d ad lib (F)		100[b]	250 (reduced F1 and F2 pup weights during lactation)		EPA 1989	

Table 3-2 Levels of Significant Exposure to DEET - 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								
36	Rat (CD)	104 wk ad lib (F)	Resp	400 F			Schoenig et al. 1999	Highest dose in males was 100 mg/kg/day; no effects were reported in males.
			Cardio	400 F				
			Gastro	400 F				
			Hemato	400 F				
			Musc/skel	400 F				
			Hepatic	100	400 F (increased serum cholesterol)			
			Renal	400 F				
			Endocr	400 F				
			Dermal	400 F				
			Ocular	400 F				
			Bd Wt	100	400 F (>10% reduced terminal body weight)			
			Metab	400				

Table 3-2 Levels of Significant Exposure to DEET - 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	Mouse (CD-1)	78 wk ad lib (F)	Resp	1000			Schoenig et al. 1999	NOAELs are for tissues and organs histopathology.
			Cardio	1000				
			Gastro	1000				
			Hemato	1000				
			Musc/skel	1000				
			Hepatic	1000				
			Renal	1000				
			Endocr	1000				
			Dermal	1000				
			Bd Wt	500	1000 (>10% reduced terminal body weight)			
Immuno/ Lymphoret								
38	Rat (CD)	104 wk ad lib (F)		100 M 400 F			Schoenig et al. 1999	NOAELs are for histopathology of lymphoreticular organs.
39	Mouse (CD-1)	78 wk ad lib (F)		1000			Schoenig et al. 1999	NOAEL is for histopathology of lymphoreticular organs.

Table 3-2 Levels of Significant Exposure to DEET - 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								
40	Rat (CD)	104 wk ad lib (F)		100 M 400 F			Schoenig et al. 1999	NOAELs are for histopathology of brain and sciatic nerve.
41	Mouse (CD-1)	78 wk ad lib (F)		1000			Schoenig et al. 1999	NOAEL is for histopathology of nervous system tissues.
Reproductive								
42	Rat (CD)	104 wk ad lib (F)		100 M 400 F			Schoenig et al. 1999	NOAELs are for histopathology of reproductive organs.
43	Mouse (CD-1)	78 wk ad lib (F)		1000			Schoenig et al. 1999	NOAEL is for histopathology of reproductive organs.

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

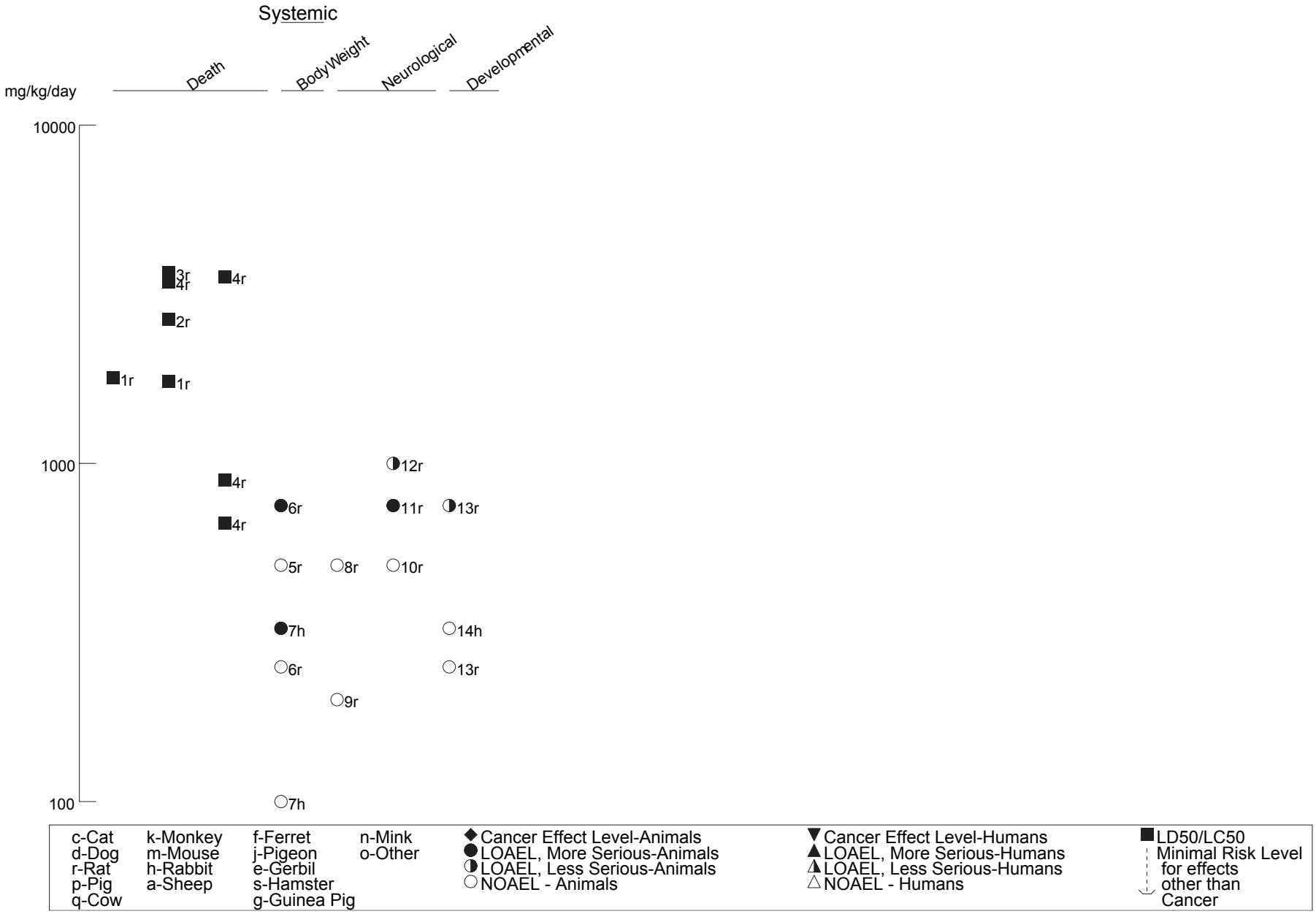
b Used to derive an intermediate-duration oral minimal risk level (MRL) of 1.0 mg/kg/day for DEET; the MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) = gavage in oil; Hemato = hematological; Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; Metab = metabolic; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; x = time(s); wk = week(s)

3. HEALTH EFFECTS

Figure 3-2 Levels of Significant Exposure to DEET - Oral

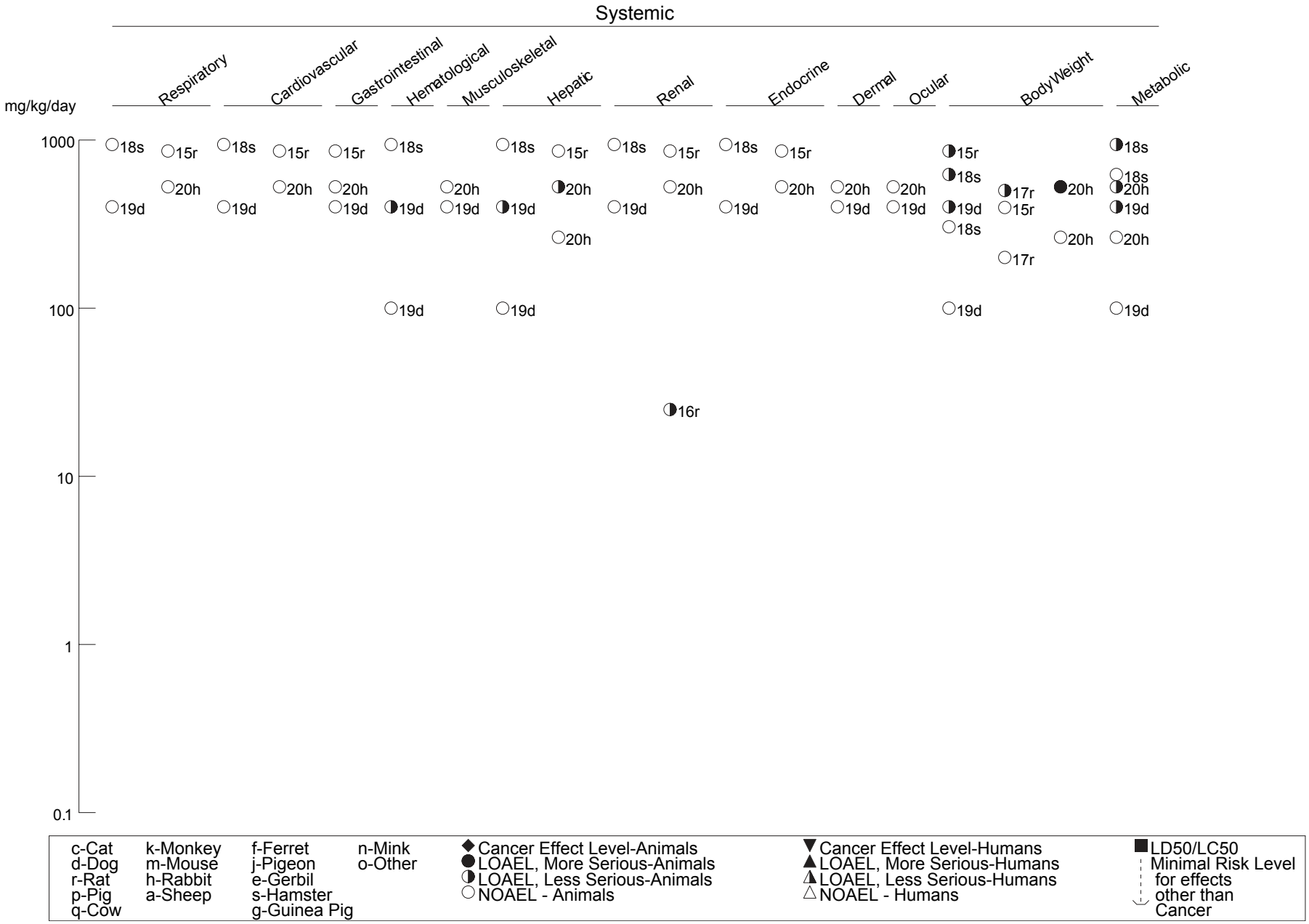
Acute (≤14 days)



3. HEALTH EFFECTS

Figure 3-2 Levels of Significant Exposure to DEET - Oral *(Continued)*

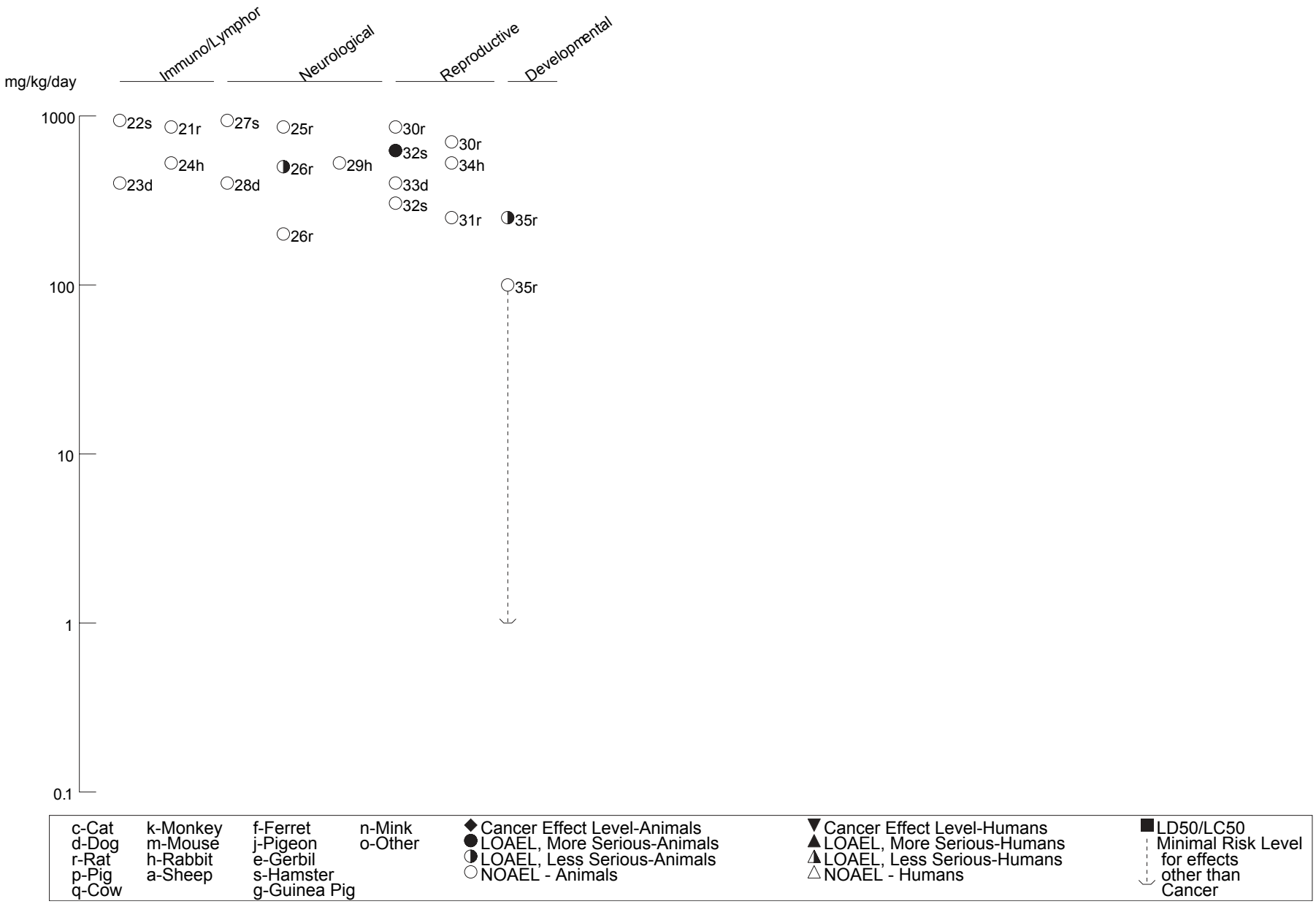
Intermediate (15-364 days)



3. HEALTH EFFECTS

Figure 3-2 Levels of Significant Exposure to DEET - Oral *(Continued)*

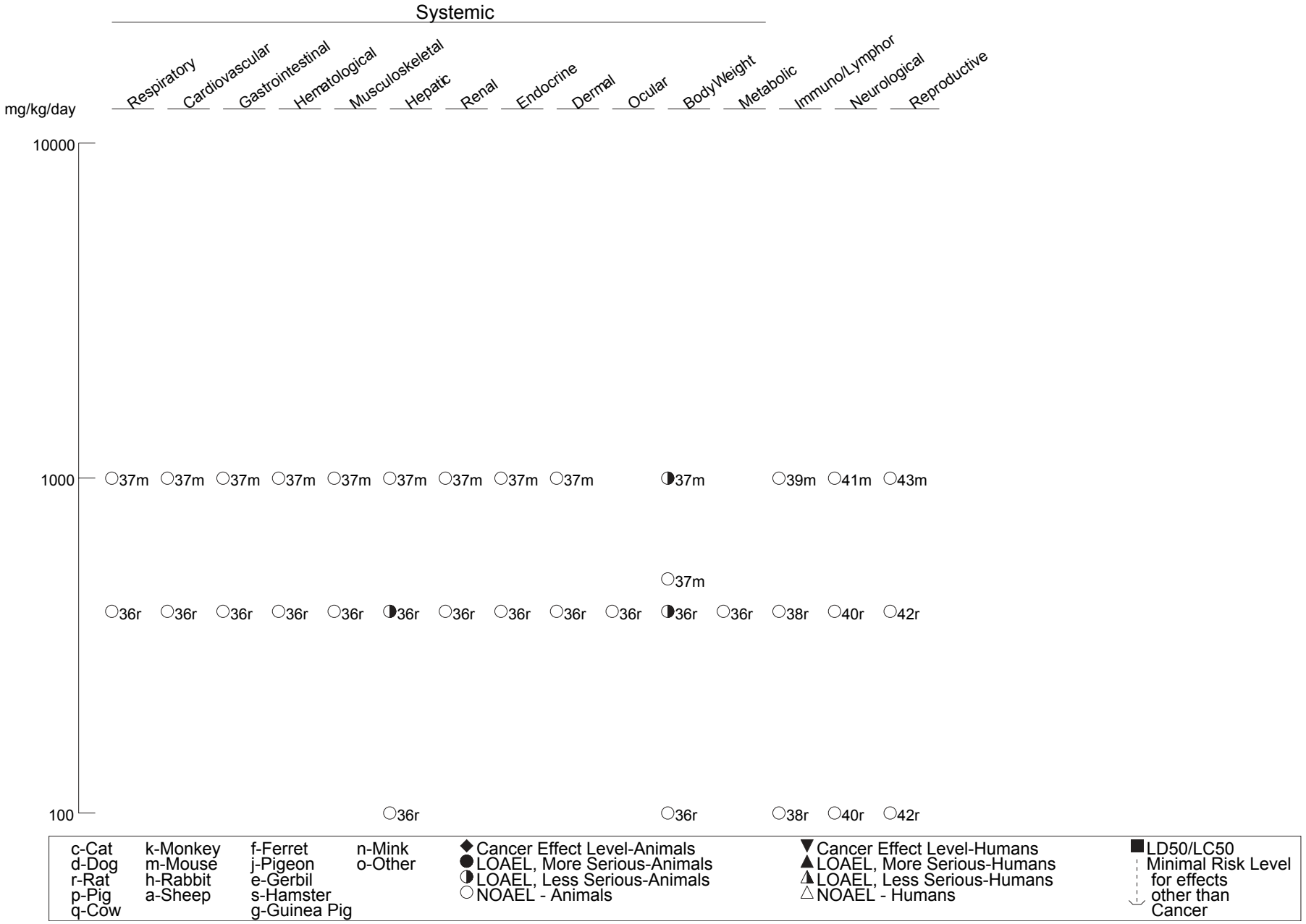
Intermediate (15-364 days)



3. HEALTH EFFECTS

Figure 3-2 Levels of Significant Exposure to DEET - Oral *(Continued)*

Chronic (≥365 days)



Respiratory Effects. No information was located regarding respiratory effects in humans following oral exposure to DEET.

Several intermediate-duration (i.e., 15 days to 52 weeks) and one chronic-duration (18 months to 2 years) oral study conducted gross and microscopic examinations of the lungs of animals (i.e., rats, mice, hamsters, dogs, rabbits) following oral exposure to DEET and did not find significant treatment-related alterations. Reported NOAELs for respiratory effects included 701 and 863 mg DEET/kg/day in male and female albino rats, respectively, treated for 200 days (Ambrose 1959), 940 mg DEET/kg/day in male and female Golden Syrian hamsters treated for 90 days (EPA 1990b), 400 mg DEET/kg/day in Beagle dogs treated for 52 weeks (Schoenig et al. 1999), and 528 mg/DEET/kg/day in New Zealand White rabbits treated for 15 days (Army 1980b).

In chronic-duration studies, the highest doses of DEET tested (100 mg/kg/day in male CD rats and 400 mg/kg/day in female CD rats treated for 2 years; 1,000 mg/kg/day in male and female CD-1 mice treated for 18 months) did not induce morphological alterations in the lungs (Schoenig et al. 1999).

Cardiovascular Effects. An abnormal ECG was reported in a 19-year-old woman 1 hour after ingesting 15–25 mL of an insect repellent containing 95% DEET (Fraser et al. 1995). The ECG indicated right and left atrial enlargement, diffuse ST-T abnormalities, and a normal QT interval. Within 24 hours, the ECG returned to baseline. An unremarkable ECG was described in a 3-year-old girl who ingested an estimated 800 mg of DEET (4 mL of a 20% solution) (Petrucci and Sardini 2000). Hypotension (blood pressure 80/50 mm Hg) was reported in a 33-year-old woman approximately 1 hour after ingesting an unknown amount of an insect repellent containing 95% DEET along with presumably excessive amounts of prescription chlorpromazine hydrochloride and hydralazine hydrochloride (Tenenbein 1987). The same investigator reported hypotension in a 16-year-old girl (blood pressure 90/50 mm Hg) and in a 14-year-old girl (systolic 60 mm Hg) following ingestion of DEET. Tachycardia, hypotension, and altered ECG were reported in a 37-year-old man who ingested 6 ounces of a repellent containing 40% DEET (approximately 748 mg DEET/kg) (Wiles et al. 2014). No further relevant information was located regarding cardiovascular effects in humans following oral exposure to DEET.

No treatment-related gross or microscopic alterations in the heart were reported in intermediate- and chronic-duration oral studies in albino or CD rats (Ambrose 1959; Schoenig et al.1999), Golden Syrian hamsters (EPA 1990b), beagle dogs (Schoenig et al. 1999), New Zealand White rabbits (Army 1980b),

and CD-1 mice (Schoenig et al. 1999). The NOAELs were the highest doses tested and were the same as indicated above for Respiratory Effects.

Gastrointestinal Effects. In a study of 20,764 human exposures involving insect repellents containing DEET that were reported to poison control centers from 1993 to 1997, 10,748 were identified as being exposed predominantly by ingestion (Bell et al. 2002). Of these, 770 exhibited gastrointestinal effects that included stomach irritation, vomiting, and nausea.

Albino rats treated with DEET in the diet (701 mg/kg/day in males, 863 mg/kg/day in females) for 200 days did not show treatment-related gross or microscopic alterations in the stomach or small intestine (Ambrose 1959). Similar findings were reported regarding the gastrointestinal tract of Beagle dogs dosed with 400 mg DEET/kg/day for 52 weeks (Schoenig et al. 1999), and New Zealand White rabbits dosed with 528 mg DEET/kg/day for 15 days (Army 1980b). The same was reported in CD rats dosed with DEET for 104 weeks (100 mg/kg/day in males, 400 mg/kg/day in females) and CD-1 mice dosed with 1,000 mg DEET/kg/day for 78 weeks (Schoenig et al. 1999).

Hematological Effects. The leukocyte count reported in a 3-year-old girl who ingested an estimated 800 mg DEET (4 mL of a 20% insect repellent solution) was within normal limits (Petrucci and Sardini 2000). No explicit statements regarding hematology tests were provided in other cases of acute intoxication with DEET that were reviewed.

Hematological tests conducted in Golden Syrian hamsters after 90 days of dosing with up to 940 mg DEET/kg/day showed sporadic inconsistent changes in certain parameters without dose-response and were not considered treatment-related by the investigators (EPA 1990b). A 52-week oral study in Beagle dogs reported that doses of 400 mg DEET/kg/day induced significant reductions in hemoglobin and hematocrit in males and females after 6 and 12 months of dosing and significant increases in platelets in females (Schoenig et al. 1999). Hematological tests were conducted in CD rats and CD-1 mice during chronic exposure to DEET (100 mg/kg/day in male rats; 400 mg/kg/day in female rats; 1,000 mg/kg/day in mice) and did not show report treatment-related hematological alterations (Schoenig et al. 1999).

Musculoskeletal Effects. Skeletal muscle and bone were examined in intermediate-duration studies in Beagle dogs (Schoenig et al. 1999) and New Zealand White rabbits (Army 1980b) and in chronic-duration studies in CD rats and CD-1 mice (Schoenig et al. 1999). None of these studies found treatment-related gross or microscopic alterations in bone or muscle. NOAELs for musculoskeletal effects were

400 mg/kg/day in dogs, 528 mg/kg/day in rabbits, 100 and 400 mg/kg/day in male and female rats, respectively, and 1,000 mg/kg/day in mice.

Hepatic Effects. Of the few reported cases of ingestion of DEET by humans, only a report by Petrucci and Sardini (2000) explicitly indicated that liver function studies were conducted and were unremarkable in a 3-year-old girl who ingested an estimated 800 mg DEET. No explicit statements regarding liver function tests were provided in other cases of acute intoxication with DEET that were reviewed.

No significant changes in clinical chemistry parameters or in gross or microscopic appearance of the liver were reported in Golden Syrian hamsters dosed with up 940 mg DEET/kg/day for 90 days (EPA 1990b). In a 52-week study in male Beagle dogs treated with 400 mg DEET/kg/day, a significant increase in serum alkaline phosphatase activity (49% at 6 months) and a significant reduction in serum cholesterol (37% at 6 months and 35% at 12 months were observed) (Schoenig et al. 1999). No significant changes occurred in dogs dosed with 100 mg DEET/kg/day. Gross and microscopic examination of the dogs' liver did not show treatment-related alterations. New Zealand White rabbits treated with 528 mg DEET/kg/day for 15 days showed changes consisting of rare to minimal fatty change in hepatocytes (Army 1980b). These changes were seen primarily midzonal, but clear vacuolated hepatocytes were also seen in central and portal areas. Clinical chemistry tests showed significant increases in serum cholesterol and triglycerides (about 4-fold each). The NOAEL for liver effects was 264 mg DEET/kg/day. A chronic-duration dietary study in CD rats also reported significant increases in serum cholesterol (2–4-fold) during the study in females dosed with 400 mg DEET/kg/day, but not 100 mg DEET/kg/day (Schoenig et al. 1999). In the chronic study there were no gross or microscopic lesions in the liver attributable to treatment with DEET.

Renal Effects. Petrucci and Sardini (2000) mentioned that creatinine levels were within normal limits in a 3-year-old girl who ingested an estimated 800 mg of DEET. No further explicit information regarding renal effects in humans following oral exposure to DEET was located.

In an early dietary study in albino rats, examination of the kidneys of the animals treated with the highest doses (701 mg/kg/day in males and 863 mg/kg/day in females) for 200 days only showed increased relative weight of the organs (12%) (Ambrose 1959). There were no treatment-related gross or microscopic alterations in the kidney that were not seen in control rats. Interestingly, in a 2-generation reproductive study in Sprague-Dawley rats, hyaline nephropathy was reported in adult F1 males from all

treated groups (doses of DEET mixed in the food were 0, 25, 100, or 250 mg/kg/day) (EPA 1989). F1 males had been produced by F0 females that had been dosed with DEET for at least 80 days before mating and presumably during gestation and lactation. F1 males were therefore exposed *in utero* and then directly for at least 93 days. The kidneys from F0 males were not examined microscopically because they did not show gross alterations (EPA 1989). Other intermediate-duration studies did not observe adverse kidney effects in Golden Syrian hamsters dosed with up to 940 mg DEET/kg/day for 90 days (EPA 1990b), Beagle dogs dosed with up to 400 mg DEET/kg/day for 52 weeks (Schoenig et al. 1999), or New Zealand White rabbits dosed with up to 528 mg DEET/kg/day for 15 days (Army 1990).

Chronic-duration studies in rats and mice did not report treatment-related kidney lesions at termination, but did report relative high incidences of chronic progressive nephropathy in male and female CD rats and chronic nephritis in male and female CD-1 mice, which also occurred in control groups and were considered unrelated to the test material (Schoenig et al. 1999). In these studies, male and female rats were dosed with up to 100 and 400 mg DEET/kg/day, respectively, for 104 weeks and male and female mice were dosed with up to 1,000 mg DEET/kg/day for 78 weeks.

Endocrine Effects. Several intermediate-duration and one chronic-duration oral study conducted gross and microscopic examinations of endocrine glands of animals following oral exposure to DEET and did not find significant treatment-related alterations. Glands examined included the adrenals, pituitary, thyroid, and parathyroid. Reported NOAELs included 701 and 863 mg DEET/kg/day in male and female albino rats, respectively, treated for 200 days (Ambrose 1959); 940 mg DEET/kg/day in male and female Golden Syrian hamsters treated for 90 days (EPA 1990b); 400 mg DEET/kg/day in Beagle dogs treated for 52 weeks (Schoenig et al. 1999); and 528 mg/DEET/kg/day in New Zealand White rabbits treated for 15 days (Army 1980b).

In chronic-duration studies, the highest doses of DEET tested (100 mg/kg/day in CD male rats; 400 mg/kg/day in CD female rats; 1,000 mg/kg/day in male and female CD-1 mice) did not induce morphological alterations in adrenals, thyroid, or pituitary glands (Schoenig et al. 1999).

Dermal Effects. No treatment-related skin alterations were reported in Beagle dogs dosed with up to 400 mg DEET/kg/day for 52 weeks (Schoenig et al. 1999) or in New Zealand White rabbits dosed with up to 528 mg DEET/kg/day for 15 days (Army 1980b). Similar observations were made regarding the skin of CD-1 mice dosed with up to 1,000 mg DEET/kg/day for 78 weeks or male and female CD rats dosed with up to 100 or 400 mg DEET/kg/day, respectively, for 104 weeks (Schoenig et al. 1999).

Ocular Effects. Lacrimation and chromodacryorrhea were reported in rats administered lethal doses of DEET by gavage (Ambrose 1959). Three studies provided additional data regarding ocular effects in animals exposed orally to DEET. No significant morphological alterations were seen in the eyes of Beagle dogs dosed with up to 400 mg DEET/kg/day for 52 weeks (Schoenig et al. 1999), New Zealand White rabbits dosed with up to 528 mg DEET/kg/day for 15 days (Army 1980b), or male and female CD rats dosed with up to 100 or 400 mg DEET/kg/day, respectively, for 104 weeks (Schoenig et al. 1999).

Body Weight Effects. Several studies provide information regarding body weight effects in animals after oral exposure to DEET; not all of the studies, however, provided data on food consumption. In general, reductions in body weight gain relative to controls were associated with reductions in food consumption. In acute-duration studies, Schoenig et al. (1993) reported that a single dose of up to 500 mg DEET/kg did not affect body weight or food consumption in CD rats over a 14-day observation period.

Administration of 750 mg DEET/kg/day to pregnant CD rats on GDs 6–15 or 325 mg DEET/kg/day to pregnant New Zealand White rabbits on GDs 6–18, however, reduced maternal weight gain by 35 and 69%, respectively (Schoenig et al. 1994); the corresponding NOAELs were 250 and 100 mg/kg/day. In both cases, food consumption was reduced.

In intermediate-duration oral studies, significant reductions in terminal body weight (≥10% differences with controls) were seen at DEET doses of 701 mg/kg/day in albino rats (Ambrose 1959), 500 mg/kg/day in CD rats (Schoenig et al. 1993), 624 mg/kg/day in Golden Syrian hamsters (EPA 1990b), and 400 mg/kg/day in Beagle dogs (Schoenig et al. 1999). In these studies, DEET was administered via the food, except in dogs, which were treated with DEET in capsules. In a 15-day study in male New Zealand White rabbits in which DEET was administered by gavage, doses of 528 mg DEET/kg/day caused a 22% reduction in body weight (rabbits lost weight) (Army 1980b); body weight showed a rapid and linear decrease throughout the study with no indication of reversal. No significant effects appeared to occur at 264 mg/kg/day, while the 132 mg/kg/day animals retained a higher portion of initial body weight compared to controls, and by day 12, diverged positively from controls. No data on food consumption were provided in this study. In the 2-generation reproductive study in Sprague-Dawley rats (EPA 1989), decreased body weight was reported in adult F0 and F1 males and females at various time points during the study and occurred mainly in rats in the 100 and 250 mg/kg/day dose groups. Some of differences with the control groups were statistically significant, but only in one case (high-dose F1 females at 18 weeks of age) was the difference with controls >10% (15.4%). Significant decreases in food

consumption relative to controls were also reported at various times. Only in adult F1 high-dose females was reduced food consumption >10% (15 and 14% at 12 and 16 weeks of age, respectively).

In chronic-duration studies, doses of 400 mg DEET/kg/day reduced terminal body weight in female CD rats by 10% and a similar effect was reported in CD-1 mice dosed with 1,000 mg DEET/kg/day (Schoenig et al. 1999); the corresponding NOAELs were 100 and 500 mg/kg/day.

Metabolic Effects. Serum electrolytes within normal limits were reported in an 18-month-old child who had ingested an unknown, but probably small, amount of an insect repellent containing DEET the day prior to being admitted to the hospital (Zadikoff 1979). Petrucci and Sardini (2000) also reported electrolytes and glucose within normal limits in a 3-year-old girl who ingested an estimated 800 mg of DEET. Metabolic acidosis was reported in a 37-year-old man who ingested 6 ounces of a repellent containing 40% DEET (approximately 748 mg DEET/kg) (Wiles et al. 2014). No further relevant information was located regarding metabolic effects in humans after oral exposure to DEET.

A few alterations in serum electrolytes were reported in studies in animals. Increases in serum potassium of 10 and 16% were reported in male and female Golden Syrian hamsters, respectively, following doses of 940 mg DEET/kg/day for 90 days (EPA 1990b); no significant changes were reported at ≤624 mg DEET/kg/day. Serum potassium was also significantly increased (23%) in male Beagle dogs after receiving doses of 400 mg DEET/kg/day for 6 months; no significant alterations were reported in dogs dosed with ≤100 mg DEET/kg/day or in dogs dosed with 400 mg DEET/kg/day for 12 months (Schoenig et al. 1999). In a study in male New Zealand White rabbits, serum calcium was significantly decreased (14%) following dosing with 528 mg DEET/kg/day, but not 264 mg/kg/day, for 15 days (Army 1980b). No significant alterations in serum electrolytes or glucose were reported in a chronic-duration study in CD rats (Schoenig et al. 1999); the highest doses tested were 100 mg DEET/kg/day in males and 400 mg/kg/day in females.

3.2.2.3 Immunological and Lymphoreticular Effects

No information was located regarding immunological effects in humans following oral exposure to DEET.

No relevant information was located regarding effects in acute-duration studies in animals. Intermediate-duration studies did not find gross or microscopic lesions in lymphoreticular organs of Beagle dogs

(Schoenig et al. 1999), albino rats (Ambrose 1959), Golden Syrian hamsters (EPA 1990b), or New Zealand White rabbits (Army 1980b) exposed to doses of DEET ranging from 400 to 863 mg/kg/day. Similar results were reported in a chronic-duration study in CD rats dosed with up to 400 mg/kg/day DEET or CD-1mice dosed with up to 1,000 mg/kg/day DEET (Schoenig et al. 1999). None of these studies, however, conducted tests to examine immunocompetence.

The highest NOAEL values for effects on lymphoreticular organs in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

All of the reported cases of acute oral intoxication with insect repellents containing DEET reported adverse neurological effects in the patients described by some as toxic encephalopathy. Opisthotonic episodes followed by generalized seizures with clonic movement of the facial muscles were described in a 3-year-old girl who ingested an estimated 800 mg of DEET (Petrucci and Sardini 2000). Opisthotonus is a postural abnormality characterized by hyperextension of the back and neck muscles, with retraction of the head, and arching forward of the trunk. Edwards and Johnson (1987) described a similar case of a child who developed toxic encephalopathy after ingesting an unknown amount of a product containing 10% DEET. The five cases of oral ingestion of DEET described by Tenenbein (1987) showed neurological signs within several hours of ingestion of the chemical including a hypertonic condition with Babinski signs, tremors, seizures, opisthotonic spells, and coma. Opisthotonic posture and bizarre movements were also described in a young child who ingested a small amount of an insect repellent containing DEET (Zadikoff 1979). Wiles et al. (2014) reported that a man suffered a seizure within minutes of ingesting 6 ounces of a repellent containing 40% DEET (approximately 748 mg DEET/kg) and was unresponsive and areflexic over the next 3 days before being declared brain dead.

Oral studies in animals have examined neurobehavioral parameters as well as the gross and microscopic morphology of tissues of the nervous system following exposure to DEET. An acute-duration study that performed a functional observational battery (FOB) and a motor activity test in CD rats reported a decrease in vertical activity and delayed response to thermal stimuli following a single dose of 500 mg/kg, the highest dose tested; the NOAEL was 200 mg/kg (Schoenig et al. 1993). A similar study in Sprague-Dawley rats, however, did not report significant alterations in locomotor activity and thigmotaxis (response to touch) following a dose of 500 mg DEET/kg (Hoy et al. 2000a). In a study aimed at determining oral LD_{50} values for DEET in Wistar rats, no clinical signs were seen in rats treated

with single doses of <1,500 mg DEET/kg in arachis oil (Verschoyle et al. 1992). Doses between 2,000 and 3,000 mg/kg, however, decreased reactivity and muscle tone. Central nervous system depression was occasionally interrupted by seizures; mostly qualitative data were presented in this study. Spikes in the electroencephalogram (EEG) arising from the auditory cortex were recorded in rats with implanted electrodes. In rats given single doses of 1,000–3,000 mg DEET/kg, light microscopy showed histological changes in the brain consisting of vacuolization of myelin sheaths mainly in cerebellar roof nuclei. Axons usually appeared normal. Also seen were single or multiple, clear cytoplasmic clefts in neurons diffusely distributed throughout the brain. Rats with these lesions usually were severely prostrated or ataxic. Electron microscopy showed extensive edematous swelling of the inner loop of the myelin sheaths and splitting of the innermost myelin lamellae occurring at the intraperiod line.

In intermediate-duration studies, dietary treatment of albino rats with up to 863 mg DEET/kg/day for 200 days did not induce gross or microscopic alterations in the brain (Ambrose 1959). A similar lack of effects was reported in multiple tissues of the central and peripheral nervous tissue from CD rats following dietary doses of up to 500 mg DEET/kg/day for 9 months, but this dietary level of DEET induced transient increases in motor activity (Schoenig et al. 1993). Golden Syrian hamsters dosed with up to 940 mg DEET/kg/day for 90 days (EPA 1990b), New Zealand white rabbits dosed with up to 528 mg DEET/kg/day for 15 days (Army 1980b), or Beagle dogs dosed with up to 400 mg DEET/kg/day for 52 weeks (Schoenig et al. 1999) did not show gross or microscopic alterations in tissues of the nervous system. In the study in dogs, doses of 400 mg DEET/kg/day induced occasional tremors in some dogs as well as excessive salivation.

In chronic-duration studies, dietary doses of up 100 mg DEET/kg/day in male CD rats, 400 mg DEET/kg/day in female CD rats, or 1,000 mg DEET/kg/day in CD-1 mice did not induce morphological alterations in central or peripheral nervous tissues (Schoenig et al. 1999).

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

No information was located regarding reproductive effects in humans following oral exposure to DEET.

Intermediate- and chronic-duration studies provide information regarding reproductive effects in animals after oral exposure to DEET. In a 2-generation continuous feeding study in Sprague-Dawley rats, fertility was not affected by treatment with up to approximately 250 mg DEET/kg/day (EPA 1989). In addition, gross and microscopic examination of the reproductive organs of the F0 generation and F1 weanlings did not show morphological alterations. In an earlier study, treatment of male and female albino rats with up to 701 or 863 mg DEET/kg/day, respectively, in the diet for 200 days did not induce gross or microscopic changes in the reproductive organs (Ambrose 1959). A 52-week study in male and female Beagle dogs dosed with up to 400 mg DEET/kg/day via capsules (Schoenig et al. 1999) or a 15-day study in male New Zealand White rabbits treated with up to 528 mg/DEET/kg/day (Army 1980b) also did not observe morphological alterations in the animals' reproductive organs. A 90-day dietary study in male and female Golden Syrian hamsters, however, reported an increased incidence of tubular degeneration in the testes and accumulation of cellular debris in the lumens of the epididymides from males dosed with ≥624 mg DEET/kg/day; the NOAEL was 305 mg DEET/kg/day (EPA 1990b). No significant alterations were observed in females.

Chronic-duration studies did not report gross or microscopic alteration in the reproductive organs from male CD rats dosed with up to 100 mg DEET/kg/day, female CD rats dosed with up to 400 mg DEET/kg/day, or male and female CD-1 mice dosed with up to 1,000 mg DEET/kg/day (Schoenig et al. 1999).

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

No information was located regarding developmental effects in humans following oral exposure to DEET.

