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The use of company or product name(s) is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry.
UPDATE STATEMENT

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333
FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987, October 20, 1988, October 26, 1989, and on October 17, 1990.

Section 104 (I) (3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. Each profile must include the following content:

(A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order 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 which present a significant risk to human health of acute, subacute, and chronic health effects, and

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

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and EPA. The original guidelines were published in the Federal Register on April 17, 1987. Each profile will be revised and republished as necessary, but no less often than every three years, as required by SARA.

The ATSDR toxicological profile is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but 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.

Each toxicological profile begins with a public health statement, which describes in nontechnical language a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

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

Agency for Toxic Substances and Disease Registry
Division of Toxicology
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Atlanta, Georgia 30333

This profile reflects our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control and Prevention, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers and is being made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and Disease Registry
QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by route of exposure, by type of health effect (death, systemic, immunologic, reproductive), and by length of exposure (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

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

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 2.7 Children’s Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.8 Biomarkers of Exposure and Effect
Section 2.11 Methods for Reducing Toxic Effects

ATSDR Information Center
Phone: 1-888-42-ATSDR or 404-639-6357 Fax: (404) 639-6359
E-mail: atsdric@cdc.gov Internet: http://www.atsdr.cdc.gov

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

Case Studies in Environmental Medicine: Taking an Exposure History—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include Reproductive and Developmental Hazards; Skin Lesions and Environmental Exposures; Cholinesterase-Inhibiting Pesticide Toxicity; and numerous chemical-specific case studies.
Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—Medical Management Guidelines for Acute Chemical Exposures—is a guide for health care professionals treating patients exposed to hazardous materials.

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

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

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, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.
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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 Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.
A peer review panel was assembled for DDT, DDE, and DDD. The panel consisted of the following members:

1. Dr. Martin Alexander, Professor, Cornell University, Ithaca, NY;
2. Dr. Daland Juberg, Senior Scientist, ICTM, Rochester, NY;
3. Dr. Donald Morgan, Private Consultant, Cedar Rapids, IA; and
4. Dr. Gary Pascoe, Scientist, EA Engineering Science and Technology, Bellevue, WA.

These experts collectively have knowledge of DDT, DDE, and DDD'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. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

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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***DRAFT FOR PUBLIC COMMENT***
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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about DDT, DDE, and DDD and the effects of exposure.

The 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 the sites targeted for long-term federal cleanup activities. DDT, DDE, and DDD have been found in at least 397 of the 1,560 current or former NPL sites. However, the total number of NPL sites evaluated for these substances is not known. As more sites are evaluated, the sites at which DDT, DDE, and DDD are found may increase. This information is important because exposure to these substances may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to DDT, DDE, and DDD, many factors determine whether you’ll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with them. You must also consider the other chemicals you’re exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

While this document is specifically focused on the primary forms or isomers of DDT, DDE, and DDD (namely \(p,p'-\text{DDT}, p,p'-\text{DDE},\) and \(p,p'-\text{DDD}\)), other isomers of these compounds will be discussed when appropriate. In some cases, the term DDT will be used to refer to the collection of all forms of DDT, DDE, and DDD. Should this not be clear from the context, the term \(\Sigma\text{DDT}\) (\(\Sigma\) is used to mean sum of) will be used.
1. PUBLIC HEALTH STATEMENT

1.1 WHAT ARE DDT, DDE, AND DDD?

DDT (1,1,1-trichloro-2,2-bis(p-chlorophenyl)ethane) was a widely used chemical to control insects on agricultural crops and insects that carry diseases like malaria and typhus. Technical grade DDT is a mixture of three forms, \( p,p' \)-DDT (85%), \( o,p' \)-DDT (15%), and \( o,o' \)-DDT (trace amounts). All of these are white, crystalline, tasteless, and almost odorless solids. Technical grade DDT may also contain DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene) and DDD (1,1-dichloro-2,2-bis(p-chlorophenyl)ethane) as contaminants. DDD was also used to kill pests, but to a far lesser extent than DDT. One form of DDD (\( o,p' \)-DDD) has been used medically to treat cancer of the adrenal gland. Both DDE and DDD are breakdown products of DDT.

DDT does not occur naturally in the environment. After 1972, the use of DDT was no longer permitted in the United States except in cases of a public health emergency. It is, however, still used in some other areas of the world. The use of DDD to kill pests has also been banned in the United States.

You will find further information on the physical properties and uses of DDT, DDE, and DDD in Chapters 3 and 4 of this profile.

1.2 WHAT HAPPENS TO DDT, DDE, AND DDD WHEN THEY ENTER THE ENVIRONMENT?

Before 1973 when it was banned, DDT entered the air, water, and soil during its production and use as an insecticide. DDT is present at many waste sites, including NPL sites; releases from these sites might continue to contaminate the environment. Most DDT in the environment is a result of past use; DDD was also used as a pesticide to a limited extent in the past. DDT still enters the environment because of its current use in other areas of the world. DDE is only found in the environment as a result of contamination or breakdown of DDT. DDD also enters the environment during the breakdown of DDT.
Large amounts of DDT were released into the air and on soil or water when it was sprayed on crops and forests to control insects. DDT was also sprayed in the environment to control mosquitoes. Although the use of DDT is no longer permitted in the United States, DDT may still be released into the atmosphere in other countries where it is still manufactured and used, including Mexico. DDT, DDE and DDD may also enter the air when they evaporate from contaminated water and soil. DDT, DDE, and DDD in the air will then be deposited on land or surface water. This cycle of evaporation and deposition may be repeated many times. As a result, DDT, DDE, and DDD can be carried long distances in the atmosphere. These chemicals have been found in bogs, snow, and animals in the Arctic and Antarctic regions, far from where they were ever used. Some DDT may have entered the soil from waste sites. DDT, DDE, and DDD may occur in the atmosphere as a vapor or be attached to solids in air. Vapor phase DDT, DDE, and DDD may break down in the atmosphere due to reactions caused by the sun. As a result, the half-life of these chemicals in the atmosphere as vapors (the time it takes for one-half of the chemical to turn into something else) is approximately 1.5–3 days.

DDT, DDE, and DDD last in the soil for a very long time. Eventually, most DDT breaks down into DDE and DDD, generally by the action of microorganisms. DDE and DDD also last in soil for long periods. These chemicals may also evaporate into the air and be deposited in other places. They stick strongly to soil, and therefore generally remain in the surface layers of soil. Some soil particles with attached DDT, DDE, or DDD may get into rivers and lakes in runoff. Only a very small amount, if any, will seep into the ground and get into groundwater. The length of time that DDT will last in soil depends on many factors including temperature, type of soil, and whether the soil is wet. DDT lasts for a much shorter time in the tropics where the chemical evaporates faster and where microorganisms degrade it faster. DDT disappears faster when the soil is flooded or wet than when it is dry. DDT disappears faster when it initially enters the soil. Later on, evaporation slows down and some DDT moves into spaces in the soil that are so small that microorganisms cannot reach the DDT to break it down efficiently. In tropical areas, ΣDDT may disappear in much less than a year. In temperate areas, half of the ΣDDT initially present usually disappears in about 5 years. However, in some cases, half of the ΣDDT initially present will remain for 20, 30, or more years.
In surface water, DDT will bind to particles in the water, settle, and be deposited in the sediment. DDT is taken up by small organisms and fish in the water. It accumulates to high levels in fish and marine mammals (such as seals and whales), reaching levels many thousands of times higher than in water. In these animals, the highest levels of DDT are found in the fat. DDT in soil can also be absorbed by some plants and by the animals or people who eat those crops.

More information about what happens to DDT, DDE, and DDD in the environment can be found in Chapter 5.

1.3 HOW MIGHT I BE EXPOSED TO DDT, DDE, AND DDD?

People are exposed to DDT, DDE, and DDD mainly by eating foods containing small amounts of these compounds. Even though DDT has not been used in this country since 1972, soil may still contain some DDT that may be taken up by plants and eaten by animals and people. DDT from contaminated water and sediment may be taken up by fish. The amount of DDT in food has greatly decreased since DDT was banned and should continue to decline. In the years 1986 to 1991, the average adult in the United States consumed an average of 0.8 micrograms (a microgram is a millionth of a gram) of DDT a day. Adults consumed slightly different amounts based on their age and sex. The largest fraction of DDT in a person’s diet comes from meat, fish, poultry, and dairy products. Leafy vegetables generally contain more DDT than other vegetables, possibly because DDT in the air is deposited on the leaves. Infants may be exposed by drinking breast milk.

DDT or its breakdown products are still present in some air, water, and soil samples. However, levels in most air and water samples are presently so low that exposure is of little concern. DDT levels in air have declined to such low levels that it often cannot be detected. In cases where DDT has been detected in air, it is associated with air masses coming from regions where DDT is still used or from the evaporated DDT from contaminated water or soil. *p,p’*-DDT and *p,p’*-DDE concentrations measured in air in the Great Lakes region in 1990 reached maximum levels of 0.035 and 0.119 nanograms (a nanogram is a billionth of a gram) of chemical per cubic meter of air (ng/m³), respectively. Levels were generally much lower, especially during the winter.
months. In 1995–1996, soils in the corn belt, where DDT was heavily used in the past, contained on the average about 10 nanograms of DDT in a gram of soil. In recent years, most surface water has not contained detectable amounts of DDT.

People who work or live around NPL sites or work with contaminated soil or sediment would most likely be exposed by accidentally swallowing soil, having skin contact with the soil, or breathing in DDT in dust.

You can find more information on exposure to DDT, DDE, and DDD in Chapter 5 of this profile.

1.4 HOW CAN DDT, DDE, AND DDD ENTER AND LEAVE MY BODY?

DDT, DDE, or DDD enters the body mainly when a person eats contaminated food. The actual amounts of DDT, DDE, and DDD absorbed from foods depends on both the concentration of chemical in the food and the amount of food eaten. Small amounts of DDT, DDE, and DDD may also be breathed in and absorbed into the body. DDT, DDE, and DDD are often attached to particles too large to pass very far into the lungs after air containing them is breathed. These particles are more likely to be carried upward in the mucus of the air passages and swallowed than for the DDT to be absorbed in the lungs. DDT, DDE, and DDD do not enter the body through the skin very easily.

Once inside the body, DDT can break down to DDE or DDD. DDE and DDD, in turn, break down to other substances (called metabolites). DDT, DDE, and DDD are stored most readily in fatty tissue. Stored amounts leave the body very slowly. Levels in fatty tissues may either remain relatively the same over time or even increase with continued exposure. However, as exposure decreases, the amount of DDT in the body also decreases. DDT metabolites leave the body mostly in urine, but may also leave by breast milk. See Chapter 2 for more information on how DDT, DDE, and DDD enter and leave the body.
1.5 HOW CAN DDT, DDE, AND DDD AFFECT MY HEALTH?

Eating food with large amounts of DDT over a short time would most likely affect the nervous system. People who swallowed large amounts of DDT became excitable and had tremors and seizures. They also experienced sweating, headache, nausea, vomiting, and dizziness. These effects on the nervous system went away once exposure stopped. Tests in laboratory animals confirm the effect of DDT on the nervous system.

No effects have been reported in people given small daily doses of DDT by capsule for 18 months. People exposed for a long time to small amounts, such as people who worked in factories where DDT was made, had some reversible changes in the levels of liver enzymes in the blood.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Animal studies show that long-term exposure to DDT may affect the liver. Tests in animals also suggest that short-term exposure to DDT and metabolites in food may have a harmful effect on reproduction. In addition, we know that some breakdown products of DDT can cause harmful effects on the adrenal gland. This gland is situated near the kidney and produces hormones.

Studies in animals have shown that oral exposure to DDT can cause liver cancer. Studies of DDT-exposed workers did not show increases in deaths or cancers. The Department of Health
and Human Services has determined that DDT may reasonably be anticipated to be a human carcinogen. The International Agency for Research on Cancer (IARC) has determined that DDT may possibly cause cancer in humans. EPA has determined that DDT, DDE, and DDD are probable human carcinogens. See Chapter 2 for more information on the health effects associated with exposure to DDT, DDE, and DDD.

1.6 HOW CAN DDT, DDE, AND DDD AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Children can be exposed to DDT, DDE, or DDD by eating food contaminated with these compounds. DDT is a pesticide, and even though it has not been used in this country since 1972, soil has small amounts and, under certain conditions, contaminated soil transfers DDT to crops. Children can be exposed also by eating food imported from countries where DDT is still being used. Because of their smaller weight, children’s intake of DDT per kilogram of body weight may be greater than that of adults. In the United States between 1985 and 1991, the average 8½-month-old infant consumed 4 times as much DDT for each pound of body weight than the average adult. However, the amounts of DDT consumed were very small.

DDT from the mother can enter her unborn baby through the placenta. DDT has been found in human placentas, fetuses, and umbilical cord blood. Because DDT has been measured in human milk, nursing infants are also exposed to DDT. However, in most cases, the benefits of breast-feeding outweigh any risks from exposure to DDT in mother’s milk.