Limited data are available in animals. Gavage administration of 750 mg DEET/kg to pregnant CD rats on GDs 6–15 resulted in a 6% reduction in fetal weight measured at sacrifice on GD 21 (Schoenig et al. 1994). The NOAEL was 250 mg DEET/kg/day (Schoenig et al. 1994). It should be noted that the 750 mg/kg/day dose level induced neurological signs in the dams during treatment as well as a significant (35%) reduction in maternal weight gain relative to controls. Examination of the fetuses did not show treatment-related increases in external, visceral, or skeletal variations or malformations. In the same study, gavage administration of up to 325 mg DEET/kg to pregnant New Zealand White rabbits on

GDs 6–18 did not result in embryotoxic or teratogenic effects in the offspring, despite the fact that maternal weight gain was reduced by about 69% during treatment.

In a 2-generation continuous feeding study in Sprague-Dawley rats that included exposure for at least 80 days before mating, treatment of the F0 generation and later of the F1 generation with 250 mg DEET/kg/day resulted in significantly reduced (>10%) F1 and F2 pup weights on lactation days 14 and 21 (EPA 1989). No significant differences with controls were observed at 100 mg DEET/kg/day compared to controls. In addition, F1 males from all treated groups (25, 100, and 250 mg/kg/day) showed a dose-related increased incidence of gross and microscopic lesions in the kidneys. The lesions included inflammation, hyaline droplet and granular cast formation, and regeneration of tubules. The reduction in pup weights was used to derive an intermediate-duration oral MRL for DEET.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No studies were located regarding cancer effects in humans following oral exposure to DEET.

One publication of three studies was located that examined the potential carcinogenicity of DEET in animals following oral exposure, and negative results were reported in the three species tested (dogs, rats, and mice) (Schoenig et al. 1999). Male and female Beagle dogs were dosed by capsule with up to 400 mg DEET/kg/day for 52 weeks; male CD rats were dosed with up to 100 mg/kg/day and female CD rats were dosed with up to 400 mg/kg/day via the diet for 104 weeks; and male and female CD-1 mice were dosed with up to 1,000 mg/kg/day via the diet for 78 weeks.

3.2.3 Dermal Exposure

3.2.3.1 Death

Five deaths have been associated with dermal exposure to DEET and three of them occurred in children. Zadikoff (1979) reported the case of a 5-year-old girl who had been sprayed nightly for almost 3 months with an insect repellent containing 10% DEET and subsequently developed progressively severe headaches starting 10 days prior to hospitalization. On admission, the child was extremely agitated, restless, and irritable with constant involuntary movements involving the head, trunk, and all limbs. This

was interrupted periodically by short episodes of quiet, shaking, crying, and screaming. Shortly thereafter, she developed a generalized convulsion and for the next 24 days, she was treated with various combinations and doses of drugs to control the hyperactivity, which eventually become intractable even with haloperidol treatment. An autopsy revealed generalized edema of the brain with intense congestion of the brain and meninges. The second case was a 6-year-old girl who in response to repeated black fly bites used a spray containing 15% DEET on at least 10 occasions on extensive areas of skin and developed a clinical picture similar to Reye syndrome or ornithine carbamoyl transferase deficiency (Heick et al. 1980). On the fifth day in the hospital, the child developed generalized convulsions followed by coma, and on the seventh and eighth day, the EEG became flat and supportive therapy was discontinued. Autopsy showed edematous brain. Based on tests, it was hypothesized that the child might have been a carrier of OCT deficiency, a potential lethal hyperammonemic condition, which may have contributed to her death. Pronczuk de Garbino et al. (1983) briefly described the case of a 17-month-old girl who was admitted to the hospital with a diagnosis of acute encephalopathy of unknown origin. During 3 weeks prior to admission, the child had received repeated applications of a lotion containing DEET. The child rapidly deteriorated and died before further toxicological information could be obtained, but DEET-induced toxicity was strongly suspected. In a study of insect repellent reports to the AAPCC, Bell et al. (2002) identified two deaths (a 26-year-old male and a 34-year-old female) following dermal exposure to >50% DEET. The male, who had applied a 52% DEET repellent liberally throughout the day, developed dyspnea, seized, vomited, unsuccessfully underwent cardio-pulmonary resuscitation, and was taken to the emergency department where he died within 2 hours of the initial seizure. Of the tissues tested, DEET levels were elevated only in the blood. Little information was available for the female, but exposure duration was reported as chronic with the only effect being an adverse dermal reaction. It should be noted that in all of these cases, excessive exposure appears to have occurred.

Limited information was located regarding lethal doses in animals exposed dermally to DEET. Carpenter et al. (1974) reported that the dermal LD_{50} in New Zealand White rabbits was 3,167 mg/kg (per Table 3-3). DEET was applied to a shaved area of the skin that was covered for 24 hours; the observation period was 14 days. EPA (1998b) indicated that the dermal LD_{50} in rabbits (strain not specified) was 4,280 mg/kg.

The LD_{50} from the Carpenter et al. (1974) is presented in Table 3-3.

Table 3-3 Levels of Significant Exposure to DEET - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
ACUTE EXPOSURE									
Death									
Rabbit (New Zealand)	24 hr					3167 M mg/kg	(LD50)	Carpenter et al. 1974	
Systemic									
Gn Pig (albino)	10 d 1 x/d	Dermal		1 mL	(slight erythema)			Ambrose 1959	10% DEET was used. DEET was not a skin sensitizer.
Rabbit (albino)	24 hr	Dermal	4000 mg/kg					Ambrose 1959	Reported erythema was due to mechanical irritation.
Rabbit (albino)	once	Ocular				0.05 mL	(severe eye irritation)	Ambrose 1959	
Rabbit (New Zealand)	once	Ocular		10 mg	(moderate eye irritation)			MacRae et al. 1984	

Table 3-3 Levels of Significant Exposure to DEET - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
INTERMEDIATE EXPOSURE							
Systemic							
Rat (CD)	13 wk 1 x/d	Resp	1000 B mg/kg/day			EPA 1988	NOAELs are for organs or tissue histopathology.
		Cardio	1000 B mg/kg/day				
		Gastro	1000 B mg/kg/day				
		Hemato	1000 B mg/kg/day				
		Musc/skel	1000 B mg/kg/day				
		Hepatic	1000 B mg/kg/day				
		Renal		100 M mg/kg/day (granular casts; inflammation, hyaline droplets)			
		Endocr	1000 B mg/kg/day				
		Dermal		100 B mg/kg/day (skin scaling; acanthosis/hyperkeratosis)			
		Ocular	1000 B mg/kg/day				
		Bd Wt	1000 B mg/kg/day				

Table 3-3 Levels of Significant Exposure to DEET - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Rat (CD)	13 wk 1 x/d	Metab	1000 B mg/kg/day				EPA 1988	NOAELs are for organs or tissue histopathology.
Rat (CD)	90 d 5 d/wk	Renal		1000 M mg/kg/day	(hyaline nephropathy)		EPA 1990a	
		Dermal		1000 M mg/kg/day	(increased incidence of erythema)			
		Bd Wt	1000 M mg/kg/day					
Rat (Sprague-Dawley)	9 wk 5 d/wk	Hepatic	1000 M mg/kg/day				Lebowitz et al. 1983	Liver and kidney NOAELs are for organ weight.
		Renal	1000 M mg/kg/day					
		Bd Wt	1000 M mg/kg/day					
Rabbit (albino)	13 wk 5 d/wk	Dermal		1000 B mg/kg	(skin irritation)		Ambrose 1959	
		Bd Wt	1000 B mg/kg					

Table 3-3 Levels of Significant Exposure to DEET - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
Pig Micropigs	90 d 5 d/wk	Resp	1000 B mg/kg/day			EPA 1992a	NOAELs are for organ and tissue histopathology.
		Cardio	1000 B mg/kg/day				
		Gastro	1000 B mg/kg/day				
		Hemato	1000 B mg/kg/day				
		Musc/skel	1000 B mg/kg/day				
		Hepatic	1000 B mg/kg/day				
		Renal	1000 B mg/kg/day				
		Endocr	1000 B mg/kg/day				
		Dermal		100 B mg/kg/day	(skin desquamation; hyperkeratosis)		
		Ocular	1000 B mg/kg/day				
		Bd Wt	1000 B mg/kg/day				

Table 3-3 Levels of Significant Exposure to DEET - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious		Serious			
Pig Micropigs	90 d 5 d/wk	Metab	1000 B mg/kg/day					EPA 1992a	NOAELs are for organ and tissue histopathology.
Immuno/ Lymphoret									
Rat (CD)	13 wk 1 x/d		1000 B mg/kg/day					EPA 1988	NOAEL is for histopathology of lymporeticular organs.
Pig Micropigs	90 d 5 d/wk		1000 B mg/kg/day					EPA 1992a	NOAEL is for histopathology of lymphoreticular tissues.
Neurological									
Rat (Sprague-Dawley)	60 d 1 x/d					40 M mg/kg/day	(diffuse neuronal cell death in brain regions)	Abdel-Rahman et al. 2001	
Rat (Sprague-Dawley)	30 d 1 x/d					40 M mg/kg/day	(neuronal degeneration in brain; impaired neurobehavior)	Abdel-Rahman et al. 2004	
Rat (Sprague-Dawley)	60 d 7 d/wk			4 M mg/kg/day	(impaired sensorimotor performance)			Abou-Donia et al. 2001a	
Rat (Sprague-Dawley)	45 d 1 x/d			40 M mg/kg/day	(impaired sensorimotor function)			Abou-Donia et al. 2001b	

Table 3-3 Levels of Significant Exposure to DEET - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference Chemical Form	Comments
Rat (CD)	13 wk 1 x/d		1000 B mg/kg/day			EPA 1988	NOAEL is for histopathology of the brain and spinal cord.
Rat (Sprague-Dawley)	30 d 1 x/d		40 B mg/kg/day			Fediuk et al. 2010	NOAEL is for neurobehavioral function.
Pig Micropigs	90 d 5 d/wk		1000 B mg/kg/day			EPA 1992a	NOAEL is for histopathology of brain, spinal cord, and sciatic nerve.
Reproductive							
Rat (CD)	13 wk 1 x/d		1000 B mg/kg/day			EPA 1988	NOAEL is for histopathology of the reproductive organs.
Rat (Sprague-Dawley)	9 wk 5 d/wk		1000 M mg/kg/day			Lebowitz et al. 1983	NOAEL is for testes histopathology and sperm count and viability.
Pig Micropigs	90 d 5 d/wk		1000 B mg/kg/day			EPA 1992a	NOAEL is for histopathology of reproductive organs.

Table 3-3 Levels of Significant Exposure to DEET - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL		Reference Chemical Form	Comments
				Less Serious	Serious		
CHRONIC EXPOSURE							
Systemic							
Mouse Swiss	140 wk 2 x/wk	Dermal	20 F mg			Stenback 1977	
		Bd Wt	20 F mg				
Rabbit (New Zealand)	90 wk 2 x/wk	Dermal	20 B mg			Stenback 1977	

B = both; Bd Wt = body weight; d = day(s); F = Female; Gn pig = guinea pig; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; wk = weeks(s); x = time(s)

3.2.3.2 Systemic Effects

No studies were located regarding body weight effects in humans following dermal exposure to DEET.

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

Respiratory Effects. The only information regarding respiratory effects in humans exposed to DEET is that provided by a survey of 143 workers of the Everglades National Park, Florida (NIOSH 1986). Based on the reported use of insect repellent sprays or lotions, the workers were classified as low exposure (n=44, non-users), medium exposure (n=55; <4.25 g DEET/week), or high exposure (n=44, >4.25 g DEET/week). Concentrations of DEET in the repellents used varied from 15 to 75% in the sprays and from 30 to 100% in the lotions. The survey found that complaints of chest pain or wheezing were significantly elevated ($p<0.05$) in the high-exposure group (30%) compared to the medium- (9%) or low-exposure (11%) groups. It should be noted that exposure was inferred from only survey responses, a notable weakness. Because no actual quantification was possible, the findings from this report should be interpreted with caution.

Application of up to 1,000 mg DEET/kg/day for 13 weeks onto the shaved back of micropigs or CD rats did not induce gross or microscopic alterations in the respiratory tract, although details were not reported (EPA 1988, 1992a).

Cardiovascular Effects. Hypotension and orthostatic change in blood pressure were described in a case of an adult woman after spraying herself with a DEET-containing insect repellent (Clem et al. 1993). For years she had used a product containing 14.25% DEET without adverse effects, but, that day she used a product with higher (but unspecified) percent of DEET and completely wetted most of her body with it. An ECG performed on admission showed marked sinus bradycardia (44 beats/min), but a repeat ECG performed 1 hour later showed no abnormalities. In a case report of an 18-month-old boy who was having seizures after being applied an unknown amount of an insect repellent containing 17.6% DEET, an ECG performed on arrival to a medical center was within normal limits (Briassoulis et al. 2001).

Blood pressure appeared unaffected in two case reports of death from DEET overexposure, with respective values of 110/65 mm Hg for a 5-year-old girl (Zadikoff 1979) and 108/68 mm Hg for a 6-year-old girl (Heick et al. 1980), but was slightly elevated at 140/86 mm Hg in a 27-year-old man who

survived after significant medical treatment (Hampers et al. 1999). Heart rate was elevated in the first case (135/min), normal in the second (66/min), and elevated in the third (104/min). A study conducted in nine volunteers to determine the impact of 33% DEET lotion on various physiological measures, including heart rate, during exercise-heat stress reported no significant differences in heart rate between controls and those who applied DEET (Kenefick et al. 2011). The investigators had hypothesized that DEET lotion would impair measures of sweating and evaporation and thus increase strain and discomfort, which it did not.

Application of up to 1,000 mg DEET/kg/day, 5 days/week for 13 weeks onto the shaved back of micropigs or CD rats did not induce gross or microscopic alterations in the heart and aorta, although details were not reported (EPA 1988, 1992a).

Gastrointestinal Effects. The only relevant information with regard to gastrointestinal effects is from a report by Clem et al. (1993), which states that a 61-old-woman developed nausea, vomiting, and explosive diarrhea after spraying herself liberally with a high percentage DEET insect repellent. The possibility that this was coincidental, however, cannot be ruled out.

Application of up to 1,000 mg DEET/kg/day, 5 days/week for 13 weeks onto the shaved back of micropigs or CD rats did not induce gross or microscopic alterations in the gastrointestinal tract, although details were not reported (EPA 1988, 1992a).

Hematological Effects. Several studies provided information regarding hematological effects following dermal exposure to insect repellents that contained DEET. The majority involve single case reports of children 6-years-old or younger that found no significant deviations from normal limits for red and white blood cell counts (Briassoulis et al. 2001; Heick et al. 1980; Lipscomb et al. 1992; Roland et al. 1985; Zadikoff 1979). The one case in which leukocytosis (16,900/mm^3 or $1.69x10^{10}$/L) was observed involved an 18-months-old girl who had been sprayed daily with an insect repellent containing 20% DEET for approximately 3 months prior to admission (Edwards and Johnson 1987). Clem et al. (1993) and Hampers et al. (1999) reported single cases of intoxication in adults. Both cases had signs and symptoms severe enough to warrant a visit to the emergency department. Hematological parameters were measured and were within normal limits.

Application of up to 1,000 mg DEET/kg/day, 5 days/week for 13 weeks days onto the shaved back of micropigs or CD rats did not induce significant alterations in hematological parameters, although details were not reported (EPA 1988, 1992a).

Musculoskeletal Effects. In the survey of 143 employees of the Everglades National Park, Florida, symptoms of muscle cramping were significantly ($p<0.05$) increased in the medium- (24%) and high- (25%) exposure groups compared to the low-exposure (7%) group (NIOSH 1986).

Application of up to 1,000 mg DEET/kg/day, 5 days/weeks for 13 weeks onto the shaved back of micropigs or CD rats did not induce gross or microscopic alterations in skeletal muscle or bone (femur), although details were not reported (EPA 1988, 1992a).

Hepatic Effects. Four case reports of intoxication of children following dermal exposure to insect repellents containing DEET stated that liver function tests performed shortly after admission to an emergency center were within normal limits (Edwards and Johnson 1987; Lipscomb et al. 1992; Roland et al. 1985; Zadikoff 1979). In the case reported by Zadikoff (1979), the 5-year-old girl died 24 days after admission. In an additional case of dermal intoxication of a 6-year-old girl who eventually died 8 days after admission to the hospital, Heick et al. (1980) reported significantly elevated serum enzymes measured on the fifth day in the hospital. Necropsy showed an enlarged liver with no other abnormalities in appearance. Histological and ultrastructural examination of the liver suggested a nonspecific hepatic injury.

Liver weight was increased, but not significantly, in male Sprague-Dawley after receiving applications of up to 1,000 mg undiluted DEET/kg/day onto the shaved dorsal skin 5 days/week for 9 weeks (Lebowitz et al. 1983). Application of 1,000 mg DEET/kg/day (the highest dose tested) onto the shaved back of male and female CD rats for 13 weeks induced significant increases in absolute and relative liver weight; the same was observed in females that received doses of 300 mg DEET/kg/day (EPA 1988). In addition, males from all treated groups (100, 300, and 1,000 mg DEET/kg/day) had vacuolar change in the liver (significant only in the mid-dose group), which were considered an adaptive response; no vacuolar changes were seen in females. Application of up to 1,000 mg DEET/kg/day, 5 days/week for 13 weeks onto the shaved back of micropigs did not induce gross or microscopic alterations in the liver, nor did it affect serum levels of transaminases, although details were not provided (EPA 1992a).

Renal Effects. Few studies reported the results of renal tests following dermal intoxication with insect repellents containing DEET. Two case reports of children (Briassoulis et al. 2001; Roland et al. 1985) and one case of an adult exposed to DEET (Clem et al. 1993) all reported levels of blood urea nitrogen and creatinine within normal limits in the patients upon arrival at the emergency department.

Application of up to 1,000 mg undiluted DEET/kg/day onto the shaved back of male Sprague-Dawley rats 5 days/week for 9 weeks increased kidney weight at 36, 65, and 95 days, and the increase was significant at 65 days (Lebowitz et al. 1983). A study on male CD rats that received applications of 1,000 mg undiluted DEET/kg/day, 5 days/week for 90 days with microscopic examination of the kidneys reported a significant increased incidence of granular casts and hyaline droplets, as well as inflammation and regeneration of renal tubular epithelium in treated rats compared to controls in both castrated and non-castrated rats (EPA 1990a). The test was performed to assess whether testosterone caused greater effects of DEET on males, but both relative kidney weights and histopathology results indicated that the renal effects of DEET were not enhanced by this hormone. A similar study in CD rats reported slight, but statistically significant, increases in blood urea nitrogen in males exposed to ≥300 mg DEET/kg/day (EPA 1988). In addition, gross necropsy showed enlarged kidneys in males from all exposed groups (100, 300, and 1,000 mg DEET/kg/day), with pale and granular appearance in males exposed to ≥300 mg/kg/day. Microscopic examination showed an increased incidence of renal lesions in all males consisting of granular casts, inflammation, regeneration, and hyaline droplets. High-dose females had a small increase in hyaline casts and inflammation, but the hyaline cast in females was, reportedly, different from that of males (no further details were provided). As mentioned in Chapter 2, the hydrocarbon-induced nephropathy has only been demonstrated in adult male rats and has been linked to a specific protein, $\alpha_{2\mu}$-globulin, which is produced under hormonal control by the liver (Alden 1986; Swenberg 1993). However, the $\alpha_{2\mu}$-globulin is unique to male rats and is not present in human kidneys. Hence, this particular nephropathy has no significance for humans and would therefore be inappropriate to use for evaluation of human health effects or risk assessment. Application of up to 1,000 mg DEET/kg/day, 5 days/week for 13 weeks onto the shaved back of micropigs did not induce gross or microscopic alterations in the kidneys, nor did it affect serum creatinine levels, although details were not reported (EPA 1992a).

Endocrine Effects. In the case report of a 5-year-old girl admitted to the emergency department after being sprayed repeatedly with an insect repellent containing 10% DEET, Zadikoff (1979) stated that thyroid function studies were within normal limits. No other study provided information regarding endocrine effects in humans following dermal exposure to DEET.

Application of up to 1,000 mg DEET/kg/day, 5 days/week for 13 weeks onto the shaved back of micropigs or CD rats did not induce gross or microscopic alterations in the adrenals, thyroid, parathyroid, or pituitary glands, although details were not provided (EPA 1988, 1992a).

Dermal Effects. A low incidence of adverse dermal effects has been reported in humans following application of insect repellents containing DEET in the form of lotions or sprays. It should be noted, however, that the paucity of consumer adverse effect reports, considering the billions of product applications that have occurred in the 60-year history of DEET usage as an active ingredient in insect and acarid repellent, suggests that DEET is generally safe for consumer use if instructions for application are followed.

In an early study in five volunteers (for which further information on informed consent was not provided), application of 1mL of a 50% solution of DEET in isopropanol to the face and 2 mL to the arms once per day for 5 consecutive days did not cause irritation on the arms, but caused a feeling of dryness and astringency in both face and arms (Ambrose 1959). DEET applied to the face also caused desquamation around the nose and some feeling of dryness and astringency. One subject who applied undiluted DEET to the face for 6 weeks showed desquamation around the nose after the third day; each time desquamation appeared, applications were stopped and desquamation disappeared usually within 2 days, and then treatment was resumed. No other signs or symptoms were noted.

MMWR (1989) and Wantke et al. (1996) reported two cases of children who developed non-immunological urticaria following applications of insect repellents containing DEET. In the case described by Wantke et al. (1996), a 4-year-old boy with no history of prior insect repellent application developed urticarial and a generalized itch within minutes of applying a 25% DEET product. Patch testing revealed that the boy's skin was highly sensitive, and that his cutaneous hyperreactivity was not specific to DEET. Wantke et al. (1996) concluded that the boy appeared to have developed non-immunologic, chemical-induced generalized urticaria from the insect repellent. Roland et al. (1985) reported the case of an 8-year-old girl with reportedly sensitive skin who developed a raised, erythematous pruritic rash on her face and extremities 2 days after applying copious amounts of Off!® to those skin areas for that period. On the third day that she applied Muskol®, she experienced convulsions and seizures by the next morning, and was hospitalized. After a 2-day stay at a hospital to treat neurological effects, the rash faded. Results indicated this was a hypersensitivity reaction to DEET.

A group of soldiers developed acute dermatitis 18–24 hours after applying an insect repellent containing 50% DEET before sleep to the uncovered skin of the face, neck, upper part of the trunk, and legs (Reuveni and Yagupsky 1982). All of the subjects complained of a burning sensation and showed erythema of the antecubital fossa of one or both arms where applications could pool or be confined and macerated with sweat in the flexures. Subsequent examination showed progression of the erythema to hemorrhagic blister formation, and in some cases deep ulcerations in 1–2 days. Amichai et al. (1994) reported another single case of acute dermatitis of the antecubital fossa in a soldier who developed a burning sensation and skin eruption about 8 hours after applying an insect repellent containing 33% DEET the previous night. The symptoms did not recur following re-exposure. A survey of 143 employees of the Everglades National Park, Florida, who used DEET regularly in their work, showed that more highly exposed workers had a significantly higher ($p<0.05$) prevalence (27%) of skin rash and blisters than those with medium exposure (14%) or those with low (7%) exposure (NIOSH 1986).

An acute study with occluded application of 2 or 4 mL undiluted DEET (approximately 2,000 or 4,000 mg) to the depilated torsos of albino rabbits (of which the skin was slightly abraded on half of the animals) for 24 hours resulted in mild to moderate erythema on all animals (Ambrose 1959). Slightly more erythema was present on the abraded areas of skin and on the ventral compared with flanks and dorsal surfaces. An evaluation concluded that the greater degree of erythema observed on ventral surfaces was due to mechanical action rather than to increased heat in that area.

Uncovered repeated application of 1 mL DEET/kg (approximately 1,000 mg/kg/day) to albino rabbits 5 days/week for 13 weeks resulting in cutaneous irritation starting at about the third application of DEET Ambrose 1959). The effect was characterized by slight to moderate erythema, desquamation, and dryness of the skin. The erythema disappeared over the weekend but not the desquamation or skin dryness. The skin became leathery, hard, and dry and fissures developed after the third or fourth week of treatment in some rabbits. Desquamation persisted and remained throughout the study. Although scarring was present in some rabbits, most skin alterations had disappeared three weeks after the last dose. Application of doses of 1,000 mg neat technical DEET/kg/day to the back of male CD rats 5 days/week for 90 days resulted in increased incidence of erythema (EPA 1990a). A similar study in which CD rats received applications of 100, 300, or 1,000 mg DEET/kg/day (in volumes of 0.1, 0.3, and 1.0 mL/kg) for 13 weeks reported increased incidence of red and scabbed areas at the application site for both male and female rats (EPA 1988). Microscopic examination of the skin showed increased incidence of acanthosis and/or hyperkeratosis. Application of ≥100 mg DEET/kg/day (as a mixture consisting of equal parts of technical-grade DEET from four manufacturers) to the back of micropigs 5 days/week for 13 weeks

resulted in skin desquamation (EPA 1992a). Microscopic examination of two unspecified application sites on dorsal and lateral surfaces at termination showed dose-related increased incidence of hyperkeratosis at ≥100 mg DEET/kg/day in males and ≥300 mg DEET/kg/day in females. Acanthosis at application site A was observed only in males and showed a threshold response at 1,000 mg DEET/kg/day, while at site B/C, the effect was dose-related at ≥300 mg DEET/kg/day (EPA 1992a).

No skin lesions were reported in a chronic-duration study in male Swiss mice and in male and female New Zealand White rabbits that received applications of 0.02 mL of a 10, 50, or 100% solution of DEET (2, 10, or 20 mg DEET) for 2 times/week (140 weeks in mice, 90 weeks in rabbits) (Stenback 1977).

DEET was not a skin sensitizer in guinea pigs or in rabbits (Ambrose 1959).

Ocular Effects. In the study of 20,764 human exposures involving insect repellents containing DEET that were reported to poison control centers from 1993 to 1997, 4,422 were identified as being exposed predominantly by accidental contact of an insect repellent spray with the eyes (Bell et al. 2002). Six of those (three children and three adults) experienced major ocular symptoms. Common signs and symptoms reported in these subjects included ocular irritation/pain and lacrimation.

A study in CD rats applied up to 1,000 mg DEET/kg/day onto the shaved back daily for 13 weeks reported that ophthalmological examinations conducted at week 13 showed no compound-related effects (EPA 1988). A study in albino rabbits examined the ocular effects of three different DEET preparations: 100% undiluted (1 drop, 0.04 mg), 30% DEET in cottonseed oil (3 drops, ~0.04 mg), or a 40% emulsion in vegetable lecithin with ethanol and water (3 drop, ~0.05 mg) (Ambrose 1959). Two hours after application to the conjunctival sac, there did not seem to be significant differences in the degree of eye injury induced by the three preparations, but it appeared that the emulsion was slightly more irritating. DEET induced moderate to marked edema of the nictitating membrane, lacrimation, conjunctivitis, and pus, which were still present 48 hours after application. Three rabbits also showed some cloudiness. All treated eyes showed varying degrees of injury as revealed by fluorescein staining. Some effects seen at 48 hours were still seen 72 hours after application, but were not as severe. After 5 days, fluorescein staining was negative and all eyes were considered to have a normal appearance by the investigator, suggesting that the eye injuries were probably not permanent. Another study in rabbits reported that 0.01 mL of undiluted DEET (approximately 10 mg) caused moderate eye irritation, as indicated by increased corneal thickness and fluorescein staining, swelling of the conjunctiva, corneal cloudiness, and iris reaction (MacRae et al. 1984). The eye returned to a normal appearance by 168 hours. Application of up

to 1,000 mg DEET/kg/day 5 days/week for 13 weeks onto the shaved back of micropigs did not induce gross or microscopic alterations in the eyes, although details were not provided (EPA 1992a).

Body Weight Effects. Repeated applications of approximately 1,000 mg DEET/kg/day to a shaved area of the skin of Sprague-Dawley rats or albino rabbits did not significantly affect body weight (Ambrose 1959; Lebowitz et al. 1983). Similar findings were reported in male Swiss mice applied 20 mg DEET (approximately 666–1,000 mg/kg/day assuming a body weight of 0.02–0.03 kg for the mice) for 140 weeks (Stenback 1977). Body weight was not significantly affected (<10% difference with controls) in CD rats or micropigs that received applications of up to 1,000 mg DEET/kg/day onto the shaved back for 13 weeks (EPA 1992a).

Metabolic Effects. Several studies of children intoxicated after skin application of insect repellents containing DEET reported levels of glucose and serum electrolytes within normal limits upon admission to emergency centers (Briassoulis et al. 2001; Edwards and Johnson 1987; Gryboski et al. 1961; Heick et al. 1980; Roland et al. 1985; Zadikoff 1979). Similar findings were reported by Hampers et al. (1999) in their description of an adult case of poisoning.

Application of up to 1,000 mg DEET/kg/day, 5 days/week for 13 weeks onto the shaved back of micropigs did not induce alterations in serum electrolytes or glucose levels, although details were not reported (EPA 1992a). Tests conducted in male and female CD rats that received applications of 1,000 mg DEET/kg/day, 5 days/week for 13 weeks showed a significant decrease in serum glucose in males, which was considered not biologically significant by the investigators (EPA 1988). Serum electrolyte levels were within normal ranges in that study.

3.2.3.3 Immunological and Lymphoreticular Effects

A few cases of contact urticaria by immunological mechanisms have been reported in humans after using products containing DEET. Immunological contact urticaria is a type I hypersensitivity reaction that is mediated by antigen-specific IgE in individuals who previously have been sensitized (Shutty et al. 2013). Maibach and Johnson (1975) reported the case of an elderly woman who discovered that she had allergic contact dermatitis to DEET containing products after self-experimentation with insect repellents over four summers (applying them, observing a rash form immediately, and then noting that the rash disappeared upon washing off the 0.1, 1, and 100% substance). Patch test application of three active ingredients of repellents (dimethylphthalate, DEET, and butopyronoxyl), along with their inactive components, to intact

skin showed that DEET was the substance causing the immediate urticaria. Application of pure samples of DEET gave similar responses. Testing with 18 structurally-related analogs of DEET and similar substances showed that the response depended on the nature and positions of those substances that were substituted on the benzene ring. It was determined that active structures required *ortho*, *meta*, or both positions to be fluoromethylated, inactivation occurred if the *para* position was so filled (as if full activation needed access to the *meta* site for hydroxylation), the molecule needed a benzoyl structure, and the response may be mediated by histamine. Serum from the patient was injected into two volunteers who had an injection site response to DEET, indicating the patient's response could be passively transferred. Results suggested that the mechanism of action was immunologic, and its passive transferability indicated a deficiency in the patient's immune system. A similar case was reported by Vozmediano et al. (2000) in a 16-year-old girl who historically experienced disproportional reactions to insect bites and developed a skin reaction accompanied by increasingly evident edema and severe pruritus after regularly applying a lotion containing 20% DEET. The authors conducted an open skin test using that product and 0.1%, 1% and 100% DEET. The product and higher two concentrations resulted in a raised area, considered to be an immunologic contact urticarial. More recently, Shutty et al. (2013) described the case of a 22-year-old man who developed contact urticaria immediately after application of an insect repellent. The patient reported consistently avoiding DEET-containing products since previous contact with them had resulted in welts, and he had recently developed hives after contact with individuals who had used DEET-containing repellents. Because it was unclear what ingredient produced the urticaria, open patch testing of the patient with DEET and picaridin (another common insect repellent) was conducted. There were positive responses in tests areas receiving applications of 7% DEET and 7% DEET in ethanol, but no dermal response in areas to which 5% picaridin and 5% picaridin in ethanol were applied.

Application of up to 1,000 mg DEET/kg/day, 5 days/week for 13 weeks onto the shaved back of CD rats or micropigs did not induce gross or microscopic alterations in spleen, thymus, or lymph nodes, although details were not provided (EPA 1988, 1992a).

3.2.3.4 Neurological Effects

There have been sporadic reports over the last several decades of adverse neurological effects in adults and children following dermal application of insect repellents containing DEET. It should be noted, however, that in all cases, excessive amounts of the insect repellent may have been applied. A few representative studies are mentioned below, and additional references can be found in review articles

(Antwi et al. 2008; Bell et al. 2002; Osimitz and Murphy 1997; Qiu et al. 1998; Sudakin et al. 2003; Veltri et al. 1994). In almost all cases, exposure involved repeated applications of an insect repellent on multiple days but in at least three cases, neurological effects developed after a child received a single application (Briassoulis et al. 2001; Lipscomb et al. 1992) and after an adult received a few applications in the same day (Hampers et al. 1999). The amount applied was not known in either case, but Lipscomb et al. (1992) reported that the child received a virtual total body application of an insect repellent containing 95% DEET. Hampers et al. (1999) reported that the adult male had applied 20% DEET sunscreen lotion early in the day and a 25% DEET spray several times later that day to his arms, neck, and legs, resulting in the acute onset of parathesias of limbs and face, then progressive hallucinations and confusion, followed by combativeness. The emergency department neurological examination identified tremors in all extremities and a hypertonic state. He was unresponsive to haloperidol, diazepam, and phenytoin treatment, and required further medication, intubation, and mechanical ventilation. On day 2, he was off the ventilator, and on day 3, his mental state appeared normal, although he still had headaches. All effects had resolved after a week.

Neurological signs and symptoms reported in children and adults include seizures, ataxia, restlessness, uncontrolled limb movements, agitation, aggressive behavior, combativeness, impaired cognitive functioning, and opisthotonos (Briassoulis et al. 2001; Edwards and Johnson 1987; Gryboski et al. 1961; Hampers et al. 1999; Heick et al. 1980; NIOSH 1986; Pronczuk de Garbino et al. 1983; Roland et al. 1985; Snyder et al. 1986; Zadikoff 1979), or headaches that progressively worsen or are long lasting (Hampers et al. 1999; Zadikoff 1979). Some milder symptoms included insomnia, muscle cramping, mood disturbances, and difficulty with starting or stopping urination (NIOSH 1986). The combination of some of these signs and symptoms has been described as toxic encephalopathy, and Zadikoff (1979) considered that this spectrum of symptoms could result in misdiagnosis as viral encephalitis. Five deaths occurred among these cases (Bell et al. 2002; Heick et al. 1980; Pronczuk de Garbino et al. 1983; Zadikoff 1979). Osimitz and Murphy (1997) examined 14 cases that reported neurological effects following dermal exposure to DEET and concluded that causality is difficult to establish because of limitations in clinical details provided in the reports. The investigators noted that 8 of the 14 patients may have had idiopathic seizures, 1 may have had an exanthematous illness and a convulsion, 3 may have had an inflammatory process affecting the central nervous system, and 1 was heterozygous for ornithine carbamoyl transferase deficiency, but synergisms with DEET were not excluded. There was insufficient information on an additional patient to determine if there were alternate explanations for the patient's encephalopathy.

In a study of 20,764 human exposures involving insect repellents containing DEET that were reported to poison control centers from 1993 to 1997, 2,179 were identified as having been exposed predominately by skin contact (Bell et al. 2002). Of these, 118 exhibited minor neurologic symptoms that included dizziness/vertigo, headache, and drowsiness/lethargy. The severe symptoms among these cases included tremors (15), single seizures (8), muscle weakness (10), muscle rigidity (5), peripheral neuropathy (5), slurred speech (3), and paralysis (1).

In an early study in five volunteers, application of approximately 1 mL of a 50% solution of DEET in isopropanol to the face (i.e., enough to completely wet each area) once per day for 5 consecutive days induced a slight tingling sensation in all the subjects (Ambrose 1959). No other neurological signs or symptoms were noted.

Haley and Kurt (1997) conducted a cross-sectional survey of 249 Gulf War veterans in order to identify risk factors of war-related syndromes. The extent of exposure to DEET was assessed by self-estimation of the number of times per day repellent was typically applied. Independent risk factors were identified by performing a series of adjusted, stepwise logistic regression analyses that required a level of significance of $p<0.005$ for a variable to enter and remain in a logistic regression model. The results of the analyses showed that the prevalence of a syndrome termed arthro-myo-neuropathy increased with the amount of insect repellent used ($p<0.005$ for a univariate association and $p<0.001$ for trend). This association held true for those who used government-issued repellent (75% DEET in ethanol) (odds ratio [OR] of 1.54; 95% confidence interval [CI] of 1.17–2.03), but not for those who reported using a formulation containing ≤31% DEET or one containing no DEET. While the latter gives biological plausibility to the results, assessing exposure by self-recollection limits the validity of the study conclusions.

A series of animal studies have been conducted to examine the neurological effects of DEET applied to the skin of animals alone and in combination with other chemicals used by military personnel in the Persian Gulf War. This section summarizes the effects of DEET alone; information regarding interactions of DEET with other chemicals is presented in Section 3.9, Interactions with Other Chemicals. It should be mentioned, however, that some of these studies seem to have some deficiencies in reliability, as explained below (Jortner 2006; Schoenig 2002).

In an intermediate-duration study, relatively low doses of 4 mg/kg/day DEET (as 10 mg/mL in 70% alcohol) applied daily to 1 in^2 of the back of the neck skin of male Sprague-Dawley rats for 60 days did

not affect simple sensorimotor reflexes tested 30–60 days after exposure ceased, but affected some sensory parameters such as performance on a beam, grip strength, and performance on an inclined plane (Abou-Donia et al. 2001a). In addition, doses ≥4 mg DEET/kg/day decreased the permeability of the blood brain barrier mainly in the brainstem but also in the cerebellum, doses ≥40 mg DEET/kg/day decreased the permeability in the midbrain, and 400 mg DEET/kg/day decreased the permeability in the cortex. In a companion study, similar treatment with 40 mg DEET/kg/day (only dose tested) for 45 days was shown to significantly increase (by ~40%) acetylcholinesterase (AChE) activity in the brainstem but not in other brain areas and also to significantly increase (by ~20%) choline acetyltransferase (ChAT) activity in the cortex but not in the brainstem (Abou-Donia et al. 2001b). DEET also significantly increased ligand binding to m2 muscarinic acetylcholine receptors in the cortex, but did not affect ligand binding of nicotinic receptors in the cortex. Gross and microscopic examination of the brain of the treated rats showed neuronal degeneration principally in the motor cerebral cortex, dentate gyrus, CA1 and CA3 subfields of the hippocampus, and the Purkinje cell layer of the cerebellum (Abdel-Rahman et al. 2001). In a subsequent study, the same group of investigators confirmed the findings regarding the neurobehavioral effects and histological effects in the various brain areas (Abdel-Rahman et al. 2004). Contrary to what was reported in a previous study (Abou-Donia et al. 2001b), however, in the more recent study (Abdel-Rahman et al. 2004), DEET was reported to statistically significantly increase (rather than have no effect) AChE activity in the cortex and cerebellum but not in the brainstem (which earlier was increased by 40%) and to have no significant effect on the ligand binding to m2 muscarinic acetylcholine receptors in the cortex. No explanation was provided for these apparent discrepancies. It should also be mentioned that Fediuk et al. (2010) applied doses of 40 mg DEET/kg/day (as 100 mL DEET in 70% alcohol) to 4 cm^2 of the shaved back of Sprague-Dawley rats for 30 days, as did Abdel-Rahman et al. (2004) to 2.5 cm^2 (dose applied in 1 mL of 70% ethanol in water) for 60 days, and reported no significant alterations in various neurobehavioral tests that assessed arousal, locomotion, habituation, and motor coordination. The reason for the difference in the result between these two studies (other than the area of skin exposed, duration of exposure, and concentration of DEET in the alcohol vehicle) is not apparent. Regarding the histological findings in the Abdel-Rahman et al. (2001, 2004) reports, it was noted that there may have been misinterpretation of the findings (Jortner 2006). The main concern is that the report of “degenerating” or “dying” neurons in this article is actually the result of poor handling and inadequate fixation of the brain tissue and is a “dark” neuron artifact. The presence of this artifact suggests that both the neuron counting and the immunostaining procedures may have been compromised.

The studies by Abou-Donia and Abou-Rahman state that the doses of DEET, pyridostigmine bromide (PB), and permethrin used in their studies of rats were considered comparable to exposures received by

service members during the Persian Gulf War. The National Academy of Sciences (NAS) stated that "the primary studies of Veterans deployed to the Gulf War compared to Veterans not deployed do not demonstrate differences in cognitive and motor measures as determined through neurobehavioral testing." The NAS update committee concluded that "there is inadequate or insufficient evidence to determine if an association exists between deployment to the Gulf War and neurocognitive and neurobehavioral performance" (DVA 2011).

In studies in CD rats and micropigs, application of up to 1,000 mg DEET/kg/day to the shaved back 5 days/week for 13 weeks did not induce gross or microscopic alterations in the brain, sciatic nerve, or spinal cord, although details were not reported (EPA 1988, 1992a).

The NOAELs and LOAELs for neurological effects from the animal studies summarized above are presented in Table 3-3.

3.2.3.5 Reproductive Effects

No information was located regarding reproductive effects in humans following dermal exposure to DEET.

Three studies were located with information regarding reproductive effects in animals following dermal exposure to DEET. Application of up to 1,000 mg undiluted DEET/kg/day onto the shaved dorsal skin of male Sprague-Dawley rats for 5 days/week over a total for 9 weeks did not significantly affect sperm count or viability, nor did it induce sperm head abnormalities (Lebowitz et al. 1983). Application of 4–400 mg DEET/kg/day for 60 days to 1 cm^2 of skin on the necks of male Sprague-Dawley rats decreased blood-testis barrier permeability (but not in a dose-related manner) to approximately 75% of the control value (Abou-Donia et al. 2001). In addition, treatment with DEET did not affect testes weight, nor did it induce compound-related lesions in the testes. Application of up to 1,000 mg DEET/kg/day to the shaved back of CD rats or micropigs 5 days/week for 13 weeks did not induced gross or microscopic alterations in the reproductive organs, although details were not reported (EPA 1988, 1992a).

The doses of 1,000 mg DEET/kg/day (the highest dose tested) in rats and pigs is listed as a NOAEL for reproductive effects in Table 3-3.

3.2.3.6 Developmental Effects

Limited information is available regarding developmental effects in humans following dermal exposure to DEET from two single cases and two cohort studies. Schaefer and Peters (1992) reported the case of a 34-year-old woman who had been working in Africa where she continuously applied a lotion containing 25% DEET in addition to taking prophylactic chloroquine against malaria. Pregnancy was without complications and she delivered a boy of normal weight at the estimated date of birth. However, the boy was born with antimongoloid slant of the palpebral fissures, hypertelorism, thin lips, poorly developed philtrum, and a broad nasal bridge. During the first months of life, the boy developed statomotor retardation, muscular hypotonia, central hearing loss, and strabismus. Genetic testing did not show inborn errors of metabolism and there was no family history of genetic disorders. A possible role for chloroquine was ruled out given the safety of its prophylactic use. A causal relationship with DEET was not established. Hall et al. (1975) described two cases of children born with cardiac anomalies leading to congestive heart failure and diagnosis of coarctation of the aorta. The mothers, who were sisters, had used large amounts of insecticides (containing N-octyl bicycloheptene dicarboximide, piperonyl butoxide, allethrin, pyrethrins, and 2,2-dichlorovinyl dimethyl phosphate) and DEET in the insect repellent Off!® during a camping trip at about 8 weeks into their pregnancies. It is worth noting that the sisters were only together during the camping trip, that defects in the aortic arch segment occur between gestational weeks 6 and 10, and that there was a family history of heart problems on the father's side of one of the boys. In this study, the role of DEET, if any, cannot be determined. Although Hall et al. (1975) indicated that that multiple cases of familial coarctation are rare, others (e.g., Perera et al. 2014; Atalay and Kichilas 2011) have reported congenital aortic coarctation phenotypic malformations, and the latter reported three such individuals in two generations of the same family.

McGready et al. (2001) studied the effects of application of 1.7 g DEET/day in the second and third trimesters of 449 pregnant women as part of a double-blind trial of insect repellents in the prevention on malaria in Thailand. Controls consisted of 449 women who did not apply DEET. Women were followed for the duration of their pregnancy. Newborns were assessed for head and arm circumference and length; gestational age was assessed within 5 days of birth and neurological tests were conducted that assessed tone, movement, behavior, and visual and auditory alertness. Infants were followed up until 12 months of age for growth and basic developmental milestones. DEET was not detected in 30 urine samples from DEET-exposed women, but was detected in 4 of 50 samples of cord blood from women exposed to DEET. The results of the analyses did not reveal significant differences in the outcomes measured between offspring from exposed and non-exposed women. More recently, Barr et al. (2010) studied the

association between exposure to various pesticides (DEET among them) in a cohort of 150 New Jersey women and birth outcomes (birth weight, head circumference, abdominal circumference, and birth length). Exposure was assessed by measuring pesticides in maternal serum prior to birth and in cord blood after delivery. DEET was one of the pesticides most frequently detected in maternal and cord serum; the corresponding mean concentrations were 3.21 ng/g (range 1.82–18.84 ng/g) and 3.12 ng/ng (range 2.06–13.07 ng/g). The results of multivariable regression analyses carried out to minimize biases due to confounding factors ascertained that there was no significant association between DEET and the birth outcomes measured. The investigators noted that since blood was collected at birth, the exposure measured did not necessarily precede the birth outcomes measured. Also, there was no documentation of exposure by environmental measurements. Finally, many of the concentrations measured were near the limit of detection (LOD) of the analytical method.

No studies were located regarding developmental effects of DEET in animals following dermal exposure.

3.2.3.7 Cancer

Limited information exists regarding exposure to DEET and cancer in humans. A case-control study of testicular cancer and occupational exposures was conducted in Sweden (Hardell et al. 1998). Exposure to multiple occupations and chemical agents was assessed by self-administered questionnaires. The final analysis comprised 148 cases and 363 controls. The risk for testicular cancer among workers who used insect repellents (most containing DEET) for <115 days was not elevated based on 15 cases (OR 1.2, 95% CI 0.6–2.5). The OR for those using repellents for >115 days, however, was 2.3 (95% CI 1.2–4.4), based on 24 cases. Little information was presented in this study regarding how potential confounders were controlled; however, multivariate analysis found a significant interaction for those who were co-exposed to insect repellents and video display units (OR 2.5, CI 1.1–5.4). The investigators also noted that a previous study of this cohort had found an increased risk for testicular cancer associated with exposure to polyvinyl chloride (PVC) and that additives in PVC may also be used in the manufacture of insect repellents. Finally, assessment of exposure by self-recollection is known to be unreliable.

Another case-control study involved 513 men with non-Hodgkin's lymphoma (NHL) and 1,506 controls (McDuffie et al. 2005). The study found that simultaneous use of the pesticide mecoprop and DEET by farmers who wore rubber gloves resulted in higher odds ratios for NHL (OR 3.86, 95% CI 1.57–9.49) than farmers who either did not use DEET or did not use rubber gloves. The results were explained by DEET presumably increasing the permeability of the gloves to the phenoxyherbicide. Co-exposure to

DEET and the herbicide dicamba also resulted in increased risk with rubber gloves (OR 2.04, CI 1.02–4.06) or without them (OR 1.84, CI 1.23–2.75).

Only one study was located regarding cancer in animals after dermal exposure to DEET. In that study, 0.02 mL of a 10, 50, or 100% solution of DEET (2, 10, or 20 mg DEET) was applied over 1 in^2 of the skin of Swiss mice (50/exposure group, 100 unexposed controls) 2 times/week for 140 weeks. The incidence of tumors on the application site or at any remote site compared to controls did not increase (Stenback 1977). Additionally, fewer DEET-exposed mice developed tumors (36–50 vs. 58% for controls), and they had higher long-term survival rates (e.g., 12–26 vs. 6% for controls at 100 weeks). Dosing New Zealand White rabbits (5/group) in the same manner for 90 weeks also yielded negative cancer results (Stenback 1977).

3.3 GENOTOXICITY

No studies were located regarding genotoxic effects in humans exposed to DEET.

The only information regarding genotoxicity following *in vivo* exposure is that from a study in which Sprague-Dawley rats were applied a single dermal dose of 400 mg DEET/kg in 70% ethanol and the urine was collected and analyzed for the biomarker of DNA damage 8-hydroxy-2'-deoxyguanosine (Abu-Qare and Abou-Donia 2000). The results showed a significant increase ($p<0.05$) in the levels of the biomarker in urine over a 72-hour period after dosing. Maximum excretion was reached 24 hours after dosing, after which time excretion of 8-hydroxy-2'-deoxyguanosine leveled off.

Few studies have examined the genotoxicity of DEET in *in vitro* assays. Exposure of primary human nasal mucosal cells from the inferior and the middle turbinate to concentrations of DEET ranging from 0.5 to 1.0 mM (~0.1–0.2 µL/mL) for 60 minutes induced significant DNA damage, as quantified by the comet assay (Tisch et al. 2002). In another study with mammalian cells, DEET assayed to a cytotoxic level of ≥1.0 µL/mL for 18–20 hours did not induce unscheduled DNA synthesis in primary rat hepatocytes (EPA 1990c). In yet another study in mammalian cells, incubation of Chinese hamster ovary cells with up to 1.0 µL DEET/mL without activation (16 hours) or up to 0.5 µL DEET/mL with activation (2 hours) did not induce chromosomal aberrations (EPA 1990c). Mutagenicity studies conducted in prokaryotic organisms with or without metabolic activation yielded negative results (EPA 1990c; Zeiger et al. 1992). The results of the *in vitro* genotoxicity studies with DEET are summarized in Table 3-4.

Table 3-4. Genotoxicity of DEET *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	–	–	EPA 1990c
S. typhimurium TA98, TA100, TA1535, TA1538	Reverse mutation	–	–	Zeiger et al. 1992
Mammalian cells:				
Cultured primary human nasal mucosal cells	DNA damage	+	No data	Tisch et al.1992
CHO cells	Chromosomal aberrations	–	–	EPA 1990c
Rat hepatocytes	Unscheduled DNA synthesis	No data	–	EPA 1990c

+ = positive results; – = negative results; DNA = deoxyribonucleic acid; CHO = Chinese hamster ovary

3.4 TOXICOKINETICS

No data on the toxicokinetics of DEET in humans exposed via inhalation or oral routes were located in the literature reviewed. Similarly, there are no animal data on toxicokinetics of inhaled DEET. Data on absorption of orally-administered DEET are limited to a single rat study (Schoenig et al. 1996) that showed rapid and nearly complete >90% absorption of DEET. Dermal absorption of DEET has been extensively studied in humans, laboratory animals and in *in vitro* test systems. The rate and extent of dermal uptake are affected by species, sex, vehicle and/or formulation in which DEET is applied, dose, and evaporation rate; thus, estimates are highly variable. Based on urinary excretion of radioactivity, the available estimates of the extent of dermal ^{14}C-DEET absorption in humans have ranged between 3.8 and 17% of the applied radioactivity (Blomquist and Thorsell 1977; Feldman and Maibach 1970; Selim et al. 1995).

No specific deposition site has been identified for DEET. After oral or dermal exposure, DEET is widely distributed. It has been detected in the brain, liver, lung, spleen, kidney, fat, lacrimal glands, and nasal mucosa of exposed animals. The one study examining the potential for transplacental transfer of ^{14}C-DEET in rabbits did not detect radioactivity in the fetuses at the end of 29 days of daily dermal applications to the does. After intravenous exposure of pregnant rabbits on 1 day, low levels of radioactivity, however, were detected in the fetuses. DEET did not bind to human serum albumin (HSA) in *in vitro* tests, but did bind to bovine serum albumin (BSA).

The primary metabolites of DEET in humans and laboratory mammals exposed via oral, dermal, or intraperitoneal injection routes are *m*-(diethylaminocarbonyl) benzoic acid (DCBA) and *m*-(ethylaminocarbonyl) benzoic acid (EACB) (Sandstrom et al. 2005; Schoenig et al. 1996; Selim et al. 1995; Taylor and Spooner 1990). It should be noted that some older studies referred to DCBA as *m*-(diethylamino carbonyl)benzoic acid and used the acronym DACB. Metabolism has not been examined in other species or after inhalation exposure. In humans, DCBA was produced by ring methyl oxidation via the intermediate N,N-diethyl-3-hydroxymethyl-benzamide (DHMB), primarily by cytochrome (CYP) 1A2 and 2B6. EACB resulted from N-dealkylation via the intermediate, N-ethyl-*m*-toluamide (ET), by CYP2C19 and CYP3A4. At low substrate concentrations, the ring methyl oxidation pathway was expected to predominate due to higher substrate affinities of the relevant cytochrome P-450 isozymes. There was evidence that DEET induced CYP3A, thereby inducing its own metabolism (Abu-Qare and Abou-Donia 2001a; Usmani et al. 2002). Other metabolites identified in human urine include N-ethyl-N-(1-hydroxyethyl)-3-methylbenzamide and 3-((carboxymethyl)

(hydroxymethyl)carbamoyl)benzoic acid (Wu et al. 1979), while *m*-(aminocarbonyl)benzoic acid (ACB) and *m*-toluic acid were also identified in rat urine (Taylor and Spooner 1990).

Available information from animal studies suggested that metabolism occurred rapidly and mainly in the liver. Limited information suggested that there might be gender differences in the metabolism of DEET, such that males might metabolize DEET faster than females. Females may produce more of the intermediate ET than DHMB at higher doses (Schoenig et al. 1996; Yeung and Taylor 1988).

DEET was rapidly cleared from the plasma after dermal exposure, with plasma elimination half-lives ranging from 2.5 to 9 hours in animals (Fediuk et al. 2011; Kasichayanula et al. 2007; Qiu et al. 1997a, 1997b). The primary route of elimination after oral, dermal, or intravenous exposure was via urinary excretion of metabolites, although some unchanged DEET was excreted in the urine after a high-dose or long-term exposures. Biliary excretion of DEET or its metabolites was observed in animals. It is not known whether this is a significant excretory pathway in humans.

3.4.1 Absorption

The available literature did not include any studies of the absorption of DEET after inhalation exposure. Data on absorption of orally-administered DEET are limited to two rat studies (Hoy et al. 2000a; Schoenig et al. 1996). Schoenig et al. (1996) showed rapid and nearly complete absorption (>90%) in CD rats, while Hoy et al. (2000a) reported that oral administration of 200 mg DEET/kg to Sprague-Dawley rats resulted in blood serum concentrations 30 minutes after administration that were approximately 3.5, 8.5, and 13 ng/mL in males, pre-estrus females, and met-estrus females, respectively. Dermal absorption of DEET has been extensively studied in humans, laboratory animals, and *in vitro* test systems. Estimates of the rate and extent of dermal uptake vary widely and these parameters may be affected by species (Moody and Nadeau 1993), sex (Snodgrass et al. 1982), vehicle and/or the formulation in which DEET is applied (Fediuk et al. 2011; Iscan et al. 2006; Karr et al. 2012; Kasting et al. 2008; Qiu et al. 1997a, 1997b), dose (Moody et al. 1995; Santhanam et al. 2005), and evaporation rate (Reifenrath et al. 1991; Santhanam et al. 2005). The sunscreen, oxybenzone, if applied after DEET application, has been shown to enhance the penetration of DEET across animal skin *in vivo* and *in vitro* (Chen et al. 2010; Gu et al. 2005; Kasichayanula et al. 2007; Ross et al. 2004; Wang and Gu 2007) as has mechanical action (Ambrose 1959).

3.4.1.1 Inhalation Exposure

No quantitative information on the absorption of DEET in humans or animals exposed via inhalation was located. Many exposures reported to poison control centers from 1993 to 1997, however, were identified as involving predominantly inhalation exposure and the adverse signs and symptoms exhibited by these subjects suggest that absorption by this route may have occurred (Bell et al. 2002). Toxic effects seen in rats and mice after acute inhalation exposure to high concentrations of DEET also provide indirect evidence of absorption of DEET through the lungs (Ambrose 1959; Army 1979; Deb et al. 2010; EPA 1998c).

3.4.1.2 Oral Exposure

The many case reports of adverse health effects in humans following accidental or intentional ingestion of insect repellents containing DEET mentioned in Section 3.2.2, Oral Exposure, provide evidence of gastrointestinal absorption of this substance.

One study in CD rats examined absorption, distribution, metabolism, and elimination of radioactivity after administration of ring-labeled ^{14}C-DEET by gavage (Schoenig et al. 1996). The time of peak radioactivity in plasma was 30 minutes postdosing in males and 2 hours postdosing in females (Schoenig et al. 1996), indicating rapid uptake. Data from this study suggest that up to 91% of an oral dose of 100–500 mg DEET/kg was absorbed based on urinary recovery of radioactivity.

Hoy et al. (2000a) demonstrated oral absorption of DEET in Sprague-Dawley rats by measuring DEET in blood serum 30 minutes after oral administration of 200 mg/kg via gavage. The measured blood serum concentrations were approximately 3.5, 8.7, and 13 μg/mL in male, pre-estrus females, and met-estrus female rats, respectively.

3.4.1.3 Dermal Exposure

Small quantities of DEET are rapidly absorbed across human skin, based on appearance in the plasma. Selim et al. (1995) evaluated the rate of absorption of DEET applied to the arms of volunteers. ^{14}C-DEET (~0.5 mg/cm^2) was applied either neat or in a 15% solution in ethanol to 24 cm^2 areas on the arms of six male volunteers and left for 8 hours. Doses of DEET in both applications were similar (~15 mg and 37 μCi in the neat application and about 12 mg and 36 μCi in ethanol). The peak radioactivity in plasma occurred 6 hours after application of neat DEET and 4 hours after application of DEET in ethanol,

indicating that the ethanol solvent slightly enhanced absorption. Smallwood et al. (1992) detected DEET in serum (by high performance liquid chromatography [HPLC] analysis) within 1 hour after dermal application of an insect repellent at estimated doses of 0.14–1.86 g. The peak serum concentration typically occurred within 1–2 hours after application of the repellent (Smallwood et al. 1992). The authors estimated dermally applied doses ranging from 0.31 to 5.99 $\mu g/cm^2x10^3$ and observed a correlation ($r=0.80$, $p=0.01$) between applied dose ($\mu g/cm^2x10^3$) and area under the serum concentration vs. time curve (through the 6-hour measurement); in units of hour · μg/g). Feldman and Maibach (1970) observed the maximum rate of absorption during the first 12 hours after administration of 4 μg DEET/cm^2 to the skin of volunteers, when the absorption rate was estimated as 0.773% per hour.

Estimates of the extent of DEET absorbed across the skin of humans have been made based on urinary excretion of radioactivity; these estimates range between 3.8 to 17% of the applied radioactivity, a primary factor for the difference may be the time that DEET was left on the skin. Based on the cumulative amount of radioactivity excreted in urine collected during the 5 days after dosing in the human study by Selim et al. (1995), 5.6– 8.3% of the applied radioactivity was absorbed on average. In two experiments with the same female volunteer exposed for 8 hours to 0.12 mg/kg ^{14}C-DEET via topical application, absorption was at least 3.8–5.5% of the applied radioactivity based on cumulative urinary excretion of radioactivity during the 48 hours following commencement of exposure (Blomquist and Thorsell 1977). Feldman and Maibach (1970) reported total absorption of ~17% of a topically applied dose of 4 μg/cm^2 (total area of 13 cm^2) ^{14}C-DEET (left untouched for 24 hours) to the forearm of volunteers (ages and genders not reported); absorption was based on cumulative urinary excretion of radioactivity over 5 days.

Dermal absorption of DEET in CD rats occurred rapidly, with peak blood levels occurring within 2–3 hours after the commencement of exposure. A single dermal application of 100 mg/kg ring-labeled ^{14}C-DEET (the vehicle was not reported) to the shaved backs (12.5 cm^2) of fasted rats was studied. Radioactivity levels in blood peaked 2 hours after application in males (at 333 dpm/0.1 mL) and 3 hours after application in females (255 dpm/0.1 mL), and persisted at a high level for the duration of the exposure, indicating ongoing absorption from the application site (Schoenig et al. 1996). The application site was covered with a glass rectangular enclosure to minimize evaporative losses. In a study in which evaporative losses were not prevented, a peak plasma concentration of 0.3 μg DEET/mL was reached 90 minutes after the end of the 24-hour exposure (Fediuk et al. 2011). Dermal absorption was rapid in Beagle dogs; plasma concentrations of DEET in dogs exposed to two different formulations (a novel formulation with 7.5% DEET and Off!: Skintastic II® containing 7.125% DEET) showed a similar time

profile, with the peak concentrations of 154.3 and 196.5 ng/mL (for the two formulations) occurring at 1.25 hours postdosing (Qiu et al. 1997a, 1997b). DEET was detected in plasma at 15 minutes postexposure for both formulations, but the rate of absorption from the formulation with 7.5% DEET was slower, based on the lower plasma concentration observed at that time (17.7 vs. 101 ng/mL) (Qiu et al. 1997a).

The extent of DEET absorbed across the skin of rats has been reported to be as low as 15% and as high as 78% due a variety of factors, including dose, vehicle and/or formulation in which DEET is applied, and evaporation rate. Schoenig et al. (1996) measured radioactivity in urine collected for 7 days after a single dermal application of 100 mg/kg ring-labeled ^{14}C-DEET (a vehicle was not reported) to the shaved backs (12.5 cm2) of fasted CD rats. Based on the urinary radioactivity levels, approximately74–78% of the applied dose was absorbed across rat skin (Schoenig et al. 1996). When male and female Wistar rats were treated topically with 50 mg/kg ^{14}C-DEET on the shaved upper back (1.5–2 cm^2 area), 52–54% of the applied radioactivity was excreted in the urine within the first 48 hours, indicating dermal absorption of at least 52% of the administered dose (Taylor and Spooner 1990). Moody et al. (1995) estimated dermal absorption of DEET by Sprague-Dawley rats to be 15.1, 26.8, and 20.3% of doses of 4.7, 6.7, and 31.8 mg DEET/cm^2 (respectively) in various formulations, based on urinary, fecal, and tissue recovery of radioactivity, indicating a J-shaped dose-response.

Available *in vivo* information on species differences in dermal uptake are limited but suggest that the differences among laboratory animals may be small. When dermal absorption was estimated based on cumulative urinary and fecal excretion of radioactivity over 7 days after a single dermal application of 4 µg ^{14}C-DEET/cm^2, estimates of 44, 33, 38, and 31% absorption were reported for male Sprague-Dawley rats, female Sprague-Dawley rats, female New Zealand White rabbits, and male Beagle dogs, respectively (Snodgrass et al. 1982). While the species differences were small in this study, the data did suggest gender differences, with male rats absorbing a greater percentage than females.

Fediuk et al. (2011) reported the relative bioavailability in rats of dermally-applied DEET in ethanol (100 mg/kg) to Sprague-Dawley rats as 1.5% based on the ratio of the dermal and intravenous plasma area under the curve values (24 hours after the end of exposure). The study authors attributed the low bioavailability in this study to the use of the ethanol vehicle which may have enhanced evaporation. However, it should be noted that others have shown that 30–45% ethanolic solutions of DEET increased permeation of DEET into human's skin *in vitro* compared to DEET alone or to 60–90% ethanolic solutions (Stinecipher and Shah 1997). These investigators suggested that at low ethanol concentrations,

extraction of skin lipids associated with alteration of polar pathways results in increased permeation of DEET. However, higher concentrations of ethanol may extract lipids from the skin and alter the barrier function and decrease uptake by the skin resulting in decreased permeation of DEET.

In addition to evaporation, a variety of other factors can affect the dermal uptake of DEET. These factors are most notably the vehicle and/or formulation of the product containing DEET, but articles often provide little or no information regarding inert ingredients in the product being evaluated or any vehicle that was used. Qiu et al. (1997a, 1997b) evaluated the dermal bioavailability of two different DEET formulations in Beagle dogs. One was a novel formulation (7.5% DEET) and the second was Off! Skintastic® containing 7.125% DEET. Using the ratio of area under the plasma concentration-time curve to dose after dermal (15 mg/kg) and intravenous (2.5 mg/kg) exposures, the study authors estimated the absolute dermal bioavailability of the two formulations to be 14% (Off! Skintastic®) and 18% (novel formulation). More recently, Brand et al. (2006) showed that administration of a single gavage dose of ≥4.3 g ethanol/kg to rats significantly increased skin absorption of DEET when a piece of the rat's skin was tested 2 hours later in an *in vitro* flow-through diffusion cell system. The ethanol-induced enhancement of DEET absorption was dose-related. A mechanism for these findings was not explored in the study. Their conclusion was that acute and chronic consumption of alcoholic beverages compromises the skin barrier and increases the dermal absorption of DEET; this enhancement remains for at least 24 hours after blood alcohol levels subside since ethanol clears from the skin more slowly than from blood.

The sunscreen, oxybenzone, has been demonstrated to enhance the dermal penetration of DEET in both *in vivo* (Kasichayanula et al. 2007; Wang and Gu 2007) and *in vitro* studies (Chen et al. 2010; Gu et al. 2005; Ross et al. 2004). Kasichayanula et al. (2007) evaluated the absorption of DEET across the shaved skin of 3-week-old piglets. The test materials were a commercial insect repellent containing 9% DEET and a combined sunscreen/repellent that contained 9% DEET. One gram of the product was applied to a surface area of 150 cm^2. Plasma samples were collected at regular intervals between 0 and 48 hours after application for HPLC analysis. When the repellent was applied alone, the concentration of DEET in the plasma peaked at ~28 µg/mL 2 hours after dosing, declined rapidly over the next 10 hours, and then declined very gradually for the subsequent 36 hours. A similar profile was seen with the combination product. The area under the curve of the plasma concentration:time plot was higher after application of the combined repellent/sunscreen product (446.21 µg hour/mL) compared with repellent alone (286.59 µg hour/mL), indicating enhanced absorption of DEET from the combination product. Wang and Gu (2007) used the same experimental design as Gu et al. (2005) and had similar methodological issues. For example: (1) the human skin samples were prepared very aggressively with freezing, thawing, scraping,

and cutting, but the integrity of the skin samples used for the experiments was only visual; a more rigorous and standardized approach to evaluate the integrity of skin samples, such as ^3H_2O penetration (Santhanam et al. 2005), would have been more appropriate, and (2) it was stated that the amount of test sample in direct contact with the skin surface (0.64 cm^2) in the diffusion cells was measured to be 0.1 g (equivalent to approximately 100 µL/cell and 156,250 µg/cm^2 skin); this appears to be an enormous dose in comparison to human use of DEET and sunscreen products and to the *in vitro* study of Santhanam et al. (2005) in which Franz diffusion cells with DEET applied to human skin samples used doses of 5 µL/cell in most experiments and a maximum dose of 20 µL/cell.

Moody and Nadeau (1993) compared the *in vitro* dermal permeability of ^{14}C-DEET across skin samples from several animal species and humans. Doses varied approximately 2-fold across the experiments from 12.5 to 44.7 µg/cm^2; the skin thickness was the same (0.5±0.01 mm) for all samples except human foreskin, which was 0.3 mm. Table 3-5 shows the pharmacokinetic parameters calculated from the experiments. The maximum rate of permeability was greatest across mouse skin (2.9 µg/cm^2/hour) and lowest across guinea pig skin (0.4 µg/cm^2/hour). The maximum rate of permeability of DEET across human skin *in vitro* was between 1 and 2 µg/cm^2/hour (Moody and Nadeau 1993).

In vitro estimates of DEET skin permeability vary significantly depending on the vehicle in which it is applied (Qiu et al. 1998; Moody et al. 1995; Stinecipher and Shah 1997). Qiu et al. (1998) reported 10–23% reductions in the flux of DEET across the skin with the use of 20% (w/w) PEG 400, 1% (w/w) Tween 80, or 75% (v/v) ethanol in Carbopol 940 NF and Pemulun TR-2 formulations when compared with a commercially-available preparation containing an equivalent concentration of DEET. *In vitro* measurements of flux and permeability across human skin were higher for DEET in 30–45% ethanol solutions compared with 75–90% ethanol solutions (Stinecipher and Shah 1997). Similarly, in a study by Iscan et al. (2006), *in vitro* skin permeation rates were shown to vary depending on the concentration of ethanol; flux rates were 0.41, 0.14, and 0.09 mg/cm^2-second at 45, 70, and 95% ethanol, respectively (Iscan et al. 2006).

The percent of applied dose that is absorbed across human skin appears to depend on dose and integrity of the skin samples. Santhanam et al. (2005) evaluated *in vitro* permeability of DEET across human cadaver skin at doses ranging from 0.02 to 11,000 µg/cm^2. The percent penetration increased with dose up to 680 µg/cm^2 and then declined at higher doses. Moody et al. (1995) observed lower absorption of ^{14}C-DEET from higher doses of DEET. Based on a methodology of recovery from receiver solution, skin extraction with methanol and skin digest, the authors estimated 48, 36, and 17% absorption across human

Table 3-5. Species Differences in *In Vitro* Estimates of DEET Dermal Permeability

Species (site of skin sample)	Applied dose (µg/cm^2)	Permeability based on receiver solution (%)	Permeability based on receiver solution, skin wash and skin digest (%)	Maximum rate of permeability (µg/cm^2/hour)	Lag time[a] (hours)
Mouse (back)	33.3	36.2±27.5	39.0±29.0	2.9±1.81	1.4±0.45
Rat (back)	38.7	21.4±2.17	64.8±2.70	1.3±0.07	1.9±0.08
Guinea pig (back)	12.5	10.9±1.40	38.4±4.46	0.4±0.14	1.3±0.20
Yorkshire pig (back)	19.4	15.3±0.82	28.9±5.17	0.7±0.12	1.4±0.20
Human (abdomen)	44.7	27.7±4.24	28.1±4.28	2.0±0.58	0.6±0.28
Human (neonatal foreskin)	27.9	13.1±9.58	13.8±9.59	0.98±0.91	1.6±1.73

[a]Time to appearance in receiver fluid.

Source: Moody and Nadeau (1993)

skin at applied doses of 16.7, 25.3, and 97.3 mg DEET/cm^2, respectively, in three different commercial preparations. Similar experiments conducted with rat skin showed little or no difference in percent absorption across a similar dose range and the same preparations (Moody et al. 1995).

A number of studies have examined alternative formulations of DEET intended to minimize skin permeation and maximize the duration of insect repellent effectiveness by prolonging evaporation time.

Karr et al. (2012) showed that microencapsulation formulations resulted in lower penetration across split-thickness human cadaver skin tested in Franz cells modified to allow controlled airflow trapping. Kasting et al. (2008) reported a similar observation; microencapsulation using walled polysaccharide microcapsules diminished the dermal uptake of DEET by 25–35% (compared with an ethanol vehicle) in *in vitro* tests using human cadaver skin. Similarly, Iscan et al. (2006) incorporated DEET into solid lipid particles as a colloidal solution and observed decreased permeation across human donor skin from plastic surgery patients when compared to free DEET in the same preparation. Wang et al. (2014) showed that oil-in-water emulsions significantly lowered percutaneous permeation of DEET through isolated human skin compared to water-in-oil emulsions. Experiments also showed that the addition of xanthan gum to the oil-in-water emulsion reduced the size of oil droplets containing DEET and increased penetration of DEET through human skin.

Exposure to other compounds prior to dermal exposure to DEET may also alter skin permeability. Kaushik et al. (2010) observed that pretreatment of human skin *in vitro* with different compounds (laurocapram, iminosulfuram, and others) could enhance or retard the rate of skin penetration depending on the vehicle in which the pretreatment was applied.

Airflow across exposed skin affects dermal penetration of DEET by its effect on volatilization. Santhanam et al. (2005) observed lower penetration across human skin tested *in vitro* under a fume hood with higher airflow compared with tests conducted on a laboratory workbench with lower airflow. Reifenrath et al. (1991) observed reduced (one-third as high) dermal penetration of ^{14}C-DEET across excised pig skin *in vitro* when air flow was increased by 10-fold.

3.4.2 Distribution

Limited data regarding distribution of DEET in humans indicate that DEET can distribute to cord blood following dermal exposure of pregnant women (Barr et al. 2010; McGready et al. 2001). No data were located regarding distribution following inhalation or oral exposure.

Distribution data are available in animals exposed orally or dermally. A single study of CD rats exposed via gavage (Schoenig et al. 1996) indicated distribution to a number of organs (liver, lung, spleen, kidney, and fat) without identifying specific deposition sites for DEET. Similar findings were reported after dermal exposure to DEET in rats, rabbits, and dogs (Fediuk et al. 2010; Schoenig et al. 1996; Snodgrass et al. 1982). An older study that used whole-body autoradiography to assess distribution after dermal exposure to ^{14}C-DEET reported high levels of radioactivity in the lacrimal glands and nasal mucosa of albino mice (Blomquist and Thorsell 1977); these tissues were not assessed in other studies. When pregnant New Zealand White rabbits were exposed topically to ^{14}C-DEET (50, 100, or 500 mg/kg/day) for 29 days, radioactivity was not detected in the fetuses at the end of treatment (Snodgrass et al. 1982).

After intravenous exposure, DEET undergoes extensive extravascular distribution; estimates of steady-state volume of distribution in beagle dogs (Qiu et al. 1997b) and Sprague-Dawley rats (Fediuk et al. 2011) exceeded the total body water of these species. Some evidence for transplacental transfer of intravenously-administered DEET was provided in studies of pregnant mice and rabbits exposed intravenously to ^{14}C-DEET; radioactivity was detected at low levels in the fetuses of both species (Snodgrass et al. 1982; Blomquist et al. 1975).

DEET did not bind to plasma proteins in *in vitro* tests conducted with HSA; the fraction of unbound DEET after a 60-minute incubation of DEET in saline with up to 10 μg/mL HSA was 95% (Abu-Qare and Abou-Donia 2002). Kasting et al. (2008) measured the binding of DEET to BSA in saline using equilibrium dialysis in side-by-side diffusion cells (one side containing BSA and one side saline only). Equilibrium was reached in 2–3 days, and the fraction unbound was calculated to be 0.189±0.008 (Kasting et al. 2008).

3.4.2.1 Inhalation Exposure

No information on the tissue distribution of DEET in humans or animals exposed via inhalation was located.

3.4.2.2 Oral Exposure

When CD rats were given single doses of 100 or 500 mg/kg ring-labeled ^{14}C-DEET in corn oil via gavage and sacrificed 7 days later for tissue analysis, total tissue residues of ^{14}C activity ranged from 0.15 to 0.67% of administered radioactivity and the distribution of radioactivity showed highest concentrations in the liver, lung, spleen, kidney, and fat. The percent of administered radioactivity reaching systemic circulation and the tissues was much higher for animals administered ^{14}C-DEET orally than for animals administered ^{14}C-DEET dermally (Schoenig et al. 1996).

3.4.2.3 Dermal Exposure

McGready et al. (2001) studied the distribution of 1.7 g DEET/day in the second and third trimesters of 449 pregnant women as part of a double-blind trial of insect repellents in the prevention of malaria in Thailand. DEET was not detected in 30 urine samples from DEET-exposed women, but was detected in 4 of 50 samples of cord blood from women exposed to DEET. Barr et al. (2010) assessed the distribution of DEET by measuring pesticides in maternal serum prior to birth and in cord blood after delivery. DEET was one of the pesticides most frequently detected in maternal and cord serum; the corresponding mean concentrations were 3.21 ng/g (range 1.82–18.84 ng/g) and 3.12 ng/ng (range 2.06–13.07 ng/g).

Schoenig et al. (1996) measured tissue concentrations of radioactivity in CD rats 7 days after a single dermal application of 100 mg/kg ring-labeled ^{14}C- DEET. Radioactivity levels were low (<0.4 ppm) in all tissues; apart from the carcass, the highest concentrations were in the liver (0.21 and 0.22 ppm in males and females, respectively), kidneys (0.08 and 0.02 ppm in males and females, respectively), and blood (0.04 and 0.05 ppm in males and females, respectively).

Fediuk et al. (2010) detected DEET in the liver and brain of male and female Sprague-Dawley rats that had received daily topical applications of 40 mg DEET/kg (2,500 μg/cm^2 skin), either alone or in combination with the sunscreen, oxybenzone, for 30 days. The median concentration in liver was significantly higher when DEET was applied with oxybenzone (350.8 ng/g) than when applied alone (95.9 ng/g). In contrast, the concentrations in the brain (7.6–8.5 ng/g) were similar with both treatments (Fediuk et al. 2010). In a related study also conducted in rats, a single, 24-hour dermal exposure to 100 mg DEET/kg yielded liver and kidney concentrations of 14.6 and 12.2 ng/g, respectively (Fediuk et al. 2011). The study authors noted that the use of an ethanol vehicle for the latter study likely facilitated evaporation of DEET, decreasing the quantities that reached the liver and kidney.

Snodgrass et al. (1982) measured the tissue distribution of ^{14}C-DEET in small groups of Sprague-Dawley rats (n=6/sex), New Zealand White rabbits (n=6 females), and Beagle dogs (n=3 males) 7 days after dermal application of 4 μg/cm^2, and observed the highest levels in the lung and spleen of dogs, lung of rabbits, and liver and kidney of female rats. The levels, however, varied among individual animals; radioactivity was not detected in these organs in some animals. Using whole-body autoradiography, Blomquist and Thorsell (1977) measured the highest levels of radioactivity in the lacrimal gland, liver, kidney, and nasal mucosa of albino mice 2 hours after a topical application of 15 mg ^{14}C-DEET/kg for 2 hours.

Dermal application of ^{14}C-DEET at doses of 50, 100, or 500 mg/kg/day to pregnant New Zealand White rabbits on GDs 1–29 did not result in detectable radioactivity in the fetuses at sacrifice at the end of exposure (Snodgrass et al. 1982).

3.4.2.4 Other Routes of Exposure

Intravenously administered DEET undergoes extensive extravascular distribution, as shown by the volume of distribution in dogs and rats. Qiu et al. (1997b) calculated a mean steady-state volume of distribution of 6.21 L/kg in Beagle dogs exposed to 2.5 or 6.0 mg DEET/kg via intravenous injection; this volume is 10 times higher than the total body water of a lean dog (~0.6 L/kg; Davies and Morris 1993) and demonstrates extravascular distribution. Similarly, Fediuk et al. (2011) calculated a steady-state volume of distribution of 5.6 L/kg in Sprague-Dawley rats receiving intravenous injections of DEET (2 mg/kg); this compares with a total body water of ~0.7 L/kg in rats (Davies and Morris 1993).

In albino mice exposed to ^{14}C-DEET (0.05 μCi/g body weight) via intravenous injection and evaluated by whole-body autoradiography, the highest concentrations of radioactivity were detected (in descending order) in the lacrimal gland, liver, kidney, and nasal mucosa (Blomquist et al. 1975). Radioactivity persisted for 24 hours postdosing in the lacrimal gland, liver, nasal mucosa, urinary bladder, and intestinal contents, but none was detected on the autoradiograms 3 days later (four days post-dosing). When male albino mice were fasted for 18–24 hours prior to treatment, lower concentrations of radioactivity were detected in the liver and kidney compared with levels in mice allowed to feed prior to exposure (Blomquist et al. 1975).

A similar pattern of radioactivity was seen in a pregnant albino mouse examined 20 minutes after injection of DEET; the concentration of radioactivity in the fetus was low. The highest concentrations in

the fetus were in the kidney, urinary bladder, gastric mucosa, lens, and liver. Very little radioactivity was detected in the fetus 4 hours after exposure of the pregnant dam (Blomquist et al. 1975). Snodgrass et al. (1982) observed low levels of radioactivity (about one-sixth of the corresponding maternal blood levels) in the fetuses of New Zealand White rabbits treated with a single intravenous injection of 140.6 μg ^{14}C-DEET on GD 15.