We do not know whether children differ from adults in their susceptibility to health effects from DDT. There have been few studies of health effects in young children exposed to DDT. A child who drank DDT in kerosene vomited and had tremors and convulsions and eventually died; however, we do not know how much of this was caused by the kerosene. Adults who swallowed DDT in much greater amounts than those found in the environment had effects on their nervous
systems. The same harmful effects will probably happen to young children if they eat food or drink liquids with large amounts of DDT. However, because DDT is no longer used or made in the United States, such exposure is not likely to happen. Two studies have shown a higher dose of DDT is needed to kill newborn and young rats than adult rats. In one study, when the dose was divided up and given over four days, the same dose of DDT killed rats of all ages.

There is no evidence that exposure to DDT at levels found in the environment causes birth defects or other developmental effects in people. Studies in animals have shown that DDT given during pregnancy can slow the growth of the fetus, but there is no evidence that exposure to DDT causes structural birth defects in animals. However, exposure to DDT or its metabolites during development may change how the reproductive and nervous systems work. Male rats exposed to the DDT breakdown product, \( p,p' \)-DDE, as fetuses or while nursing, showed changes in the development of their reproductive system. One study found that the beginning of puberty is delayed in male rats given relatively high amounts of \( p,p' \)-DDE as juveniles. Also, one study showed that exposure of mice to DDT during the first weeks of life resulted in neurobehavioral problems when tests were done later in life. These studies raise concerns that exposure to DDT early in life might cause harmful effects that remain or begin long after exposure has stopped.

More information regarding children’s health and DDT and related compounds can be found in Section 2.8.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO DDT, DDE, AND DDD?

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

At this time, most people are exposed to DDT and its breakdown products as a result of eating foods or drinking liquids that may be contaminated with small amounts of DDT. DDT is a pesticide, but it was banned in the United States in 1972. However, because of its chemical
characteristics, it has stayed in the environment and low levels of DDT may be present in foods (i.e., fruits, vegetables, meat, and fish) for many years. Studies have shown that cooking will reduce the amount of DDT in fish. Many other countries still use DDT; therefore, food brought into the United States from these countries may contain DDT. The Food and Drug Administration (FDA) analyzes a wide variety of imported food items (coffee, tropical fruits, etc.) as well as domestic products to determine if pesticide residues are above EPA tolerances. DDT has been found in both root and leafy vegetables. DDT attaches to the roots of plants, but it does not easily move to other parts of the plants. Washing fruits and vegetables before eating them is a good idea.

You and your children may be exposed to DDT by eating certain types of fish or wildlife caught from certain locations. Some states, Native American tribes, and U.S. territories have issued fish and wildlife advisories to warn people about DDT-contaminated fish and turtles. Each state, Native American tribe, or U.S. territory sets its own criteria for issuing fish and wildlife advisories. A fish advisory will specify which bodies of water have restrictions. The advisory will tell you what type and sizes of fish are of concern. The advisory may completely ban eating fish or tell you to limit your meals of a certain fish type. For example, an advisory may tell you to eat a certain type of fish no more than once a month. The advisory may tell you only to eat certain parts of the fish or turtle and how to prepare or cook the fish or turtle to decrease your exposure to DDT. The fish or wildlife advisory may be stricter to protect pregnant women, nursing mothers, and young children. To reduce your children’s exposure to DDT, obey fish and wildlife advisories. Information on fish and wildlife advisories in your state is available from your state health or natural resources department. Signs may also be posted in certain fishing areas.

More information regarding exposure to DDT can be found in Sections 5.5, 5.6, and 5.7.
1.8 **IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO DDT, DDE, AND DDD?**

DDT, DDE, and DDD can be measured in fat, blood, urine, semen, and breast milk. Samples of blood and urine are easy to get, and levels in these samples may help show the amount of exposure. These tests are not readily available at your doctor's office, but your doctor can tell you where they can be done. Tests may show low, moderate, or excessive exposure to these compounds. However, such tests cannot show the exact amount of DDT, DDE, or DDD to which a person was exposed, or predict the chance of health effects in the person. See Section 2.6 and Chapter 6 for more information on tests to detect these compounds in the body.

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

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

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that
provides it. Some regulations and recommendations for DDT, DDE, and DDD include the following:

All uses of DDT were banned by EPA in 1972, except in cases of public health emergencies. DDT was banned because the chemical was building up in the environment and possibly hurting wildlife. Also, some cancer tests in laboratory animals showed positive results. Although DDT is no longer used in the United States, federal regulations still control the amounts of DDT allowed in food and water.

OSHA states that workers may not be exposed to amounts of DDT greater than 1 milligram of DDT per cubic meter of air (1 mg/m³) for an 8-hour workday, 40-hour work week. EPA estimates that drinking 2 liters of water per day containing 0.59 nanograms of DDT per liter of water (1 nanogram is one billionth of a gram) and eating 6.5 grams of fish and shellfish per day (from waters containing 0.59 nanograms DDT per liter) would be associated with an increased lifetime cancer risk of one in one million. Fish and shellfish tend to concentrate DDT from the surrounding water in their tissues. The FDA sets standards for almost all foods. See Chapter 7 for more information on regulations.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry  
Division of Toxicology  
1600 Clifton Road NE, Mailstop E-29  
Atlanta, GA 30333

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)  
Fax: (404) 639-6359
ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000
2. HEALTH EFFECTS

2.1 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 DDT, DDE, and DDD. 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. Information on the effects of DDT, DDE, and DDD in humans and in animal species traditionally used in laboratory experiments is presented in Section 2.2 Discussion of Health Effects by Route of Exposure, whereas information on the effects of these compounds in wildlife is presented in Section 2.3 Health Effects in Wildlife Potentially Relevant to Human Health.

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

While this document is specifically focused on the primary forms or isomers of DDT, DDE, and DDD (namely \(p,p\)'-DDT, \(p,p\)'-DDE, and \(p,p\)'-DDD), other isomers of these compounds will be discussed when appropriate. In some cases, the term DDT will be used to refer to the collective forms of DDT, DDE, and DDD. Should this not be clear from the context, the term \(\Sigma\)DDT (\(\Sigma\) is used to mean sum of) will be used.

Typically, people are not exposed to DDT, DDE, or DDD individually, but rather to a mixture of all three compounds since DDE and DDD are contaminants, as well as degradation and metabolic products, of DDT. In addition, DDT, DDE, and DDD each can exist in three isomeric forms based on the relative position of the chlorine substitutions on the two chlorophenyl rings (Chapter 3). The most prevalent isomer of DDT, DDE, or DDD in the environment is the \(p,p\)'-isomer. Technical grade DDT contains 65–80% \(p,p\)'-DDT, 15–21% \(o,p\)'-DDT, and up to 4% of \(p,p\)'-DDD (Metcalf 1995). When the toxicity of the isomers of DDT, DDE, or DDD reported in the experimental data differ in an organ system, such as the reproductive or developmental systems, isomer-specific results are presented, when available. Therefore, the data presented in this document include some relevant toxicity information on DDE and DDD analogues and on the \(o,p\)'- and \(p,p\)'-isomers of DDT and technical grade DDT.
2. HEALTH EFFECTS

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) 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.
Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of DDT, DDE, and DDD are indicated in Table 2-1 and Figure 2-1. Because cancer effects could occur at lower exposure levels, Figure 2-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of $1 \times 10^{-4}$ to $1 \times 10^{-7}$, as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for DDT, DDE, and DDD. 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 1990a), 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.

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.

### 2.2.1 Inhalation Exposure

Occupational exposure to DDT involved multiple routes of exposure. The primary routes of exposure were probably inhalation and dermal; however, absorption of DDT from the lungs may not have been significant, and ingestion due to the mucociliary apparatus of the respiratory tract is more likely. Therefore, with the exception of a report on lung cancer, epidemiological studies of occupational exposure will be discussed under oral exposure and the following section refers to nonoccupational inhalation exposure.
2. HEALTH EFFECTS

2.2.1.1 Death

No studies were located regarding death in humans or animals after inhalation exposure to DDT, DDE, or DDD.

2.2.1.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, or dermal effects in humans or animals after inhalation exposure to DDT, DDE, or DDD.

Respiratory Effects. Volunteers were exposed by inhalation of aerosols containing DDT at concentrations that left a white deposit on the nasal hair (Neal et al. 1944). Except for moderate irritation of the nose, throat, and eyes, which may have been related to the vehicle to disperse DDT in an aerosol, no significant changes were reported. This study had several limitations. The study did not provide information concerning conditions of exposure, dose, or information on persons exposed.

No studies were located regarding the respiratory effects in animals after inhalation exposure to DDT, DDE, or DDD.

Ocular Effects. Reports of ocular effects in humans exposed to DDT in the air are limited to the study by Neal et al. (1944). In this study, moderate, nonspecific eye irritation was reported by volunteers exposed to an aerosol containing DDT. This effect is assumed to have been caused by direct contact of the aerosol with the eye and not by inhalation of the aerosol. No information on the length of exposure or the concentration of DDT in air was provided. Irritation may have been related to the vehicle in which DDT was dissolved.

No studies were located regarding the ocular effects in animals after inhalation exposure to DDT.
No studies were located regarding the following effects in humans or animals after inhalation exposure to DDT, DDE, or DDD:

**2.2.1.3 Immunological and Lymphoreticular Effects**

**2.2.1.4 Neurological Effects**

**2.2.1.5 Reproductive Effects**

**2.2.1.6 Developmental Effects**

**2.2.1.7 Genotoxic Effects**

*In vitro* genotoxicity studies are discussed in Section 2.6.

**2.2.1.8 Cancer**

Occupational exposure to DDT was associated with increased lung cancer in a case control study of the Uruguayan work force (De Stefani et al. 1996). Elevated, but not statistically significant, odds ratios (OR) for any type of lung cancer were observed in 34 workers who had been exposed for 1 to 20 years (OR=1.6; 95% confidence interval [CI]=0.9 to 4.6), in 16 workers who had been exposed for greater than 20 years (OR=2.0; 95% CI=0.9 to 4.7), and in 50 workers who had ever been exposed to DDT (OR=1.7; 95% CI=1.0 to 2.8). Significantly elevated odds ratios were reported in a subset of 33 DDT-exposed lung cancer patients with small cell cancer (OR=3.6; 95% CI=1.5 to 8.9) or in 57 with adenocarcinoma (OR=2.3; 95% CI=1.2 to 4.7). Analyses were adjusted for age, residence, education, tobacco smoking, and alcohol consumption.

Several additional studies of workers occupationally exposed to DDT are discussed in Section 2.2.2.8 as exposure most probably occurred by ingestion of trapped particles rather than by inhalation.

No studies were located regarding cancer in animals after inhalation exposure to DDT, DDE, or DDD. EPA (IRIS 1999a) calculated an inhalation unit risk of 9.7x10^{-5} per µg/m³ for DDT from oral data in animals (Section 2.2.2.8). The air concentrations corresponding to excess cancer risk levels of 1x10^{-4}, 1x10^{-5}, 1x10^{-6}, and 1x10^{-7} are 1x10^{-3}, 1x10^{-4}, 1x10^{-5}, and 1x10^{-6} mg/m³, respectively.
2. HEALTH EFFECTS

2.2.2 Oral Exposure

Table 2-1 and Figure 2-1 present the health effects observed in humans and animals associated with levels of significant oral exposure for each designated exposure duration. The levels of exposure to humans below which the risk of adverse effects (other than cancer) is presumed to be minimal are also presented.

Occupational exposure to DDT has involved multiple routes of exposure, the most significant of which involved ingestion of DDT particles via the mucociliary apparatus of the respiratory tract. Therefore, epidemiological studies of occupational exposure to DDT are discussed in this section.

2.2.2.1 Death

Only one case of fatal poisoning in humans after accidental oral exposure to DDT has been documented (Hill and Robinson 1945). One ounce of 5% DDT in kerosene was ingested by a 1-year-old child. Clinical signs included coughing and vomiting followed by tremors and convulsions. The child then became comatose and died; however, the contribution of the kerosene solvent to DDT toxicity was not clear. Doses as high as 285 mg DDT/kg body weight have been accidentally ingested by humans with no fatal results (Garrett 1947).

In a follow-up study to Morgan and Lin (1978) (see Section 2.2.2.2), Morgan et al. (1980) analyzed morbidity and mortality in an extensive cohort of workers exposed to organochlorine pesticides. The follow-up included 73% of an original cohort of 2,600 workers. Disease incidence rates were studied in relation to occupational subclasses and to serum levels of organochlorine pesticides measured in the original study. There were no significant differences in mortality patterns between pesticide-exposed workers and controls except for an excess of deaths by accidental trauma in workers engaged in structural pesticide application.