3.4.3 Metabolism

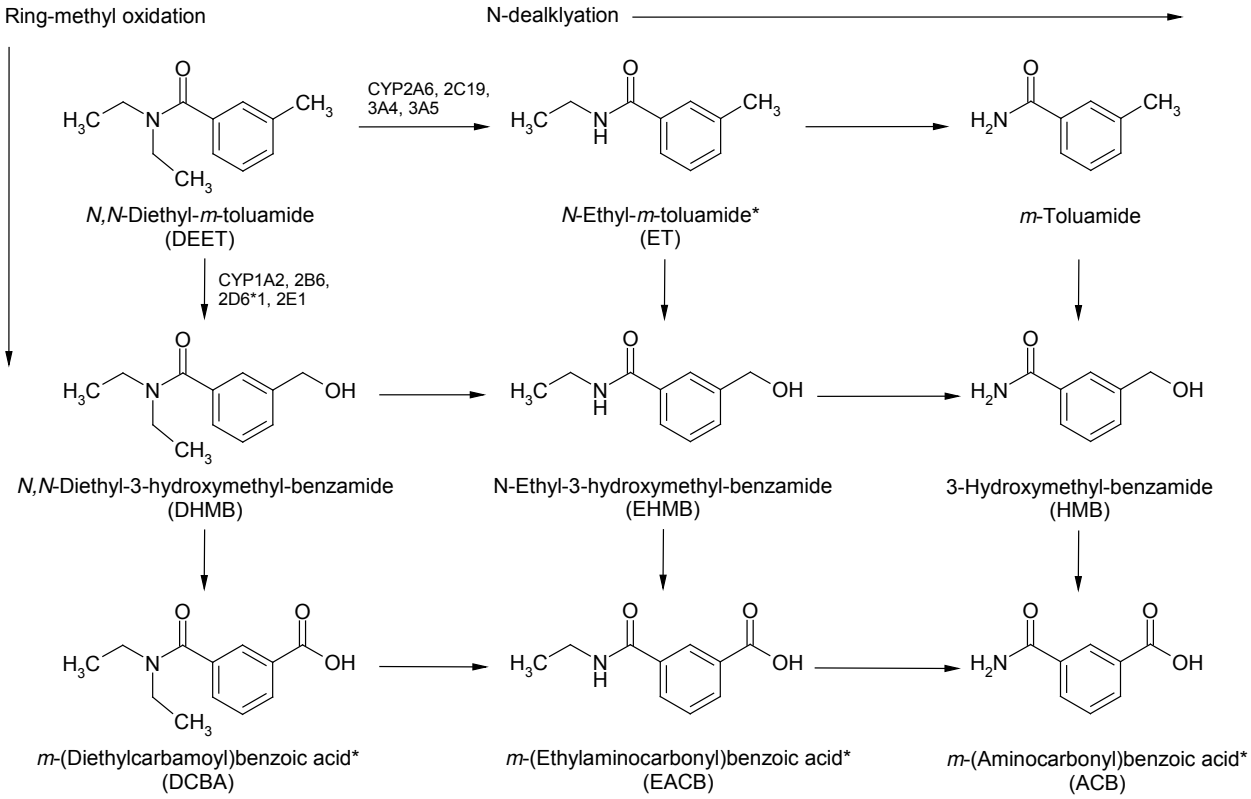
The major metabolic pathways for DEET are shown in Figure 3-3. The primary metabolites of DEET in humans exposed dermally (Selim et al. 1995) and in rats exposed via oral, dermal, or intraperitoneal injection routes (Schoenig et al. 1996; Taylor and Spooner 1990) are DCBA and EACB; metabolism has not been examined after inhalation exposure. ET occurs in urine as the glucuronide conjugate and has been identified in acid-hydrolyzed human (Tian and Yiin 2014; Wu et al. 1979) and rat (Taylor and Spooner 1990) urine. Other metabolites identified in human urine include N-ethyl-N-(1-hydroxyethyl)-3-methylbenzamide and 3-((carboxymethyl)(hydroxymethyl)carbamoyl)benzoic acid (Wu et al. 1979), while ACB and *m*-toluic acid have also been identified in rat urine (Taylor and Spooner 1990).

DHMB is produced by oxidation of the methyl group on the benzene ring to carboxylic acid, a reaction mediated primarily by CYPs 1A2 and 2B6 in humans (Usmani et al. 2002). ET results from dealkylation of the amide group; the primary cytochrome P-450 isozymes that catalyze this reaction are CYP2C19 and CYP3A4 (with small contributions from CYPs 2A6 and 3A5) in humans (Usmani et al. 2002). Other minor metabolites have been observed after incubation of DEET with liver microsomes, including N,N-diethyl-*m*-formylbenzamide and N-ethyl-*m*-hydroxymethylbenzamide (EHMB) (Taylor et al. 1986).

Metabolism via one or the other of these pathways will be favored in humans with higher levels of the corresponding CYPs (Usmani et al. 2002). At low substrate concentrations, the ring methyl oxidation pathway is expected to predominate due to higher substrate affinities of the relevant cytochrome P-450 isozymes (Usmani et al. 2002). There is evidence that DEET can induce CYPs 3A4, 2B6, 2A6, 1A1, and 1A2 translation and transcription, thereby inducing its own metabolism (Abu-Qare and Abou-Donia 2001a; Usmani et al. 2002).

Available information suggests that metabolism occurs rapidly; metabolites were detected in the plasma of rats as soon as 30 minutes after a 24-hour dermal exposure (Fediuk et al. 2012). The liver is the primary site of metabolism (Abu-Qare and Abou-Donia 2008). Limited *in vivo* and *in vitro* data suggest

Figure 3-3. Primary Metabolic Pathways of DEET in Rodents and Humans



*Detected in human urine as free or conjugated metabolite

Sources: Constantino and Iley 1999; Schoenig et al. 1996; Selim et al. 1995; Taylor 1986; Taylor and Spooner 1990; Usmani et al. 2002; Wu et al. 1979

the possibility of gender differences in metabolism of DEET (Schoenig et al. 1996; Yeung and Taylor 1988); males may metabolize DEET faster than females, and females may produce more EACB than DCBA at higher doses.

3.4.3.1 Inhalation Exposure

No information on the metabolism of DEET in humans or animals exposed via inhalation was located.

3.4.3.2 Oral Exposure

A single rat study provides information on metabolism of DEET after oral exposure. Schoenig et al. (1996) administered ^{14}C-DEET in corn oil via gavage to male and female CD rats and collected urine samples over the next 36–72 hours. Analysis of urine samples by HPLC showed complete metabolism of DEET at both low (100 mg/kg) and high (500 mg/kg) doses (no DEET was detected in urine). The majority of the excreted radioactivity (~50–60% of administered radioactivity depending on dose and regimen) was associated with the metabolite DCBA, which resulted from oxidation of the methyl group to carboxylic acid. A second metabolite, EACB, resulting from dealkylation of the amide group, accounted for between 3 and 17% of the administered radioactivity (Schoenig et al. 1996). No effort was made to identify the minor metabolites.

3.4.3.3 Dermal Exposure

Selim et al. (1995) analyzed the urine of human volunteers exposed to undiluted DEET or 15% DEET in ethanol via dermal application (~0.5 mg/cm^2). Unchanged DEET was not detected in the urine. Six peaks were separated by HPLC; these six accounted for the majority (>60%) of urinary radioactivity after either form of DEET was applied. By comparing the HPLC profile from human urine with the profile from the urine of rats treated with DEET, the authors identified two of the metabolites; 24–42% of the urinary radioactivity consisted of DCBA, while between 7.6 and 26% consisted of EACB (a coeluting peak prevented more precise quantification of this metabolite).

Wu et al. (1979) identified (but did not quantify) DEET metabolites in the urine of a 30-year old, 78 kg male subject who applied 10.4 g of DEET in a repellent to ~75% of his body; the duration of treatment was not specified. Four possible metabolic pathways were identified, and five metabolites resulting from three of the pathways were identified by electron impact ionization and chemical ionization mass spectrometry. The metabolites were identified as: DCBA; the glucuronide conjugate of ET; N-ethyl-

N-(1-hydroxyethyl)-3-methylbenzamide; and 3-((carboxymethyl)(hydroxymethyl)carbamoyl)benzoic acid and a small amount of DHMB was tentatively identified.

Tian and Yiin (2014) reported that application of 10 mL of a repellent containing 12% DEET to the arms or legs of children (5–7 years old) and adults (23–25 years old) resulted in urinary excretion mainly of DCBA and ET and a small amount of unchanged DEET over an 8-hour period after the application. DCBA constituted 78.2% of the total metabolites in children and 46.1% in adults. No significant differences regarding metabolic profile were observed between male and female subjects. Expressed as DEET equivalents, a greater amount of metabolites were recovered from children (1,116 µg) than from adults (446 µg). The reason for this difference was not totally clear, but no details were provided regarding the exposure conditions.

The urinary metabolite profile observed in Wistar rats exposed to 100 mg DEET/kg via dermal application was similar to that seen after oral exposure (Schoenig et al. 1996). The major urinary metabolites were DCBA, which represented 47–48% of the administered radioactivity, and EACB, which represented 3–13% of administered radioactivity. Female rats excreted higher amounts of EACB (13%) than males (3%). Taylor and Spooner (1990) administered 50 mg ^{14}C-DEET/kg by topical application to the backs of male and female Wistar rats. DCBA and EACB were the primary urinary metabolites, accounting for ~36–37% and ~11–12% of the administered radioactivity, respectively, in the first 48 hours (metabolites were quantified in two 24-hour urine samples). Minor metabolites identified in the rat urine were ACB and *m*-toluic acid; these were not quantified. Analysis of acid-hydrolyzed urine revealed the presence of ET; the authors suggested that it was conjugated with glucuronide in urine. In contrast to the results reported by Schoenig et al. (1996), Taylor and Spooner (1990) detected unchanged DEET in the urine, accounting for 4.7–5.5% of the applied dose in the first 48 hours after dosing.

Fediuk et al. (2012) measured the levels of DHMB and ET in the plasma of Sprague-Dawley rats as soon as 30 minutes after the end of a 24-hour dermal treatment with 100 mg/kg (4 mg/cm^2) DEET. Plasma was not analyzed for any other metabolites or for DEET. The plasma concentrations of both DHMB and ET continued to increase for 24 hours postexposure. At the end of the 24-hour observation period, concentrations of DHMB and ET were ~140 and 120 ng/mL, respectively. In a repeated exposure experiment conducted by the same authors, the concentrations of DHMB and ET were ~150 and 350 ng/mL, respectively, after a 30-day repeated application of 40 mg/kg (10 mg/cm^2) DEET.

In liver samples taken at sacrifice at the end of the 24-hour exposure to 100 mg DEET/kg, the concentrations of DHMB and ET were similar at 29±2.9 and 36±4.2 ng/g, respectively (Fediuk et al. 2012). In contrast, after 30 days of repeated dermal dosing with 40 mg DEET/kg, the concentration of DHMB in the liver was ~3 times higher (384.3±87.3 ng/g) than that of ET (139.6±57.1 ng/g).

DHMB and ET were measured in urine samples taken from piglets 48 hours after dermal application of a repellent lotion containing 9% DEET (1 g quantity) to a shaved area of 150 cm^2 (Kasichayanula et al. 2005). Urine was not analyzed for other metabolites. The concentration of DHMB in urine was about twice that of ET (0.99 vs. 0.55 µg/mL, respectively); no parent compound was detected.

3.4.3.4 Other Routes of Exposure

After intraperitoneal administration of 50 mg ^{14}C-DEET/kg, male Wistar rats excreted 55–66% of the administered dose as DCBA in the first 24 hours after dosing; an additional 16–22% was excreted as EACB in the same time period (Taylor and Spooner 1990). As with dermal exposure, two additional urinary metabolites were identified (*m*-aminocarbonyl) benzoic acid and *m*-toluic acid; these metabolites were not quantified (Taylor and Spooner 1990). Acid hydrolysis of the urine revealed ET, which was likely present in urine as the glucuronide conjugate (Taylor and Spooner 1990).

In vitro experiments with liver microsomes show metabolism of DEET to DHMB and ET. Based on studies in DEET-exposed humans and rats (Schoenig et al. 1996; Selim et al. 1995; Taylor and Spooner 1990), these compounds appear to be intermediates and/or minor *in vivo* metabolites of DEET. Incubation of 1,000 nmol DEET with phenobarbital-induced male rat liver microsomes for 45 minutes resulted in metabolism of at least 65% of the DEET (of the total 71% recovered; Taylor 1986). The major metabolite was DHMB (422.2 nmol), followed by ET (222.5 nmol); only 62.8 nmol of DEET was recovered at the end of the experiments (Taylor 1986). Metabolism varied with pH. At pH 8.6, two minor metabolites, N,N-diethyl-*m*-formylbenzamide and EHMB were detected at low levels. At pH (7.4), metabolism of DEET was virtually abolished (<7% was metabolized).

Using baculovirus-infected insect cells expressing specific human cytochrome P-450 isozymes, Usmani et al. (2002) demonstrated that the two primary metabolites of DEET are each produced by specific isozymes, with no cross-reactivity. Specifically, DHMB is formed by CYPs 1A2, 2B6, 2D6*1, and 2E1, while ET is formed by CYPs 2A6, 2C19, 3A4, and 3A5. Table 3-6 shows the activity of each isozyme on the DEET substrate; as the table shows, CYP2E1 has relatively low activity compared with the other

Table 3-6. CYP-Specific Metabolism of DEET by Human CYPs Expressed in Baculovirus-Infected Insect Cells

		Kinetic parameters		
CYP isoform	Activity at 1,000 or 3,000 µM DEET (nmol/nmol isoform/minute)	V_{max} (nmol/mg protein/minute)	K_m (µM)	CL_{int} (10^{-6}/nmol isoform/minute)
DHMB formation (ring methyl oxidation)				
CYP1A2	68.94±2.64	24.5±1.2	41.0±2.0	598.7±39.6
CYP2B6	69.51±1.83	22.3±2.1	40.2±1.2	552.0±40.4
CYP2D6*1	56.56±2.52			
CYP2E1	3.34±0.17			
ET formation (N-deethylation)				
CYP2A6	4.55±0.30			
CYP2C19	8.96±0.82			
CYP3A4	5.05±0.20			
CYP3A5	5.81±0.24			

Source: Usmani et al. (2002)

DHMB-forming isozymes. Usmani et al. (2002) also evaluated species differences in metabolism of DEET by human, Long-Evans rat, and CD-1 mouse microsomes *in vitro*; the calculated intrinsic clearances of human and mouse microsomes were similar, while much higher clearance (>2-fold) was calculated from data in rat microsomes (Table 3-7).

Abu-Qare and Abou-Donia (2008) showed that DEET is primarily metabolized in the liver rather than in plasma. The authors incubated human plasma with DEET for 60 minutes and measured the disappearance of DEET over time; the half-life for DEET in plasma was calculated to be 665 minutes. In contrast, when DEET was incubated with human liver microsomes, the disappearance half-life was 60 minutes. When the experiments were conducted in the presence of pyridostigmine bromide and/or permethrin, the plasma disappearance half-life decreased by more than half (indicating accelerated metabolism), while the liver microsome half-life increased by 2.6–5.3-fold (indicating slowed metabolism) (Abu-Qare and Abou-Donia 2008). The study authors identified *m*-toluamide as a metabolite of DEET in the human liver microsomes, and reported K_m and V_{max} values of 62 μM and 112 pmol/minute/mg protein, respectively, for the formation of this metabolite.

Gender differences in the rate of DEET metabolism were demonstrated in a study by Yeung and Taylor (1988). When liver microsomes from male and female Wistar rats were incubated with DEET for 2 hours, microsomes from male rats metabolized DEET much faster than those from female rats, as measured by the disappearance of DEET from incubation solution and appearance of DHMB and ET metabolites. Table 3-8 compares the microsomal metabolism data for males and females.

3.4.4 Elimination and Excretion

There are no studies of the excretion of DEET in humans or animals exposed via inhalation in the available scientific literature.

DEET is rapidly cleared from the plasma after dermal or intravenous exposure. Wu et al. (1979) evaluated the metabolism of DEET in a 30-year-old, 78-kg subject who applied 10.4 g of DEET in a repellent to ~75% of his body. Urine was collected for 36 hours, and the rate of excretion of unchanged DEET via urine was estimated as 10–14% in the first hour and was reduced to 2% by the fourth hour. After dermal exposure, the plasma elimination half-life has been reported to be ~6–9 hours in rats (Fediuk et al. 2011), 2.5–2.7 hours in Beagle dogs (Qiu et al. 1997a, 1997b), and 7.3 hours in piglets

Table 3-7. *In vitro* Liver Microsomal Metabolism Parameters of DEET

Species	V_{max} (nmol/mg protein/minute)	K_m (μM)	CL_{int} (10^{-6}/mg protein/minute)
DHMB formation (ring methyl oxidation)			
Human	12.9±1.6	67.6±4.2	191.5±15.4
Rat	17.6±1.2	38.3±0.2	461.3±23.5
Mouse	6.8±1.4	43.4± 0.6	156.8±23.8
Mouse treated *in vivo* (200 mg/kg/day)	16.4±3.4	42.6±13.6	385.1±52.6
ET formation (N-deethylation)			
Human	20.5±3.4	842.5±49.9	24.4±5.1
Rat	19.2±2.8	214.3±26.1	89.5±10.9
Mouse	14.5±2.9	660.6±59.5	21.7±3.9
Mouse treated *in vivo* (200 mg/kg/day)	22.9±2.9	630.9±128.0	38.3±5.1

Source: Usmani et al. (2002)

Table 3-8. Gender Differences in *In Vitro* Rat Liver Microsomal Metabolism of DEET

Parameter	Male	Female
Percent metabolized at 2 hours	58±4.8[a]	17±1.6
Rate of DEET disappearance (minute^{-1})	0.0667±0.007[b]	0.0467±0.002
Half-life for DEET disappearance (minutes)	10±1.5[b]	15±1.1
Rate of DHMB appearance (minute^{-1})	0.0777±0.009[a]	0.0273±0.001
Rate of ET appearance (minute^{-1})	0.970±0.011[a]	0.346±0.002

[a]Significantly different from female, $p<0.001$.
[b]$p<0.05$.

DHMB = N,N-diethyl-*m*-hydroxymethylbenzamide; ET = N-ethyl-*m*-toluamide

Source: Yeung and Taylor (1988)

(Kasichayanula et al. 2007). After intravenous exposure, plasma elimination half-lives of 1.7 hours in rats (Fediuk et al. 2011) and 2.56 hours in Beagle dogs (Qiu et al. 1997a, 1997b) have been reported.

After oral, dermal, or intravenous exposure, the primary route of elimination is via urinary excretion of metabolites (Blomquist and Thorsell 1977; Schoenig et al. 1996; Selim et al. 1995; Snodgrass et al. 1982). At high dermal doses and/or after long-term repeated dermal exposure, some unchanged DEET is excreted in the urine (Smallwood et al. 1992; Taylor and Spooner 1990). A small amount of DEET is eliminated via the bile (Blomquist and Thorsell 1977; Moody et al. 1995; Qiu et al. 1997b; Schoenig et al. 1996; Selim et al. 1995; Snodgrass et al. 1982).

3.4.4.1 Inhalation Exposure

No information on the elimination of DEET in humans or animals exposed via inhalation was located.

3.4.4.2 Oral Exposure

Available data on elimination of DEET after oral exposure is limited to a single study using gavage administration in CD rats (Schoenig et al. 1996). In this study, up to 91% of an administered dose of 100–500 mg DEET/kg was recovered in the urine, with 3–6% recovered in feces, within 7 days of exposure (Schoenig et al. 1996). The rate of urinary excretion was high in the first 12 hours, during which ~75% of the low dose (100 mg/kg) and ~35–50% of the high dose (500 mg/kg) was excreted. Urinary excretion was minimal after 24 hours at both doses (Schoenig et al. 1996).

3.4.4.3 Dermal Exposure

Urinary excretion was the primary route of elimination in volunteers exposed to ^{14}C-DEET via dermal application (Selim et al. 1995). After application of ~0.5 mg DEET/cm^2 (neat or as a 15% solution in ethanol) to the arms of male volunteers, 5.6–8.3% of the administered radioactivity was excreted in the urine, and 0.02–0.08% was excreted in feces over the first 5 days post-application. The highest rates of urinary excretion occurred during the first 12 hours, and cumulative excretion increased very little after 24 hours (Selim et al. 1995). When a female volunteer was exposed for 8 hours to 0.12 mg^{14}C-DEET/kg via topical application, 3.8–5.5% of the applied radioactivity was excreted via the urine during the 48 hours following commencement of exposure (Blomquist and Thorsell 1977). The maximum rate of excretion (~0.23% per hour) occurred ~4–6 hours after the end of exposure.

Smallwood et al. (1992) developed a technique to analyze DEET in urine and tested the method on eight National Park employees who regularly used a DEET-containing insect repellent and on nine naïve volunteers exposed in a laboratory. The National Park employees were observed to apply sufficient quantities of the repellent, which contained 71% DEET, to yield a daily application of approximately 1 g of DEET. Concentrations of DEET in 24-hour urine samples collected from eight employees after the third day of the work week ranged from below the quantification limit of 0.18 µg/mL up to 5.69 µg/mL. Urinary concentrations were positively correlated ($p<0.05$) with estimated exposure (details not provided) among the eight employees. When nine volunteers without prior exposure were exposed in a laboratory to a DEET-containing repellent at doses between 0.14 and 1.86 g DEET, however, only two of the nine 24-hour urine samples showed DEET concentrations above the quantification limit; concentrations reported for these two volunteers ranged between 0.31 and 2.02 µg/mL; in the remaining seven volunteers, the concentrations of DEET in urine were <0.09 µg/mL, the LOD.

Wu et al. (1979) measured DEET in the urine of a 30-year-old, 78-kg male subject who applied 10.4 g of DEET in a repellent to ~75% of his body. The duration of treatment was not specified. The rate of excretion of unchanged DEET via urine was reported to be 10–14%/hour in the first hour and 2%/hour in the fourth hour. Unchanged DEET was detected in the urine up to 18 hours after application. Because 10.4 g is a very high dose, this may have caused saturation of metabolism pathways, which may have contributed to the detection of unchanged DEET in the urine.

Fediuk et al. (2011) calculated a plasma elimination half-life of ~6 hours in Sprague-Dawley rats exposed for 24 hours to 100 mg DEET/kg in ethanol via topical treatment. Co-treatment with oxybenzone yielded a 44% decrease in plasma elimination half-life (Fediuk et al. 2011). After 30 days of topical exposure (40 mg DEET/kg/day or 2,500 µg/cm^2/day), the plasma concentration of DEET declined with an apparent elimination half-life of 9.1 hours (Fediuk et al. 2010). DEET was still detected in the plasma 24 hours after the last treatment. Qiu et al. (1997a, 1997b) reported a plasma elimination half-life of 2.5–2.7 hours in Beagle dogs exposed to two different formulations of DEET via dermal application; these values were similar to the plasma elimination half-life after intravenous exposure (2.56 hours). Kasichayanula et al. (2007) reported a plasma elimination half-life of 7.3 hours for DEET in piglets exposed via the skin to either a commercial insect repellent containing 9% DEET or a sunscreen/repellent that also contained 9% DEET (for each product, 1 g was applied to 150 cm^2).

When CD rats received a 100 mg/kg dermal application of ^{14}C- DEET under occlusion, 74–78% of the administered radioactivity was recovered in the urine and 4–7% was recovered in the feces (Schoenig et

al. 1996). The rate of urinary elimination was slower than after oral exposure; only ~22–28% of the administered radioactivity was recovered in urine samples over the first 24 hours after dermal application, compared with up to 75% after oral dosing (Schoenig et al. 1996). Snodgrass et al. (1982) compared the 7-day excretion profiles of male and female Sprague-Dawley rats, female New Zealand rabbits, and male Beagle dogs following topical application of ^{14}C-DEET. The cumulative excretion was essentially complete in all species by 3–4 days postdosing. Species differences in cumulative excretion were not apparent.

Although the group sizes were small in this study (three animals each), the excretion profiles suggested a sex difference in excretion by rats; males exhibited a higher percent total excretion (~44% including urinary and fecal excretion) compared with females (~33% including urinary and fecal excretion; Snodgrass et al. 1982).

The detection of radioactivity in feces after dermal exposure suggests that rats, rabbits, and dogs eliminate a small amount of DEET via enterohepatic circulation (Moody et al. 1995; Schoenig et al. 1996; Snodgrass et al. 1982). An older study in albino mice provided direct evidence for biliary excretion of DEET. Blomquist and Thorsell (1977) reported high levels of radioactivity in the bile and intestinal tract (as well as the urine) when whole-body autoradiography of mice was performed after 2-hour dermal exposure to 15 mg ^{14}C-DEET/g.

3.4.4.4 Other Routes of Exposure

Clearance of DEET from plasma is rapid after intravenous administration. Fediuk et al. (2011) reported a clearance rate of 67 L/hour/kg and elimination half-life of 103 minutes in Sprague-Dawley rats after intravenous injection of 2.5 mg DEET/kg. Qiu et al. (1997a, 1997b) reported a plasma elimination half-life of 2.56 hours in Beagle dogs exposed intravenously to 2.5 mg DEET/kg. Qiu et al. (1997b) calculated the clearance of DEET in this study to be 2.66 L/hour/kg, and noted that this value exceeded the renal blood flow rate (1.38 L/hour/kg) and thus provided evidence for intrahepatic clearance of DEET in beagle dogs.

Snodgrass et al. (1982) observed species differences in excretion of intravenously-administered DEET, with lower cumulative excretion (about half as much, based on visual inspection of data shown graphically) in male beagle dogs than male or female rats or female rabbits.

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. However, if the uptake and disposition of the chemical substance(s) are adequately described, 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 3-4 shows a conceptualized representation of a PBPK model.

If PBPK models for DEET 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.

No PBPK modeling studies were located for DEET.

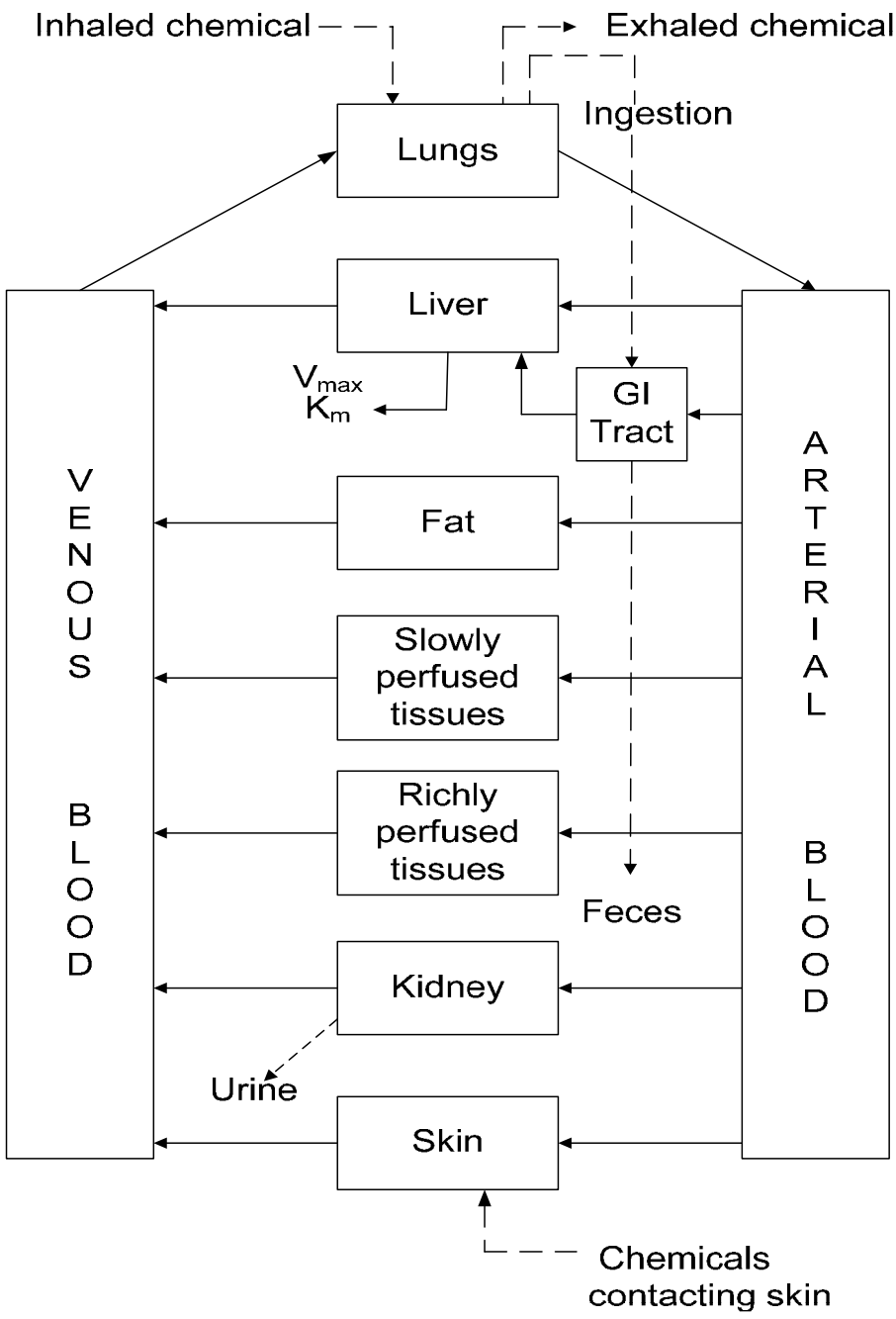
3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

As discussed in detail in Section 3.4 (Toxicokinetics), DEET is absorbed following oral or dermal exposure. No studies examining the mechanisms of DEET absorption were located in the available literature. The dermal absorption of DEET may be affected by species (Moody and Nadeau 1993), sex (Snodgrass et al. 1982), vehicle and/or formulation in which DEET is applied (Fediuk et al. 2011; Iscan et al. 2006; Karr et al. 2012; Kasting et al. 2008; Qiu et al. 1997a, 1997b), dose (Moody et al. 1995; Santhanam et al. 2005), evaporation rate (Reifenrath et al. 1991; Santhanam et al. 2005), and coexposure to other compounds. In particular, the sunscreen, oxybenzone, has been shown to increase the dermal absorption of DEET (Chen et al. 2010; Gu et al. 2005; Kasichayanula et al. 2007; Ross et al. 2004; Wang and Gu 2007).

Available studies provide somewhat disparate findings on the plasma protein binding of DEET; Abu-Qare and Abou-Donia (2002) observed little or no binding to HSA, but the incubation time was short (60 minutes). In contrast, Kasting et al. (2008) used an equilibrium dialysis method to estimate that ~81% of DEET is bound to BSA; equilibrium was reached at about 2–3 days of incubation, suggesting that the incubation time may have been too short in the earlier study. The significance of equilibrium being

Figure 3-4. 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: Krishnan and Andersen 1994

reached in days is unclear since dermally applied DEET in humans is eliminated within hours (Selim et al. 1995).

The role of metabolism on the toxicity of DEET is not known. The two major pathways of DEET metabolism (ring methyl oxidation and N-deethylation) depend on specific CYP isozymes (oxidation via CYPs 1A2, 2B6, 2D6*1, and 2E1 and N-deethylation via CYPs 2A6, 2C19, 3A4, and 3A5); thus, the rate of metabolism and the nature of the metabolites produced may vary among individuals due to variations in these isozymes and their activities. Specifically, metabolism via one or the other of these pathways will be favored in humans with higher levels of the corresponding CYPs (Usmani et al. 2002). At low substrate concentrations, the ring methyl oxidation pathway is expected to predominate due to higher substrate affinities of the relevant cytochrome P-450 isozymes (Usmani et al. 2002). There is evidence that DEET can induce CYPs 3A4, 2B6, 2A6, 1A1, and 1A2 translation and transcription, thereby inducing its own metabolism (Abu-Qare and Abou-Donia 2001a; Usmani et al. 2002).

No information was located regarding mechanisms of elimination and excretion of parent compound or metabolites of DEET.

3.5.2 Mechanisms of Toxicity

In rare instances, DEET has been shown to induce adverse neurological effects in humans including seizure, ataxia, restlessness, uncontrolled limb movements, agitation, aggressive behavior, combativeness, impaired cognitive function, and opisthotonos. Studies in animals have reproduced some of these effects following high oral bolus exposure to DEET. In a repeated dose dermal study in rats, doses of ≥40 mg DEET/kg/day decreased the permeability of the blood-brain barrier (BBB) in various brain areas, but significantly only in the brainstem (Abou-Donia et al. 2001b). Investigators in this study provided several speculative hypotheses regarding DEET's effects on decreasing the permeability of the BBB, including regulation of expression of the cerebral endothelial multidrug transporter, *p*-glycoprotein (*p*-gp), which serves to protect the central nervous system by inducing efflux of drugs and chemicals; modulating levels of cyclic adenosine monophosphate (cAMP) after prolonged exposure, as high levels of cAMP have been shown to reduce BBB permeability; causing a hypothermic response, which may be responsible for the BBB permeability changes; and regulating the expression of proteins at tight junctions in the BBB resulting in reduced blood flow, and thus, reduced entry of chemicals into the brain. It should be noted that in this study, impaired sensory performance was reported at 4 mg DEET/kg/day, 1/10 the dose level that affected BBB permeability, and that doses up to 400 mg DEET/kg/day did not induce observable

clinical signs such as seizures, ataxia, or other signs. This lack of clinical signs suggests that the altered sensory performance may not be caused by alterations in BBB permeability and that changes of greater magnitude in BBB permeability or recruitment of additional brain areas are necessary for overt signs such as tremors or seizures to occur. The results of another dermal exposure study in rats from the same group of investigators suggested that DEET might affect cholinergic and noradrenergic pathways innervating brain areas involved in specific behaviors such as limb placing or beam-walking performance (Abou-Donia et al. 2001b). In a subsequent study of repeated-dosing dermal exposure of rats, DEET was shown to induce neuronal degeneration in the dentate gyrus, CA1 and CA3 subfields of the hippocampus, midbrain, brainstem, and Purkinje cell layer of the cerebellum (Abdel-Rahman et al. 2004). Possible mechanisms discussed by the investigators that could explain these morphological alterations included DEET-induced oxidative stress leading to the generation of free radicals and alterations in antioxidants, and induction of acetylcholinesterase in various brain areas leading to neuronal damage and subsequent apoptosis. As noted earlier, Jortner (2006) published his concerns about the misinterpretation of the histopathological findings reported in Abdel-Rahman et al. (2001) and other related publications. The main concern is that the report of "degenerating" or "dying" neurons in this article is the result of poor handling and inadequate fixation of the brain tissue and is a "dark" neuron artifact. The presence of this artifact suggests that both the neuron counting and the immunostaining procedures may have been compromised in the Abdel-Rahman et al. (2001) study and in subsequent studies at this laboratory.

Studies by Chaney et al. (1999) also provide information regarding possible mechanisms of DEET toxicity. Treatment of mice with DEET by intraperitoneal injection resulted in seizures that could not be prevented by pretreatment with standard anticonvulsive drugs or anticholinergic agents. These results suggested that DEET-induced seizure activity is mediated by a non-cholinergic pathway.

3.5.3 Animal-to-Human Extrapolations

Exposure of animals to DEET has resulted in effects similar to those reported in cases of intoxication in humans. There does not seem to be an animal species that can be used as a preferred animal model for studies of DEET.

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).

No studies were located regarding endocrine disruption in humans after exposure to DEET. Intermediate- (Ambrose 1959; Army 1980b; Schoenig et al. 1999) and chronic-duration (Schoenig et al. 1999) oral studies in animals that conducted gross and microscopic examination of endocrine glands found no evidence that DEET is an endocrine disruptor.

No *in vitro* studies were located regarding endocrine disruption of DEET.

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 most 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 adverse health effects from exposure to hazardous chemicals, but whether there is a difference depends on the chemical(s) (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to exposure-related 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 that are most sensitive to disruption from exposure to hazardous substances. Damage from exposure in one stage 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). Past literature has often described the fetus/infant as having an immature (developing) blood-brain barrier that is leaky and poorly intact (Costa et al. 2004). However, current evidence suggests that the blood-brain barrier is anatomically and physically intact at this stage of development, and the restrictive intracellular junctions that exist at the blood-CNS interface are fully formed, intact, and functionally effective (Saunders et al. 2008, 2012).

However, during development of the brain, there are differences between fetuses/infants and adults that are toxicologically important. These differences mainly involve variations in physiological transport

systems that form during development (Ek et al. 2012). These transport mechanisms (influx and efflux) play an important role in the movement of amino acids and other vital substances across the blood-brain barrier in the developing brain; these transport mechanisms are far more active in the developing brain than in the adult. Because many drugs or potential toxins may be transported into the brain using these same transport mechanisms—the developing brain may be rendered more vulnerable than the adult. Thus, concern regarding possible involvement of the blood-brain barrier with enhanced susceptibility of the developing brain to toxins is valid. It is important to note however, that this potential selective vulnerability of the developing brain is associated with essential normal physiological mechanisms; and not because of an absence or deficiency of anatomical/physical barrier mechanisms.

The presence of these unique transport systems in the developing brain of the fetus/infant is intriguing; whether these mechanisms provide protection for the developing brain or render it more vulnerable to toxic injury is an important toxicological question. Chemical exposure should be assessed on a case-by-case basis. Research continues into the function and structure of the blood-brain barrier in early life (Kearns et al. 2003; Saunders et al. 2012; Scheuplein et al. 2002).

Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns given their low glomerular filtration rate and not having 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).

As indicated throughout Section 3.2, Discussion of Health Effects by Route of Exposure, there are reports that provide information regarding health effects in children exposed to DEET. Most of these cases involved oral or dermal exposure and some cases resulted in death (Heick et al. 1980; Pronczuk de Garbino et al. 1983; Zadikoff 1979). The most common manifestation of intoxication were neurological effects including agitation, hypertonia, seizures, ataxia, restlessness, and uncontrolled limb movements (Edwards and Johnson 1987; Gryboski et al. 1961; Heick et al. 1980; Lipscomb et al. 1992; MMWR 1989; Petrucci and Sardini 2000; Roland et al. 1985; Tenenbein 1987; Zadikoff 1979). The combination of some of these signs and symptoms has been described as toxic encephalopathy. The putative association between exposure to DEET and seizures needs to be interpreted with caution since, as noted by Koren et al. (2003), a relatively high percentage (23–29%) of children are exposed to DEET in the United States and seizure disorders occur in approximately 3–5% of children from any cause, making it possible, just by chance alone, to erroneously find an association. This had been discussed earlier by MMWR (1989), which pointed out that "since the exact circumstances under which DEET-related neurotoxicity may occur are unclear, DEET should not be accepted as the cause of a seizure until appropriate evaluation has reliably excluded other possible etiologies." Also, in its Registration Eligibility Document for DEET, EPA (EPA 1998b) stated the following: "One possible explanation for the seizures [reported for children] is coincidence. Seizure coinciding with DEET is not unexpected, given an estimated 15,000–20,000 afebrile seizures in children (ages zero-19 years) estimated annually and an estimated 17 million children using DEET 10 times a year."

In the study of 9,086 human exposures involving insect repellents containing DEET reported to Poison Control Centers from 1985 to 1989 the majority of exposures were accidental and occurred in children (Veltri et al. 1994). These investigators also did not find a relationship between age and the severity of the reaction or with gender. They noted that "children less than six years of age were not more likely to develop adverse effects from DEET-containing products than older children or adults and the effects that did occur in children were not more serious" and that "exposed females were not more likely to develop adverse effects nor were the effects more severe than in exposed males."

An epidemiological study in which women applied DEET themselves in the second and third trimester of pregnancy did not find significant differences between exposed and controls regarding head and arm circumference or length or in a series of neurological tests in newborn infants (McGready et al. 2001). Another epidemiological study did not find significant associations between DEET concentration in maternal blood or cord serum and birth weight, head circumference, abdominal circumference, or birth length in newborn infants (Barr et al. 2010).