A historical prospective mortality study was conducted on 3,600 white male workers employed between 1935 and 1976 in occupations that involved exposures to various brominated compounds, organic and inorganic bromides, and DDT (Wong et al. 1984). Among individuals exposed to DDT, overall mortality, expressed as the standard mortality ratio (SMR), was not elevated over expected values.

However, there was an excess in deaths from respiratory cancer. Several factors confound these results: those individuals exposed to DDT also were potentially exposed to other chemicals, and smoking history
<table>
<thead>
<tr>
<th>Key to figure</th>
<th>Species (Strain)</th>
<th>Exposure/duration/frequency (Specific route)</th>
<th>System</th>
<th>NOAEL (mg/kg/day)</th>
<th>Less serious (mg/kg/day)</th>
<th>Serious (mg/kg/day)</th>
<th>Reference</th>
<th>Chemical Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rat (NS)</td>
<td>Once (NS)</td>
<td></td>
<td></td>
<td>300 (LD50)</td>
<td></td>
<td>Ben-Dyke et al. 1970</td>
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</tr>
<tr>
<td>2</td>
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<td>Once (NS)</td>
<td></td>
<td></td>
<td>400 (LD50)</td>
<td></td>
<td>Ben-Dyke et al. 1970</td>
<td>DDD, NS</td>
</tr>
<tr>
<td>3</td>
<td>Rat (NS)</td>
<td>Once (G)</td>
<td></td>
<td></td>
<td>800 (LD50)</td>
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<td>Cameron and Burgess 1945</td>
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<td>4</td>
<td>Rat (Sherman)</td>
<td>Once (G)</td>
<td></td>
<td></td>
<td>113 (LD50)</td>
<td></td>
<td>Gaines 1969</td>
<td>DDT, p.p'</td>
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<tr>
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<td>Rat (Sherman)</td>
<td>Once (G)</td>
<td></td>
<td></td>
<td>4000 (LD50)</td>
<td></td>
<td>Gaines 1969</td>
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<tr>
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<td>Rat (Sherman)</td>
<td>Once (G)</td>
<td></td>
<td></td>
<td>880 (LD50)</td>
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<td>Gaines 1969</td>
<td>DDE, Tech</td>
</tr>
<tr>
<td>7</td>
<td>Rat (NS)</td>
<td>4 d (G)</td>
<td></td>
<td></td>
<td>279.2 (4-day LD50, preweanling; cumulative dose)</td>
<td></td>
<td>Lu et al. 1965</td>
<td>DDT, Tech</td>
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<td>8</td>
<td>Rat (NS)</td>
<td>4 d (G)</td>
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<td></td>
<td>285.6 (4-day adult LD50; cumulative dose)</td>
<td></td>
<td>Lu et al. 1965</td>
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<td>9</td>
<td>Rat (NS)</td>
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<td></td>
<td></td>
<td>355.2 (LD50, weanling rats)</td>
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<td>Lu et al. 1965</td>
<td>DDT, Tech</td>
</tr>
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<td>194.5 (LD50, adult rats)</td>
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<td>Lu et al. 1965</td>
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<td>Species (Strain)</td>
<td>Exposure/duration/frequency (Specific route)</td>
<td>System</td>
<td>NOAEL (mg/kg/day)</td>
<td>Less serious (mg/kg/day)</td>
<td>Serious (mg/kg/day)</td>
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<td>(G)</td>
<td>4000 (LD50, newborn rats)</td>
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<td>Lu et al. 1965 DDT, Tech</td>
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<td>437.8 (LD50, preweanling rats)</td>
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<td>Lu et al. 1965 DDT, Tech</td>
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<td>Mouse (Inbred Swiss)</td>
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<td>(G)</td>
<td>300 M (LD50)</td>
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<tr>
<td>14</td>
<td>Mouse (C3H)</td>
<td>6 d</td>
<td>(F)</td>
<td>85.7 F (50% of mice killed after a 6-day feeding period)</td>
<td></td>
<td>Okey and Page 1974 DDT, p.p'</td>
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</tr>
<tr>
<td>15</td>
<td>Mouse (CF1)</td>
<td>Once</td>
<td>(G)</td>
<td>1466 (LD50)</td>
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<td>Tomatis et al. 1972 DDD, p.p'</td>
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<tr>
<td>16</td>
<td>Mouse (CF1)</td>
<td>Once</td>
<td>(G)</td>
<td>810 (LD50)</td>
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<td>Tomatis et al. 1972 DDE, o.p'</td>
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<td>Once</td>
<td>(G)</td>
<td>237 (LD50)</td>
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<td>Tomatis et al. 1972 DDT, Tech</td>
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<td>Goat (NS)</td>
<td>Once</td>
<td>(G)</td>
<td>400 (LD50)</td>
<td></td>
<td>Cameron and Burgess 1945 DDT, NS</td>
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<tr>
<td>19</td>
<td>Rabbit (NS)</td>
<td>Once</td>
<td>(G)</td>
<td>300 (LD50)</td>
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<td>Cameron and Burgess 1945 DDT, NS</td>
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<tr>
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<tr>
<td>20</td>
<td>Monkey (Rhesus)</td>
<td>Once (G)</td>
<td>Hepatic</td>
<td>150</td>
<td>(increased serum LDH, AP, and transaminases)</td>
<td>Agarwal et al. 1978 DDT, NS</td>
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<td>21</td>
<td>Rat (Wistar)</td>
<td>12 d (G)</td>
<td>Hepatic</td>
<td>40</td>
<td>(18% increase in relative liver weight; increased liver GSH and AHH enzyme activities)</td>
<td>DeWaziers and Azais 1987 DDT, NS</td>
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<tr>
<td>22</td>
<td>Rat (Sprague Dawley)</td>
<td>Once (GO)</td>
<td>Endocr</td>
<td>25</td>
<td>50</td>
<td>(reduced capacity to concentrate iodine in thyroid)</td>
<td>Goldman 1981 DDT, Tech</td>
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<tr>
<td>23</td>
<td>Mouse (CF1)</td>
<td>1 wk (F)</td>
<td>Hepatic</td>
<td>42.9</td>
<td>(29% increase absolute liver weight; increase cytochrome-c reductase and P-450)</td>
<td>Pasha 1981 DDE, NS</td>
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<td>24</td>
<td>Dog (NS)</td>
<td>14 d (NS)</td>
<td>Cardio</td>
<td>50</td>
<td>(decrease in contractile force)</td>
<td>Cueto 1970 DDD, o,p'</td>
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<td></td>
<td>Endocr</td>
<td>50</td>
<td>(decreased plasma glucocorticoids)</td>
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<td>25</td>
<td>Dog (NS)</td>
<td>10 d (C)</td>
<td>Endocr</td>
<td>50</td>
<td>(adrenal hemorrhage)</td>
<td>Kirk et al. 1974 DDD, o,p'</td>
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<td>26</td>
<td>Dog</td>
<td>Once (C)</td>
<td>Endocr</td>
<td>200</td>
<td>(reversible degenerative adrenal changes)</td>
<td>Powers et al. 1974 DDD, Tech</td>
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<td>27</td>
<td>Dog (Mongrels and Beagles)</td>
<td>6 d or 15d (C)</td>
<td>Endocr</td>
<td>100</td>
<td>(necrosis, adrenal)</td>
<td>Powers et al. 1974 DDT, Tech</td>
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<td>28</td>
<td>Rabbit</td>
<td>10 d (New Zealand)</td>
<td>(G)</td>
<td>4.3</td>
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<td>Shiplov et al. 1972 DDT, NS</td>
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<td>29</td>
<td>Human</td>
<td>Once (F)</td>
<td></td>
<td>10.3</td>
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<td>16 (convulsions)</td>
<td>Heieh 1954 DDT, NS</td>
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<td>30</td>
<td>Monkey (Rhesus)</td>
<td>Once (G)</td>
<td></td>
<td>150</td>
<td>(decrease CNS total lipids, phospholipids and cholesterol)</td>
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<td>Sanyal et al. 1986 DDT, Tech</td>
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<td>31</td>
<td>Rat (Wistar)</td>
<td>Once (GO)</td>
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<td></td>
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<td>160 (tremors)</td>
<td>Hietanen and Vainio 1976 DDT, NS</td>
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<td>32</td>
<td>Rat (Fischer)</td>
<td>Once (G)</td>
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<td>25</td>
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<td>50 (tremors)</td>
<td>Hong et al. 1986 DDT, p,p'</td>
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<td>Rat (Albino Sprague Dawley)</td>
<td>Once (G)</td>
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<td>100 (myoclonus)</td>
<td>Hwang and Van Woert 1978 DDT, p,p'</td>
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<td>34</td>
<td>Mouse (albino)</td>
<td>once (GO)</td>
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<td>160 M (tremors)</td>
<td>Hietanen and Vainio 1976 DDT, p,p'</td>
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<td>35</td>
<td>Mouse (Albino)</td>
<td>Once (G)</td>
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<td>200 (convulsions)</td>
<td>Matlin et al. 1981 DDT, p,p'</td>
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Table 2-1. Levels of Significant Exposure to DDT, DDE, DDD – Oral (continued)

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<th>Chemical Form</th>
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<td>36</td>
<td>Gn Pig (NS)</td>
<td>Once (G)</td>
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<td>160 (paralysis of hind legs)</td>
<td>Hietanen and Vainio 1976 DDT, NS</td>
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<td>37</td>
<td>Hamster (NS)</td>
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<td>160</td>
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<td>Hietanen and Vainio 1976 DDT, NS</td>
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<td><strong>Reproductive</strong></td>
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<td>Rat (Wistar)</td>
<td>7 d (F)</td>
<td></td>
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<td>100 (increased uterus weight; premature vaginal opening)</td>
<td>Clement and Okey 1972 DDT, o,p'</td>
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<td>39</td>
<td>Rat (Long-Evans)</td>
<td>1 x/d (GO)</td>
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<td></td>
<td>200 M (reduced seminal vesicle and ventral prostate weight)</td>
<td>Kelce et al. 1995 DDE, p,p'</td>
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<td>40</td>
<td>Rat (Sprague-Dawley)</td>
<td>1 x/d (GO)</td>
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<td></td>
<td>200 M (reduced seminal vesicle and ventral prostate weight)</td>
<td>Kelce et al. 1997 DDE, p,p'</td>
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<td>Rabbit (New Zealand)</td>
<td>Gd7-9 (GO)</td>
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<td>50 (increased resorptions, 1.8% in controls, 25% in treated)</td>
<td>Hart et al. 1971 DDT, p,p'</td>
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<td>42</td>
<td>Rabbit (New Zealand)</td>
<td>Gd7-9 (GO)</td>
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<td></td>
<td>10 (increased resorptions, 1.3% in controls, 9.5% in treated)</td>
<td>Hart et al. 1972 DDT, p,p'</td>
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<td></td>
<td><strong>Developmental</strong></td>
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<td>Gallert and Heinrichs 1975 DDE, o,p'</td>
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<td>43</td>
<td>Rat (Sprague Dawley)</td>
<td>Gd15-19 (G)</td>
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<tr>
<td>44 Rat (Sprague Dawley)</td>
<td>Gd15-19 (G)</td>
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<td>Gellert and Heinrichs 1975 DDT, o,p'</td>
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<tr>
<td>45 Rat (Sprague Dawley)</td>
<td>Gd15-19 (G)</td>
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<td>Gellert and Heinrichs 1975 DDT, p.p'</td>
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<tr>
<td>46 Rat (Sprague Dawley)</td>
<td>Gd15-19 (G)</td>
<td></td>
<td>28 (delayed vaginal opening)</td>
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<td>Gellert and Heinrichs 1975 DDD, o,p'</td>
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<tr>
<td>47 Rat (Long-Evans)</td>
<td>1 x/d Gd 14-18 (GO)</td>
<td></td>
<td>100 M (males: reduced anogenital distance at birth; pdp 13 retained thoracic nipples)</td>
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<td>Kelce et al. 1995 DDE, p,p'</td>
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<td>48 Rat (Holtzman)</td>
<td>1 x/d Gd 14-18 (GO)</td>
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<td>50 M (reduced anogenital distance on pdp1 and relative ventral prostate weight on pdp21)</td>
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<td>Loeffler and Peterson 1999 DDE, p,p'</td>
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<tr>
<td>49 Rat (Long-Evans)</td>
<td>1 x/d Gd 14-18 (GO)</td>
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<td>100 M (reduced anogenital distance on pdp2; retained thoracic nipples on pdp13)</td>
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<td>You et al. 1998 DDE, p,p'</td>
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<td>50 Rat (Sprague Dawley)</td>
<td>1 x/d Gd 14-18 (GO)</td>
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<td>10 M (pdp13 males retained thoracic nipples)</td>
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<td>You et al. 1998 DDE, p,p'</td>
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<td>Serious (mg/kg/day)</td>
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<tr>
<td>51</td>
<td>Mouse (NMRI)</td>
<td>Once ppd 10 (GO)</td>
<td></td>
<td></td>
<td>0.5² M (increased motor activity at 4 months)</td>
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<td>52</td>
<td>Mouse (NMRI)</td>
<td>Once ppd 10 (GO)</td>
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<td>0.5 M (decrease in cerebral cortex muscarinic acetylcholine receptors at 4 months)</td>
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<td>53</td>
<td>Mouse (NMRI)</td>
<td>once ppd 10 (GO)</td>
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<td>0.5 M (decreased muscarinic receptors in cerebral cortex; increased spontaneous activity at 5 months)</td>
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<td>54</td>
<td>Mouse (NMRI)</td>
<td>once ppd 10 (GO)</td>
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<td>0.5 M (decreased muscarinic receptors in cerebral cortex; increased spontaneous activity at 5 and 7 months)</td>
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<td>55</td>
<td>Mouse (CF1)</td>
<td>1 x/d Gd 11-17 (GO)</td>
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<td>0.018 M</td>
<td>1.82 M (altered behavior; increase urine marking in a novel territory)</td>
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<td>56</td>
<td>Rabbit (New Zealand)</td>
<td>Gd4-7 (G)</td>
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<td>1 (decreased fetal weight)</td>
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<td>57</td>
<td>Rabbit (New Zealand)</td>
<td>Gd7-9 (GO)</td>
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<td>50 (22% decreased offspring weight)</td>
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Table 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)