Studies in rats and rabbits exposed orally to DEET during gestation did not find fetotoxicity or teratogenicity (Schoenig et al. 1994). In both species, exposure to the highest doses (750 mg DEET/kg/day in rats and 325 mg DEET/kg/day in rabbits) resulted in significant reductions in maternal weight gain during the dosing period. In addition, rats treated with 750 mg DEET/kg/day showed a series of neurological signs during the dosing period including hypoactivity, ataxia, decreased muscle tone, and foot splay. A 2-generation reproductive study in rats reported significantly reduced body weight in F1 and F2 male and female pups on days 14 and 21 of lactation at maternal doses of 250 mg DEET/kg/day (EPA 1989).

Only one study was located that showed greater susceptibility to DEET in young animals compared to adults (Verschoyle et al. 1992). The study reported that the oral LD_{50} for DEET in 11-day-old Wistar rats was 4–5 times lower than in adult rats.

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).

The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of a generalizable sample 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 DEET from this report is discussed in Section 6.5. 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 DEET 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 DEET 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.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to DEET

Measurement of DEET in urine may not be a reliable biomarker of exposure, as this compound is rapidly metabolized after oral and dermal exposure, and the parent compound has rarely been detected in urine of animals or humans (Selim et al. 1995; Schoenig et al. 1996; Taylor and Spooner 1990) other than for high doses resulting in death (Ambrose 1959). Urinary metabolites of DEET appear to be better markers of exposure than the parent compound (Calafat et al. 2016, see below).

Smallwood et al. (1992) assessed the correlation between dermal exposure to DEET and urine and serum levels of DEET in a group of chronically-exposed workers and in a group of naïve volunteers, observing that neither urine nor serum levels were related to exposure estimates at low doses, but that urine samples may be correlated with exposure at higher doses or in individuals exposed regularly. The authors attributed the lack of correlation at low doses to the complex toxicokinetic behavior of DEET applied to the skin. As part of an effort to develop techniques to analyze DEET in urine and serum, Smallwood et al. (1992) tested the method on eight National Park employees who regularly used a DEET-containing insect repellent, and nine naïve volunteers (for whom information on informed consent was not provided)

exposed in a laboratory. The National Park employees were observed to apply sufficient quantities of the repellent, which contained 71% DEET, to yield an average daily application of approximately 1 g of DEET. Concentrations of DEET in spot urine samples collected from eight employees after the third day of the work week ranged from below the quantitation limit of 0.18 µg/mL up to 5.69 µg/mL. The authors reported that urinary concentrations were positively correlated (r=0.7) with estimated exposure among the eight employees; the wide range of urinary levels (0.18–5.69 µg/mL), however, appears to have no relationship to the single 1-g dermal dose that each individual reportedly received, suggesting that there may have been a wide range of applied doses. When nine volunteers without prior exposure were exposed in a laboratory to a DEET-containing repellent at doses between 0.14 and 1.86 g DEET per volunteer, the serum of all volunteers contained detectable DEET at concentrations ranging from 0.15 to 1.17 µg/g (Smallwood et al. 1992). Spot urine samples from only two of the nine volunteers, however, showed DEET concentrations above the detection limit of 0.09 µg/mL, and these subjects did not have the highest exposures (based on flux estimates). DEET concentrations in urine reported at various times (between 4 and 22 hours after application) for these two subjects ranged between 0.31 and 2.02 µg/mL (Smallwood et al. 1992). Dermal dose and application area were not readily correlated with spot urine or serum levels at any time point up to 6 hours after application among the volunteers, but the areas under the serum DEET concentration vs. time curves for the volunteers, integrated over 6 hours, were shown to correlate with the calculated flux of DEET across the skin (flux estimates ranged between 0.31 and 5.99 µg-cm^{2}x10^9).

Urinary metabolites of DEET are useful biomarkers of exposure. Kuklenyik et al. (2013) developed an HPLC/isotope dilution tandem mass spectrometry (MS) method to measure DEET and two of its oxidative metabolites (DHMB and DCBA) in the urine of humans and tested the technique on 75 anonymously collected samples from U.S. adults without known exposure. The authors reported that DCBA was detected most frequently and at the highest concentrations, indicating that this may be a useful biomarker of DEET exposure (Kuklenyik et al. 2013). Because no volunteer had any known exposure to DEET, however, the presence of DCBA in urine may in fact be indicative of exposure to the metabolite DCBA, perhaps in drinking water. This theory is consistent with reports that DEET metabolites are not effectively removed by waste water treatment facilities and may thus be available for subsequent public exposure.

Arcury et al. (2007) analyzed the urine of children of North Carolina farmworkers for metabolites of pesticides and reported that DEET metabolites were detected in the urine of 6 of 60 children. The median concentration of DEET metabolites in urine was 0.08 µg/g creatinine. The report did not clearly report

the metabolites analyzed in the urine. Recently, Calafat et al. (2016) published the results of analyses of 5,348 urine samples from persons ≥6 years old in a representative sample of the U.S. general population in the 2007–2010 NHANES. DEET was detected in only 3% of the samples (0.08–45.1 µg/L), DCBA was detected in approximately 84% of the samples (>0.48–30,400 µg/L), and DHMB was detected in approximately 15.5% of the samples (>0.09–332 µg/L). Adjusted concentrations of DCMB were found to be dependent on season of the year (higher in May through September than in October through April), race/ethnicity highest in non-Hispanic whites, possibly reflecting different lifestyle uses), household income, and age. In general, children had higher adjusted concentrations of DCBA than adults, which the investigators attributed to a higher rate of application to children by the parents than to themselves. Urine is the normal medium for assessing human exposure to DEET, and due to the high metabolic rate of DEET, both DCBA and DHMB are more sensitive biomarkers of exposure than DEET itself.

3.8.2 Biomarkers Used to Characterize Effects Caused by DEET

There are no specific biomarkers of effect for DEET exposure. Exposure to products containing DEET has been associated with neurological effects such as seizures, ataxia, hypertonia, uncontrolled movements and agitation, as well as with skin irritation. These and other symptoms including hypotension, nausea and vomiting, and skin rashes can be the result of exposure to many other chemicals or can be caused by conditions unrelated to chemical exposures.

3.9 INTERACTIONS WITH OTHER CHEMICALS

A series of animal studies have been conducted that examined the effects of combined application of DEET and other chemicals that were implicated in the development of neurological alterations and other symptoms among veterans of the Persian Gulf War, termed Gulf War Syndromes or Gulf War illness. Some investigators (Abou-Donia et al. 1996) have proposed that the combination of chemicals, namely, DEET, permethrin, and pyridostigmine bromide (PB), possibly caused some of the range of symptoms reported. Permethrin is a type I pyrethroid insecticide that was applied to the clothing of the military personnel. Pyridostigmine bromide is a reversible inhibitor of AChE that was used orally. A summary of the findings from these studies is provided below.

A 60-day study of daily dermal applications of 4, 40, or 400 mg of 97.7% DEET/kg/day to 1 cm^2 of shaved backs of rats found decreases in permeability of the BBB [^{3}H]hexamethomium of 78, 66, and 65%, respectively, in the brainstem, which was the most sensitive area (Abou-Donia et al. 2001a). Although dermally applied permethrin at doses up to 1.3 mg/kg/day had no significant effect on BBB

permeability, DEET and permethrin in combination significantly decreased BBB permeability in the cortex. None of the treatments affected simple sensorimotor reflexes, but DEET alone at the lowest dose, 4 mg/kg, and the combination with permethrin affected some sensory parameters such as performance on a beam, grip strength, and performance on an inclined plane. The combination of the two drugs resulted in poorer performance in some tests, but only at the highest doses.

In a subsequent study of DEET (40 mg/kg/day dermally) that also included PB (1.3 mg/kg/day in drinking water) and permethrin (0.13 mg/kg/day dermally), in doses stated to be comparable to those received by service members during the Persian Gulf War, none of the single treatments affected postural reflexes, limb placing, or vibrissae touch (Abou-Donia et al. 2001b). Beam walking time (but not beam walking score) was increased over time by coexposure to DEET with PB (but not DEET with permethrin), and was affected most by the 3 substances in combination, but was unaffected by DEET or permethrin alone. Each of the 3 substances alone and in any combination reduced performance on the incline plane and especially reduced forepaw grip strength to <10% of controls. There is no indication in the literature that service members comparably exposed to these substances were unable to lift items and function on the battlefield, perhaps indicating that rats are an exquisitely sensitive species, and more sensitive than humans. DEET produced occasional diarrhea, which has not been reported in other studies conducted at higher dose levels. In general, combination with PB produced the most marked deficits. DEET alone increased AChE by about 40% in the brainstem but not in other brain areas. In combination with PB, AChE in brainstem was decreased. The three drugs together decreased AChE in brainstem and midbrain. DEET alone caused a significant increase (about 20%) in choline acetyltransferase (ChAT, the enzyme responsible for the synthesis of acetylcholine) activity in the cortex and a non-significant increase in the brainstem, the only two places measured. DEET alone and with permethrin significantly increased ligand binding density of m2 muscarinic acetylcholine receptors in the cortex. DEET alone did not affect ligand binding of nicotinic receptors in the cortex; nor did exposure to PB plus DEET only, or the three drugs together.

A study that conducted microscopic examination of the brain in rats exposed to the same service member related doses of DEET, permethrin, or the combination showed that DEET alone induced neuronal degeneration principally in the motor cerebral cortex, dentate gyrus, *cornu ammonis* (CA) subfields 1 and 3 of the hippocampus, and the Purkinje cell layer of the cerebellum (Abdel-Rahman et al. 2001). In the cerebral cortex DEET alone generally appeared to cause more damage than permethrin alone and degeneration appeared to occur earlier in rats treated with the combination than with either chemical alone, but the combination did not induce enhanced neuron loss. In the dentate gyrus, there was a greater

level of neuron loss with DEET or permethrin alone than with the combination; the authors suggested that concurrent exposure to chemicals can decrease their absorption. As mentioned earlier, concerns have been expressed about the misinterpretation of the histopathological findings reported in Abdel-Rahman et al. (2001) and other related publications. The main concern is that the report of "degenerating" or "dying" neurons in this article is actually the result of poor handling and inadequate fixation of the brain tissue and is a "dark" neuron artifact. The presence of this artifact suggests that both the neuron counting and the immunostaining procedures may have been compromised in the Abdel-Rahman et al. (2001) study and in other studies conducted at this laboratory in this timeframe.

Yet another study that included DEET, permethrin, and malathion showed that all three chemicals alone altered neurobehavioral parameters (Abdel-Rahman et al. 2004). The combination of DEET with these other chemicals altered the effects of DEET alone. DEET with permethrin significantly increased AChE activity in the cortex and cerebellum, and significantly decreased AChE activity in the midbrain. Similar, but less marked, changes were seen in the group with DEET plus malathion. DEET plus malathion and DEET plus permethrin significantly increased butyrylcholinesterase in plasma. Treatment with DEET alone or DEET combined with permethrin or malathion did not significantly affect muscarinic acetylcholine receptor binding. DEET alone induced neuronal degeneration in the dentate gyrus, CA1 and CA3 subfields of the hippocampus, midbrain, brainstem, and Purkinje cell layer of the cerebellum. These studies used doses of DEET, PB, and permethrin at doses stated to be comparable to those received by military personnel during the Persian Gulf War.

Similar studies in rats to those conducted by Abou-Donia and coworkers, but with DEET administered orally once or daily over 7 days were conducted by Hoy et al. (2000a, 2000b). In the single-dose study, up to 500 mg DEET/kg had no significant effect on locomotor activity except in met-estrus female rats for which speed was reduced at the highest dose. Administration of DEET (100 mg/kg) and permethrin (15 mg/kg) significantly reduced locomotor activity in male but not female rats to 2.06 meters/min compared to 2.24 and 2.50 meters/min achieved for each substance individually administered at twice those doses. Despite DEET having a greater effect on male mobility, uptake to blood serum was 2–3 times greater in females. Also, the administration of PB tended to decrease oral uptake of DEET in female but not in male rats. In the 7-day study, administration of DEET (200 mg/kg/day) or permethrin (60 mg/kg/day) by gavage or PB (7.5 mg/kg/day) by intraperitoneal injection did not cause significant alterations in locomotor activity. Administration of the combination PB/DEET (at half doses), however, resulted in significantly lower locomotor rates, while the combination permethrin/DEET (at half doses) significantly increased locomotor rates. Administration of the three drugs together (at one third doses)

caused no significant effect. The competition between drugs is consistent with the suggestion by Hoy et al. (2000a) that PB uptake might protect rats from the effects of permethrin.

While the results summarized above suggest that the combination of PB and insect repellents may have synergistic neurological effects, the results of a more recent acute exposure study in humans did not support these findings. Roy et al. (2006) conducted a multicenter, prospective, double-blind, placebo-controlled crossover trial, approved by human use committees at the Uniformed Services University, Bethesda, Maryland; Naval Health Research Center, San Diego, California, Office of the Surgeon General of the Army; and Navy Bureau of Medicine and Surgery. The 64 volunteers completed informed consent forms and were exposed to permethrin-impregnated uniforms continuously; a DEET-containing skin cream (33% DEET) twice daily to neck, face, and legs, and oral pyridostigmine bromide (30-mg tablets) every 8 hours for a full day before each part was conducted. The 4-part crossover design ensured exposure of all participants to all treatments and placebos under both mental plus physical stress and rest conditions. The outcomes examined included biochemical assays and parameters of physical performance, neurocognitive responses, and self-reported adverse effects. The results showed significant increases in systolic blood pressure and heart rate, and increased serum levels of adrenaline, noradrenaline, and lactate during stress sessions; however, none of these were influenced by treatment. None of the exposure combinations significantly affected diastolic blood pressure or serum dopamine or cortisol levels. In addition, neurocognitive performance, as measured by the WinSCAT battery, did not differ with exposure to treatments compared to placebos and showed a slight non-statistical improvement with stress. Finally, self-reported effects did not differ by exposure group. Roy et al. (2006) attributed the difference between their results and those of Abou-Donia and coworkers to the different dose levels used and routes of administration. Roy et al. (2006) noted that in their study, permethrin-treated uniforms did not lead to measurable permethrin in the blood stream.

In an additional study examining the interactive effects of DEET, PB, and permethrin in animals, McCain et al. (1997) reported that the simultaneous administration of the three chemicals to rats significantly increased the lethality compared to expected additive values. Concurrent administration of PB and DEET caused a significant increase in lethality compared to expected additive values. The investigators suggested that possible mechanisms could involve facilitated absorption of PB in the gut by DEET or inhibition of detoxification systems.

In studies in rats, intraperitoneal administration of 200 mg DEET/kg (at levels expected to produce 10–20% lethality) did not significantly alter the inhibition of cholinesterase activity in the heart (20%

reduction), diaphragm (30% reduction), or whole blood (15% increase), whereas intraperitoneal administration of only 1 or 3 mg PB/kg resulted in significant 80–90% reductions of cholinergic activity in those areas (Chaney et al. 2000). Co-administration of 200 mg DEET/kg with 1 or 3 mg PB/kg, however, reduced ChE activity to levels achieved solely by PB, except in whole blood for which the high PB dose resulted in levels comparable to unexposed controls. No dose of PB alone significantly altered cholinesterase activity in the brain. DEET alone slightly reduced brain ChE activity, and DEET plus the high PB dose reached statistical significance at 40% inhibition of brain cholinesterase. These results were interpreted as DEET not altering the inhibition of ChE activity induced by PB in the heart, diaphragm, or whole blood, and that DEET increased the permeability of the brain to PB rather than directly affecting PB-induced cholinesterase inhibition. The same group of investigators also reported that intraperitoneal co-administration of PB and DEET to rats caused a profound and rapid decrease in heart rate that did not occur with either chemical alone that eventually resulted in death (Chaney et al. 2002). The investigators noted that the primary cause of death appeared to be circulatory failure and proposed the following sequence of events: DEET may have depressed central cardiorespiratory centers and altered sympathetic outflow from the brain. PB aggravated DEET-induced toxicity presumably by promoting accumulation of acetylcholine at peripheral cholinergic receptor sites. This accumulation at cholinergic sites resulted in bradycardia and further reduced cardiac output, which caused the development of progressive circulatory shock. It is worth noting that the relevance of injection studies of DEET to safety assessment of DEET exposure in humans is, at best, questionable.

It should also be noted that while the studies that examined the interactive action of DEET, permethrin, and PB provide valuable information for understanding potential mechanisms that could explain some health outcomes manifested in the Gulf War Syndrome, it is difficult to see their relevance to civilian exposures to DEET and other chemicals.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to DEET than will most persons exposed to the same level of DEET in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of DEET, or compromised function of organs affected by DEET. Populations who are at greater risk due to their unusually high exposure to DEET are discussed in Section 6.7, Populations with Potentially High Exposures.

No populations that are unusually susceptible to adverse health effects from exposure to DEET were identified in the literature reviewed. A study of 9,086 human exposures involving insect repellents containing DEET reported to Poison Control Centers from 1985 to 1989 found that children younger than 6 years of age were not more likely to develop adverse effects from DEET-containing insect products than older children or adults, and the effects that occurred in children were not more serious (Veltri et al. 1994). AAPCC (2013) reported that 57%, or 2,316 case reports, of exposure to DEET were in children ≤5 years of age. This may indicate a propensity for parents to apply DEET more liberally to protect their youngest children from insect bites, rather than a differential susceptibility. Neurological effects, specifically seizures, have been reported in children and adults following oral or dermal exposure to products containing DEET. Thus, the question arose as to whether subjects with known prior seizure disorders would be more susceptible to DEET. In a study of 296 major and moderate severity cases included in the DEET Registry from 1995 to 2001, people with an underlying neurological disorder or a history of seizures prior to the first documented use of DEET were not disproportionally represented in the Registry (Osimitz et al. 2010).

Verschoyle et al. (1992) evaluated acute toxicity in rats and noted that neonates were significantly more sensitive than adult rats to DEET-induced lethality; however, no sensitivity generalizations can be made based on a single study, nor is it possible to make inferences about sensitivity at the lower doses to which humans are more likely to be exposed.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to DEET. 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 DEET. When specific exposures have occurred, poison control centers, board certified medical toxicologists, board-certified occupational medicine physicians and/or other medical specialists with expertise and experience treating patients overexposed to DEET can be consulted for medical advice.

DEET has a low order of toxicity if used properly; however, it is prudent to avoid the overuse of DEET, which could result in adverse health effects (AAP 2015; Holland 2015).

The following texts provide specific information about treatment following exposures to DEET:

Borron SW. 2007. Pyrethrins, repellents, and other pesticides. In: Shannon MW, Borron SW, Burns MJ, eds. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: Saunders Elsevier, 1185-1194.

Osmundson M. 1998. Insecticides and pesticides. In: Viccellio P, ed. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers, 401-413.

Holland MG. 2015. Insecticides: Organochlorines, pyrethrins/pyrethroids, and insect repellents. In: Hoffman RS, Howland MA, Lewin NA, eds. Goldfrank's toxicologic emergencies. 10th ed. New York, NY: McGraw-Hill Education, 1435–1448.

Additional relevant information can be found in the front section of this profile under QUICK REFERENCE FOR HEALTH CARE PROVIDERS.

3.11.1 Reducing Peak Absorption Following Exposure

The following information was extracted from the books listed above; specific chapters were written by Borron (2007), Osmudsen (1998), and Holland (2015). It is recommended, however, that this information be used along with consultation with a medical specialist with expertise and experience treating/managing patients with DEET poisoning.

In cases of accidental dermal overexposure, skin decontamination with copious amounts of soap and water should be a priority to prevent further absorption. In cases of eye exposure, irrigation of the eyes with isotonic saline or copious amounts of room temperature water for at least 15 minutes is recommended. In cases of oral ingestion, one report recommended administration of a single dose of activated charcoal if clinically indicated (Holland 2015). However, only one case report of treating a DEET-overexposed individual with activate charcoal was located (Tenenbein 1987). Since the patient died, the efficacy of using activated charcoal is unclear.

3.11.2 Reducing Body Burden

No information was located regarding reducing the DEET body burden following exposure to this substance, but studies in volunteers indicate that it is rapidly cleared from the body (Selim et al. 1995; Wu et al. 1979).

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Overexposure to DEET has been associated mainly with neurological effects such as seizures and hyperactivity, and skin effects, if exposure was dermal. The mechanisms by which these effects occur have not been elucidated. Management of suspected DEET-related toxicity is essentially supportive and aimed primarily to treat the neurological effects. Benzodiazepines may be used to treat seizures. Refractory seizures may be treated with phenobarbital.

3.12 ADEQUACY OF THE DATABASE

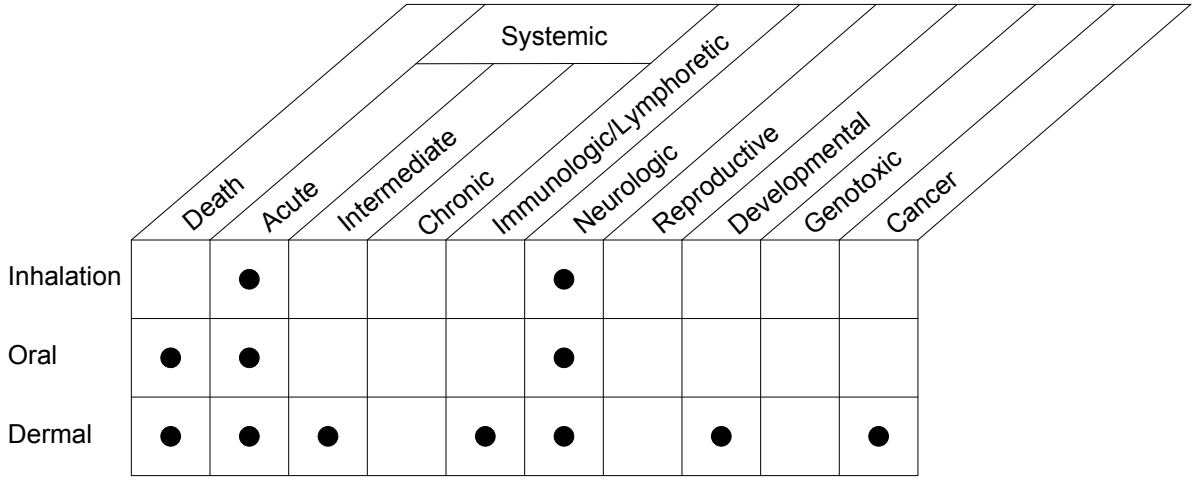
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of DEET is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of DEET.

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 risk 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.

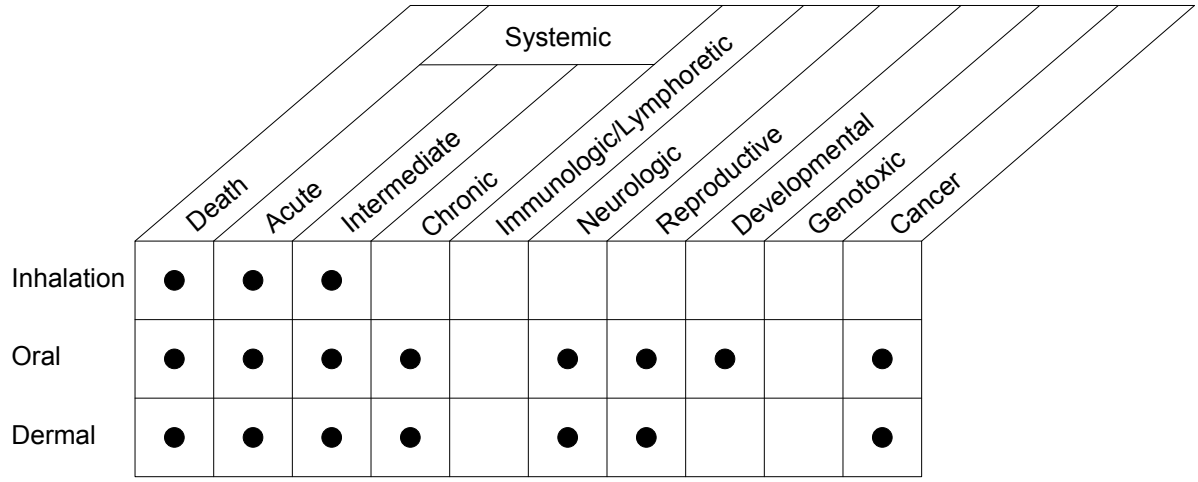
3.12.1 Existing Information on Health Effects of DEET

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to DEET are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of DEET. 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.

Figure 3-5. Existing Information on Health Effects of DEET



Human



Animal

● Existing Studies

Most of the literature reviewed concerning the health effects of DEET in humans described case reports of acute dermal exposure to DEET. There are also surveys involving great numbers of individuals from the general population compiled from records kept in public and private poison control centers. These individuals were exposed to products containing DEET by the inhalation, oral, or dermal route. Also available are a few studies of occupational exposure and controlled dermal exposure in volunteers. No reliable estimates of quantitative exposure could be obtained from case reports.

The database in animals is extensive. As can be seen in Figure 3-5, most studies in animals have been conducted by the oral and dermal routes of exposure. There is more information regarding the health effects of DEET following intermediate exposure than regarding acute or chronic exposure. There is no evidence suggesting that the toxicity of DEET is route-specific. The intake and uptake rates from oral exposure, however, are faster than those by the dermal route of exposure, so greater peak concentrations in liver and nervous system tissues are achieved.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Information is lacking concerning actual dermal exposures of individuals who use DEET-containing products, and the AAPCC database only addresses the percentage of DEET in products for which reports are made to poison control centers. Since environmental and public health agencies recommend the use of DEET to avoid insect and acarid bites, developing a standard for conducting dermal dosimetry and adding dose information to poison control center reports could help improve recommendations for safely applying DEET.

Information is available regarding the effects of acute-duration exposure in humans following inhalation (Bell et al. 2002), oral (Edwards and Johnson 1987; Fraser et al. 1995; Petrucci and Sardini 2000; Tenenbein 1987; Wiles et al. 2014; Zadikoff 1979), and dermal exposure (Ambrose 1959; Briassoulis et al. 2001; Clem et al. 1993; Edwards and Johnson 1987; Gryboski et al. 1961; Hampers et al. 1999; Heick et al. 1980; Lipscomb et al. 1992; Maibach and Johnson 1975; MMWR 1989; Reuveni and Yagupsky 1982; Roland et al. 1985; Shutty et al. 2013; Vozmediano et al. 2000; Wantke et al. 1996; Zadikoff 1979). Deaths have been reported following oral and dermal exposure to products containing DEET (Heick et al. 1980; Pronczuk de Garbino et al. 1983; Tenenbein 1987; Veltri et al. 1994; Wiles et al. 2014; Zedikoff 1979). The main target of toxicity in humans and animals following acute, high-level exposure by any route is the nervous system (Army 1979; Briassoulis et al. 2001; Gryboski et al. 1961; Lipscomb et al.

1992; Petrucci and Sardini 2000; Verschoyle et al. 1992; Zadikoff 1979). No reliable exposure concentrations were available in surveys of people reporting to emergency departments after inhalation exposure to insect repellents containing DEET; therefore, no acute-duration inhalation MRL could be derived using human data. Very limited inhalation data in animals were located and the available studies (Ambrose 1959; Army 1979; Deb et al. 2010) have significant limitations rendering them inadequate for MRL derivation. Studies that examine a comprehensive number of end points to possibly construct dose-response relationships would seem warranted; the need to fill this data gap, however, needs to be balanced with the fact that, assuming proper use, it is unlikely that significant inhalation of DEET will occur based on its estimated half-life in air of 5 hours (EPIWIN 2012), which makes persistence and long-range transport of DEET in air negligible. There is no information from humans who ingested DEET that is useful for derivation of an acute-duration oral MRL for DEET. Studies in animals provided information regarding lethal doses (Ambrose 1959; Carpenter et al. 1974; EPA 1998c; McCain et al. 1997; Verschoyle et al. 1992), developmental effects in rats and rabbits (Schoenig et al. 1994), and neurological effects in rats (Schoenig et al. 1993; Verschoyle et al. 1992). These studies did not identify a sensitive target for DEET. Studies that provide comprehensive information regarding potential gross and microscopic alterations in major organs and tissues would be valuable. Based on an incomplete database, an acute-duration oral MRL was not derived for DEET. Case reports of people who used insect repellents containing DEET in the form of aerosols or lotions provide information regarding cardiovascular, gastrointestinal, hematological, hepatic, renal, endocrine, dermal, ocular, immunological, and neurological effects (Amichai et al. 1994; Bell et al. 2002; Briassoulis et al. 2001; Clem et al. 1993; Hampers et al. 1999; Heick et al. 1980; Lipscomb et al. 1992; Maibach and Johnson 1975; MMWR 1989; Reuveni and Yagupsky 1982; Roland et al. 1985; Zadikoff 1979). A study in volunteers provided information on dermal effects of DEET (Ambrose 1959). A limited number of studies in animals provided information on lethal doses (Carpenter et al. 1974; EPA 1998c) and on dermal and ocular effects (Ambrose 1959; MacRae et al. 1984). Normal use of products containing DEET involves direct skin exposure. Therefore, animal studies that examine a wide range of end points (systemic, immunological, neurological, reproductive, and developmental) and establish dose-response relationships would be valuable.

Intermediate-Duration Exposure. There are no studies of humans exposed to DEET for intermediate durations by the inhalation or oral routes. Two inhalation studies in animals were available for review. A limited-scope study reported unspecified alterations in the lungs and trachea of rats following a 7-week exposure period (Ambrose 1959). A 13-week study in rats examined a comprehensive number of end points, including organ and tissue histopathology and hematological and

clinical chemistry parameters and found no significant effects (Army 1980a). In the absence of a LOAEL being identified, an intermediate-duration inhalation MRL was not derived for DEET. As mentioned above, it is unlikely that humans will be exposed to significant amounts of DEET in the air; therefore, it does not appear that additional inhalation studies are necessary at this time. Intermediate-duration oral studies in animals provided information on systemic (Ambrose 1959; Army 1980b; EPA 1989, 1990b; Schoenig et al. 1993, 1999), immunological (Ambrose 1959; Army 1980b; EPA 1990b; Schoenig et al. 1999), neurological (Ambrose 1959; Army 1980b; EPA 1990b; Schoenig et al. 1993, 1999), reproductive (Ambrose 1959; EPA 1989), and developmental effects (EPA 1989). Although a clear target for DEET toxicity was not apparent, a developmental study that identified the lowest LOAEL (EPA 1989) was adequate and was used to derive an intermediate-duration oral MRL for DEET. Additional intermediate oral studies do not seem necessary at this time. Limited information is available regarding intermediate-duration dermal exposure in humans. Workers at a national park who used insect repellents or lotions containing DEET repeatedly during the summer season complained more often of chest pain or wheezing, muscle cramping, skin rashes and blisters, dizziness, disorientation, and difficulty concentrating than workers who used the products less often or did not use them at all (NIOSH 1986). In addition, a case report of an 18-month-old girl who received daily applications of an insect repellent containing 20% DEET for approximately 3 months reported hematological and neurological effects, but no evidence of altered liver function (Edwards and Johnson 1987). Further studies of workers exposed seasonally to DEET would be valuable, especially if exposure can be better characterized. Intermediate-duration dermal studies in animals provide information regarding systemic effects (Ambrose 1959; EPA 1988, 1990a, 1992a; Lebowitz et al. 1983), neurological effects (Abdel-Rahman et al. 2001, 2004; Abou-Donia et al. 2001a, 2001b), and reproductive effects (Lebowitz et al. 1983). Two of these studies (EPA EPA1988, 1992a) conducted a comprehensive examination of the major organs and tissues from rats and micropigs to identify possible histological alterations; these studies also monitored hematological and clinical parameters. Therefore, additional intermediate-duration animal studies by the dermal route do not seem warranted at this time.

Chronic-Duration Exposure and Cancer. There are no studies of humans exposed chronically to DEET by any route with the exception of a study that monitored birth outcomes in women exposed to various pesticides (Barr et al. 2010) and a study of testicular cancer in Sweden (Hardell et al. 1998). The assumption is that in both studies, the subjects may have been exposed for extended periods of time (see specific sections below). There are no chronic-duration inhalation studies in animals. Based on use patterns and physical properties of DEET, however, chronic-inhalation exposure to DEET is not expected; therefore, chronic-inhalation studies may not be necessary at this time. Chronic-duration oral

studies have been conducted with DEET in rats and mice (Schoenig et al. 1999). These studies provided information on a comprehensive number of end points including clinical signs, gross and microscopic appearance of tissues and organs, hematological parameters, and clinical chemistry and ophthalmology in rats. A chronic-duration oral MRL however, was not derived because the few alterations reported were of questionable toxicological significance. In addition, the available studies did not test for end points such as subtle neurobehavioral effects, which have been reported at relative low doses in intermediate-duration dermal studies in rats (Abou-Donia et al. 2001a) and in humans following seasonal used of DEET-containing insect repellents (NIOSH 1986). It would be useful to have this information because populations living near hazardous waste sites could be exposed orally via contaminated water. Only one chronic-duration dermal study in animals was available for review. That study examined gross lesions in mice and rabbits that had DEET applied onto the skin for 140 or 90 weeks, respectively, but did not provide information regarding possible non-neoplastic changes in tissues and organs (Stenback 1977). Based on decades of experience with humans applying DEET to the skin repeatedly and because chronic dermal exposure is not expected except in unusual circumstances (e.g., long-term use in tropical areas where biting insects are active throughout the year, or in the field by military personnel), additional chronic-duration dermal studies do not seem necessary at this time.

Very limited information is available regarding exposure to DEET and cancer in humans. A study of testicular cancer and occupational exposures in Sweden found an increased risk among workers who used insect repellents for more than 115 days (Hardell et al. 1998). Studies of cancer need to be conducted among groups identified as having long-term exposure to DEET, such as those involved in the manufacture of the chemical and those who use it for extended periods during the year, such as park workers. DEET has been examined for carcinogenicity in oral studies in rats, mice, and dogs (Schoenig et al. 1999) and in dermal studies in mice and rabbits (Stenback 1977). The results were negative in all the species tested. Additional cancer studies in animals do not seem necessary.

Genotoxicity. There are no genotoxicity studies of humans exposed to DEET. Individuals involved in the manufacture and long-term use of DEET could be tested for possible genomic alterations. A single *in vivo* study reported an increase in a biomarker of DNA damage in rats that had application of a single dermal dose of DEET (Abu-Qare and Abou-Donia 2000). Additional studies *in vi*vo that examine whether DEET is a clastogenic substance would be valuable. A limited number of studies of reverse mutation in *Salmonella* gave negative results (EPA 1990c; Zeiger et al. 1992); additional studies seem unwarranted. Studies in mammalian cells gave mixed results. Evidence of DNA damage was reported in

cultured primary human nasal mucosal cells (Tisch et al. 2002). It would be useful to try to replicate the findings from Tisch et al. (2002).

Reproductive Toxicity. No studies were located regarding reproductive effects in humans exposed to DEET by any route. No data on reproductive toxicity were located in animals exposed to DEET by inhalation. Intermediate- and chronic-duration oral studies did not find significant gross or microscopic alterations of the reproductive organs of male and female animals (Ambrose 1959; Army 1980b; EPA 1989; Schoenig et al. 1999) except for tubular degeneration of the testes in hamsters (EPA 1990b). Fertility was evaluated only in a 2-generation continuous feeding study in rats and was not affected by treatment with DEET (EPA 1989). An intermediate-duration dermal exposure study in rats did not find significant histological alterations in the testes or in sperm parameters (Lebowitz et al. 1983). Two additional intermediate-duration dermal studies did not observe morphological alterations in the reproductive organs from rats or micropigs (EPA 1988, 1992a). Further reproductive studies are unlikely to provide new key information.

Developmental Toxicity. Two studies provided information regarding developmental effects in humans following exposure to DEET (Barr et al. 2010; McGready et al. 2001). In the latter study, controlled dermal exposure of pregnant women to DEET during the second and third trimesters did not affect developmental outcomes at birth and up to 1 year of age. Follow-up studies of these infants would have been useful. In the Barr et al. (2010) study of the general population, there was no significant association between levels of DEET in maternal blood and cord serum and developmental outcomes. Studies in rats and rabbits exposed orally to DEET during gestation showed only a slight decrease in fetal weight in rats and no significant fetotoxicity in rabbits at dose levels that induced maternal toxicity (Schoenig et al. 1994). No teratogenicity was reported in either study. In a 2-generation continuous feeding study in rats, the only significant effect observed was a reduction in F1 and F2 pup body weight on days 14 and 21 of lactation (EPA 1989). Since the birth weight of pups was not significantly different from controls, the possibility exists that DEET was transferred to the pups via the milk or that there was insufficient milk production by the exposed dams, or both. Experiments could be designed to test these hypotheses. Cross-fostering experiments could provide information regarding the relative importance of exposure to DEET through the placenta vs. via lactation.

Immunotoxicity. A few studies have reported that exposure to DEET can cause contact urticaria by immunological mechanisms in humans (Maibach and Johnson 1975; Shutty et al. 2013; Vozmediano et al. 2000). Intermediate- and chronic-duration oral studies in animals have mainly showed that exposure

to DEET did not induce gross or microscopic alterations in lymphoreticular organs and tissues (Ambrose 1959; Army 1980b; EPA 1990b; Schoenig et al. 1999). Because parameters of immunocompetence were affected in a study in mice administered DEET by subcutaneous injection (Keil et al. 2009), and because immunocompetence has been affected in animals by exposure to other chemicals at relatively low doses (Abadin et al. 2007), it would be useful to conduct pilot studies, especially by the dermal route of exposure, to test whether exposure to DEET can also affect immunocompetence.

Neurotoxicity. Adverse neurological effects have been reported in humans following inhalation, oral, or dermal exposure to insect repellents containing DEET. In most cases, this has occurred following exposure to what appears to have been excessive amounts. Signs and symptoms reported include seizures, ataxia, restlessness, uncontrolled limb movements, agitation, aggressive behavior, combativeness, impaired cognitive functioning, and opisthotonos (Briassoulis et al. 2001; Edwards and Johnson 1987; Gryboski et al. 1961; Hampers et al. 1999; Heick et al. 1980; NIOSH 1986; Petrucci and Sardini 2000; Pronczuk de Garbino et al. 1983; Roland et al. 1985; Snyder et al. 1986; Wiles et al. 2014; Zadikoff 1979). Continued follow-up of the individuals with the most severe effects (i.e., seizures) would provide valuable information regarding possible long-term effects (or lack thereof) due to acute exposure. In a 1-year follow-up of 35 of these cases of seizures after exposure to DEET, medical tests showed evidence of an underlying neurological disorder in 5 of these cases (Osimitz et al. 2010). Studies in animals have reported neurobehavioral alterations (Abdel-Rahman et al. 2004; Abou-Donia et al. 2001a; Army 1979; Schoenig et al. 1993), morphological alterations (Abdel-Rahman et al. 2001; Verschoyle et al. 1992), and neurochemical alterations (Abou-Donia et al. 2001b). As mentioned in Section 2.2, Summary of Health Effects, there are some unexplained inconsistencies between the results from some of these studies that need to be resolved. With regard specifically to morphological alterations, as mentioned earlier, findings reported by Abdel-Rahman et al. (2001, 2004) have been questioned as possible artifacts (Jortnet 2006), so it would be useful to try to replicate their findings. The mechanism by which DEET (or a metabolite) induces neurological alterations has not been elucidated, so further research in this area is needed.