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<th>LOAEL Serious (mg/kg/day)</th>
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<td>58</td>
<td>Rabbit</td>
<td>Gd7-9 (New Zealand)</td>
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<td>10 (11% decreased fetal weight on day 28)</td>
<td>50 (19% decreased fetal weight on day 28)</td>
<td>Hart et al. 1972 DDT, p.p'</td>
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### Table 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)

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<td>59</td>
<td>Monkey</td>
<td>2.4 or 6 mo</td>
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<td>50 (death of 6/6 in 14 weeks)</td>
<td>Cranmer et al. 1972a</td>
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<td></td>
<td>(Squirrel)</td>
<td>(G)</td>
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<tr>
<td>60</td>
<td>Mouse</td>
<td>6wk</td>
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<td>35 F (4 out 5 died)</td>
<td>NCI 1978</td>
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<td>(B6C3F1)</td>
<td>(F)</td>
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<td>DDT, Tech</td>
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<td>61</td>
<td>Mouse</td>
<td>6wk</td>
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<td>66 M (4 out of 5 died)</td>
<td>NCI 1978</td>
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<td>62</td>
<td>Rat</td>
<td>120 d</td>
<td>Endocr</td>
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<td>0.2 M (degeneration of adrenal cortex and medulla)</td>
<td>Chowdhury et al. 1990</td>
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<td>(albino)</td>
<td>(GO)</td>
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<td>Bd Wt</td>
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<td>0.2 M (30% reduced body weight gain)</td>
<td>Gupta et al. 1989</td>
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<td>63</td>
<td>Rat</td>
<td>3 wk</td>
<td>Hepatic</td>
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<td>15 (significant increase in liver weight and in cytochrome P-450 enzymes)</td>
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<td>Jonsson et al. 1981</td>
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<td>(GO)</td>
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<td>64</td>
<td>Rat</td>
<td>36 wk</td>
<td>Hepatic</td>
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<td>6.6 (focal necrosis/regeneration)</td>
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<td>Laug et al. 1950</td>
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<td>(Sprague Dawley)</td>
<td>7d/wk</td>
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<td>65</td>
<td>Rat</td>
<td>15-27 wk</td>
<td>Hepatic</td>
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<td>0.05c (cellular hypertrophy, cytoplasmic eosinophilia)</td>
<td>0.25</td>
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<td>(Osborne-Mendel)</td>
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<td>66</td>
<td>Rat</td>
<td>6 wk (Osborne-Mendel)</td>
<td>Bd Wt</td>
<td>28 M</td>
<td>50 M (16% reduced body weight gain)</td>
<td>.97 F (45% reduced body weight gain)</td>
<td>NCI 1978 DDT, Tech</td>
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<td>67</td>
<td>Rat</td>
<td>6 wk (Osborne-Mendel)</td>
<td>Bd Wt</td>
<td>88 M</td>
<td>88 M (11% decrease in body weight gain)</td>
<td>157 M (22% decrease in body weight gain)</td>
<td>NCI 1978 DDE, p.p'</td>
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<tr>
<td>68</td>
<td>Rat</td>
<td>2-18 mo (Sherman)</td>
<td>Hepatic</td>
<td>2.5 M</td>
<td>2.5 M (minor liver vacuolation, hypertrophy and cell margination)</td>
<td>Ortega 1955 DDT, Tech</td>
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<td>69</td>
<td>Mouse</td>
<td>6 wk (B6C3F1)</td>
<td>Bd Wt</td>
<td>310 F</td>
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<tr>
<td>70</td>
<td>Mouse</td>
<td>6 wk (B6C3F1)</td>
<td>Bd Wt</td>
<td>101 F</td>
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<td>Mouse</td>
<td>6 wk (B6C3F1)</td>
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<td>72</td>
<td>Mouse</td>
<td>28 d (NMRI)</td>
<td>Hepatic</td>
<td>6.25</td>
<td>6.25 (increased liver weight and P-450 induction)</td>
<td>Orberg and Lundberg 1974 DDT, p.p'</td>
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<td>73</td>
<td>Dog</td>
<td>36-150 d (NS)</td>
<td>Endocr</td>
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<td>50 (adrenocortical necrosis)</td>
<td>Kirk and Jenson 1975 DDD, o.p'</td>
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<td>74</td>
<td>Rat</td>
<td>4 wk (Wistar)</td>
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<td>2.3 M</td>
<td>5.7 M (decreased IgG and IgM, increased albumin/globulin ratio)</td>
<td>Banerjee et al. 1995 DDT, p.p'</td>
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<td>75</td>
<td>Rat (albino)</td>
<td>31 d 24 hr/d (F)</td>
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<td>1.9 (decreased mast cells)</td>
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<td>Gablits et al. 1975 DDT, NS</td>
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<td>76</td>
<td>Rat (Sprague-Dawley)</td>
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<td>121 (atrophy thymus)</td>
<td>Hamid et al. 1974 DDD, o.p'</td>
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<td>77</td>
<td>Mouse (Hissar)</td>
<td>3-12 wk (F)</td>
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<td>10.5 21 M (decreased IgM antibody titer)</td>
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<td>Banerjee 1987a DDT, NS</td>
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<td>Neurological</td>
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<td>50 (staggering, weakness, loss equilibrium)</td>
<td>Cranmer et al. 1972a DDT, p.p'</td>
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<td>78</td>
<td>Monkey (Squirrel)</td>
<td>2, 4, or 6 mo (G)</td>
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<td>10 (15-20% decrease in brain lipids, CNS phospholipids, and cholesterol)</td>
<td>Sanyal et al. 1986 DDT, Tech</td>
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<td>79</td>
<td>Monkey (Rhesus)</td>
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<td>80</td>
<td>Rat (Osborne-Mendel)</td>
<td>26 wk (F)</td>
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<td>16 F (body tremors)</td>
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<td>81</td>
<td>Rat (Wistar)</td>
<td>9 wk (F)</td>
<td></td>
<td></td>
<td>34.1 F (tremors in 80% of females after 9 weeks of treatment)</td>
<td>Rossi et al. 1977 DDT, Tech</td>
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<td>Reproductive</td>
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<td>7.5 (sterility)</td>
<td>Jonsson et al. 1976 DDT, Tech</td>
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<td>Rat (Sprague Dawley)</td>
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<td>3.75</td>
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### Table 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)

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<td>83</td>
<td>Rat (Long-Evans)</td>
<td>1 x/d Ppd 21-57 (GO)</td>
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<td>100 M (delayed onset of puberty by 5 days)</td>
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<td>Kelce et al. 1995 DDE, p,p'</td>
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<td>84</td>
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<td>Komburst et al. 1986 DDE, p,p'</td>
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<td>85</td>
<td>Rat (Wistar)</td>
<td>3 wk 3 x/wk (GO)</td>
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<td>100 (marginal, but significant decrease in testosterone in the testis)</td>
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<td>Krause 1977 DDT, NS</td>
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<td>86</td>
<td>Rat (NS)</td>
<td>ppd 4-23 (G)</td>
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<td></td>
<td>200 (decreased absolute testis weight)</td>
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<td>Krause et al. 1975 DDT, NS</td>
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<td>Rat (Wistar)</td>
<td>20 wk (F)</td>
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<td>Wrenn et al. 1971 DDT, o,p'</td>
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<td>88</td>
<td>Mouse (C-57)</td>
<td>60-90 d (F)</td>
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<td>51.4 (78% decreased fertility)</td>
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<td>Bernard and Gaertner 1984 DDT, Tech</td>
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<td>Mouse (B6C3F1)</td>
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<td>Ledoux et al. 1977 DDT, Tech</td>
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<td>90</td>
<td>Mouse (NMRI)</td>
<td>7d/wk 12 wk (F)</td>
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<td>1.67 (decreased implanted ova, increased-persistent-estrus)</td>
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<td>Lundberg 1974 DDT, p,p'</td>
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<td>91</td>
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<td>1.67 (decreased corpora lutea and Lundberg implants)</td>
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<td>Key to figure</td>
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<td>92</td>
<td>Mouse (NMRI)</td>
<td>28 d</td>
<td>G</td>
<td>6.25</td>
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<td>Orberg and Lundberg 1974</td>
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<td>Mouse (BALB/c)</td>
<td>120 d</td>
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<td>1.3</td>
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<td>Ware and Good 1967</td>
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<td>DDT, Tech</td>
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<td>94</td>
<td>Rabbit (New Zealand)</td>
<td>3 x/wk</td>
<td>GO</td>
<td>3 F (reduced ovulation rate and slight decrease circulating progesterone post-insemination)</td>
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<td>Lindenau et al. 1994</td>
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<tr>
<td>Developmental</td>
<td>Rat (Wistar)</td>
<td>42 d</td>
<td>Gd 1-21</td>
<td>1.7</td>
<td>16.8</td>
<td>(decreased growth of nursing pups)</td>
<td>42.1 (pup death by 10 days)</td>
<td>Clement and Okey 1974 DDT, p,p'</td>
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<td></td>
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<td>Gd 1-21</td>
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<td>Ld 1-21</td>
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<tr>
<td>96</td>
<td>Rat (Wistar)</td>
<td>pre-conception</td>
<td>Gd 1-21</td>
<td>16.8</td>
<td>84</td>
<td>(17% less weight than controls at age 21 days)</td>
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<td>Clement and Okey 1974 DDT, o,p'</td>
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<td>97</td>
<td>Mouse (CF1)</td>
<td>Gd 1-21</td>
<td>Ld 1-21</td>
<td>34.3</td>
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<td>(decreased maze performance learning at 1 and 2 months in survivors)</td>
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<td>Craig and Ogilvie 1974 DDT, Tech</td>
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<td>Cancer</td>
<td>Mouse (CF1)</td>
<td>15-30 wk</td>
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<td>42.8 (liver hepatomas)</td>
<td>Tomatis et al. 1974b DDT, p.p'</td>
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### Table 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)

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<th>Species (Strain)</th>
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<tr>
<td>99</td>
<td>Rat (Osborne-Mendel)</td>
<td>78wk (F)</td>
<td>Cardio</td>
<td>0.61</td>
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<tr>
<td>100</td>
<td>Mouse (B6C3F1)</td>
<td>78wk (F)</td>
<td>Hemato</td>
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<tr>
<td>102</td>
<td>Human</td>
<td>12-18 mo (F)</td>
<td>Cardio</td>
<td>0.61</td>
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<td>Hayes et al. 1956</td>
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<td>103</td>
<td>Monkey (Rhesus)</td>
<td>3.5-7 yr (F)</td>
<td>Hepatic</td>
<td>3.9</td>
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<td>Durham et al. 1963</td>
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19 F (16% death rate compared to 0% in controls) NCI 1978 DDE, p,p'  
15.0 F (10% mortality compared to 0% in controls) NCI 1978 DDT, Tech  
49 F (40% death rate compared to 5% in controls) NCI 1978 DDE, p,p'
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<td>104 Rat</td>
<td>27 mo</td>
<td>Resp</td>
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<td>Deichmann et al. 1967</td>
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<td>Hemato</td>
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<td>10 (hemolysis in spleen)</td>
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<td>Hepatic</td>
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<td>10 (focal hepato-cellular necrosis)</td>
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<td>Renal</td>
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<td>10 (some tubular epithelial necrosis and polycystic degeneration; small hemorrhages)</td>
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<td>105 Rat</td>
<td>2 yr</td>
<td>Hepatic</td>
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<td>7 (focal hepatocellular necrosis)</td>
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<td>Fitzhugh and Nelson 1947</td>
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<td>106 Rat</td>
<td>Resp</td>
<td>78 wk</td>
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<td>45 M</td>
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<td>Musc/skel</td>
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<td>Hepatic</td>
<td>23 M (fatty metamorphosis)</td>
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<td>Bd Wt</td>
<td>32 F (20% decrease in body weight gain)</td>
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<td>231 M</td>
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<td>Gastro</td>
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<td>Renal</td>
<td>66 F (chronic inflammation of the kidney)</td>
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Table 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)

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<td>Bd Wt</td>
<td>142 F (28% decrease in body weight gain)</td>
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71 F (17% decrease in body weight gain)
### Table 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)

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<td>49 F</td>
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<td>Bd Wt</td>
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<td>112 Hamster (Syrian)</td>
<td>life (F)</td>
<td>Hepatic</td>
<td>20</td>
<td>40 (focal necrosis)</td>
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<td>Cabral et al. 1982a</td>
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<td>(50% increase in relative liver weight)</td>
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<td>116 Human</td>
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**Neurological**

**Reproductive**

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<td>1.9</td>
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<td>life</td>
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<td>19.7 (liver tumors, NS)</td>
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<td>34.1 (liver cell tumors; 33.3% incidence, 0% in controls)</td>
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<tr>
<td>140 Mouse</td>
<td>(BALB/c)</td>
<td>life 2-gen (F)</td>
<td></td>
<td></td>
<td></td>
<td>32.5 (liver tumors in F0 and F1)</td>
<td>Terracini et al. 1973</td>
</tr>
</tbody>
</table>
Table 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)

<table>
<thead>
<tr>
<th>Key to figure</th>
<th>Species (Strain)</th>
<th>Exposure/ duration/ frequency (Specific route)</th>
<th>System</th>
<th>NOAEL (mg/kg/day)</th>
<th>Less serious (mg/kg/day)</th>
<th>Serious (mg/kg/day)</th>
<th>Reference</th>
<th>Chemical Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>141 Mouse (CF1)</td>
<td>2 yr (F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15.8 (liver tumors, NS)</td>
<td>Thorpe and Walker 1973</td>
<td>DDT, p,p'</td>
</tr>
<tr>
<td>142 Mouse (CF1)</td>
<td>life multi-gen (F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.38 M (liver tumors in F0 and F1)</td>
<td>Tomatis et al. 1972</td>
<td>DDT, Tech</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>45.5 F (liver tumors in F0 and F1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>143 Mouse (CF1)</td>
<td>130 wk (F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42.6 M (significant increase in liver tumors)</td>
<td>Tomatis et al. 1974a</td>
<td>DDE, p,p'</td>
</tr>
<tr>
<td>144 Mouse (CF1)</td>
<td>130 wk (F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42.6 M (significant increase in lung and liver tumors)</td>
<td>Tomatis et al. 1974a</td>
<td>DDD, p,p'</td>
</tr>
<tr>
<td>145 Mouse (CF1)</td>
<td>6 gen (F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.33 (liver tumors, NS)</td>
<td>Turusov et al. 1973</td>
<td>DDT, Tech</td>
</tr>
<tr>
<td>146 Hamster (Syrian)</td>
<td>128 wk (F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>95 (CEL: adrenal neoplasms; 14% in controls, 34% in treated)</td>
<td>Rossi et al. 1983</td>
<td>DDT, Tech</td>
</tr>
</tbody>
</table>
Table 2-1. Levels of Significant Exposure to DDT, DDE, DDD—Oral (continued)

<table>
<thead>
<tr>
<th>Key to figure</th>
<th>Species (Strain)</th>
<th>Exposure/duration/frequency (Specific route)</th>
<th>System</th>
<th>NOAEL (mg/kg/day)</th>
<th>Less serious (mg/kg/day)</th>
<th>Serious (mg/kg/day)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>147 Hamster</td>
<td>(Syrian)</td>
<td>128 wk</td>
<td></td>
<td></td>
<td></td>
<td>47.5</td>
<td>(CEL: hepatocellular tumors; Rossi et al. 0/73, 11/69, 14/78)</td>
</tr>
<tr>
<td></td>
<td>(F)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DDE, p.p'</td>
</tr>
</tbody>
</table>

*The number corresponds to entries in Figure 2-1.

*Used to derive an acute oral minimal risk level (MRL) of 0.0005 mg/kg-day for DDT. The MRL was derived by dividing the LOAEL by an uncertainty factor of 1000 (10 to account for interspecies variability, 10 for interspecies variability, and 10 for the use of a LOAEL).

*Used to derive an intermediate minimal risk level (MRL) of 0.0005 mg/kg/day for DDT. The MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 to account for interspecies variability and 10 for intraspecies variability). See Appendix A, ATSDR Minimal Risk Level Worksheets, for explanation of how dietary concentrations were converted to doses.

Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; CNS = central nervous system; d = day(s); (F) = food; Endocr - endocrine; F = female; (G) = gavage; gastro = gastrointestinal; Gd = gestation day; gen = generation(s); (GO) = gavage in oil; Hemato = hematological; hr = hour(s); kg = kilogram; ld = lactation day; LD₅₀ = lethal dose, 50% kill; LOAEL = lowest-observable-adverse-effect level; M = male; mg = milligram; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; PND = postnatal day; ppd = postpartum day; Resp = respiratory; wk = week(s); x = times
Figure 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral
Acute (≤ 14 days)

The number next to each point corresponds to entries in the accompanying table.

- c-Cat  - Humans  f-Ferret  n-Mink  ▲ Cancer Effect Level-Animals  ▼ Cancer Effect Level-Humans  □ LD50/LC50
- d-Dog  k-Monkey  j-Pigeon  o-Other  ● LOAEL, More Serious-Animals  ▲ LOAEL, More Serious-Humans  Minimal Risk
- r-Rat  m-Mouse  e-Gerbil  ● LOAEL, Less Serious-Animals  ▲ LOAEL, Less Serious-Humans  for effects
- p-Pig  h-Rabbit  s-Hamster  ○ NOAEL - Animals  △ NOAEL - Humans  other than Cancer
- q-Cow  a-Sheep  g-Guinea Pig
Figure 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)

Acute (≤ 14 days)

The number next to each point corresponds to entries in the accompanying table.

<table>
<thead>
<tr>
<th>Animal</th>
<th>Hazard Category</th>
<th>Human Effect</th>
<th>Animal Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>c-Cat</td>
<td>-Humans</td>
<td></td>
<td>Cancer Effect Level-Humans</td>
</tr>
<tr>
<td>d-Dog</td>
<td>k-Monkey</td>
<td>LOAEL, More Serious-Humans</td>
<td></td>
</tr>
<tr>
<td>r-Rat</td>
<td>m-Mouse</td>
<td>LOAEL, Less Serious-Humans</td>
<td></td>
</tr>
<tr>
<td>p-Pig</td>
<td>h-Hamster</td>
<td>NOAEL - Humans</td>
<td></td>
</tr>
<tr>
<td>d-Cow</td>
<td>a-Sheep</td>
<td></td>
<td>Cancer Effect Level-Humans</td>
</tr>
<tr>
<td></td>
<td>g-Guinea Pig</td>
<td></td>
<td>LD50/LC50 Minimal Risk for effects other than Cancer</td>
</tr>
</tbody>
</table>
Figure 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)
Intermediate (15-364 days)

The number next to each point corresponds to entries in the accompanying table.

* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for cancer end point.
Figure 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)

Chronic (≥ 365 days)

The number next to each point corresponds to entries in the accompanying table.

<table>
<thead>
<tr>
<th>c-Cat</th>
<th>d-Dog</th>
<th>r-Rat</th>
<th>p-Pig</th>
<th>q-Cow</th>
<th>f-Ferret</th>
<th>k-Monkey</th>
<th>m-Mouse</th>
<th>h-Rabbit</th>
<th>a-Sheep</th>
<th>n-Mink</th>
<th>o-Other</th>
<th>Cancer Effect Level-Animals</th>
<th>Cancer Effect Level-Humans</th>
<th>LD50/LC50</th>
<th>Minimal Risk for effects other than Cancer</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td>LOAEL, More Serious-Animals</td>
<td>LOAEL, More Serious-Humans</td>
<td></td>
<td>Minimal Risk for effects other than Cancer</td>
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<td></td>
<td>LOAEL, Less Serious-Animals</td>
<td>LOAEL, Less Serious-Humans</td>
<td></td>
<td>Minimal Risk for effects other than Cancer</td>
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<td></td>
<td>NOAEL - Animals</td>
<td>NOAEL - Humans</td>
<td></td>
<td>Minimal Risk for effects other than Cancer</td>
</tr>
</tbody>
</table>

---

[Diagram showing levels of exposure with various symbols and values]
Figure 2-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (continued)

Chronic (≥ 365 days)

The number next to each point corresponds to entries in the accompanying table. * Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for cancer end point.

<table>
<thead>
<tr>
<th>mg/kg/day</th>
<th>Endocrine</th>
<th>Dermal</th>
<th>Body Weight</th>
<th>Neurological</th>
<th>Reproductive</th>
<th>Developmental</th>
<th>Cancer*</th>
</tr>
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<tbody>
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<th>Systemic</th>
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<tbody>
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<td>· 110m</td>
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<tr>
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<tr>
<td>· 1E-7</td>
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</tbody>
</table>

Legend:
- Cancer Effect Level-Animals
- Cancer Effect Level-Humans
- LOAEL, More Serious-Animals
- LOAEL, More Serious-Humans
- LOAEL, Less Serious-Animals
- LOAEL, Less Serious-Humans
- NOAEL - Animals
- NOAEL - Humans
- LD50/LC50
- Minimal Risk
- Estimated Upper-Bound Human Cancer Risk Levels
- for effects other than Cancer

2. HEALTH EFFECTS

...DRAFT FOR PUBLIC COMMENT...

...DRAFT FOR PUBLIC COMMENT...
was not included in the analysis. Brown (1992) conducted an update of an historical prospective mortality study of workers in five pesticide manufacturing plants. In the plant where primary exposure was DDT (320 persons and 90 deaths since 1964), there was a significant excess of deaths (11) from stroke. The SMR was 2.38. The study is limited by insufficient exposure data, possible confounding exposures, and by relatively small numbers of deaths from stroke.

The LD$_{50}$ values reported in rats exposed to single oral doses of DDT ranged from 113 to 800 mg/kg (Ben-Dyke et al. 1970; Cameron and Burgess 1945; Gaines 1969). Results from a study by Lu et al. (1965) revealed age-dependent LD$_{50}$ values in rats. The LD$_{50}$ values in newborn, preweanling, weanling, and adult rats were >4,000, 438, 355, and 195 mg/kg, respectively. However, when preweanling and adult rats were administered one-quarter of the LD$_{50}$ daily for 4 days, there was no significant difference in the 4-day LD$_{50}$ between the two age groups. Lu et al. (1965) suggested that the elimination mechanism in the preweanling rats is less well developed, thus making them more susceptible to repeated doses than adults. The age-dependent susceptibility to single high oral doses of DDT in rats was confirmed by others who suggested that seizures and hyperthermia, observed in the adults but not in young rats, as well as less resistance to hypoxia, contribute to the apparent higher sensitivity of the adult rat (Henderson and Wooley 1969b, 1970).

In male and female mice, a single oral dose of >237 mg technical grade DDT/kg caused death (Kashyap et al. 1977; Tomatis et al. 1972), and a daily dietary dose of about 85.7 mg $p,p'$-DDT/kg killed 50% of a group of mice after a 6-day feeding period (Okey and Page 1974). Exposure of pregnant mice to 34.3 mg technical DDT/kg on gestation days 1–21 followed by cross-fostering of the pups resulted in preweanling death in 39% of the neonates exposed in utero and through lactation and 10% of the pups exposed only through lactation (Craig and Ogilvie 1974). No deaths occurred in pups exposed in utero only. The LD$_{50}$ values for guinea pigs and rabbits after oral exposure to DDT were 400 and 300 mg/kg, respectively (Cameron and Burgess 1945). Four out of five female B6C3F1 mice fed a diet that provided approximately 35 mg technical DDT/kg/day for 6 weeks died; the cause of death was not discussed (NCI 1978). Four out of six monkeys treated by gavage with 50 mg $p,p'$-DDT/kg/day died after four weeks of treatment; two additional monkeys died during the weeks nine and fourteen of treatment, the cause of death was not specified (Cranmer et al. 1972a). A 10% mortality rate (relative to 0% in controls) was observed in the 78-week NCI (1978) bioassay for female B6C3F1 mice treated with approximately 15 mg technical DDT/kg/day; in the high-dose group (30.2 mg/kg/day), the mortality rate was 28%. There was no positive association between dose of DDT and mortality in male mice (NCI 1978).
2. HEALTH EFFECTS

DDT, DDE, and DDD mortality studies also have been conducted. An LD$_{50}$ of 880 mg/kg was reported for male Sherman rats (Gaines 1969). Death occurred in mice after single oral doses of $o,p'$-DDE ranging from 810 to 880 mg DDE/kg (Tomatis et al. 1974a).