Epidemiological and Human Dosimetry Studies. Most of the literature reviewed concerning the health effects of DEET in humans described case reports of accidental or intentional ingestion, or dermal exposure to DEET by the general population (Barr et al. 2010; Briassoulis et al. 2001; Clem et al. 1993; Edwards and Johnson 1987; Fraser et al. 1995; Gryboski et al. 1961; Hampers et al. 1999; Heick et al. 1980; Lipscomb et al. 1992; Maibach and Johnson 1975; MMWR 1989; Petrucci and Sardini 2000; Pronczuk de Garbino et al. 1983; Roland et al. 1985; Shutty et al. 2013; Tenenbein 1987; Vozmediano et

al. 2000; Wantke et al. 1996; Wiles et al. 2014; Zadikoff 1979), and exposure of workers (NIOSH 1986), volunteers (Ambrose 1959; McGready et al. 2001), and military personnel (Amichai et al. 1994; Haley et al. 1997; Reuveni and Yagupsky 1982). Only in four of these studies was there information regarding dose/exposure concentrations. Wiles et al. (2014) reported that a man who ingested 6 ounces of a repellent containing 40% DEET (748 mg/DEET/kg) suffered a seizure, became unresponsive, and was declared brain dead 3 days after poisoning. Ambrose (1959) reported that 1–2 mL of a 50% DEET solution applied on to the face of volunteers for 5 days caused some desquamation. McGready et al. (2001) reported that dermal application of 1.7 g DEET/day to women during the second and third trimester of pregnancy did not affect developmental outcomes. In NIOSH (1986), estimates of exposure to >4.25 g DEET/week (based on survey recall data) were associated with chest pain or wheezing, skin rash and blisters, and impaired cognitive functioning. Follow-up of individuals who have experienced the most severe effects (i.e., seizures) would help determine possible long-term effects of acute high exposure. Continuous evaluation of park workers who have used insect repellents during part of the year for several years could provide valuable information including reproductive data in both males and females and pregnancy outcomes in women as well as potential health effects in their offspring.

Biomarkers of Exposure and Effect.

Exposure. Further studies correlating urinary levels of DEET or its metabolites with exposure measures could provide valuable information to validate the use of these metrics as biomarkers of exposure to DEET, as available studies are limited (Calafat et al. 2016).

Effect. There are no DEET-specific effects following exposure to this substance. Neurological and dermal effects that have been associated with exposure to DEET can also be induced by exposure to other chemicals or can even be caused by conditions unrelated to chemical exposures. Any research aimed at identifying a specific biomarker of effect for DEET would be valuable.

Absorption, Distribution, Metabolism, and Excretion. No information on the toxicokinetics of DEET in humans or animals exposed via inhalation was available in the literature reviewed. Studies aimed at characterizing the behavior of DEET entering systemic circulation through the inhalation route of exposure would be valuable, even though inhalation is an unlikely route of exposure to DEET if products containing DEET are used properly. Only one study (Schoenig et al. 1996) examined the toxicokinetics of DEET after a single oral exposure in rats; studies examining other exposure regimens would provide useful information on the effects of exposure frequency or duration on toxicokinetics, and

studies in other species would help determine whether there are species differences in toxicokinetics after oral exposure. The role of metabolism on the toxicity of DEET is not known; therefore, studies designed to provide information on this issue seem warranted.

Comparative Toxicokinetics. There is suggestive evidence for species differences in the absorption, metabolism, and/or elimination of DEET. As only one study in rats examined toxicokinetics after oral exposure to DEET (Schoenig et al. 1996), the lack of information on species differences in toxicokinetics of orally-administered DEET represents an important data gap. Additional information comparing dermal absorption by rodents with absorption by humans under the same treatment conditions would be useful, as cross-study comparisons are hampered by differences in exposure conditions that can markedly affect the rate or extent of absorption. Likewise, there are suggestive, but not conclusive, data indicating gender differences in metabolism and/or excretion of DEET. Further studies comparing male and female animals or humans are needed to provide a basis for conclusions regarding gender differences in the toxicokinetics of DEET.

Methods for Reducing Toxic Effects. There are no DEET-specific effects following exposure to this chemical. Overexposure to DEET has been associated mainly with neurological effects such as seizures and hyperactivity, and dermatitis, if exposure was through skin contact. The mechanisms by which these effects occurred have not been elucidated. Management of suspected DEET-related toxicity is essentially supportive and aimed primarily to treat the neurological effects. Publishing treatments that have proved to be effective in randomized controlled trials in medical journals could improve and/or prevent secondary effects and speed recovery in the most severe cases.

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.

Information on the effects of DEET in children is derived mainly from case reports of accidental ingestion of insect repellents containing DEET or after receiving excessive dermal applications of the repellents. The most common manifestation of intoxication were neurological effects including agitation, hypertonia, seizures, ataxia, restlessness, and uncontrolled limb movements (Edwards and Johnson 1987; Gryboski et al. 1961; Heick et al. 1980; Lipscomb et al. 1992; MMWR 1989; Petrucci and Sardini 2000; Roland et al. 1985; Tenenbein 1987; Zadikoff 1979). Evaluation of poisoning cases reported to Poison Control Centers from 1983 to 1989 did not suggest that children are more sensitive to DEET than adults (Veltri et al.

1994). Only one study in animals was located that examined the acute toxicity of DEET in relation to age (Verschoyle et al. 1992). That study reported that neonatal rats were significantly more sensitive than adult rats to DEET-induced lethality. No generalization, however, can be made based on a single study, nor can inferences be made about sensitivity at the nonlethal dose levels to which humans are exposed. Additional studies would be useful.

Limited information is available regarding developmental effects of DEET in humans. A study of women who applied a known amount of DEET onto the skin during the second and third trimesters did not affect developmental outcomes at birth and up to 1 year after birth (McGready et al. 2001). Follow-up studies of these infants would have been useful. A study of the general population did not find significant associations between levels of DEET in maternal blood and cord serum and developmental outcomes (Barr et al. 2010). Conventional developmental studies in rats and rabbits did not find adverse developmental effects in the offspring at maternal sacrifice on the last day of gestation (Schoenig et al. 1994). In the 2-generation continuous feeding study in rats, male and female F1 and F2 pups, however, had significantly reduced body weight on lactation days 14 and 21 (EPA 1989). As mentioned before, because birth weight was not affected by treatment with DEET, the reduced body weight in the pups could have been due to reduced milk production or quality, or transfer of DEET and/or metabolites in the milk to the pups. Further studies regarding possible transfer of DEET and/or metabolites to the offspring via maternal milk seem appropriate.

There are no adequate data to evaluate whether pharmacokinetics of DEET in children are different from adults. To the extent that various cytochromes P450 that are involved in the metabolism of DEET in humans (Usmani et al. 2002) are developmentally regulated (Tateishi et al. 1997), the metabolism of DEET in neonates and infants, however, will likely differ from adults. Whether this would result in increased susceptibility of the young is not known because it is also not known whether metabolism of DEET represents activation or detoxification. No information was located regarding levels of DEET (or metabolites) in human milk. DEET, however, has been measured in cord blood (Barr et al. 2010). Further information on the dynamics of DEET and metabolites during pregnancy would be useful.

Biomarkers of exposure need to be further studied to better estimate human exposure at all age levels following exposure to DEET. There are no data on the interaction of DEET with other chemicals in children. The information available indicates that methods used to mitigate the effects of DEET in adults are applicable to children.

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

No relevant ongoing studies pertaining to DEET were identified in RePorter (2017).

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

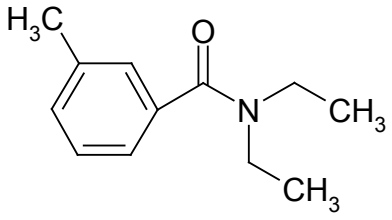
Information regarding the chemical identity of DEET is located in Table 4-1.

DEET is the chemical, N,N-diethyl-*meta*-toluamide, *ortho* and *para* isomers are present at low concentrations. DEET is an N,N-disubstituted aromatic carbonamide, which is used as an active ingredient in insect repellents. DEET was registered for commercial use by the general public in 1957. In December 1980, DEET was issued a Registration Standard (PB81-207722) followed by a Data Call-In in September 1988 requiring additional mammalian and avian toxicity data (EPA 1998c). Technical-grade DEET is typically formulated with carriers and solvents (such as ethanol, isopropanol, or water) for use in commercial products. Commercial product formulations include microencapsulated, pressurized sprays or aerosols, impregnated materials such as towelettes and roll-ons, and ready-to-use solutions such as non-aerosol pump sprays, liquids, creams, lotions, and foams. Some DEET products are also formulated with sunscreen. (EPA 2014l, 2014m; HSDB 2001). The DEET concentration in commercial products varies according to country and can range from 4 to 100% (by weight) in the United States. Technical-grade DEET typically contains 95% *meta*-isomer, the most effective form of the chemical (EPA 1998b, 1998c; O'Neil et al. 2013). The EPA does not require expiration dates to be included on the label of DEET products manufactured in the United States (EPA 1998b).

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of DEET is located in Table 4-2.

Table 4-1. Chemical Identity of DEET (N,N-Diethyl-*meta*-Toluamide)

Characteristic	Information	
Chemical name	N,N-Diethyl-*meta*-toluamide	
Synonym(s)	Benzamide, N,N-diethyl-3-methyl; N,N-diethyl-3-methylbenzamide; diethyltoluamide; diethyl toluamide; N,N-diethyl-*m*-toluamide; 3-methyl-N,N-diethylbenzamide; *m*-toluamide, N,N-diethyl; *m*-toluic acid diethylamide; *m*-delphene	ChemIDplus 2013; HSDB 2001
Registered trade name(s)	DEET; Delphene®; MGK diethyltoluamide; Detamide®; Detamine; Metadelphene®; Skeeter Skat®; Autan® (some formulations); Amincene C 140®; Amincene C-EM®; Bepper-DET®; DET®; DETA®; DET-20®; DETA-20®; Flypel®; Muscol®; Muskol®; Off!®; Repel®; Repper-DET®; Repudin-Special®; Chemform®; Cutter®; Old Time Woodsman®	ChemIDplus 2013; EPA 1998b, 1998c; HSDB 2001
Chemical formula	$C_{12}H_{17}NO$	HSDB 2001
Chemical structure		
Identification numbers:		
CAS registry	134-62-3	HSDB 2001
NIOSH RTECS	No data	
EPA hazardous waste	No data	
DOT/UN/NA/IMDG shipping	UN; IMO	
HSDB	1582	HSDB 2001
NCI	No data	
EPA Pesticide Chemical Code	080301	ChemIDplus 2013; HSDB 2001

CAS = Chemical Abstracts Service; DOT/UN/NA/IMDG = 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; RTECS = Registry of Toxic Effects of Chemical Substances

Table 4-2. Physical and Chemical Properties of DEET

Property	Information	Reference
Molecular weight	191.27	HSDB 2001
Color	Nearly colorless liquid	EPA 1998b, 2012c
Physical state	Liquid	HSDB 2001
Melting point	-45°C -44.3°C	PhysProp 2014 Weeks et al. 2012
Boiling point	284-285°C 284.2°C 160°C at 19 mm Hg 111°C at 1.0 mm Hg 290°C 760 mm Hg	Weeks et al. 2012 ECHA 2010 HSDB 2001 O'Neil 2013 PhysProp 2014
Density:		
at 20°C/4°C	0.996 g/cm^3 1.01 g/cm^3 0.998 g/cm^3	HSDB 2001 Weeks et al. 2012 Weeks et al. 2012
Odor	Faint, characteristic odor	EPA 1998b, 2012c
Odor threshold:		
Water	No data	
Air	No data	
Taste threshold	No data	
Solubility:		
Water at 25°C	11,200 mg/L >1,000 mg/L at room temperature; 9,900 mg/L at 25°C	Weeks et al. 2012 CITI 1992; HSDB 2001 O'Neil et al. 2013
Organic solvent(s)	Miscible in benzene, carbon disulfide, chloroform, ethanol, ether, and isopropanol; soluble in hexane, acetonitrile, toluene, methylene chloride, and methanol; practically insoluble in glycerin	HSDB 2001; O'Neil et al. 2013; Weeks et al. 2012
Partition coefficients:		
Log K_{ow}	2.02 2.18 2.4 at 22°C and pH 6 2.66	Moody 1987; HSDB 2001 PhysProp 2014 ECHA 2010 CITI 1992; Weeks et al. 2012
K_{oc}	300 47–126	HSDB 2001 ECHA 2010; Weeks et al. 2012
Vapor pressure		
at 20°C	0.0056 mm Hg 0.00167 mm Hg at 25°C 0.00013 mm Hg at 25°C	HSDB 2001 O'Neil et al. 2013 Weeks et al. 2012
Henry's law constant	5.1 x10^{-8} atm-m^3/mol at 25°C	EPIWIN 2012
Autoignition temperature	No data	
Flashpoint	155°C 144°C	O'Neil et al. 2013 ECHA 2010

Table 4-2. Physical and Chemical Properties of DEET

Property	Information	Reference
Flammability limits	No data	
Explosive limits	No data	

5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.1 PRODUCTION

No information is available in the TRI database on facilities that manufacture or process DEET 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 2005).

DEET was developed in 1946 by the U.S. Army and has become the world's standard insect repellent. As of March 2017, there were 27 companies in the United States that manufactured approximately 119 federally active consumer products containing DEET (NPIRS 2017). DEET is produced globally, with commercial production achieved via reaction of *m*-toluoyl chloride and diethylamine in benzene or ether as a solvent (O'Neil et al. 2013). Data for production volumes were not located. DEET is designated by the U.S. EPA as a registered "pesticide" (type of pesticide is an insect and acarid repellent). EPA (1998b) reregistered its use in products available to the general public, except for products and formulations that combine DEET and sunscreen, or those that are corrosive to the eye or cause corneal involvement or irritation persisting for ≥21 days.

In the environment, *Pectinophora gossypiella*, commonly known as the pink bollworm, naturally produces DEET; however, this source would not accumulate levels of environmental significance (Knepper 2004).

5.2 IMPORT/EXPORT

The U.S. EPA estimated that the annual U.S. production and import volumes of DEET range from approximately 2.6 to 4.5 million pounds (EPA 2007; ILS 1999).

5.3 USE

DEET is used globally. The major use for DEET is as an insect and acarid repellent intended to repel, but not kill, biting insects. Commercial products are used in residential settings and are applied directly on the human body or hair and/or personal clothing, footwear, shoes, and hats while being worn, on cats, dogs, and horses, or on pet living and sleeping quarters (EPA 2014m). Data from 1998 and the Centers for Disease Control and Prevention (CDC) report there are over 225 commercial insect repellents that

range in concentration from 4 to 100%; DEET use in formulations with dermal sunscreens were also reported (Brausch and Rand 2011; CDC 2009; EPA 1998b, 1998c, 2014l). In 1998, EPA (1998b) stated that the reregistration eligibility decision (RED) does not include products/formulations that combine DEET and sunscreen; however, in the EPA (2012c) environmental fate and ecological risk assessment for registration review of DEET, 10 end-use products/formulations with sunscreen were reported. As of March 2017, 27 companies in the United States reported the manufacture of approximately 119 consumer products containing DEET (NPIRS 2017). Products include lotions, creams, sticks, aerosol and non-aerosol sprays, foams, gels, and wipes or towelettes. According to EPA, as of February 2014, there were 123 active registrations for DEET, including co-formulations with other chemicals, formulations with sunscreen, and one registration for use on horses (EPA 2012c, 2014m). Formulations may range from 4 to 95% active ingredient, and a 100% technical-grade product also exists. Although agricultural uses have been reported (Aronson et al. 2012), DEET is currently registered by the EPA only as an insect and acarid repellent. Additional uses of DEET as a specialty solvent, surface plasticizer, pharmaceutical dermal penetration enhancer (Windhauser 1982), and other potential applications have been reported (Aronson et al. 2012; Carlson 2000; EPA 1998b, 1998c; Weeks et al. 2012). The chemical properties that enable DEET to dissolve certain plastics along with its strong smell are potential disadvantages for some applications (Wang et al. 2013).

Wang et al. (2013) evaluated DEET against other repellents for effectiveness against bed bugs moving into an area in which a CO_2 cue was present. Bed bugs are currently of international concern following a population rebound after the termination of DDT use. Filter papers in petri dishes were treated with a repellent over half of the surface and with the vehicle on the other half, entirely bathed in CO_2. After nine males and six large nymphs (immature bedbugs) were released at the center, the portion avoiding the repellent side was recorded over time. Complete effectiveness for 24 hours was found for 5% DEET as well as for two naturally occurring repellents (3-methyl-5-hexyl-2-cyclohexanone [isolongifolenone] or propyl dihydrojasmonate [isolongifolanone]). A minimum of 10% DEET was required to repel at least 93% of bed bugs for 9 hours, and 25% DEET was effective for 14 days. Two other substances were ineffective (7% picaridin repellent or 0.5% permethrin insecticide). Current production volumes for DEET were not available in the EPA Inventory Update Reporting Database or the Chemical Data Reporting Database. According to 1990 data, the EPA Registration Eligibility Decision document for DEET reported annual use of approximately 4 million pounds (active ingredient) and about 30% of the U.S. population used DEET annually as an insect and acarid repellent (EPA 1998b, 1998c, 2014l). Approximately 19% of households used it on household members, and about 4% of households that had cats and/or dogs applied DEET to pets. The average annual domestic use of DEET has been estimated as

approximately 5–7 million pounds based on product sales (EPA 2004). According to the California Environmental Protection Agency, approximately 577,874 pounds (active ingredient) of DEET were sold in California alone in 2008 (Aronson et al. 2012).

Since 1998, in Germany, DEET has been replaced by 1-piperidine carboxylic acid 2-(2-hydroxy-ethyl)-1-methylpropylester (Bayrepel) in some products (Knepper 2004).

5.4 DISPOSAL

According to the Material Safety Data Sheet for one DEET product, the disposal method noted that waste must be disposed of in accordance with federal, state, and local environmental control regulations; the container must not be reused; it may be placed in the trash for disposal; absorbents should be disposed of in the trash (Sawyer 2010). It is assumed that most products containing DEET are discarded into landfills following their disposal in common household waste. Large spillages of DEET should be decontaminated by rinsing with a 5% solution of sodium hydroxide (WHO 1987).

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6. POTENTIAL FOR HUMAN EXPOSURE

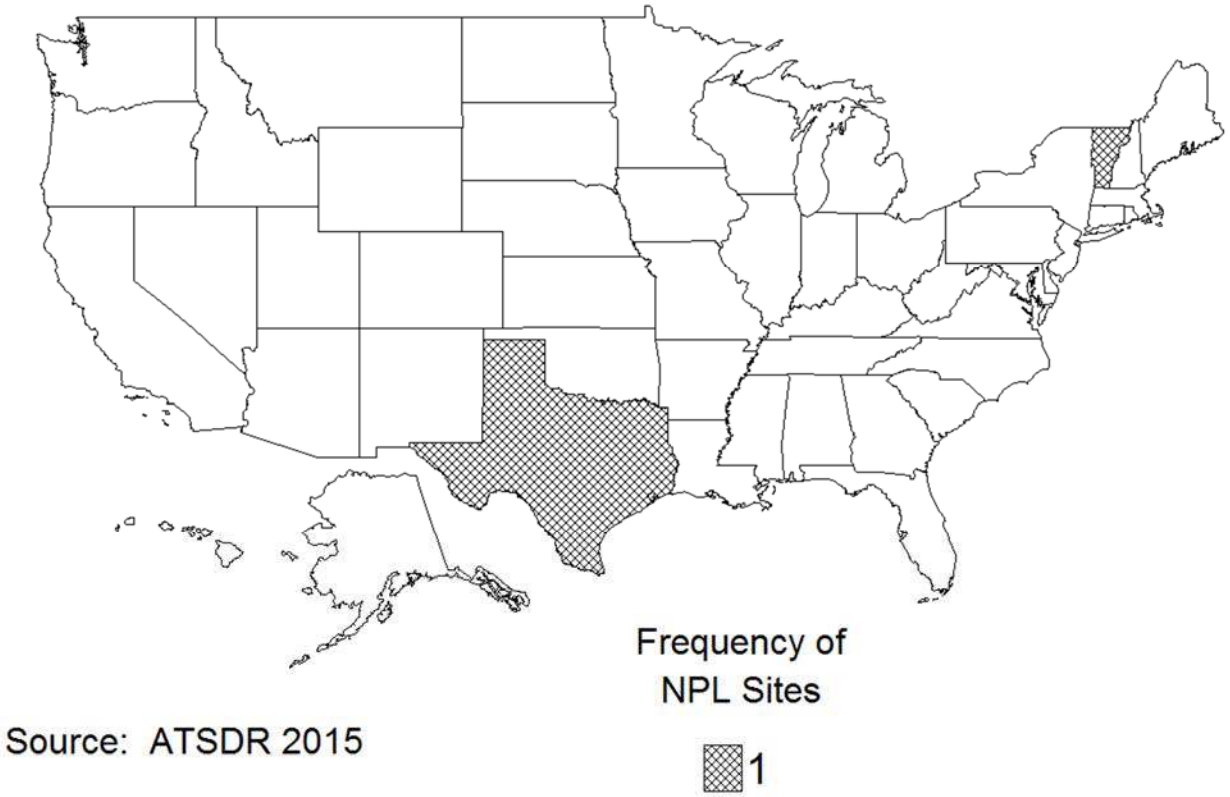
6.1 OVERVIEW

DEET was previously identified in at least 2 of the 1,832 hazardous waste sites across the United States (a refining operation in Friendswood, Texas and a municipal landfill in Bennington, Vermont) that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2015). The concentrations of DEET found at these two NPL sites were not considered a health concern (ATSDR 2015). Figure 6-1 shows the states with DEET-contaminated NPL sites, and the frequency or number of occurrences of these sites in each state. However, recent NPL site information indicates that DEET is no longer identified as an existing contaminant at any of the 1,832 hazardous waste sites across the United States that are listed as of that date on the NPL (EPA 2017a, 2017b). The EPA Superfund program is a dynamic system that continually evaluates sites across the United States for inclusion and deletion from the NPL; therefore, the exact number of hazardous waste sites may vary with time. The site in Texas is no longer on the NPL (EPA 2014g) and the site narrative for the Vermont site does not identify DEET as a major contaminant (EPA 2014h). However, the number of sites evaluated for DEET is not known.

DEET enters the environment via direct and indirect sources through its use as a commercial product. DEET is an insect and acarid repellent intended for indoor and outdoor residential human use. Water is the most common environmental medium in which DEET has been detected. DEET has been detected in surface water, groundwater, and drinking water. DEET enters aquatic systems as a result of common human activities, such as showering or bathing and laundering of clothes after products containing DEET have been applied. DEET is expected to be moderately mobile and has the potential to leach into groundwater. It is not expected to undergo hydrolysis in aquatic environments, and biodegradation under anaerobic conditions is negligible. However, DEET is considered inherently and readily biodegradable (Weeks et al. 2012) and is not considered a persistent or bioaccumulative substance.

The most important route of exposure to the general population is through dermal contact via intentional application to the skin of consumer products containing DEET. Dermal application of DEET can result in absorption through the skin. Exposure via inhalation, ocular and oral routes may be possible; however, due to the intended use of end products, these routes are minimal in comparison with dermal exposure.

Figure 6-1. Frequency of NPL Sites with DEET Contamination



Occupational exposure may occur via dermal contact and inhalation where DEET is manufactured or used. DEET has been monitored in human urine and blood samples.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

DEET may be released to the environment directly or indirectly through its use in commercial products. There are no natural sources of DEET known to be environmentally significant.

6.2.1 Air

There is no information on releases of DEET to the atmosphere from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

DEET is released into the atmosphere solely by human activities associated with its production and use as an insect and acarid repellent. DEET can enter the air during spray application onto skin or clothing. It has been reported that evaporation from human skin is 9.6% in 1 hour (Spencer et al. 1979). Cheng et al. (2006) surmised that the presence of DEET in air of the Lower Fraser Valley of Canada was primarily due to its widespread use by the Canadian population during the summer. Levels in the urban forest showed a diurnal change (3.03 ng/m^3 during the day and 1.25 ng/m^3 at night), while those near highly visited Golden Ear Provincial Park were higher (11.1–11.4 ng/m^3 in the day and up to 37.1 ng/m^3 at night when insect density may have been greatest). The lowest levels measured (0.53–0.78 ng/m^3) were at a

remote location and were considered to be the ambient background for the area resulting from spraying livestock in that rural area.

6.2.2 Water

There is no information on releases of DEET to the water from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

DEET is frequently detected in the aquatic environment (Knepper 2004; Kolpin et al. 2002; Sandstrom et al. 2005). DEET can enter surface waters directly due to recreational activities such as swimming, via swimmers with DEET products on their skin or clothing, or indirectly from overspray during application. Because of its limited absorption through human skin, the majority of applied DEET is washed off the skin (Selim et al. 1995). DEET is released into water systems through routine human activities such as showering and bathing of individuals who have recently applied DEET products. DEET applied to clothing may end up in waste water treatment plants (WWTPs) or may be released with gray water after the clothes are laundered and enter the environment after passing through the WWTPs or domestic septic systems. Additionally, sewage effluent may contain DEET and DEET metabolites due to human absorption and excretion (Aronson et al. 2012; Costanzo et al. 2007). Monitoring data indicate that the highest concentration of DEET in aquatic environments correlates with its increased application during the summer months (Knepper 2004; Sandstrom et al. 2005) and late winter (Sandstrom et al. 2005). DEET can enter groundwater from contaminated surface waters or leachate from landfills (Cordy et al. 2004).

6.2.3 Soil

There is no information on releases of DEET to the soil from manufacturing and processing facilities because these releases are not required to be reported (EPA 2005).

DEET may be released to soil as a result of overspray during application as a repellent or irrigation of soils with reclaimed water in which DEET is present. DEET may also be released to soil when it is disposed of in landfills or from accidental spills of products or wastes containing DEET during overland transportation.

6.3 ENVIRONMENTAL FATE

The environmental fate of DEET, which includes the transport, partitioning, and transformation of this substance, is controlled by various physicochemical properties, degradation, and other loss processes. According to European Union (EU) regulatory criteria and the overall data presented below, DEET is unlikely to bioaccumulate and is not expected to be highly persistent in the environment (Aronson 2012; Weeks et al. 2012).

6.3.1 Transport and Partitioning

Based on its vapor pressure of $5.6x10^{-3}$ mm Hg at 20°C, DEET will exist solely as a vapor if released to the atmosphere. Vapor-phase DEET is expected to degrade in the atmosphere via reaction with photochemically-produced hydroxyl radicals, with an estimated half-life of 5 hours (EPIWIN 2012). Therefore, persistence and long-range transport of DEET in air is not expected.

Monitoring data indicate water as the major environmental sink for DEET. If released to water, DEET is not expected to accumulate in aquatic organisms. Experimental bioconcentration factors (BCFs) of 0.8–2.4 L/kg at 0.5 mg/L and <2.4 at 0.05 mg/L measured in carp indicate that the potential for bioconcentration in aquatic organisms is low (CITI 1992; Weeks et al. 2012). Volatilization of DEET from water surfaces is not expected to be an important fate process based on its estimated Henry's Law constant of $4.5x10^{-8}$ atm-m^3/mole (EPIWIN 2012).

DEET is expected to have low adsorption to soils and sediment; therefore, leaching into groundwater is possible and removal by sludge adsorption in sewage treatment plants is incomplete. Experimental soil sorption K_{oc} factors have been reported as 43.3 L/kg resulting from a high-performance liquid chromatography (HPLC) estimation and 47–126 L/kg from an Organization for Economic Co-operation (OECD) guideline method (Adsorption-Desorption Using a Batch Equilibrium Method) using five soils (ECHA 2010; Weeks et al. 2012). Secondarily-treated effluent from a municipal waste treatment plant containing DEET was applied to a 2.4-m soil column packed with Mohall-Laveen sandy loam soil over 23 days in a study assessing the potential for compounds to persist and possibly enter groundwater upon recharge. DEET was detected in the column inflow at the beginning and the end of the experiment at concentrations of 1.4 and 1.6 µg/L, respectively. DEET was finally detected in the drainage samples at the end of the experiment at a concentration of 2.3 µg/L (Cordy et al. 2004).

6.3.2 Transformation and Degradation

DEET can partition into various environmental compartments and is subject to abiotic and biotic degradation processes.

6.3.2.1 Air

The major removal process for DEET in the atmosphere is photooxidation via reaction with hydroxyl radicals. The estimated half-life for this reaction is 5 hours, based on an estimated rate constant of $2.5x10^{-11}$ cm^3/molecule-second at 25°C (EPIWIN 2012). Direct photolysis in the ambient atmosphere is not expected to be an important fate process because DEET does not absorb light at environmentally relevant wavelengths (EPA 2014m; Weeks et al. 2012).

6.3.2.2 Water

DEET is considered to be hydrolytically stable; results from guideline studies however, indicate that DEET will be biodegradable under environmental conditions and should not be persistent in the environment.

Using the Japanese Ministry of International Trade and Industry (MITI) test based on OECD Guideline 301C, DEET, at 100 mg/L, achieved 0% of its theoretical biochemical oxygen demand (BOD) after 4 weeks using a sewage inoculum maintained under aerobic conditions and was not considered readily biodegradable (CITI 1992). DEET was degraded 48.6% after 28 days using the closed bottle (OECD Guideline 301D) test and it was concluded that DEET was probably inherently biodegradable but did not meet the criteria to be classified as readily biodegradable (Weeks et al. 2012). In another guideline study, DEET achieved 83.8% of its theoretical CO_2 evolution after a 28-day incubation period using the modified Sturm (OECD Guideline 301B) test and was considered readily biodegradable (Weeks et al. 2012). The discrepancies in results could be attributed to the toxic effects of DEET on microbial populations at high concentrations, such as those used in OECD Guideline 301C. Testing indicated that DEET only caused minor inhibitory effects on microbial activity and was not typically a concern at environmentally relevant concentrations (ECHA 2010; Weeks et al. 2012).

Hydrolysis in water is not expected to be an important fate process. Results from two studies following OECD Guideline 111, EPA Method 835.2110, and EC C.7 demonstrate that DEET is hydrolytically

stable at 50°C and pH 4, 7, and 9 (EPA 1998b, 1998c, 2002; Weeks et al. 2012). The UV/visible absorption spectrum for a 10 ppm DEET solution in methanol of 200–225 nm (EPA 2014m) suggests that this chemical does not absorb at wavelengths >290 nm and therefore would not be expected to undergo direct photolysis in sunlight. Direct photolysis in sterile water did not contribute to decomposition in a simulation experiment by Calza et al. (2011) and in a 7-day experiment using distilled water and a xenon arc light (Weeks et al. 2012). Indirect photolysis in river water, however, resulted in degradation. Photocatalytic degradation experiments in river water under illumination and in the dark resulted in half-lives of 5 and 15 days, respectively (Calza et al. 2011). The main transformation products identified were N,N-diethyl-3-hydroxymethyl-benzamide, N,N-diethyl-*m*-benzamide, N-ethyl-*m*-formylbenzamide, and N-ethyl-*m*-toluenamide (Calza et al. 2011). Confirmed DEET microbial degradates that have been reported include 3-methylbenzoate (which further degrades to 3-methylcatechol), N,N-diethyl-*m*-toluamide-N-oxide, and N-ethyl-*m*-toluamide (which further degrades to N-ethyl-*m*-toluamide-N-oxide) (Aronson et al. 2012). Of the degradation products detected in the river water study, it was noted that several resulted from biotic processes, while others were formed from indirect photolysis. Indirect photolysis in sunlit surface waters and biotic degradation under aerobic conditions are the most important removal processes for DEET (Calza et al. 2011). Biotic degradation processes produce products via monohydroxylation (or N-oxidation), N-dealkylation, and demethylation on the benzene ring (Calza et al. 2011; Rivera-Cancel et al. 2007; Seo et al. 2005).

Anaerobic biodegradation of DEET using aquifer slurries obtained from the Norman municipal landfill in Oklahoma was shown to be negligible. Measured DEET concentrations at 0, 1, 8, and 11 months of incubation were 171, 194, 198, and 199 μM, respectively, in aquifer slurries from a sulfate reducing site. DEET did not biodegrade in an aquifer slurry from a methanogenic site; at 0, 1, 8, and 11 months of incubation, concentrations of DEET were 194, 192, 190, and 199 μM, respectively (Kuhn and Sulflita 1989).

6.3.2.3 Sediment and Soil

No biodegradation studies in soil samples were located; OECD guideline studies and aquifer studies, however, suggest that DEET is biodegradable under aerobic conditions, but biodegrades slowly under anaerobic conditions (Kuhn and Sulflita 1989; Weeks et al. 2012).

6.3.2.4 Other Media

Results from pure culture studies have demonstrated the ability of *Pseudomonas putida DTB* to metabolize DEET by hydrolyzing the amide bond resulting in two degradation products, 3-methylbenzoate and diethylamine (Rivera-Cancel et al. 2007). 3-Methylbenzoate has been shown to be readily biodegradable, and predictive methods have suggested that other DEET metabolites are not expected to persist in the environment (Aronson et al. 2012). An additional study on the metabolism of DEET by soil fungi (*Cunninghamella elegans*) identified three metabolites: N,N-diethyl-*m*-toluamide-N-oxide, N-ethyl-*m*-toluamide-N-oxide, and N-ethyl-*m*-toluamide (Seo et al. 2005). It should be noted that these studies were not with mixed microbial populations typically found in natural systems and should therefore not be considered definitively representative of the biodegradation of DEET in the environment.

DEET removal from WWTPs varies depending on the specific conditions of each site. Aronson et al. (2012) summarized several studies in which removal from WWTPs ranged from 10 to 99%. Removal from trickling filter treatment plants was generally lower than activated sludge plants. Knepper (2004) observed that elimination rates in WWTPs varied with influent concentration levels of DEET. Elimination rates were negligible in winter and spring months and increased in late summer up to 90% when concentration levels of DEET peak.

The removal of DEET from drinking water and waste water treatment plants located in South Korea was assessed by Kim et al. (2007). Various removal systems including membrane bioreactors, reverse osmosis, nanofiltration, and ultraviolet (UV) irradiation were analyzed. Minimal removal was reported with membrane systems; the other systems, however, removed DEET to concentrations <1 ng/L (initial concentrations averaged 18 ng/L). Utilizing granulated activated carbon was the most efficient removal system for drinking waters.

6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to DEET depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of DEET 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 DEET 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 DEET in a variety of environmental media are detailed in Chapter 7.

Care should be taken when assessing analytical results for which a limit of detection (LOD) or similar sensitivity value is not provided for the substance of interest, as well as the study reports not having detected that substance; failing to detect a substance does not mean that it is not present.

6.4.1 Air

DEET was detected in an air quality study of <2.5 μm aerosol samples performed in Canada from August 1 to 30, 2001. Samples were taken both at daytime and nighttime at five locations: Golden Ears Park (in a forested area), Cassiar Tunnel, Slocan Park (low-density urban surrounding), Langley Lochiel (a rural environment), and an elevated Sumas Eagle Ridge (forest/urban area). DEET concentrations ranged from 0.95 to 15.4 ng/m^3 (Cheng et al. 2006).

DEET was detected, but not quantified, in the atmosphere of Rome, Italy in the winter and summer of 2009 (Balducci et al. 2012).

6.4.2 Water

DEET has been detected in streams, surface water and groundwater systems, and sewage treatment plant effluents throughout the United States (Glassmeyer et al. 2005; Kolpin et al. 2002; Sandstrom et al. 2005). A summary of published studies by Brausch and Rand (2011) reported measured concentrations for DEET in 188 surface waters samples throughout the United States ranging from 13 to 660 ng/L (0.013–0.66 μg/L), with a median value of 55 ng/L (0.055 μg/L). A review by Costanzo et al. (2007) reported that DEET has been detected and reported in worldwide water samples, such as drinking water, streams, marine waters, groundwater, and treated effluent at concentrations of 40–3,000 ng/L (0.04–3.0 μg/L) and has also been detected in coastal waterways in Australia at concentrations of 8–1,500 ng/L (0.008–1.5 μg/L). DEET was detected in 8 of 50 groundwater samples from unconfined (<30 m) and confined (up to 500 m) aquifers in Tokyo taken between October and November 2007 (Kuroda et al. 2012). The arithmetic mean limit of quantification (LOQ) for the study was reported as 20.8 ng/L (0.0208 μg/L). The concentrations in these groundwater samples were lower on average, yet were comparable to sewage influent concentrations of DEET (503 ng/L [0.503 μg/L]) measured in the WWTPs of Tokyo in a previous study (Kuroda et al. 2012). DEET was detected in 83.5% of groundwater samples

(n=164) obtained from 23 European countries at an average concentration of 9 ng/L (0.009 µg/L) (Loos et al. 2010). Knepper (2004) investigated WWTP samples from June 1998 until October 2002 in Wiesbaden, Germany. During the winter and spring months of 1999, influent and effluent concentrations were comparable, yielding concentrations as high as to 0.6 µg/L. Summer influent concentrations in 1999 increased to 3 µg/L; effluent concentrations increased to 1–1.5 µg/L. Influent concentrations in November 1999 decreased from the summer month concentrations to 0.26–0.49 µg/L (Knepper 2004). Effluents from 90 WWTPs across Europe were sampled in 2010. Out of 156 chemicals targeted for analysis, DEET was one of the highest concentration chemicals found at levels up to 15.8 µg/L, with an average detection of 678 ng/L (0.678 µg/L); LOQ=1 ng/L (0.001 µg/L) (Loos et al. 2013a). DEET was detected in influent samples from three WWTPs serving large metropolitan areas of the United States at levels of 54–500 ng/L (0.054–0.5 µg/L) and in effluent samples at 100–260 ng/L (0.1–0.26 µg/L) (Trenholm et al. 2008).

Guardiola et al. (1989) identified DEET in groundwater samples from wells, which had been closed for several years due to pollution, in the Besos river basin (northeastern Spain) at concentrations up to 34 ng/L (0.034 µg/L). In a United States Geological Survey (USGS) study, samples were taken on September 6, 2000 from five multilevel monitoring wells near the Norman Landfill in Oklahoma, with reported concentrations of DEET ranging from <800 to 1,300 ng/L (<0.8–1.3 µg/L); the detection limit was 40 ng/L (0.04 µg/L). Well depths ranging from 3.26 to 6.29 m and their distances from the landfill were from 1 to 574 m (Barnes et al. 2004). DEET has been detected in surface water samples in numerous studies at concentrations of 2–2,100 ng/L (0.002–2.1 µg/L) (Dougherty et al. 2010). DEET was detected in water samples at 3 of 11 sites sampled in September and April near Liberty Bay, Washington. It was detected in one surface water sample and two groundwater samples at concentrations of 2.3–3.3 ng/L (0.0023–0.0033 µg/L). Two of the sites were also tested with polar organic chemical integrative samplers (POCIS) put in place for 62 days from January to March 2007 and again for 61 days from July to September 2007; DEET was detected at site 1 at 2.1–3.4 ng/POCIS (detection limit 1.0 ng/POCIS) and at site 2 at 3.0–6.3 ng/POCIS (Dougherty et al. 2010).

DEET was detected, but not quantified, in leachate samples of three domestic and industrial waste landfills (Eggen at al. 2010). These sites operated between 1973 and 1989 (this site also accepted separated residual domestic waste from 1985 through 2010 when the paper was written), 1974 and 2006, and 1972 and 2002.

In a USGS survey during 1999 and 2000, 139 streams from 30 states were sampled. DEET was reported in 74.1% of the samples analyzed at a median concentration of 60 ng/L (0.06 µg/L) and a maximum concentration of 1,100 ng/L (1.1 µg/L) (Kolpin et al. 2002). In the 2000 USGS survey, DEET was detected in 73.2% of 56 stream samples at a median concentration of 0.05 µg/L and a maximum concentration of 1.13 µg/L. The analytical method used methylene chloride liquid-liquid extraction (LLE) of whole water followed by capillary-column gas chromatography/mass spectrometry (GC/MS) operated in selected-ion monitoring mode, and achieved a detection level of 0.02 µg/L, if retention time and ionic abundance criteria were met; otherwise, the reporting limit was 0.08 µg/L (Sandstrom 2005). Site selection focused on urban and agricultural areas, during various seasons, at locations where there was the possibility of waste water contamination, via human, industrial, and agricultural sources, entering the streams. Levels were highest near urban areas and during summer and late winter. An attempt was made to re-analyze these samples for DEET metabolites; however, none of the chemicals could be detected in the samples. Limitations were noted and more accurate methods for their determination need further consideration (Sandstrom et al. 2005). In 2001, Kolpin et al. (2004) detected DEET in water samples collected from 23 stream locations situated upstream and downstream of 10 cities in Iowa. Stream samples were taken during high, normal, and low flow conditions. DEET was detected in the 23 normal-flow samples with a frequency of 4.3% and a maximum concentration of 62 ng/L (0.062 µg/L) and in the 30 low-flow samples with a frequency of 6.7% and a maximum concentration of 130 ng/L (0.13 µg/L). DEET was not detected in any of the 23 high-flow samples. DEET was detected in 43% of samples collected in March, April, and August of 2004 from 18 streams in north-central and northwestern Arkansas. Concentrations in the water samples were below the detection limit (0.5 µg/L) and were estimated as 18–83 ng/L (0.018–0.083 µg/L) (Haggard et al. 2006). Water samples collected from the main-stem Mississippi River during 1987 through 1992 contained DEET at concentrations of 8–110 ng/L (0.008–0.11 µg/L) (Goolsby and Pereira 1996). In 1989, DEET was detected in five of eight surface water samples taken at various locations along the Rhine River in The Netherlands at concentrations of 21–46 ng/L (0.021–0.046 µg/L) (Hendriks et al. 1994). DEET was detected in 12 of 15 sampling sites along the northern River in Germany between June 24 and July 7, 1998 at concentrations of 0.11–1.09 ng/L (0.00011–0.00109 µg/L) (Weigel et al. 2002). Po River water samples collected in July 2008 were analyzed for DEET and its degradation products. Fifteen transformation products were identified in the water samples. DEET was detected in seven of the eight samples at concentrations of 0.6–155.55 ng/L (0.0006–0.156 µg/L). The detection limit was 0.5 ng/L (0.0005 µg/L) (Calza et al. 2011). Freshwater streams were monitored in Hessisches Ried region, Germany from September 2003 to September 2006 (Quednow and Puttmann 2009); 330 samples were collected on 13 different occasions at 26 locations. The mean concentration of DEET detected was 245 ng/L (0.245 µg/L), with the highest

concentration (1.3 µg/L) occurring in June 2004. Overall, mean concentrations were higher in the summer months than during the other seasons.

Water samples taken from 0.5 m below the water surface of the Zhujiang and Shijing Rivers were collected in July and August 2011 (Yang et al. 2013). Concentrations of DEET were below the LOQ in three samples; however, concentrations ranged from 0.2 to 107 ng/L (0.0002–0.107 µg/L) in all other samples (n=24). The higher levels of DEET at some of the sites were attributed to its use as a pesticide in those areas. Water samples (n=10) taken from 0.5 m below the water surface of the Beijiang River were also collected in July and August 2011; concentrations of DEET were 3–47 ng/L (0.003–0.047 µg/L [ppb]).

Around Norway in 2002, DEET was detected in 12 seawater samples, into which sewage treatment plant effluents and non-treated sewage are discharged, at concentrations of 0.4–13 ng/L (0.0004–0.013 µg/L) (Weigel et al. 2004). Marine samples taken in February, May, and September 2011 and March 2012 from the northern Adriatic Sea approximately 50 cm below the surface contained DEET at concentrations of 0.349, 1.255, 4.995, and 0.460 ng/L, respectively (0.000349, 0.001255, 0.004995, and 0.00046 µg/L); the average LOQ was reported as 0.213 ng/L (0.000213 µg/L [ppb]) (Loos et al. 2013b).

Between November and December 2001, water samples were collected at several sites within a U.S. drinking water treatment facility in a heavily populated, urbanized drainage basin. DEET was detected in 3 of the 12 stream and raw water samples (25% frequency of detection). The highest concentration of DEET in samples of finished water was 0.066 µg/L (ppb) (reporting level 0.5 µg/L) (Stackelberg et al. 2004). DEET was not detected in 15 finished drinking water samples from four water filtration plants in San Diego County, California; the sample dates were between August 2001 and June 2002. DEET was, however, detected in 1 of 13 source water samples for four water filtration plants in San Diego County, California at a mean concentration of 0.131 µg/L (ppb); sample dates were August 2001 to November 2002 (Loraine and Pettigrove 2006). DEET was detected in two of six water samples from a waste water reclamation plant in San Diego County, California at a mean concentration of 1.31 µg/L; sample dates were September 2001 to June 2002 (Loraine and Pettigrove 2006). In samples taken during 2006 and 2007 from drinking water treatment plants across the United States, DEET was detected in the source water at 6 of 19 plants at a maximum concentration of 110 ng/L (0.11 µg/L) and a median concentration of 85 ng/L (0.085 µg/L) and in the finished water at 6 of 18 plants at a maximum concentration of 93 ng/L (0.093 µg/L) and a median concentration of 63 ng/L (0.063 µg/L [ppb]) (Benotti et al. 2009). In New York between May 2003 and January 2005, effluent concentrations, ranging from 0.3 to 15 µg/L

(ppb), from WWTPs indicated that removal rates were minimal (Phillips et al. 2005). Effluent concentrations in Las Vegas, Nevada in June 2005 and January 2006 were on average between 0.123 and 0.188 µg/L [ppb]) (Snyder 2005).

DEET was detected in water samples taken from two locations on Assunpink Creek in Trenton, New Jersey. At the first collection site downstream from a WWTP effluent discharge, DEET was detected at levels of 51–99 ng/L (0.051–0.099 µg/L). At the second site, 2 miles further downstream, DEET was detected at 45–340 ng/L (0.045–0.34 µg/L) (Alvarez et al. (2005). DEET was analyzed for in 10 WWTP-influenced sites around the United States. Samples were taken upstream from the plant, from the effluent, and two samples were taken at varying distances downstream. DEET was reported in 70% of the samples, with a median concentration of 0.097 µg/L and a maximum concentration of 2.1 µg/L; the reporting level was 0.5 µg/L (Glassmeyer et al. 2005). In July 2006, DEET was detected at concentrations of 0.09, 0.02, 0.04, and 0.065 µg/L (median detection level of 0.005 µg/L) in samples from sites on Wascana Creek, Saskatchewan, Canada. Samples were collected 31.8 km upstream from Regina, a sewage treatment plant, and 9.3, 59.8, and 104.8 km downstream from the sewage treatment plant, respectively. DEET was also detected at the same sampling sites in May 2007 (Waiser et al. 2011).

During October 2006–November 2007, Foster (2007) tested WWTPs in San Marcos, Texas and found that DEET was one of the most frequently detected compounds. The treatment plant uses activated sludge, granular activated carbon filtration, and ultraviolet disinfection. There was no detection of DEET 30 yards upstream from the effluent discharge. DEET was detected at a mean concentration of 1.7 µg/L (ppb) in 100% of the influent samples; DEET was detected at a mean concentration of 0.023 µg/L in 33% of the effluent samples and 0.009 µg/L (ppb) in 33% of the samples 30 yards downstream from the effluent discharge (detection limit=14.5 ng/L).

Through 1998 and 1999, DEET was detected in the effluents of 11 out of 19 WWTPs located in Switzerland at concentrations under the detection limit up to 1.3 µg/L (ppb) (Gerecke et al. 2002). Kim et al. (2007) reported a mean concentration of 0.0247 µg/L (ppb) for DEET in seven WWTPs located in South Korea. These plants receive about 85% domestic waste and use mainly activated sludge treatment methods.

In northeastern Kansas, Lee and Rasmussen (2006) detected median levels of DEET at 1.4 and <0.5 µg/L in the effluent of three trickling filter WWTPs and four activated sludge WWTPs (MRL 0.5 µg/L). In southeastern Miami, an activated sludge WWTP produced median effluent concentrations of

approximately 0.20 µg/L (ppb) (method detection limit=0.14 µg/L) during spring and summer months of March and July 2004 (Lietz and Meyer 2006).

In 1984 and 1991, Eckel et al. (1993) detected, but did not quantify DEET in the leachate from Hipps Road Landfill, Jacksonville, Florida, a site that received waste in 1968 and 1969. In May 1990, DEET was detected, but not quantified, in three municipal landfill leachate samples in Gryta, Vasteras, Sweden (Oman and Hynning 1993).

DEET was detected in marine coastal areas along the Florida Keys following an underwater music festival in which human recreational activities occurred in and around the water. Samples were taken before, during, and after the festival. DEET concentrations ranged from not detected to 17 ng/L (0.017 µg/L) (Chaudhary et al. 2005). DEET was detected in coastal waters of Norway at levels of 4.2–240.8 ng/L (0.0042–0.2408 µg/L) (Langford et al. 2008).

Aronson et al. (2012) reported a study in which DEET produced mean concentrations ranging from 2.6 to 4.3 µg/L (ppb) in confined animal-feeding operation waste waters in Nebraska, while feed lot lagoons in Minnesota had concentrations under the method reporting level of 0.5µg/L (ppb) (Lee et al. 2004). Additionally, these authors compiled concentrations of DEET measured in published studies from 1996 to 2010 found in influent and effluent waste waters, and published studies from 1994 to 2010 of surface waters in and outside of the United States. Kim et al. (2007) studied rivers receiving WWTP effluents and found DEET in seven out of eight samples with a mean concentration of 0.022 µg/L (ppb) (method detection limit=1 ng/L).

DEET was detected in 98% of reclaimed water samples (n=55) collected from sprinkler systems used for daily irrigation in Florida. The water had received primary and secondary treatments not designed to remove micronutrients. One sample reached the maximum concentration of approximately 14,000 ng/L (14 µg/L), while the rest were <1.5 µg/L (Wang and Gardinali 2013).

6.4.3 Sediment and Soil

No data were located on the environmental levels of DEET in sediment or soil.

6.4.4 Other Environmental Media

No data were located on the levels of DEET in other environmental media.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to DEET is expected to be relatively high based on its use as an insect and acarid repellent. Consumer products containing DEET are intended for direct application onto skin and/ or clothing while being worn. Products such as wrist bands or nets may also be impregnated with DEET. The general population is exposed to DEET via dermal contact after direct application of DEET insect repellents.

The Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2009, 2017) includes results from the assessment of DEET levels in the National Health and Nutrition Examination Survey (NHANES) for urine samples from 4,512 members of the U.S. general population surveyed during the years 1999–2000 and 2001–2002. As shown in Table 6-1 and 6-2, the average for DEET was below the detection limit (0.449 µg/L) for the survey years 1999–2000 in each selected percentile. For the survey years 2001–2002, the total geometric mean, and the 50th and 75th percentiles were also below the detection limit (0.1 µg/L). The 90th and 95th percentiles were just above the LOD and reported DEET concentrations were 0.11 and 0.18 µg/L (Table 6-1), respectively, and the creatinine corrected values were 0.27 and 0.41 µg/g creatinine, respectively (Table 6-2). For the survey years 2007–2008 and 2009–2010, the average for DEET was again below the detection limit (0.089 µg/L) in each selected percentile. Because DEET undergoes oxidative metabolism in humans, more sensitive biomarkers for assessing DEET exposure are the metabolites DCBA and DHMB (Calafat et al. 2016), which are included in the updated tables, January 2017 of the Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2017). As shown in Tables 6-3 and 6-5, for the survey years 2007–2008, the total geometric mean for DCBA was 3.50 µg/L, while that for DHMB was not determinable, and the respective 90th and 95th percentiles were 33.9 and 79.2 µg/L for DCBA and 0.229 and 0.780 µg/L for DHMB. For the survey years 2009–2010, the total geometric mean for DCBA was 4.54 µg/L, while that for DHMB was not determinable, and the respective 90th and 95th percentiles were 51.9 and 165 µg/L for DCBA and 0.455 and 1.34 µg/L for DHMB. In Tables 6-4 and 6-6, for the survey years 2007–2008, the total geometric mean for DCBA was 3.60 µg/g creatinine, while that for DHMB was not determinable, and the respective 90th and 95th percentiles were 27.3 and 70.8 µg/g creatinine for DCBA and 0.331 and 0.628 µg/g creatinine for DHMB. For the survey years 2009–2010, the total geometric mean for DCBA was 4.74 µg/g creatinine, while that for DHMB was not determinable, and the respective 90th and 95th percentiles were 44.6 and 131 µg/g creatinine for DCBA and 0.449 and 1.13 µg/g creatinine for DHMB.

Table 6-1. Geometric Mean and Selected Percentiles of Urine Concentrations of DEET (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2002, 2007–2010[a]

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	1999–2000[b]	*[d]	<LOD[f]	<LOD	<LOD	<LOD	1,977
	2001–2002[b]	*[d]	<LOD	<LOD	0.11 (0.10–0.14)	0.18 (0.14–0.22)	2,535
	2007–2008[c]	*[e]	<LOD	<LOD	<LOD	<LOD	2,565
	2009–2010[c]	*[e]	<LOD	<LOD	<LOD	<LOD	2,744
Age group							
6–11 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	480
	2001–2002	*	<LOD	<LOD	0.13 (0.10–0.18)	0.21 (0.12–0.56)	580
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	380
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	386
12–19 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	672
	2001–2002	*	<LOD	<LOD	0.13 (0.11–0.16)	0.22 (0.13–0.52)	829
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	386
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	400
20–59 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	825
	2001–2002	*	<LOD	<LOD	0.11 (<LOD–0.13)	0.17 (0.13–0.21)	1,126
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,169
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,307
≥60 years	2007–2008	*	<LOD	<LOD	<LOD	<LOD	630
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	651
Gender							
Males	1999–2000	*	<LOD	<LOD	<LOD	<LOD	964
	2001–2002	*	<LOD	<LOD	0.11 (0.10–0.15)	0.18 (0.13–0.25)	1,191
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,286
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,343
Females	1999–2000	*	<LOD	<LOD	<LOD	<LOD	1,013
	2001–2002	*	<LOD	<LOD	0.11 (0.10–0.13)	0.17 (0.13–0.21)	1,344
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,279
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,401

Table 6-1. Geometric Mean and Selected Percentiles of Urine Concentrations of DEET (in µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2002, 2007–2010[a]

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Race/ethnicity							
Mexican Americans	1999–2000	*	<LOD	<LOD	<LOD	<LOD	688
	2001–2002	*	<LOD	<LOD	0.11 (<LOD–0.14)	0.13 (0.11–0.19)	678
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	499
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	600
Non-Hispanic blacks	1999–2000	*	<LOD	<LOD	<LOD	<LOD	518
	2001–2002	*	<LOD	<LOD	0.10 (<LOD–0.14)	0.14 (0.10–0.24)	700
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	570
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	504
Non-Hispanic whites	1999–2000	*	<LOD	<LOD	<LOD	<LOD	598
	2001–2002	*	<LOD	<LOD	0.11 (0.10–0.14)	0.18 (0.13–0.27)	956
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,071
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,199

[a]Data in this table come from the National Report on Human Exposure to Environmental Chemicals and Update Tables, which is continuously updated with new measurements. The most up-to-date data for environmental chemicals and reference ranges in the U.S. general population are available at the National Report website: https://www.cdc.gov/exposurereport/.
[b]CDC 2009.
[c]CDC 2017.
[d]Not calculated; the proportion of results below limit of detection (LOD) was too high to provide a valid result. The LODs for survey years 1999–2000 and 2001–2002 were 0.449 and 0.1 µg/L, respectively.
[e]Not calculated; the proportion of results below LOD was too high to provide a valid result. The LOD for survey years 2007–2008 and 2009–2010 was 0.089 µg/L.
[f]<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.

CI = confidence interval

Table 6-2. Geometric Mean and Selected Percentiles of Urine Concentrations of DEET (Creatinine Corrected) (µg/g creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2002, 2007–2010[a]

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	1999–2000[b]	*[d]	<LOD[f]	<LOD	<LOD	<LOD	1,977
	2001–2002[b]	*[d]	<LOD	<LOD	0.27 (0.24–0.30)	0.41 (0.35–0.50)	2,534
	2007–2008[c]	*[e]	<LOD	<LOD	<LOD	<LOD	2,563
	2009–2010[c]	*[e]	<LOD	<LOD	<LOD	<LOD	2,744
Age group							
6–11 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	480
	2001–2002	*	<LOD	<LOD	0.33 (0.23–0.63)	0.64 (0.28–1.93)	580
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	380
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	386
12–19 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	672
	2001–2002	*	<LOD	<LOD	0.19 (0.15–0.24)	0.25 (0.19–0.49)	828
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	384
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	400
20–59 years	1999–2000	*	<LOD	<LOD	<LOD	<LOD	825
	2001–2002	*	<LOD	<LOD	0.27 (<LOD–0.32)	0.41 (0.37–0.50)	1,126
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,169
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,307
≥60 years	2007–2008	*	<LOD	<LOD	<LOD	<LOD	630
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	651
Gender							
Males	1999–2000	*	<LOD	<LOD	<LOD	<LOD	964
	2001–2002	*	<LOD	<LOD	0.20 (0.17–0.25)	0.32 (0.25–0.44)	1,191
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,285
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,343
Females	1999–2000	*	<LOD	<LOD	<LOD	<LOD	1,013
	2001–2002	*	<LOD	<LOD	0.33 (0.29–0.37)	0.50 (0.41–0.58)	1,343
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,278
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,401

Table 6-2. Geometric Mean and Selected Percentiles of Urine Concentrations of DEET (Creatinine Corrected) (µg/g creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 1999–2002, 2007–2010[a]

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Race/ethnicity							
Mexican Americans	1999–2000	*	<LOD	<LOD	<LOD	<LOD	688
	2001–2002	*	<LOD	<LOD	0.19 (<LOD–0.23)	0.28 (0.23–0.35)	678
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	498
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	600
Non-Hispanic blacks	1999–2000	*	<LOD	<LOD	<LOD	<LOD	518
	2001–2002	*	<LOD	<LOD	0.13 (<LOD–0.15)	0.19 (0.14–0.27)	699
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	569
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	504
Non-Hispanic whites	1999–2000	*	<LOD	<LOD	<LOD	<LOD	598
	2001–2002	*	<LOD	<LOD	0.30 (0.27–0.35)	0.48 (0.39–0.55)	956
	2007–2008	*	<LOD	<LOD	<LOD	<LOD	1,071
	2009–2010	*	<LOD	<LOD	<LOD	<LOD	1,199

[a]Data in this table come from the National Report on Human Exposure to Environmental Chemicals and Update Tables, which is continuously updated with new measurements. The most up-to-date data for environmental chemicals and reference ranges in the U.S. general population are available at the National Report website: https://www.cdc.gov/exposurereport/.
[b]CDC 2009.
[c]CDC 2017.
[d]Not calculated; the proportion of results below limit of detection (LOD) was too high to provide a valid result. The LODs (not corrected for creatinine) for survey years 1999–2000 and 2001–2002 were 0.449 and 0.1 µg/L, respectively.
[e]Not calculated; the proportion of results below LOD was too high to provide a valid result. The LOD (not corrected for creatinine) for survey years 2007–2008 and 2009–2010 was 0.089 µg/L.
[f]<LOD means less than the limit of detection for urine samples; not corrected for creatinine.

CI = confidence interval

Table 6-3. Geometric Mean and Selected Percentiles of Urine Concentrations of 3-(Diethylcarbamoyl) Benzoic Acid (DCBA) (µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2007–2010[a]

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Total	2007–2008	3.50 (2.64–4.64)	2.37 (1.88–3.10)	9.14 (5.61–14.5)	33.9 (20.5–53.1)	79.2 (37.9–145)	2,538
	2009–2010	4.54 (3.35–6.15)	3.40 (2.31–4.95)	13.8 (8.63–20.6)	51.9 (31.1–108)	165 (57.8–464)	2,735
Age group							
6–11 years	2007–2008	4.44 (3.73–5.29)	3.44 (2.70–5.87)	12.7 (9.54–15.9)	42.0 (24.2–70.4)	79.7 (44.9–114)	378
	2009–2010	6.44 (3.72–11.1)	5.35 (2.58–8.86)	18.5 (8.15–37.9)	83.8 (28.4–439)	316 (41.2–3970)	385
12–19 years	2007–2008	5.26 (3.47–7.98)	4.37 (2.68–5.98)	13.1 (6.81–25.8)	35.4 (20.4–71.2)	71.2 (30.7–700)	380
	2009–2010	6.58 (4.49–9.66)	4.63 (2.82–8.64)	18.9 (10.7–33.6)	87.8 (32.9–186)	186 (31.1–1130)	398
20–59 years	2007–2008	3.33 (2.56–4.35)	2.23 (1.83–2.90)	7.95 (5.05–14.5)	30.8 (17.4–53.1)	75.6 (39.3–131)	1,157
	2009–2010	4.39 (3.29–5.86)	3.33 (2.23–4.95)	14.0 (8.36–20.9)	51.4 (32.6–95.8)	138 (52.9–280)	1,300
≥60 years	2007–2008	2.78 (1.75–4.42)	1.64 (.936–3.06)	6.15 (3.08–16.9)	34.7 (16.3–75.4)	103 (32.4–200)	623
	2009–2010	3.42 (2.39–4.91)	2.13 (1.45–4.00)	9.63 (5.33–17.1)	35.4 (19.7–63.8)	103 (43.2–346)	652
Gender							
Males	2007–2008	4.15 (2.88–6.00)	2.90 (2.13–4.34)	11.3 (6.63–19.7)	37.7 (20.7–82.0)	112 (34.7–556)	1,269
	2009–2010	5.58 (3.94–7.90)	4.39 (2.67–6.24)	18.7 (10.8–30.6)	78.3 (37.3–174)	199 (96.2–525)	1,340
Females	2007–2008	2.97 (2.32–3.80)	2.06 (1.64–2.59)	6.84 (4.41–10.8)	30.8 (15.0–40.8)	52.6 (36.4–103)	1,269
	2009–2010	3.73 (2.79–4.98)	2.76 (1.87–4.24)	9.91 (6.35–15.9)	36.2 (22.4–70.4)	94.9 (40.2–278)	1,395

Table 6-3. Geometric Mean and Selected Percentiles of Urine Concentrations of 3-(Diethylcarbamoyl) Benzoic Acid (DCBA) (µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2007–2010[a]

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI) 50th	75th	90th	95th	Sample size
Race/ethnicity							
Mexican Americans	2007–2008	3.70 (2.57–5.33)	3.26 (1.87–5.17)	9.63 (5.93–17.6)	28.0 (14.7–69.1)	69.1 (27.5–133)	490
	2009–2010	2.63 (1.61–4.28)	2.03 (.932–4.71)	7.35 (4.22–14.5)	23.1 (12.5–48.2)	48.9 (26.0–94.3)	599
Non-Hispanic blacks	2007–2008	4.36 (3.18–5.96)	3.54 (2.24–6.04)	10.3 (6.78–17.4)	31.9 (19.3–51.6)	62.4 (40.4–103)	562
	2009–2010	3.91 (2.85–5.35)	3.22 (2.24–4.75)	9.53 (5.88–14.4)	23.4 (18.0–33.4)	38.4 (29.1–60.5)	497
Non-Hispanic whites	2007–2008	3.47 (2.35–5.14)	2.22 (1.65–3.19)	9.12 (4.82–17.0)	36.5 (17.7–82.0)	86.9 (32.9–356)	1,064
	2009–2010	5.48 (3.83–7.84)	4.31 (2.64–6.25)	17.7 (10.5–28.4)	67.9 (32.6–195)	200 (63.8–832)	1,199

[a]Data in this table come from the National Report on Human Exposure to Environmental Chemicals and Update Tables, which is continuously updated with new measurements. The most up-to-date data for environmental chemicals and reference ranges in the U.S. general population are available at the National Report website: https://www.cdc.gov/exposurereport/.

The limits of detection for survey years 2007–2008 and 2009–2010 were 0.93 and 0.475 µg/L, respectively.

CI = confidence interval

Source: CDC 2017

Table 6-4. Geometric Mean and Selected Percentiles of Urine Concentrations of 3-(Diethylcarbamoyl) Benzoic Acid (DCBA) (Creatinine Corrected) (µg/g creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2007–2010[a]

			Selected percentiles (95% CI)				
	Survey years	Geometric mean (95% CI)	50th	75th	90th	95th	Sample size
Total	2007–2008	3.60 (2.79–4.65)	2.79 (2.14–3.55)	8.55 (5.49–13.2)	27.3 (17.8–47.9)	70.8 (34.1–170)	2,537
	2009–2010	4.74 (3.48–6.46)	3.35 (2.30–5.26)	12.9 (8.53–20.6)	44.6 (28.3–86.3)	131 (47.0–405)	2,735
Age group							
6–11 years	2007–2008	5.64 (4.72–6.75)	4.84 (3.65–5.78)	14.2 (10.7–19.8)	47.7 (34.2–55.1)	88.6 (47.9–182)	378
	2009–2010	8.72 (5.03–15.1)	6.42 (4.02–11.6)	23.5 (13.2–36.7)	75.4 (28.6–673)	365 (46.2–4,980)	385
12–19 years	2007–2008	4.08 (2.81–5.93)	2.96 (2.14–5.36)	11.0 (6.38–16.0)	24.3 (14.8–53.4)	53.4 (19.3–345)	379
	2009–2010	5.65 (3.76–8.50)	3.76 (2.56–6.22)	16.5 (7.29–31.7)	68.6 (25.3–182)	154 (25.3–1,270)	398
20–59 years	2007–2008	3.34 (2.61–4.27)	2.73 (1.99–3.46)	7.57 (4.92–12.1)	24.8 (14.9–44.7)	57.8 (30.9–117)	1,157
	2009–2010	4.41 (3.25–5.97)	2.98 (2.11–5.32)	11.7 (7.71–19.6)	39.1 (24.7–82.6)	112 (51.3–228)	1,300
≥60 years	2007–2008	3.42 (2.33–5.02)	2.47 (1.45–3.64)	7.33 (4.25–16.8)	33.8 (15.9–86.0)	93.3 (34.2–244)	623
	2009–2010	4.06 (2.95–5.59)	2.68 (2.10–3.96)	10.8 (6.79–15.9)	37.7 (22.2–51.1)	108 (42.7–393)	652
Gender							
Males	2007–2008	3.46 (2.46–4.87)	2.72 (1.76–3.73)	8.68 (5.34–14.4)	27.8 (16.9–69.4)	87.0 (27.8–403)	1,269
	2009–2010	4.97 (3.49–7.08)	3.29 (2.14–5.94)	14.7 (9.13–24.0)	60.0 (28.5–134)	185 (74.8–433)	1,340
Females	2007–2008	3.74 (2.99–4.68)	2.88 (2.27–3.63)	8.55 (5.36–13.2)	27.2 (16.2–46.3)	54.8 (34.2–117)	1,268
	2009–2010	4.54 (3.40–6.05)	3.35 (2.39–4.67)	11.8 (7.55–18.4)	35.3 (24.2–53.4)	77.6 (36.7–252)	1,395

Table 6-4. Geometric Mean and Selected Percentiles of Urine Concentrations of 3-(Diethylcarbamoyl) Benzoic Acid (DCBA) (Creatinine Corrected) (µg/g creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2007–2010[a]

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Race/ethnicity							
Mexican Americans	2007–2008	3.79 (2.57–5.58)	3.60 (1.99–5.96)	9.91 (6.55–16.9)	27.8 (15.0–60.6)	60.6 (24.4–107)	490
	2009–2010	2.74 (1.75–4.28)	2.03 (1.12–5.18)	7.57 (3.92–14.0)	23.3 (13.6–31.8)	37.4 (23.6–90.5)	599
Non-Hispanic blacks	2007–2008	3.33 (2.46–4.49)	2.74 (1.91–3.76)	7.07 (4.88–11.9)	22.5 (12.6–45.1)	53.9 (28.7–103)	561
	2009–2010	2.98 (2.26–3.94)	2.41 (1.70–3.37)	6.73 (4.34–9.46)	16.5 (13.0–20.4)	30.6 (19.4–51.1)	497
Non-Hispanic whites	2007–2008	3.78 (2.69–5.32)	2.82 (2.05–4.02)	8.70 (5.23–14.9)	30.7 (16.7–57.2)	76.9 (26.7–432)	1,064
	2009–2010	5.97 (4.13–8.64)	4.41 (2.61–7.43)	17.4 (10.7–26.7)	61.1 (29.0–189)	189 (56.4–849)	1,199

[a]Data in this table come from the National Report on Human Exposure to Environmental Chemicals and Update Tables, which is continuously updated with new measurements. The most up-to-date data for environmental chemicals and reference ranges in the U.S. general population are available at the National Report website: https://www.cdc.gov/exposurereport/.

The limit of detection (not corrected for creatinine) for survey years 2007–2008 and 2009–2010 were 0.93 and 0.475 µg/L, respectively.

CI = confidence interval

Source: CDC 2017

Table 6-5. Geometric Mean and Selected Percentiles of Urine Concentrations of N,N-Diethyl-3-(Hydroxymethyl) Benzamide (DHMB) (µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2007–2010[a]

		Geometric mean (95% CI)	Selected percentiles (95% CI)				
	Survey years		50th	75th	90th	95th	Sample size
Total	2007–2008	*[b]	<LOD[c]	<LOD	0.229 (<LOD–0.525)	0.780 (0.326–1.51)	2,562
	2009–2010	*[b]	<LOD	<LOD	0.455 (0.162–0.956)	1.34 (0.644–3.10)	2,736
Age group							
6–11 years	2007–2008	*	<LOD	<LOD	0.275 (0.168–0.433)	0.640 (0.264–2.64)	380
	2009–2010	*	<LOD	<LOD	0.655 (<LOD–2.93)	2.82 (0.205–24.6)	385
12–19 years	2007–2008	*	<LOD	<LOD	0.356 (<LOD–0.879)	0.665 (0.165–8.14)	386
	2009–2010	*	<LOD	<LOD	0.472 (<LOD–1.59)	1.20 (0.201–4.11)	398
20–59 years	2007–2008	*	<LOD	<LOD	0.188 (<LOD–0.413)	0.767 (0.335–1.30)	1,167
	2009–2010	*	<LOD	<LOD	0.498 (0.172–0.956)	1.34 (0.729–2.29)	1,304
≥60 years	2007–2008	*	<LOD	<LOD	0.256 (<LOD–0.787)	0.787 (0.194–1.81)	629
	2009–2010	*	<LOD	<LOD	0.257 (0.106–0.512)	0.840 (0.521–2.46)	649
Gender							
Males	2007–2008	*	<LOD	<LOD	0.325 (0.091–0.909)	1.05 (0.249–4.86)	1,283
	2009–2010	*	<LOD	<LOD	0.744 (0.323–1.43)	1.81 (0.946–3.94)	1,339
Females	2007–2008	*	<LOD	<LOD	0.165 (<LOD–0.326)	0.512 (0.256–0.968)	1,279
	2009–2010	*	<LOD	<LOD	0.220 (<LOD–0.521)	0.796 (0.329–2.05)	1,397

Table 6-5. Geometric Mean and Selected Percentiles of Urine Concentrations of N,N-Diethyl-3-(Hydroxymethyl) Benzamide (DHMB) (µg/L) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2007–2010[a]

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Race/ethnicity							
Mexican Americans	2007–2008	*	<LOD	<LOD	0.216 (0.092–0.509)	0.509 (0.207–0.989)	499
	2009–2010	*	<LOD	<LOD	0.228 (<LOD–0.504)	0.507 (0.223–0.866)	598
Non-Hispanic blacks	2007–2008	*	<LOD	<LOD	0.310 (0.091–0.470)	0.640 (0.378–1.29)	567
	2009–2010	*	<LOD	<LOD	0.135 (<LOD–0.292)	0.449 (0.212–0.884)	503
Non-Hispanic whites	2007–2008	*	<LOD	<LOD	0.255 (<LOD–0.861)	0.884 (0.225–4.84)	1,071
	2009–2010	*	<LOD	<LOD	0.644 (0.182–1.34)	1.89 (0.770–5.34)	1,195

[a]Data in this table come from the National Report on Human Exposure to Environmental Chemicals and Update Tables, which is continuously updated with new measurements. The most up-to-date data for environmental chemicals and reference ranges in the U.S. general population are available at the National Report website: https://www.cdc.gov/exposurereport/.
[b]Not calculated; the proportion of results below limit of detection (LOD) was too high to provide a valid result. The LOD for survey years 2007–2008 and 2009–2010 was 0.083 µg/L.
[c]<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.

CI = confidence interval

Source: CDC 2017

Table 6-6. Geometric Mean and Selected Percentiles of Urine Concentrations of N,N-Diethyl-3-(Hydroxymethyl) Benzamide (DHMB) (Creatinine Corrected) (µg/g creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2007–2010[a]

		Geometric mean	Selected percentiles (95% CI)				
	Survey years	(95% CI)	50th	75th	90th	95th	Sample size
Total	2007–2008	*[b]	<LOD[c]	<LOD	0.331 (<LOD–0.452)	0.628 (0.393–1.32)	2,560
	2009–2010	*[b]	<LOD	<LOD	0.449 (0.300–0.720)	1.13 (0.548–2.41)	2,736
Age group							
6–11 years	2007–2008	*	<LOD	<LOD	0.370 (0.289–0.524)	0.831 (0.347–1.37)	380
	2009–2010	*	<LOD	<LOD	0.572 (<LOD–3.40)	3.12 (0.370–18.4)	385
12–19 years	2007–2008	*	<LOD	<LOD	0.253 (<LOD–0.555)	0.544 (0.191–1.76)	384
	2009–2010	*	<LOD	<LOD	0.436 (<LOD–0.869)	0.869 (0.246–8.42)	398
20–59 years	2007–2008	*	<LOD	<LOD	0.331 (<LOD–0.441)	0.582 (0.441–0.866)	1,167
	2009–2010	*	<LOD	<LOD	0.468 (0.300–0.702)	1.10 (0.572–1.79)	1,304
≥60 years	2007–2008	*	<LOD	<LOD	0.394 (<LOD–0.701)	1.01 (0.389–2.48)	629
	2009–2010	*	<LOD	<LOD	0.395 (0.315–0.489)	0.875 (0.548–2.41)	649
Gender							
Males	2007–2008	*	<LOD	<LOD	0.300 (0.176–0.826)	0.866 (0.304–3.33)	1,282
	2009–2010	*	<LOD	<LOD	0.524 (0.280–1.39)	1.45 (0.718–3.16)	1,339
Females	2007–2008	*	<LOD	<LOD	0.341 (<LOD–0.393)	0.572 (0.419–0.734)	1,278
	2009–2010	*	<LOD	<LOD	0.419 (<LOD–0.488)	0.723 (0.458–1.85)	1,397

Table 6-6. Geometric Mean and Selected Percentiles of Urine Concentrations of N,N-Diethyl-3-(Hydroxymethyl) Benzamide (DHMB) (Creatinine Corrected) (µg/g creatinine) for the U.S. Population from the National Health and Nutrition Examination Survey (NHANES) 2007–2010[a]

	Survey years	Geometric mean (95% CI)	Selected percentiles (95% CI)				Sample size
			50th	75th	90th	95th	
Race/ethnicity							
Mexican Americans	2007–2008	*	<LOD	<LOD	0.315 (0.203–0.446)	0.467 (0.337–0.720)	498
	2009–2010	*	<LOD	<LOD	0.297 (<LOD–0.401)	0.415 (0.299–0.718)	598
Non-Hispanic blacks	2007–2008	*	<LOD	<LOD	0.234 (0.175–0.411)	0.487 (0.315–1.05)	566
	2009–2010	*	<LOD	<LOD	0.221 (<LOD–0.262)	0.362 (0.246–0.648)	503
Non-Hispanic whites	2007–2008	*	<LOD	<LOD	0.343 (<LOD–0.583)	0.826 (0.349–2.99)	1,071
	2009–2010	*	<LOD	<LOD	0.531 (0.305–1.36)	1.59 (0.524–5.83)	1,195

[a]Data in this table come from the National Report on Human Exposure to Environmental Chemicals and Update Tables, which is continuously updated with new measurements. The most up-to-date data for environmental chemicals and reference ranges in the U.S. general population are available at the National Report website: https://www.cdc.gov/exposurereport/.
[b]Not calculated; the proportion of results below limit of detection (LOD) was too high to provide a valid result. The LOD (not corrected for creatinine) for survey years 2007–2008 and 2009–2010 was 0.083 µg/L.
[c]<LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.

CI = confidence interval

Source: CDC 2017

Records of human exposure to DEET and/or DEET and other products were compiled from centers reporting to the Toxic Exposure Surveillance System from 1993 to 1997 (Bell et al. 2002). There were 20,764 exposure cases identified. Cases involving infants, children, and teenagers accounted for 18.6, 64.5, and 3.1% respectively. Of all the exposures, 89.2% occurred at the subject's home due to misuse of the product. There were 20,346 cases that involved products intended for human use, while 418 of the cases involved DEET-containing veterinary products. Ingestion accounted for 51.8% of the exposure incidents. Ocular, dermal, and multiple route exposures accounted for 21.3, 10.5, and 13.4% respectively. Of all the cases, 6,267 involved products containing <11% DEET, 9,003 involved products containing between 11 and 50% DEET, and 2,111 involved products containing >50% DEET; 3,293 of the cases reported unknown concentrations of DEET. A similar study conducted between 1985 and 1989 evaluated 9,086 human exposures of any product containing DEET reported to Poison Control Centers (Veltri et al. 1994). Most of the exposures occurred between May and September when DEET use is at its highest. Close to two-thirds of the incidents resulted in minor symptoms or did not have any adverse effects. Forty-nine percent of the exposures were due to ingestion, 32% resulted from ocular exposure, 12% were reported from multiple exposure routes, 4.2% from dermal exposure, and 2% via inhalation. More than 65% of exposure cases involved children 2–5 years of age. In a more recent report (from the 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System [NPDS] 30th Annual Report) (AAPCC 2013), it is stated that there were 4,158 cases in which DEET was mentioned and 4,075 cases that involved solely DEET exposure. There were 3,759 cases reported as unintentional. The majority of the cases (2,316 cases) involved children ≤5 years old. The outcome of all the exposure incidents were typically minor (1,176 cases) or none at all (576 cases). Moderate (83 cases), major (3 cases), and deadly (2 cases) outcomes were rarely observed. Of the exposures reported, 88% did not produce symptoms that required treatment in a health care facility (Veltri et al. 1994).

Wu et al. (1979) found DEET in the urine sample of a 30-year-old male who applied a commercial product containing DEET 18 hours after exposure. Eight hours after application, the DEET concentration in the blood was reported at 0.3 mg%. It was concluded that DEET was absorbed through the skin and about 10–14% was excreted unchanged. Urinary metabolites such as N-ethyl-*m*-toluamide and *m*-carboxyl-N,N-diethylbenzoylamide were identified, but not quantified, in the study. In 1991, average exposure estimates were derived for DEET based on one application/day to typical amounts used per application (see Table 6-7). Daily exposure values determined were 12.10, 9.68, 21.05, and 37.63 mg/kg/day for adult males, adult females, children ages 13–17 years old, and children ≤12 years old, respectively. These values may underestimate actual exposure levels in some users as it is possible that some users may apply the product more than once per day (EPA 1998b, 1998c). Exposure

assessments considering scenarios of individual adults who applied either a spray or aerosol product have been done following Standard Operating Procedures for Residential Pesticide Assessment developed by EPA's Health Effects Division (EPA 2012c). Individuals weighing 80 kg and applying spray or aerosol products with 98% active ingredient (a.i.) were reported to be treating themselves with 9,453 and 16,771 mg a.i./day, respectively (Table 6-7).