An LD$_{50}$ was reported for rats as a range of single oral doses (400–4,000 mg/kg) in which mortality was observed in 50% of rats exposed to DDD (Ben-Dyke et al. 1970). An LD$_{50}$ for DDD in rats of >4,000 mg/kg was reported by Gaines (1969). Tomatis et al. (1974a) reported an LD$_{50}$ in mice after a single oral dose ranging from 1,466 to 1,507 mg DDD/kg.

The LD$_{50}$ values for the various isomers and technical grades of DDT, DDE, and DDD are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

**Respiratory Effects.** No studies were located regarding respiratory effects in humans after oral exposure to DDT, DDE, or DDD. Rats fed a diet containing 10 mg DDT/kg/day for 27 months did not develop adverse respiratory effects with the exception of squamous bronchial metaplasia in one rat (Deichmann et al. 1967). In the 78-week chronic bioassay conducted by NCI (1978), no adverse effects on the respiratory system were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg $p,p'$-DDE/kg/day, or 231 mg technical DDD/kg/day. The same findings were reported for B6C3F1 mice treated with up to 30.2 mg technical DDT/kg/day, 49 mg $p,p'$-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978).

**Cardiovascular Effects.** Cardiovascular performance was one of the parameters evaluated in male volunteers orally administered 3.5 or 35 mg DDT/day by capsule for 12–18 months either as recrystallized or technical grade DDT (Hayes et al. 1956). This dosing regimen resulted in administered doses of 0.038–0.063 or 0.36–0.61 mg/kg/day for 12–18 months. The background concentrations measured in the food of both controls and test subjects were 0.0021–0.0038 mg DDT/kg/day. Although some variations among individuals in heart rate (resting and with exercise), systolic blood pressure, and pulse pressure were noted, these variations did not correlate with increasing dosage of DDT or with duration of exposure. The authors concluded that DDT at these doses did not result in adverse cardiac
2. HEALTH EFFECTS

effects. Tachycardia (increased heart rate) was reported in 1 of 11 cases in humans after accidental ingestion of approximately 286–1,716 mg DDT in food, which when adjusted for individual body weights, was 5.1–120.5 mg/kg (Hsieh 1954). It is not known if the tachycardia was a direct result of damage to the heart or a result of a neurologically-mediated mechanism. A suggestive relationship between high serum levels of DDT and DDE and subsequent development of vascular disease, especially hypertension, was noted in pesticide-exposed individuals (Morgan et al. 1980). However, exposure to multiple pesticides is a significant confounding factor in this study.

In the 78-week chronic bioassay conducted by NCI (1978), no significant chemical-related adverse effects on the cardiovascular system were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg $p,p'$-DDE/kg/day, or 231 mg technical DDD/kg/day. The same findings were reported for B6C3F1 mice treated with up to 30.2 mg technical DDT/kg/day, 49 mg $p,p'$-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978).

**Gastrointestinal Effects.** No studies were located regarding the gastrointestinal effects in humans after oral exposure to DDT, DDE, or DDD. In the 78-week chronic bioassay conducted by NCI (1978), no significant chemical-related adverse effects on the gastrointestinal system were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg $p,p'$-DDE/kg/day, or 231 mg technical DDD/kg/day. The same findings were reported for B6C3F1 mice treated with up to 30.2 mg technical DDT/kg/day, 49 mg $p,p'$-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978).

**Hematological Effects.** Hematological effects of DDT (Hayes et al. 1956; Laws et al. 1967; Morgan and Lin 1978; Ortelee 1958) and DDE (Dunstan et al. 1996; Morgan and Lin 1978) have been assessed. An extensive study measuring organochlorine pesticide concentrations in the blood of 2,600 pesticide-exposed individuals was conducted (Morgan and Lin 1978). One thousand controls with minimal exposure to pesticides were recruited and monitored. However, controls were not matched to pesticide-exposed individuals for age, sex, or race. Various clinical tests, including extensive hematologic analyses were performed during 1967–1973, and $p,p'$-DDT and $p,p'$-DDE levels in blood were determined. Several of the hematological parameters measured correlated positively with DDT and/or DDE blood levels, including a positive correlation between serum DDE and total white blood cell count. Exposure to multiple pesticides is a confounding factor in this study.

Clinical and laboratory examinations were performed on 40 workers exposed to DDT, some of whom had also been exposed to other pesticides (Ortelee 1958). Exposure was reported to have occurred primarily
via dermal and inhalation routes, but absorption by these routes may not have been significant. No protective equipment was used and the workers were often coated with concentrated DDT dust. Examinations included a complete medical history, physical and neurological examination, and hematological and blood chemistry analyses. In addition, plasma and erythrocyte cholinesterase levels were determined as well as urinary excretion of bis(p-chlorophenyl) acetic acid (DDA), which is the predominant final metabolite of DDT. On the basis of DDA excretion, it was estimated that these workers received absorbed doses equivalent to oral doses of 14–42 mg/person/day (approximately 0.2–0.6 mg/kg/day). Despite this relatively high level of exposure, no correlation was found between DDT exposure and the frequency and distribution of abnormalities, including neurological effects, except for a few cases of minor skin and eye irritation.

A study was conducted on 35 workers who had been involved in the manufacture and formulation of DDT for an average of 15 years (Laws et al. 1967). Extensive medical examinations and blood, urine, and fat analyses were performed in an attempt to find any correlation between any health problems and exposure to DDT. The authors concluded that the clinical findings for this group were not significantly different from those expected in an appropriate control group with no occupational exposure to DDT. However, this study did not include a control group and comparisons of data were made by using information derived from "the general population".

Male volunteers were exposed to 3.5 or 35 mg DDT/day, resulting in administered doses of 0.038–0.063 or 0.36–0.61 mg DDT/kg/day, respectively, for 12–18 months (Hayes et al. 1956). The background concentration measured in food of both controls and test subjects was 0.0021–0.0038 mg DDT/kg/day. Although some variation among individuals in hemoglobin levels, red and white blood cell count, and percentage of polymorphonuclear leukocytes was noted, these variations did not correlate with increased dosage of DDT or with duration of exposure.

In a case-control study of patients with chronic, debilitating fatigue lasting at least 6 months, the mean concentration of \( p,p' \)-DDE in blood serum was significantly higher in case subjects (11.9 ppb; \( n=14 \)) than in controls (5.2 ppb; \( n=23 \)) (Dunstan et al. 1996). When the 37 subjects were pooled and then redivided according to high serum DDE (>6 ppb) and low serum DDE (<6 ppb), the red blood cell distribution width (not clearly defined) was significantly greater in the high DDE group than in the low DDE group; no differences were seen in other hematological parameters.
In a chronic study, exposure to DDT at 10 mg/kg/day for 27 months resulted in alterations in the spleen, which consisted of congestion and hemolysis exceeding that observed in untreated control rats (Deichmann et al. 1967). In addition, squirrel monkeys exposed orally to doses of 0.05–50 mg DDT/kg/day for up to 6 months exhibited no hematological changes; however, all monkeys in the highest dose group (six animals) died by week 14 (Cranmer et al. 1972a); the cause of death was not determined, but before death, the monkeys had apparently recovered from severe neurotoxic symptoms.

**Musculoskeletal Effects.** No studies were located regarding musculoskeletal effects in humans after oral exposure to DDT, DDE, or DDD. In the 78-week chronic bioassay conducted by NCI (1978), no significant chemical-related adverse musculoskeletal effects were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg \( p,p' \)-DDE/kg/day, or 231 mg technical DDD/kg/day. The same findings were reported for B6C3F1 mice treated with up to 30.2 mg technical DDT/kg/day, 49 mg \( p,p' \)-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978).

**Hepatic Effects.** There is limited evidence that DDT, DDD, and DDE may cause liver effects in humans, but in animals, the liver appears to be one of the primary targets of DDT. Morgan and Lin (1978) measured organochlorine pesticide concentrations in the blood of 2,600 pesticide-exposed workers. Controls were not matched for age, sex, or race to pesticide-exposed individuals. Positive correlations were reported between serum DDT and DDE and the presence of elevated serum levels of liver enzymes including alkaline phosphatase, serum glutamic oxaloacetic transaminase (SGOT; aspartate aminotransferase [AST]), serum glutamic pyruvic transaminase (SGPT; alanine aminotransferase [ALT]), and lactic dehydrogenase (LDH). Increased serum levels of these enzymes is an index of liver injury. In a follow-up study of Laws et al. (1967), Laws et al. (1973) reexamined 31 of the 35 workers who had been involved in the manufacture and formulation of DDT for an average of 15 years. These men completed detailed questionnaires concerning their daily contact with DDT. In addition, liver function tests and DDT serum sample tests were performed on 21 subjects. Despite the fact that these workers had an average exposure to DDT for 21 years at levels estimated to correspond to 3.6–18 mg daily (0.05–0.26 mg/kg/day), no evidence of hepatotoxicity, hepatic enlargement, or dysfunction (Bromsulphthalein test, also known as sulfobromophthelein sodium) was found. One subject had an elevated Bromsulphthalein retention and slightly elevated serum levels of alkaline phosphatase and aspartic aminotransferase. Hayes et al. (1956) exposed male volunteers to 3.5 or 35 mg DDT/day, resulting in administered doses of 0.038–0.063 or 0.36–0.61 mg DDT/kg/day for 12–18 months. The background concentration measured in food of both controls and test subjects was 0.0021–0.0038 mg DDT/kg/day.
No signs of illness or adverse hepatic effects were reported that were considered to be related to DDT exposure to humans.

Epidemiological studies of DDT-exposed workers often show increased activity of hepatic metabolic enzymes. Kolmodin et al. (1969) studied drug metabolism in 26 workers with occupational exposure to several pesticides, primarily DDT, chlordane, and lindane. An appropriate control group of 33 subjects was included. Xenobiotic metabolism was assessed by administering antipyrine in a single dose of 10–15 mg/kg after which blood levels were monitored. Antipyrine was chosen because it is metabolized in the liver and not appreciably bound to plasma proteins. The half-life of antipyrine (both mean and median) was shorter in workers exposed to insecticides than in control subjects. In addition, the range of the half-life was much smaller in the exposed group. These results indicate that exposure to these insecticides induces hepatic enzyme activities, but the relative contribution of DDT to the observed enzyme induction is impossible to ascertain in this study.

The effect of high DDT exposure on phenylbutazone and endogenous cortisol metabolism was investigated in exposed workers by Poland et al. (1970). Both of these compounds are metabolized via hepatic microsomal enzymes. Nineteen workers with an average of 14 years of employment in a plant producing only DDT were selected for study, and matched controls were obtained. Both groups were screened for medical history and given a physical examination, and venous blood samples were drawn. After a single dose of 400 mg phenylbutazone, serum was obtained at regular intervals beginning at 24 and ending at 120 hours after drug administration. The serum half-life of phenylbutazone was significantly shorter in DDT-exposed workers than in the control population. However, the serum half-life of phenylbutazone did not correlate with the total concentration of DDT and related compounds in the serum of either group. The urinary excretion of the cortisol metabolite, 6β-hydroxycortisol, was increased by 57% in DDT-exposed individuals when compared to controls. However, there was no significant correlation found between the absolute serum concentration of total DDT-related compounds and the urinary excretion of 6β-hydroxycortisol. These results suggest that exposure to DDT can alter normal hepatic metabolic enzyme activity.

In animals, the liver appears to be one of the primary targets of DDT toxicity. Acute, subchronic, and chronic oral administration of DDT has been shown to cause dose-related mild-to-severe hepatic effects in numerous animal studies. In addition, DDT has been demonstrated to be an inducer of microsomal mixed function oxidases of the liver by its ability to promote the biotransformation of various chemicals (Pasha 1981; Street and Chadwick 1967).
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Acute oral exposure to DDT is associated with a number of effects in animals including increased liver weights, increased serum levels of liver enzymes (suggestive of liver injury), and changes in the appearance of the liver. Both liver plasma membrane and serum gamma-glutamyl transeptidase (GGTP) were increased 2-fold in rats treated with a single dose of 200 mg DDT/kg (Garcia and Mourelle 1984). Plasma membrane enzyme activity returned to normal 48 hours after dosing, but enzyme activity in serum remained elevated for 48 hours. Relative liver weight increased 18% after 12 days exposure to 40 mg/kg/day DDT in rats previously deprived of vitamin A for several generations; DDT treatment began 1 week after vitamin A supplementation was started to increase the rats’ vitamin A intake back to “normal” (de Waziers and Azais 1987). In both “normal” and vitamin A deficient rats, 12 days of DDT treatment increased liver CYP (P450) enzyme content per gram of liver by 2-fold, benzo(a)pyrene hydroxylase (a CYP enzyme) activity by 3-fold, and glutathione-S-transferase activity by 2-fold; all of these changes were statistically significant. A recent study showed that hepatic O-dealkylation activities associated with CYP2B were induced in a dose-related manner in rats treated orally with DDT for 14 days (Nims et al. 1998). The dose range tested was approximately 0.17–36 mg/kg/day. Maximal induction was more than 21 times greater than control values. There was no effect on in vivo CYP2B induction at <0.17 mg/kg/day. Limited induction of ethoxyresorufin O-dealkylation was observed, and no induction of immunoreactive hepatic microsomal CYP1A protein was seen. DDT also induced CYP3A1 and CYP3A2 proteins. Induction activity was also accompanied by an increase in relative liver weight with doses of approximately 4.6 mg/kg/day and higher. Mice administered 42.9 mg DDT/kg/day for 1 week by oral gavage had increased liver weights and increased microsomal enzyme activities (Pasha 1981) and Rhesus monkeys exposed to one oral dose of 150 mg DDT/kg had increased alkaline phosphatase (AP), LDH, AST, and ALT activities in serum (Agarwal et al. 1978). An increase in the levels of liver metabolic enzymes by itself is not considered adverse; however, continued microsomal enzyme induction may lead to hypertrophy and contribute to morphological changes in the liver. It should be noted also that microsomal enzyme induction may lead to the activation of some chemicals to toxic metabolites and the detoxification of other chemicals. In addition, increased serum levels of liver enzymes such as transaminases, LDH and AP can be predictive of more serious liver effects on prolonged exposure since this may indicate cell death and consequent lysis of membranes and leakage of enzymes.

Hepatic cell hypertrophy, histopathologic alterations (proliferation of the smooth endoplasmic reticulum and concentric membrane arrays), and increased microsomal enzyme activity have also been seen following intermediate exposure of rats to DDT. These effects were observed in rats following 3–27 weeks of dietary exposure at doses ranging from 0.25 to 20 mg DDT/kg/day (Gupta et al.1989; Laug et al. 1950; Ortega 1956). In general, as doses increased, hepatic effects in rats became more
severe. Phase I metabolic enzymes were significantly increased in rats treated for 3 weeks with 15 mg
\( p,p' \)-DDT/kg/day (Gupta et al. 1989). Minor hepatocyte vacuolation was seen in male rats receiving
2.5 mg technical DDT/kg/day in the diet for 3 months; females exhibited liver hypertrophy at
10 mg/kg/day (Ortega 1956). Rats administered approximately \( 0.25-0.5 \) mg technical DDT/kg/day
(see Appendix A for dose calculation) in the diet for 12–27 weeks had liver changes consisting of hepatic
cell enlargement, especially in the cental lobules, increased cytoplasmic oxyphilia with sometimes a
semihyaline appearance, and more peripheral locations of the basophilic cytoplasmic granules (Laug et al.
1950). The severity of the effects was dose-related; a dose of approximately 0.05-0.09 mg/kg/day was a
NOAEL. This study (Laug et al. 1950) was used as the basis for the derivation of an intermediate-
duration oral MRL for DDT. Fitzhugh and Nelson (1947) fed female Osborne-Mendel rats a diet
containing 1000 ppm (96 mg/kg/day) technical grade DDT for 12 weeks and observed reversible changes
in the liver, including enlargement of centrolobular hepatocytes with accompanying histological changes.
Rats exposed continuously to 6.6 mg DDT/kg/day in the diet for 36 weeks exhibited spotty cellular
necrosis with moderate hepatocyte regeneration (Jonsson et al. 1981). Squirrel monkeys and mice had
increased hepatic cytochrome P-450 enzyme activities and/or increased liver weights following
short-term exposure by oral gavage to DDT. These effects were observed following doses of 1.67 or
6.25 mg DDT/kg/day for 28 days in mice (Lundberg 1974; Orberg and Lundberg 1974) and 5 mg
DDT/kg/day for up to 6 months in squirrel monkeys (Cranmer et al. 1972a).

Hepatic effects ranging from increased liver weights to cellular necrosis have been reported in animals
after chronic exposure to DDT in the diet. Necrosis, centrilocular hypertrophy, and hyperplasia have also
been reported in rats exposed to 7–56 mg DDT/kg/day for 24–27 months (Deichmann et al. 1967;
Fitzhugh and Nelson 1947). Increased incidence of fatty metamorphosis was seen in the liver of male rats
treated with approximately 23 mg technical DDT/kg/day or more and of amyloidosis in the liver of male
mice treated with about 3.7 mg DDT/kg/day for 78 weeks (NCI 1978). Increased relative liver weights,
but no increase in serum ALT, LDH, AP, cholinesterase, or in liver ALT, AST, LDH, AP, or
cholinesterase activities were reported in hamsters after exposure to 20–80 mg DDT/kg/day for life
(Graillot et al. 1975). Cabral et al. (1982a) reported a significant increase in liver necrosis in hamsters
exposed to approximately 40 mg DDT/kg/day in the diet for life, but not at lower doses. Both focal and
diffuse liver alterations were observed in dogs exposed by diet to 80 mg DDT/kg/day for 39–40 months,
but not at 16 mg/kg/day (Lehman 1965). In Rhesus monkeys given up to 3.9 mg DDT/kg/day for
3.5–7.5 years, periodic liver biopsies showed no “significant” observable alterations in liver histology and
the Bromsulphthalein clearance test was normal, indicating no functional liver changes (Durham et al.
1963).
Limited information exists on hepatic effects after oral exposure of animals to DDD or DDE. Rats exposed to two gavage doses of 350 mg DDE/kg/day exhibited an increase in enzyme levels (ornithine decarboxylase and cytochrome P-450) (Kitchin and Brown 1988), and mice showed increased liver weight, microsomal P450, cytochrome-C reductase, and serum total protein after daily gavage dosing with 42.9 mg/kg DDE/day for 7 days (Pasha 1981). Chronic exposure of rats (78 weeks) to \( p,p' \)-DDE resulted in increased incidence of fatty metamorphosis in the liver from males at a dose of approximately 31 mg/kg/day (NCI 1978). DDE produced significant induction of hepatic O-dealkylation activities associated with CYP2B in rats administered DDE in the diet at dose levels between approximately 0.15 and 36 mg/kg/day for 14 days (Nims et al. 1998). The NOEL for \textit{in vivo} CYP2B induction was 0.17 mg/kg/day. No induction of immunoreactive hepatic microsomal CYP1A protein was observed, and induction of CYP1A associated activities was limited. DDE also induced CYP3A1 and CYP3A2 proteins. Induction activity was also accompanied by a significant increase in relative liver weight at a dose level of approximately 4.1 mg/kg/day and higher. No adverse liver effects were observed in mice chronically exposed to \( p,p' \)-DDE in the diet at up to 49 mg/kg/day for 78 weeks (NCI 1978). Chronic exposure to approximately 48 mg \( p,p' \)-DDE/kg/day resulted in focal necrosis of the liver in hamsters in a 128-week study (Rossi et al. 1983).

DDD induced CYP2B associated activities in the livers of rats treated with the test material in the diet at dose levels of approximately 1.4 mg/kg/day and higher for 14 days (Nims et al. 1998). The NOEL was between 0.5 and 1.4 mg/kg/day. No induction of immunoreactive hepatic microsomal CYP1A protein was observed, and limited induction of CYP1A associated enzyme activity was seen. DDD also slightly induced CYP3A2, but not CYP3A1. No significant treatment-related nonneoplastic alterations were seen in the livers from rats or mice exposed orally to up to 231 or 142 mg technical DDD/kg/day, respectively, for 78 weeks (NCI 1978). Mice exposed orally to 42.9 mg DDD/kg/day in the diet for 1 week had no change in levels of P-450 microsomal enzymes, but showed a decrease in cytosolic-enzyme-mediated hydroxylation of 2- and 4-biphenyls with no change in liver weight (Pasha 1981).

**Renal Effects.** No studies were located regarding renal effects in humans after oral exposure to DDT, DDE, or DDD. Male and female Osborne-Mendel rats exposed orally to 10 mg DDT/kg/day in the diet for 27 months had tubular polycystic degeneration, tubular epithelial necrosis, and hemorrhage of the kidney (Deichmann et al. 1967). In the 78-week chronic bioassay conducted by NCI (1978), no significant chemical-related adverse renal effects were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, or in mice treated with up to 30.2 mg DDT/kg/day. Similarly, no adverse renal effects were seen in rats treated with up to approximately 59 mg.
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*p,p*-DDE/kg/day for 78 weeks (NCI 1978). However, chronic inflammation of the kidneys was seen in male mice treated with approximately 27 mg *p,p*-DDE/kg/day (NCI 1978); no such effect was seen in female mice treated with up to 49 mg/kg/day. Technical DDE, at a dose level of approximately 66 mg/kg/day, increased the incidence of chronic inflammation of the kidney in female rats in the 78-week NCI (1978) bioassay. No significant chemical-related increase in kidney lesions was seen in mice treated for 78 weeks treated with up to 231 mg technical DDD/kg/day (NCI 1978).

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to DDT or DDE. *o,p*-DDD has been used to treat adrenocortical carcinoma for almost four decades (Bergenstal et al. 1960; Wooten and King 1993). The therapeutic action is based on the activation of the compound by local cytochrome P-450 (CYP11β) to a reactive metabolite which binds to macromolecules in the adrenal cortex (see Section 2.6 Relevance to Public Health for further details).

In rats administered 0.2 mg technical grade DDT/kg/day for 120 days, atrophy of all zones of the adrenal gland, except the *zona glomerulosa*, was observed (Chowdhury et al. 1990). Hyalin degeneration of the medulla and cortex and a decrease in adrenal gland weight were also reported. Dogs given 1–15 oral doses of 100 mg/kg/day technical grade DDD showed degenerative changes in mitochondria in both the *zona fasciculata* and *zona reticularis* of the adrenal cortex which were reversible 56 weeks after dosing ceased (Powers et al. 1974). Similar degenerative adrenal changes were reported by Kirk et al. (1974) after dosing dogs (by capsule) with 138.5 mg/kg/day of *o,p*-DDD for 10 days. Plasma levels of cortisol were decreased and a decreased response to ACTH stimulation was observed. In one animal, there was hemorrhage, invasion by lymphocytes, and necrosis of the adrenal cortex (Kirk et al. 1974). Adrenocortical necrosis was also reported in dogs treated for 36–150 days with 50 mg *o,p*-DDD/kg/day in a capsule (Kirk and Jensen 1975). Further information regarding adrenal toxicity of *o,p*-DDD and of sulfonyl metabolites can be found in Section 2.6 Relevance to Public Health.

Reduced iodine concentrating capacity in the thyroid was reported in adult male Sprague-Dawley rats given a single oral gavage dose of 50 mg or higher of technical DDT/kg; the-no-observed-effect dose level was between 25 and 50 mg/kg (Goldman 1981).

In the 78-week chronic bioassay conducted by NCI (1978), no treatment-related adverse effects on the endocrine system (pituitary, adrenals, thyroid, parathyroid) were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg *p,p*-DDE/kg/day, or 231 mg technical...
DDT, DDE, and DDD

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DDD/kg/day. The same findings were reported for B6C3F1 mice treated with up to 30.2 mg technical DDT/kg/day, 49 mg \( p,p' \)-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978).

Further information regarding endocrine effects can be found in Sections: 2.2.2.5 Reproductive Effects, 2.2.2.6 Developmental Effects, 2.5.2 Mechanisms of Toxicity, and 2.7 Endocrine Disruption.

**Dermal Effects.** Clinical examinations with laboratory workups were performed on 40 workers exposed to DDT, some of whom had also been exposed to other pesticides (Ortelee 1958). Exposure was reported to occur primarily via dermal and inhalation routes; however, no protective equipment was used, and the workers were often coated with concentrated DDT dust. Information collected on each worker included a complete medical history, physical and neurological examination results, and hematological and blood chemistry analyses results. Plasma and erythrocyte cholinesterase levels were determined as well as urinary excretion of DDA. On the basis of DDA excretion, it was estimated that these workers received absorbed doses equivalent to oral doses of 14–42 mg/day (approximately 0.2–0.6 mg/kg/day). Despite the relatively high estimated exposure, no correlation was found between DDT exposure and the frequency and distribution of skin abnormalities, except for a few cases of minor skin irritation.

No studies were located indicating adverse dermal effects in animals after oral exposure to DDT, DDE, or DDD.

**Ocular Effects.** The only information available is that from an earlier report by Ortelee (1958) regarding 40 workers exposed to DDT, some of whom had also been exposed to other pesticides. Based on information on DDA excretion, it was estimated that these workers received absorbed doses equivalent to oral doses of 14–42 mg/day (approximately 0.2–0.6 mg/kg/day). No correlation was found between DDT exposure and the frequency and distribution of abnormalities, except for a few cases of minor eye irritation which were probably due to direct contact of the pesticides with the eye.