A survey by the DEET Joint Venture reported on the use of products containing DEET as an active ingredient: 37% of the U.S. population is expected to use insect repellents and 60% of this usage occurs in June and July. During these 2 months, repellents were used on an average of 7.5 and 5.6 days by adults and children, respectively (EPA 2002). The yearly averages for numbers of days in which insect repellents were used by the general population and children were 12.5 and 9.3 days, respectively (EPA 2002). It was estimated that either 5.9 g (aerosol), 1.0 g (lotion), or 2.3 g (pump spray) are applied as a single application either directly to skin or clothing (EPA 2002).

DEET was detected in urine samples from eight national park employees who applied approximately 1 g of lotion containing 71% DEET daily to their skin and clothes for 1 week. The DEET concentration in the urine collected mid-week ranged from <180 to 5,960 µg/L. In a laboratory study, two of nine male volunteers ages 18–34 years, who applied a DEET-containing lotion, had quantifiable levels in their urine. Levels for the subject with higher readings were 2,020, 900, and 1,050 µg/L respectively at 4, 12.5, and 22.0 hours after application. The urine concentration of the second subject with quantifiable concentrations at the last time point reported was 3-fold less at 310 µg/L. The remaining seven volunteers had levels <90 µg/L (LOD=90 µg/L); below the limit of quantification (LOQ=180 µg/L) of DEET in their urine. The highest concentration quantified was 2,020 µg/L at 4 hours after application and the lowest concentration was 310 µg/L at 22 hours after application. Blood samples from the nine volunteers had concentrations of DEET <LOQ to 1.17 µg/g (the LOQ for serum samples was 0.18 µg/g) (Smallwood et al. 1992).

Although exposure from contaminated drinking water is minimal compared to that of exposure via dermal application, DEET has been found at trace levels in water intended for human consumption (Benotti et al. 2009; Calza et al. 2011; Kim et al. 2007).

Two prenatal urine samples, the first at ~13 weeks of gestation and the second at ~26 weeks of gestation, were collected from 538 pregnant women (≥18 years of age) living in the Salinas Valley of California

Table 6-7. Estimated Daily DEET Exposures by Consumers Using Insect Repellents

Category of exposure	Amount of DEET per application (mg)	Body weight (kg)	Daily exposure (mg/kg/day)
Adult male	952.25	78.70	12.10
Adult female	649.31	67.10	9.68
Child, 13–17 years old	1,065.24	50.60	21.05
Child, ≤12 years old	940.83	25.00	37.63

Sources: EPA 1998b, 1998c

Table 6-8. Estimating DEET Exposures by Spray Treatment

Repellent[a]	Amount of DEET in product (mg a.i[b]./mg product)	Formulation application rate (mg product/cm^2 skin)	Fraction of body exposed	Surface area to body weight ratio (cm^2/kg)	Exposure time (hours/day)	Application frequency (number/hour)	Exposure (mg a.i./kg/day)[c]	Exposure (mg a.i./ individual/ day)[d]
Pump spray, adult human	0.98	0.62	0.75	280	3.7	0.25	118	9,453
Aerosol spray, adult human	0.98	1.10	0.75	280	3.7	0.25	210	16,771

[a]Without sunscreen.
[b]Active ingredient.
[c]Exposure estimated by multiplying the values in first six columns.
[d]Individual exposure estimated by multiplying estimated body weight (e.g., 80 kg) by exposure (mg a.i./kg/day).

Source: EPA 2012c

during 1999–2000. The LOD of the analytical method was reported as 0.1 µg/L. For the first and second samples, the maximum levels detected were 1.9 and 0.3 µg/L, the 95th percentile levels were 0.1 µg/L and <LOD, and detection frequencies were 5.6 and 1.9%, respectively (Castorina et al. 2010). The maximum concentrations were higher than the 95th percentile values reported during the latest monitoring period (2009–2010) by CDC (2017) in Table 6-1.

Cheng et al. (2006) reported finding DEET in air of the Lower Fraser Valley of Canada due to its widespread use during summer. The lowest levels measured (0.53–0.78 mg/m^3) at a remote location and were considered to be the ambient background for the area resulting from spraying livestock in that rural area. Higher levels in the urban forest were 3.03 ng/m^3 during the day and 1.25 ng/m^3 at night. The highest levels were in nearby Golden Ear Provincial Park, measuring 11.1–11.4 ng/m^3 in the day and up to 37.1 ng/m^3 at night when insect density and DEET use may have been greatest.

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 than adults. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and may spend more time outdoors. Children also are generally closer to the ground and have not yet developed the adult capacity to judge and take actions to avoid hazards (NRC 1993).

Data regarding the exposure of children to DEET indicate that dermal exposure from direct application of consumer products containing DEET is the most likely route. Inhalation is possible during aerosol product application, albeit a minor concern for exposure; additionally, hand-to-mouth behavior may result in oral exposure. Application of sunscreens containing DEET may result in unintentional overexposure to children if the sunscreen is applied repeatedly throughout the day as many consumer sunscreen products suggest. In 2012, AAPCC (2013) reported that 57%, or 2,316 case reports, of exposure to DEET was in

children ≤5 years of age. This may indicate a propensity for parents to apply DEET more liberally to protect their young children from insect bites, rather than a differential susceptibility. A recent interim review of DEET by the EPA, under the Registration Review Program, states that DEET is approved for use on children with no age restriction or percentage of DEET in the product; however, DEET should not be applied by children under 10 and application should follow the guidelines stated on specific product labels (EPA 2014i). In addition, the AAP recommends that repellents used on children should not contain more than 30% DEET and that no repellents should be used on infants below the age of 2 months (AAP 2015). The CDC concurs with this use profile as adjusted by AAP (CDC 2015).

Daily exposure estimates for DEET, assuming one application per day and standard body weights, were calculated as 21.05 mg/kg/day for children 13–17 years old, and 37.63 mg/kg/day for children ≤12 years old, in comparison to estimates of 93.68 mg/kg/day for adult females, and 12.10 mg/kg/day for adult males. These values may underestimate actual exposure due to individual consumer use patterns and do not include exposure via inhalation or oral routes, although these are judged to be minor (EPA 1998b, 1998c).

Menon and Brown (2005) documented patterns of children's exposure to DEET products as a result of their direct use as insect repellents. Between 31 and 65% of the subjects did not follow recommended procedures described in Chapter 1 of this document for the proper use of the products with respect to children, resulting in conditions that could lead to unnecessary overexposure. For example, when applying DEET to the facial area, first apply to your hands and then rub the product onto your face. Avoid direct spraying to the face as this could cause the product to get into your eyes, mouth, or lungs. And, be sure to take off DEET products before going to bed (by showering or using a wash cloth) to avoid overexposure. Do not apply to children's hands, and do not allow children to handle products containing DEET since this can increase internal exposure through hand-to-mouth activities typical of some children.

DEET exposure may occur during pregnancy. Schaefer and Peters (1992) reported a case in which a pregnant woman living in Africa applied a lotion with 25% DEET to her arms and legs once or twice a day during pregnancy. Bradman et al. (2003) did not detect DEET in amniotic fluid samples (15–18 weeks of gestation) from 100 women in California (LOD =0.4 μg/L). However, a study conducted from July 2003 to May 2004 of 150 women detected DEET in maternal serum samples at 1.82 to 18.84 ng/g and in corresponding cord serum at 2.06–13.07 ng/g (Barr et al. 2010). DEET was the most frequently detected (degree of frequency=100%) pesticide in both maternal and cord serum samples of

150 women in New Jersey at concentrations of 1.819–18.844 and 2.060–13.671 pg/mL, respectively (LOD=0.01 pg/mL) (Yan et al. 2009).

In 2004, Arcury et al. (2007) evaluated urine samples from 60 farm children (1–6 years old) in eastern North Carolina. Ten percent of the children had detectable levels of the metabolite for DEET (LOD=0.1 ng/mL) in their urine.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers in industries that manufacture and formulate DEET and DEET-containing products are likely to be at higher risk than the general population for DEET exposure. People who work or recreate outdoors (e.g., park rangers, hikers, hunters, campers) are more likely to be exposed to higher levels of DEET through the use of products containing this substance as opposed to people who work and recreate indoors (i.e., city dwellers) (Smallwood et al. 1992). Consumers who use commercial products containing DEET regularly, as a preventative measure for warding off insect bites, are exposed to higher levels of DEET than the general population who do not directly use DEET products. Children have the potential to be overexposed through misuse of the product (Bell et al. 2002).

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 DEET 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 DEET.

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. The physical chemical properties of DEET are summarized in Chapter 4 (HSDB 2001; O'Neil et al. 2013; Weeks et al. 2012). No data needs are identified.

Production, Import/Export, Use, Release, and Disposal. No information is available in the TRI database on facilities that manufacture or process 2-hexanone 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 2005).

Environmental Fate. Transport, partitioning, and bioconcentration data are available for DEET. The fate of DEET in WWTPs has been summarized (ECHA 2010; Weeks et al. 2012). Biodegradation in aquifer slurries and standard tests are available; however, no studies were located that assess biodegradation in soils.

Bioavailability from Environmental Media. No data were identified that assess the bioavailability of DEET from environmental media such as soil and foods.

Food Chain Bioaccumulation. Studies are available that indicate that DEET does not bioconcentrate in aquatic organisms and is not expected to bioaccumulate in the food chain (CITI 1992). No data needs are identified.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of DEET in contaminated media at hazardous waste sites are needed so that the information obtained on levels of DEET in the environment can be used in combination with the known body burden of DEET to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

Monitoring data are available for DEET in air (Balducci 2012; Cheng et al. 2006) and water (Brausch and Rand 2011; Glassmeyer et al. 2005; Kolpin et al. 2002; Sandstrom et al. 2005). No monitoring data were located for DEET in soil and sediment.

Exposure Levels in Humans. Exposure levels of DEET in human biological samples are available (CDC 2009; Wu et al. 1979). Continued biological monitoring of human serum and urine samples is useful since DEET is contained and used in many consumer products used by a high percentage of the

population. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Children are exposed to DEET by the same routes that affect adults (primarily dermal exposure). Continued monitoring of children's exposure to DEET is considered a data need. Child health data needs relating to susceptibility are discussed in Section 3.12.2, Identification of Data Needs: Children's Susceptibility.

Exposure Registries. The information 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; however, no exposure registries for DEET were located. DEET is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. DEET will be considered in the future when chemical selection is made for sub-registries to be established.

6.8.2 Ongoing Studies

No ongoing environmental fate studies for DEET were identified using the NIH RePORTER version 6.1.0 or the Defense Technical Information Center (DTIC) online database.

7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring DEET, its metabolites, and other biomarkers of exposure and effect to DEET. 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.

7.1 BIOLOGICAL MATERIALS

DEET is used globally as a commercial insect repellent, which results in the direct exposure of humans. Studies have shown that DEET is absorbed and most is metabolized before excretion. Analytical methods for the determination of DEET and its metabolites in biological materials and environmental media (e.g., waste water samples) may be used to verify that exposure and absorption has occurred.

Dermal absorption of DEET following applications of various DEET products has been reported between 5.6 and 16.7% of the amount applied (Blomquist and Thorsell 1977; Feldman and Maibach 1970; Selim et al. 1995). The majority of dermally absorbed DEET is metabolized and excreted in human urine (Selim et al. 1995). The main human urinary metabolites of DEET are DCBA and EACB. Additional metabolites may include ET, DHMB, *m*-toluic acid, and ACB. Additional information and standards relating to metabolites of DEET would prove useful for better analytical analysis of both biological and environmental samples.

Several methods have been validated for the analysis of DEET in biological samples. The principal method used for the detection of DEET and/or its metabolites in biological samples is high performance liquid chromatography (HPLC) and GC coupled with MS. Sample preparation is typically performed using solid-phase extraction (SPE) and/or LLE with organic solvents such as methanol, methylene chloride, and acetonitrile. Those methods are generally suitable for the analysis of DEET by itself or simultaneously with other similar substances (e.g., repellents and pesticides).

Identification of DEET and DEET metabolites in human urine has been performed using GC glass capillary columns and MS elucidations with both electron impact (EI) and chemical ionization-methane (MCI) mass spectra. Failure to control food and beverage intake, including caffeine, and the presence of plasticizers complicated the evaluation (Wu et al. 1979). A method for the rapid quantification of DEET in human urine using HPLC and a triple-quadrupole tandem MS using an atmospheric pressure chemical ionization application has been published (Olsson et al. 2004). Sample preparation involves enzyme hydrolysis, SPE, and concentration, and throughput is ~50 samples/day.

Qiu and Jun (1996) have used SPE and reverse-phase liquid chromatography (LC) with UV detection at 220 nm for the quantification of DEET in both dog and human plasma. Extraction was achieved with reverse-phase C_8 (yielding faster throughput) or C_{18} SPE cartridges using acetonitrile-ammonium acetate solutions as wash and elution solvent systems as well as for the mobile phase for the chromatography. This method had an overall absolute recovery of 97.7%, with a range of recovery, dependent on DEET concentration, of 96.9–100.2%, accuracy range of 1.5–5.1%, precision of 2.6–11.1%, and an LOQ of 15 ng/mL. Abu-Qare and Abou-Donia (2001c) have developed an analytical method using HPLC with reverse-phase C_{18} columns and UV detection, with a reported LOD of 50 ng/mL and LOQ of 50–100 ng/mL, for the simultaneous quantitative and qualitative detection of DEET and its metabolites, in rat plasma and urine that could be used in the monitoring of human plasma and urine. Barr et al. (2002) have developed a sensitive analytical method for quantifying serum and plasma concentrations of DEET in human blood, reporting an LOD of 10 pg/g. The method employs SPE using an OASIS cartridge with a mixed polarity phase followed by isotopic dilution GC-high resolution (HR)-MS for analysis.

Smallwood et al. (1992) demonstrated that DEET can be detected in both serum and urine after dermal exposure to DEET by HPLC. DEET quickly metabolizes in the body; therefore, urine concentrations of DEET specifically are not the most accurate reflection of dermal exposure concentrations. Kuklenyik et al. (2013) have successfully developed a rapid HPLC-MS/MS method to measure concentrations of DEET in addition to two of its oxidative metabolites, DHMB and DCBA, in human urine. Because DEET, DHMB, and DCBA undergo metabolism to form conjugates, they must be hydrolyzed in order to evaluate total concentrations. Enzymatic hydrolysis of the urine sample is achieved via previously described methods (Olsson et al. 2004) using β-glucuronidase/sulfatase. Separation is done on a reverse-phase analytical column and detection is achieved via atmospheric pressure chemical ionization in positive ion mode. Detection limits for these three chemicals are reported to be between 0.1 and 1.0 ng/mL.

Evaluation of fetal exposure is a key concern that was addressed by Bradman et al. (2003). Amniotic fluid was evaluated using an MS analytical method previously intended for detection of DEET in urine. The LOD for urine was reported as 0.1 µg/L, with 98% recovery, and the LOD for amniotic fluid was reported as 0.40 µg/L, with 100% recovery. Although DEET was not detected in the amniotic samples evaluated in the study, it was noted that the analytical method for measuring DEET in urine is transferable to amniotic fluids with little modification.

It has been reported that high-level exposure to DEET in combination with other chemicals may increase adverse effects (Abu-Qare and Abou-Donia 2001b, 2001c; Abou-Donia et al. 2001a; Kuklenyik et al. 2013). Cherstniakova et al. (2006) developed rapid and sensitive methods for simultaneous determination of DEET and permethrin, and DEET and pyridostigmine bromide, in human plasma using GC-MS and HPLC, respectively. Abu-Qare et al. (2001) found that urinary excretion of 3-nitrotyrosine (a biomarker of oxidative stress) in rats increased when an oral dose of pyridostigmine bromide and a dermal dose of DEET were administered alone and in combination. Due to the possibility of the combined exposure scenarios, the method developed by Abu-Qare and Abou-Donia (2001b) using reverse-phase HPLC and UV detection, mentioned above, was developed for the simultaneous determination of diazinon, permethrin, DEET, and their metabolites in rat plasma and urine using solid-phase extraction of DEET and its metabolites. HPLC methods for the separation and quantification of chlorpyrifos, pyridostigmine bromide, N,N-diethyl-*m*-toluamide, and their metabolites in rat plasma and urine had detection limits ranging from 20 and 150 ng/mL (Abu-Qare and Abou-Donia 2001c). HPLC methods for the simultaneous determination of malathion, permethrin, DEET, and their metabolites in rat plasma and urine have been developed (Abu-Qare and Abou-Donia 2001d).

Analytical methods for the determination of DEET in biological materials and fluids are summarized in Table 7-1.

7.2 ENVIRONMENTAL SAMPLES

Analysis of environmental samples is similar to or the same as that of biological samples. The primary methods of analyzing for DEET in water samples involve SPE or LLE followed by GC, HPLC, and MS. Those methods are generally suitable for the analysis of DEET by itself or simultaneously with other similar substances (e.g., repellents and pesticides).

Table 7-1. Analytical Methods for Determining DEET and Transformation Products in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Human blood	Blood containing heparin centrifuged and plasma collected; serum samples denatured with ammonium sulfate and centrifuged; SPE with OASIS cartridges.	GC-HR-MS	10 pg/g	43	Barr et al. 2002
Human serum	LLE with MTBE or SPE	GC-MS or HPLC-UV	Not reported	>90	Cherstniakova et al. 2006
Human urine and serum	Urine: extraction with diethyl ether; evaporation and dilution with methanol Serum: centrifuge and mix with 20% saline; SPE with C_{18} Sep-Pak Vac cartridges; wash with water; elute with methanol; evaporate	HPLC-UV	0.09 µg/mL (urine; serum)	90–91 (urine) 92–100 (serum)	Smallwood et al. 1992
Human urine	Hydrolysis with β-glucuronidase, SPE OASIS cartridge; LLE; evaporate; 50 samples/day throughput	HPLC-APCI-MS/MS/MS	0.1 ng/mL	At 5 ppb: 96 ppb (4.4 SD) At 50 ppb: 93 (2.7 SD)	Olsson et al. 2004
Human urine (DEET and selected metabolites)	Urine samples in sodium carbonate extracted with DCM/ ethyl alcohol and centrifuged; aqueous-phase pH adjusted and re-extracted; organic phase dried, evaporated, and reconstituted in methanol	GC-MS	Not reported	Not reported	Wu et al. 1979
Human urine (DEET and selected metabolites)	Hydrolysis with β-glucuronidase/ sulfatase in 0.1 M sodium acetate buffer; mixed, incubated at 37°C for 17 hours, then vortex mixed	HPLC MS/MS	0.1 ng/mL (DEET); 0.1 ng/mL (DHMB); 1 ng/mL (DCBA)	95	Kuklenyik et al. 2013
Human tissue	Minced tissue homogenized with water; HCl added and filtered; filtrate pH adjusted; hexane added and centrifuged; direct injection of hexane aliquot	GC	Not reported	45–60	Crowley et al. 1986

Table 7-1. Analytical Methods for Determining DEET and Transformation Products in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Rat plasma and urine (DEET and selected metabolites)	Acidify with 1 N acetic acid; vortex and centrifuge samples; SPE with C_{18} Sep-Pak Vac cartridges; wash with water; elute with methanol and acetonitrile	HPLC	50 ng/mL	78.4–89.1 (DEET, urine) 72.8–84.2 (DEET, plasma)	Abu-Qare and Abou-Donia 2001c
Rat plasma and urine (DEET and selected metabolites)	Acidify with 1 N acetic acid; vortex and centrifuge samples; SPE with C_{18} Sep-Pak Vac cartridges wash with water; elute with methanol and acetonitrile	HPLC	20 ng/mL	83	Abu-Qare and Abou-Donia 2001b
Dog and human plasma	Vortex sample; SPE with C_{18} cartridges; wash and elute with acetonitrile and ammonium acetate	HPLC-UV	15 ng/mL (LOQ)	96.9–100.2 based on DEET concentration	Qiu and Jun 1996

APCI = atmospheric pressure chemical ionization; DHMB = N,N-diethyl-3-(hydroxymethyl)benzamide; DCBA = *m*-diethylcarbonyl) benzoic acid; DCM = methylene chloride; GC = gas chromatography; HCl = hydrogen chloride; HPLC = high-performance liquid chromatography; LLE = liquid-liquid extraction; LOQ = limit of quantification; MS = mass spectrometry; MS/MS = isotope dilution tandem mass spectrometry; MTBE = methyl-tert-butyl ether; SD = standard deviation; SPE = solid-phase extraction; UV = ultraviolet

Cheng et al. (2006) used an accelerated solvent extractor with dichloromethane and methanol followed by separation using a silica gel chromatography column, followed by GC/MS to analyze aerosol samples.

He and Lee (1997) developed a method for combining capillary electrophoresis (CE) with field-amplified concentration (FAC) and SPE for rapid concentration, separation, and quantification of DEET and five organonitrogen pesticides in water samples. However, the method recovery for DEET was less than half that for the pesticides (5–50 ppb was recovered 40.5–37.8%) and the reason was not discovered. Knepper (2004) employed solid-phase enrichment of DEET in surface waters and WWTP effluents on a capillary column followed by quantification using GC/MS in single ion monitoring mode. LOQs for surface water and WWTP effluent were 0.03 and 0.1 µg/L, respectively. Sandstrom et al. (2005) analyzed whole surface water for DEET and a range of other substances using methylene chloride LLE followed by GC/MS operated in selected-ion monitoring mode. They achieved a detection level of 0.02 µg/L for DEET, if retention time and ionic abundance criteria were met; otherwise, the reporting limit was 0.08 µg/L. Surface water samples may be analyzed using SPE followed by ultrahigh pressure LC-MS. Loos et al. (2013b) developed a method employing these analytical techniques using a hybrid triple-quadrupole linear ion trap instrument. Wang and Gardinali (2013) reported the successful use of an SPE-HPLC-atmospheric pressure photoionization (APPI)-MS/MS method for the detection and quantification of DEET in filtered water.

Methods for analyzing DEET in soils were not readily available.

An analytical method for determination of DEET in soda water was reported by Chandramouli et al. (2004); however, analytical procedures for food were not located.

Details of commonly used analytical methods for several types of environmental samples are presented in Table 7-2.

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 DEET is available. Where adequate information is not available, ATSDR, in conjunction with NTP, is required to assure the initiation of a program of research

Table 7-2. Analytical Methods for Determining DEET and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection with quartz filters followed by extraction with DCM/methanol (3:1 v/v)	GC with mass selective detector	No data	58	Cheng et al. 2006
Waste water influent and effluent	SPE; elution with 10/90 (v/v) methanol/MTBE followed by DCM	GC-MS/MS	0.1 ng/L	70–111	Trenholm et al. 2008
Waste water	Sample extraction with 15% DCM in hexane followed by concentration	GC-FID	No data	No data	EPA 1983
Filtered waste water and natural water samples	Field sample filtration using glass-filter fibers and SPE; elution of dry SPE cartridges with dichloromethane and diethyl ether followed by evaporation	GC/MS	0.14 µg/L	100 (9% RSD)	Zaugg et al. 2002
Whole water	CLLE with DCM	Capillary-column GC/MS	0.12 µg/L	Ground-water 98.57; surface water 71.31	USGS-06.pdf
Surface water, groundwater, drinking water	SPE; elution with methanol	UHPLC-MS/MS	1.0 ng/L	Not reported	Weeks et al. 2012
Drinking water	Grab samples from tap; SPE (Oasis HLB or Empore SDVB sorbent); elution with organic solvent, dried over column of sodium sulfate followed by evaporation	GC-MS full scan, SIM or SIS mode	0.019 µg/L (Oasis); 0.0042 µg/L (Empore)	97.9–106 (finished drinking water from ground sources) 92.9–97.5 (finished drinking water from surface sources)	EPA 2012b
Surface water	LLE with DCM	GC/MS SIM mode	20 ng/L	74±10	Sandstrom et al. 2005
Surface water, marine water	SPE; elution with methanol and evaporation	UHPLC-MS/MS	0.213 ng/L (LOQ)	Not reported	Loos et al. 2013b

Table 7-2. Analytical Methods for Determining DEET and Transformation Products in Environmental Samples

Sample matrix[a]	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Collection with quartz filters followed by extraction with DCM/methanol (3:1 v/v)	GC with mass selective detector	No data	58	Cheng et al. 2006
Water, cola, and soft drinks	Extracted with DCM (water) or heptane (soda); dried with sodium sulfate; nonane added as keeper solvent; samples evaporated down to nonane amount	GC-HRMS	Not reported	Not reported	Chandramouli et al. 2004
Seawater	Extraction using a polymeric sorbent; elution with ethyl acetate followed by n-hexane/ ethyl acetate; rotary evaporation; iso-octane added as a keeper	GC/MS	26 pg/L	68±12	Weigel et al. 2002
Raw materials and cosmetic products	Samples prepared in ethyl acetate	HPTLC-UV	25 ng	Not reported	Markovic et al. 1999

CLLE = continuous liquid-liquid extraction; DCM = methylene chloride; GC = gas chromatography; FID = flame ionization detector; HLB = hydrophilic-lipophilic-balanced; HRMS = high-resolution mass spectrometry; LOQ = limit of quantification; MS = mass spectrometry; MS/MS = tandem mass spectrometry; MTBE = methyl-tert butyl ether; RSD = relative standard deviation; SDBV = styrene divinylbenzene; SIM = selected ion monitoring; SIS = selected ion storage; SPE = solid-phase extraction; UHPLC = ultra-high performance liquid chromatography; UV = ultraviolet absorbance detection

designed to determine the health effects (and techniques for developing methods to determine such health effects) of DEET.

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. Methods for the detection of DEET in human urine (Olsson et al. 2004; Smallwood et al. 1992; Wu et al. 1979) and serum (Cherstniakova et al. 2006; Smallwood et al. 1992) are available. These methods are sensitive and detect levels of DEET at background levels in the population, levels at which biological effects may occur. No data needs are identified for DEET-specific analytical methods. DEET rapidly metabolizes after absorption, however, suggesting that DEET concentrations in urine may not be the best biomarker. The Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2017) includes results from the assessment of DEET levels and its metabolites, DHMB and DCBA, in NHANES for urine samples. An analytical method for detecting the main DEET metabolites, DHMB and DCBA, in urine has been validated by Kuklenyik et al. (2013). This area may be a potential focus for further investigation.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods are available to measure levels of DEET in air (Cheng et al. 2006) and water media (including waste water) (Trenholm et al. 2008; Weeks et al. 2012; Weigel et al. 2002; Zaugg et al. 2002). Studies describing methods for identifying DEET in soil or sediment samples would be useful; however, it is likely that liquid extraction of DEET from solid media followed by standard analytical methods described above for biological or environmental samples would be effective.

7.3.2 Ongoing Studies

No ongoing analytical studies for DEET were identified using the NIH RePORTER version 6.1.0 or the DTIC online database.

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8. REGULATIONS, ADVISORIES, AND GUIDELINES

MRLs are substance-specific estimates that are intended to serve as screening levels. They 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 derived an intermediate-duration oral MRL of 1.0 mg/kg/day for DEET based on a NOAEL of 100 mg DEET/kg/day for developmental effects in rats (EPA 1989). The MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

The International Agency for Research on Cancer (IARC) has not classified DEET as to its carcinogenicity (IARC 2013). The World Health Organization (WHO) has not established any air quality or drinking water guidelines for DEET (WHO 2010, 2011).

The Occupational Safety and Health Administration (OSHA) has not established any enforceable standards for DEET (OSHA 2013b) nor has the National Institute for Occupational Safety and Health (NIOSH) or the American Conference of Governmental Industrial Hygienists (ACGIH) recommended a threshold limit value for DEET (ACGIH 2013; NIOSH 2012).

The American Industrial Hygiene Association (AIHA) and the Department of Energy (DOE) have not established any values for responding to potential releases of airborne DEET for use in community emergency planning (AIHA 2013, DOE 2012).

The Department of Health and Human Services (NTP 2016) has not classified DEET as a carcinogen. The EPA's OPP (EPA 2007) classified DEET as a Group D substance, not classifiable as a human carcinogen, based on no evidence of mutagenicity in multiple tests, or of carcinogenicity in long-term oral ingestion studies in adult rats or mice. EPA's OPP (EPA2007) has not derived inhalation or oral toxicity values for DEET.

EPA has classified DEET as an inert pesticide ingredient in pesticide products that are approved for nonfood human and veterinary use only (EPA 2014c).

The international and national regulations, advisories, and guidelines regarding DEET in air, water, and other media are summarized in Table 8-1.

Table 8-1. Regulations, Advisories, and Guidelines Applicable to DEET

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2013
WHO	Air quality guidelines	No data	WHO 2010
	Drinking water quality guidelines	No data	WHO 2011
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV-TWA	No data	ACGIH 2013
AIHA	ERPGs	No data	AIHA 2013
DOE	PACs	No data	DOE 2012
EPA	AEGLs	No data	EPA 2013a
	Second AEGL chemical priority list	No data	EPA 2014a
	Hazardous air pollutant	No data	EPA 2014b 42 USC 7412
	NAAQS	No data	EPA 2014e
NIOSH	REL	No data	NIOSH 2014
	IDLH	No data	
OSHA	PEL (8-hour TWA) for general industry	No data	OSHA 2013b 29 CFR 1910.1000, Table Z-1
	Highly hazardous chemicals	No data	OSHA 2013a 29 CFR 1910.119, Appendix A
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	No data	EPA 2013b 40 CFR 116.4
	Drinking water contaminant candidate list	No data	EPA 2009a 74 FR 51850
	Drinking water standards and health advisories	No data	EPA 2012a
	National primary drinking water standards	No data	EPA 2009b
	National recommended water quality criteria	No data	EPA 2014f
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	No data	EPA 2013d 40 CFR 117.3
c. Food			
FDA	EAFUS[a]	No data	FDA 2014

Table 8-1. Regulations, Advisories, and Guidelines Applicable to DEET

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
d. Other			
ACGIH	Carcinogenicity classification	No data	ACGIH 2013
EPA	Carcinogenicity classification	Group D[b]	EPA 2007
	RfC	Not available	
	RfD	Not available	
	Identification and listing of hazardous waste	No data	EPA 2013c 40 CFR 261, Appendix VIII
	Inert pesticide ingredients in pesticide products approved for nonfood use only	Yes	EPA 2014c
	Master Testing List	No data	EPA 2014d
	RCRA waste minimization PBT priority chemical list	No data	EPA 1998a 63 FR 60332
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	No data	EPA 2013e 40 CFR 264; Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance and reportable quantity	No data	EPA 2013f, 40 CFR 302.4
	Effective date of toxic chemical release reporting	No data	EPA 2013h, 40 CFR 372.65
	Extremely hazardous substances and its threshold planning quantity	No data	EPA 2013g, 40 CFR 355, Appendix A
	TSCA chemical lists and reporting periods	No data	EPA 2013i, 40 CFR 712.30
	TSCA health and safety data reporting	No data	EPA 2013j, 40 CFR 716.120
NTP	Carcinogenicity classification	No data	NTP 2016

[a]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.
[b]Not classifiable as a human carcinogen.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; FDA = Food and Drug Administration; FR = Federal Register; GRAS = generally recognized as safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; NAAQS = National Ambient Air Quality Standards; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PBT = persistent, bioaccumulative, and toxic; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TSCA = Toxic Substances Control Act; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

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10. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study— A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the 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 that must not be exceeded.

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 risk 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)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

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 new cases 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 hazardous substance.

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) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work 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 (insects or other organisms harmful to cultivated plants or animals).

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 blood:air 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 hazardous substance. 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 hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, 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)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

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 it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

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 substance 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 route and 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 substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that

are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-57, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: DEET
CAS Numbers: 134-62-3
Date: August 2017
Profile Status: Final
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: 35
Species: Rats

Minimal Risk Level: 1.0 [X] mg/kg/day [ ] ppm

Reference: EPA. 1989. [EPA memorandum 007645 from Whang Phang, Subject: Review of a two-generation reproduction on DEET, dated 13 December 1989]. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-080301_13-Dec-89_032.pdf. April 24, 2014.

Experimental design: Groups of Sprague-Dawley rats (28/sex/group) were fed diets containing 0, 500, 2,000, or 5,000 ppm DEET for at least 80 days before mating (EPA 1989). Using the standard conversion, 20 ppm=1 mg/kg/day (EPA 1998b), the diet provided doses of approximately 0, 25, 100, or 250 mg DEET/kg/day. Parental F0 animals were allowed to produce only one litter. Animals remained on the test diets during mating, gestation, and lactation. After weaning of F1 rats, 28 males and 28 females were randomly chosen to serve as parents for the F2 generation. F1 rats were mated after at least 93 days on the test diet. After weaning, 10 pups/sex/groups were subjected to gross necropsy. F0 females were killed after the selection of F1 parents. F1 females were sacrificed after weaning of their litters. The following parameters were used to assess toxicity: twice daily observations for deaths and clinical signs, body weight, and food consumption (not measured during the mating periods). Additionally, gross necropsy and histological examination of the ovaries, prostate, seminal vesicles, testes with epididymides, uterus, vagina, and all gross lesions were conducted in all parental rats and 10 weanlings/sex/group in the control and high-dose groups. Parameters used to assess developmental toxicity in the F1 and F2 litters included number of live and stillborn pups, external anomalies, sex and body weight grouped by sex on lactation days 0, 4, 7, and 14, sex and individual body weights (only group weights reported) on lactation day 21, viability, and behavioral abnormalities at least twice daily during lactation.

Effects noted in study and corresponding doses: There were no chemical-related deaths during the study. Hair loss appeared to be more prominent in high-dose F0 and F1 females than in other groups. Body weights of parental rats were lower in some of the mid- and high-dose groups at some points in the study, but the difference with controls was generally <10%. Changes in food consumption tended to parallel the changes in body weight and were generally <10% different than controls. F1 males showed mottled kidneys with incidences of 0/23, 2/23 (9%), 6/23 (26%), and 8/23 (35%) of the males (control and increasing dose groups). Microscopy revealed inflammation, hyaline droplet and granular cast formation, and regeneration of tubules. No explicit information was provided in the review regarding the other organs examined. The only significant reproductive/developmental effects reported were decreased F2 pup viability in the low- and high-dose groups on postnatal day 4 and reduced male and female F1 and F2 pup weights in the high-dose group on lactation days 14 and 21 (Table A-1).

Table A-1. Body Weight (g) of Rats on Lactation Day 21 in a 2-Generation Reproductive Study

Doses (mg/kg/day)	0	25	100	250
F1 males	46.2±6.50[a]	46.8±5.06	45.7±4.53	40.1±4.22[b]
F1 females	44.1±4.64	44.6±4.44	44.2±4.51	39.1±4.60[b]
F2 males	50.4±4.31	49.4±6.07	47.9±4.02	44.5±3.93[b]
F2 females	47.3±4.52	47.6±5.35	44.1±7.50	42.3±3.23[b]

[a]Mean±standard deviation.
[b]p<0.01.

Source: EPA (1989)

Dose and end point used for MRL derivation: NOAEL of 100 mg/kg/day (LOAEL of 250 mg/kg/day for reduced body weight in F1 and F2 male and female pups on lactation day 21).

[X] NOAEL [ ] LOAEL

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Yes,
20 ppm=1 mg/kg/day was used as done in EPA (1998b).

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: The intermediate-duration oral database showed relatively little toxicity for DEET. Most effects reported were of questionable toxicological significance except for the developmental effects that were used for MRL derivation. The fact that the reduction in body weight occurred in both male and female pups from both the F1 and F2 generations, provides strength to the MRL.

Intermediate-duration oral MRL is protective for chronic-duration exposure. The available chronic-duration oral database does not support derivation of a chronic-duration oral MRL for DEET. Long-term exposure, however, does not lead to more toxic effects than those reported for intermediate-duration exposure, so the intermediate-duration oral MRL of 1 mg/kg/day for DEET is protective for chronic-duration exposure.

Agency Contacts (Chemical Managers): Sam Keith

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 hazardous substance 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 include 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 adverse 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 an adverse 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

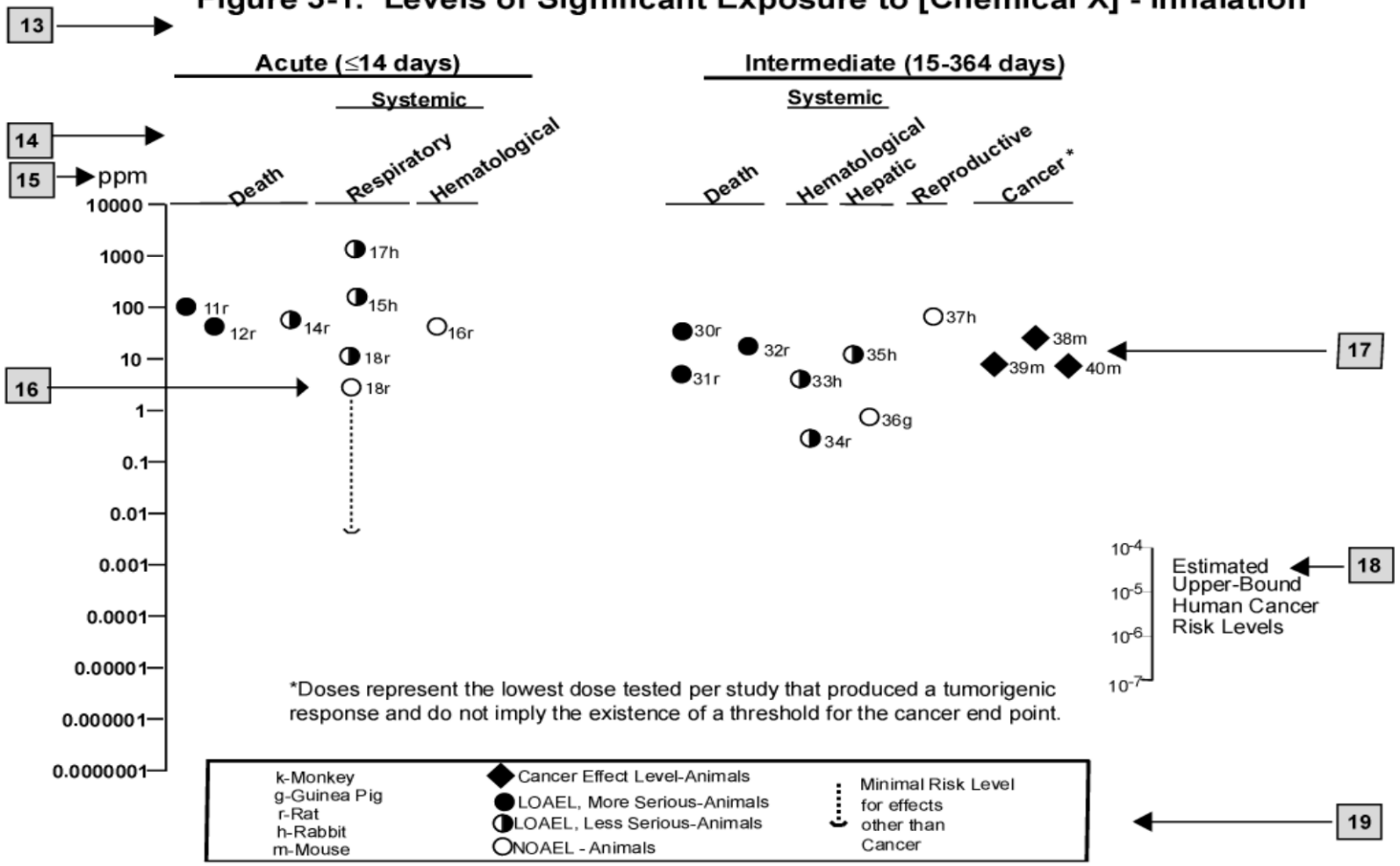
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) 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
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	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 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
mt	metric ton
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
PEL-C	permissible exposure limit-ceiling value
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
REL-C	recommended exposure level-ceiling value
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
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 (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
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
TLV-C	threshold limit value-ceiling 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