**Body Weight Effects.** No treatment-related effects on body weight were observed in a group of 51 male volunteers given daily doses of up to 0.61 mg technical DDT/kg for up to 18 months (Hayes et al. 1956).

Body weight gain was reduced by 30%, relative to controls, in male albino rats treated with 0.2 mg technical DDT/kg by gavage for 120 days; food consumption data were not provided (Chowdhury et al. 1990). Female and male Osborne-Mendel rats fed a diet that provided approximately 97 or 50 mg
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technical DDT/kg/day, respectively, for 6 weeks had a 45 and 16% reduction in body weight, respectively, at the end of the treatment period relative to controls (NCI 1978). Male and female B6C3F1 mice treated similarly with up to 35 mg technical DDT/kg/day showed no significant treatment-related alterations in body weight gain (NCI 1978). In a 78-week chronic study, female Osborne-Mendel rats showed a 20% decrease in body weight gain due to dietary administration of approximately 32 mg technical DDT/kg/day compared to controls; males exhibited a 16% decrease in weight gain with a dietary level of approximately 45 mg/kg/day (NCI 1978). B6C3F1 mice treated in the diet with up to approximately 30.2 mg technical DDT/kg/day for 78 weeks did not show treatment-related alterations in body weight (NCI 1978). Hamsters treated for life with up to 40 mg technical DDT/kg/day in the diet showed no significant treatment-related effects on body weight (Cabral et al. 1982a), but a dietary level of approximately 95 mg/kg/day of technical DDT for 128 weeks caused an unspecified reduction in body weight gain relative to controls (Rossi et al. 1983).

A 6-week treatment period with up to approximately 157 mg \( p,p' \)-DDE/kg/day in the diet induced a 22% decrease in body weight gain in male Osborne-Mendel rats, and a dose level of 88 mg/kg/day caused an 11% decrease in weight gain relative to controls (NCI 1978); a dose of 50 mg/kg/day was a NOAEL. No significant treatment-related effects on body weight were seen in female rats treated with up to 305 mg \( p,p' \)-DDE/kg/day or in B6C3F1 mice treated with up to 101 mg/kg/day (NCI 1978). Chronic administration of approximately 19 mg \( p,p' \)-DDE/kg/day in the diet to female Osborne-Mendel rats caused a 21% decrease in body weight gain; this was the lowest dose tested (NCI 1978). Female B6C3F1 mice administered approximately 28 mg \( p,p' \)-DDE/kg/day for 78 weeks had a 29% reduction in body weight gain (this was also the lowest dose tested); body weight gain in male mice was unaffected by doses of up to 47 mg \( p,p' \)-DDE/kg/day (NCI 1978). Hamsters fed a diet that provided approximately 47.5 mg \( p,p' \)-DDE/kg/day for 128 weeks showed an unspecified reduction in body weight gain compared to controls (Rossi et al. 1983).

Treatment of female Osborne-Mendel rats with approximately 97 mg technical DDD/kg/day for 6 weeks resulted in a 39% decrease in body weight gain relative to controls, but treatment with 172 mg/kg/day resulted in only a 4% reduction in weight gain (NCI 1978). In males, the highest dose tested, 279 mg/kg/day, caused a 10% reduction in weight gain at the end of the treatment period (NCI 1978). In the 78-week NCI (1978) bioassay, female rats treated with approximately 66 mg technical DDD/kg/day had a 26% decrease in weight gain compared to controls at the end of the study; this was the lowest dose level tested. In males, there was a 28% decrease in weight gain in a group dosed with approximately 116 mg/kg/day and a 39% decrease in a group receiving about 231 mg/kg/day of technical DDD.
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2.2.2.3 Immunological and Lymphoreticular Effects

Limited information was located regarding immunological effects in humans after oral exposure to DDT, DDE, or DDD. In a study in which humans were challenged with an injection of Salmonella typhimurium vaccine, serum agglutinin titers were significantly higher in three volunteers given capsules containing 5 mg DDT/day (0.07 mg/kg) for 20 days when compared to volunteers who received only the bacterial antigen; immunoglobulin levels were unaffected by treatment with DDT (Shiplov et al. 1972). The volunteers exhibited no apparent symptoms of DDT exposure. Another study assessed parameters of immunocompetence in a group of 23 men with high fish consumption from the Baltic Sea (Svensson et al. 1994). The levels of DDT in the fish were not provided. None of the subjects had symptoms of any infectious disease at the time of the study. Twenty men with almost no fish consumption served as controls. The parameters examined included white cell counts, lymphocyte levels, serum immunoglobulin levels, and lymphocyte subsets. Of all the parameters examined, only the level of natural killer (NK) cells was reduced in the fish eaters, but the difference between groups was not statistically significant. Weekly intake of fatty fish correlated significantly (r=0.32, p<0.04) with the reduction in NK cells. A correlation (r=0.72, p=0.02) was observed between NK cell level and plasma level of p,p'-DDT in 12 subjects. The toxicological significance of these findings is unknown.

Evidence of DDT-induced compromises in immune function has been obtained from studies conducted in animals. The effects of DDT on the humoral immune response were studied in mice (Banerjee 1987a; Banerjee et al. 1986, 1997b), in rats (Banerjee 1987b; Banerjee et al. 1995, 1996; Gabliks et al. 1975), and in rabbits (Shiplov et al. 1972). There was no evidence that DDT adversely affected the humoral response in rabbits; however, dosing was for only 10 days by oral gavage at a single dose level (4.3 mg/kg/day) (Shiplov et al. 1972). Following dietary dosing at levels to provide 13 mg DDT/kg/day for 3–12 weeks, mice showed an immunosuppression particularly of the secondary humoral immune response to immunization with sheep red blood cells (SRBC) or Escherichia coli lipopolysaccharide (LPS), which are T-cell dependent and T-cell-independent antigens, respectively. There was a significant reduction in splenic plaque-forming cells as well as decreased IgM titers to lipopolysaccharide compared to controls (Banerjee 1987a; Banerjee et al. 1986). Rats immunized with diptheria toxoid were fed DDT in the diet for 31 days at an intake of 1.9 or 19 mg/kg/day. When challenged with diptheria toxoid, the severity of the anaphylactic response was decreased and the number of mast cells (producing histamine) in mesenteries was significantly decreased compared to controls; antibody titers to the toxoid were not decreased (Gabliks et al. 1975). Exposure of adult mice to DDT in the diet for 16 weeks at doses of 0.0316 mg/kg/day had no effect on the humoral immune response but doses of 0.316 or 3.16 mg/kg/day
for 16 weeks significantly stimulated the primary IgM response to SRBC and the lymphoproliferative response to LPS-coated SRBC (Rehana and Rao 1992). Dosing for longer periods (20 or 24 weeks) caused a sharp reduction in both responses. Dosing of dams during pregnancy and lactation caused suppression of the immune system in offspring as discussed in Section 2.2.2.6 (Rehana and Rao 1992); however, because appropriate controls were not used, the significance of this finding is not clear.

Effects in lymphoid organs were noted in rabbits (Street and Sharma 1975) and rats (Deichmann et al. 1967; Hamid et al. 1974). Rabbits administered an oral dose of 0.18 mg DDT/kg/day in the diet for 8 weeks exhibited a significant increase in gamma globulin levels and atrophy of the thymus whereas a much higher dose, 6.54 mg/kg/day, was found to significantly decrease the skin sensitivity to tuberculin (cell mediated immunity) (Street and Sharma 1975). Rats exposed to doses of 121 mg \(o,p'\)-DDD/kg/day for 16 days had decreased (no statistical analysis) numbers of plaque-forming cells and rosette-forming cells in the spleen and thymus compared to controls and displayed atrophy of the thymus and adrenal gland (Hamid et al. 1974).

Dietary DDT increased the growth of the leprosy bacterium, *Mycobacterium leprae*, in mouse foot pads (Banerjee et al. 1997a). DDT was fed to male albino Rockfeller strain mice in the diet at 0, 20, 50, or 100 ppm (approximately 0, 4.3, 10.7, and 21.4 mg/kg/day) for 24 weeks following inoculation of the footpads of mice with the leprosy bacterium. At $50\text{ ppm}$, bacillary growth was significantly increased.

Both humoral and cell-mediated responses were adversely affected in groups of 8–12 male Wistar rats fed diets containing 200 ppm DDT, DDE, or DDD (approximately 20.2 mg/kg/day) for 6 weeks (Banerjee et al. 1996). Compared to controls, effects on the humoral immune system were seen after dietary exposure to each of the compounds, including significantly increased serum albumin/globulin ratio, suppressed serum IgM, IgG after ovalbumin immunization, and decreased antibody titer. Likewise, cell-mediated effects were seen in rats fed DDT, DDE, and DDD, including increased inhibition of leucocyte and macrophage migration, and decreased footpad thickness. Mean relative liver weight was increased compared to controls in rats fed DDT and DDE, while relative spleen weight was decreased in DDD-fed rats; no other signs of toxicity were observed.

The influence of dietary protein on the humoral and cell-mediated immunotoxicity of DDT was evaluated in groups of male Wistar rats fed diets containing 0, 20, 50, or 100 ppm DDT (approximately 0, 2.3, 5.7, and 11.4 mg/kg/day, respectively) for 4 weeks (Banerjee et al. 1995). Dose groups were divided into subgroups that received either 3, 12, or 20% protein in the diet; half of each dietary subgroup, in turn,
received a tetanus toxoid immunostimulant, resulting in allocation of 10–12 rats to each treatment group. The serum albumin/globulin ratio was significantly increased in mid- and high-DDT dose groups compared to treatment controls, but only in rats fed the low-protein diet and receiving the immunostimulant injection. Serum IgM and IgG were significantly reduced in mid- and high-DDT groups that were fed the 3% protein diet, regardless of whether they had been immunostimulated with tetanus toxoid injections. No effects were seen in any group fed diets containing 12 or 20% protein.

DDT enhanced stress-induced humoral immune response suppression in mice (Banerjee et al. 1997b). Groups of 80–90 albino male Hissar mice were fed 0, 20, 50, or 100 ppm \( p,p' \)-DDT in the diet (approximately 0, 4.1, 10.1, and 20.3 mg/kg/day, respectively). Equal subgroups were selected for SRBC or plaque-forming cell (PFC) assays. Assay subgroups were in turn divided into five equal groups, resulting in treatment groups of 8–10 mice per group; one group received no stressor, and the other four groups received one of four different combinations of temperature (3 hours at 4°C) and restraint stresses. Relative to controls, DDT alone caused no significant alterations in primary antibody titer to SRBC or in PFC response. DDT in combination with stress, and in a dose-related manner, significantly reduced both responses to a greater extent than did each stressor alone. The results of this study indicate the following: (1) certain types of stressors are sufficient to suppress the humoral immune response in mice, in the absence of known chemical stressors, and (2) dietary DDT at sufficient levels can enhance the immunosuppressant effect of other stressors that otherwise have no statistically discernable effect.

Sheep red blood cell (SRBC) antibody titers were reduced in groups of 16 or 20 male Wistar rats fed 100 or 200 ppm in the diet for 8 weeks (approximately 10.3 and 20.6 mg/kg/day, respectively); DDT dietary exposure groups were divided into two subgroups, one received ascorbic acid by gavage at 100 mg/kg/day and the other received no ascorbic acid (Koner et al. 1998). Dose-related decreases in SRBC antibody titers were seen in the DDT-treated rats compared to controls, with or without concurrent treatment with ascorbic acid; the decrease was statistically significant in the 200-ppm group. In the DDT-treated rats, the absolute decrease appeared to be attenuated in rats co-treated with ascorbic acid compared to those not receiving ascorbic acid, although statistical tests were not reported.

In the 78-week chronic bioassay conducted by NCI (1978), no treatment-related adverse effects on the thymus, spleen, or lymph nodes were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg \( p,p' \)-DDE/kg/day, or 231 mg technical DDD/kg/day. The same negative findings were reported for B6C3F1 mice treated with up to 30.2 mg technical DDT/kg/day,
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49 mg \( p,p' \)-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978). Immunocompetence was not evaluated in this study.

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.2.4 Neurological Effects

The nervous system appears to be one of the primary target systems for DDT toxicity in humans after acute, high exposures. A number of investigators conducted experimental studies on humans in the 1940s and 1950s at controlled doses that produced effects. Other data come from accidental poisonings where dose levels were crudely estimated. Persons exposed to 6 mg DDT/kg administered orally by capsule generally exhibited no illness, but perspiration, headache, and nausea have been reported (Hayes 1982). Convulsions in humans have been reported at doses of 16 mg DDT/kg or higher (Hsieh 1954). Velbinger (1947a, 1947b) exposed volunteers to oral doses of 250, 500, 750, 1,000, or 1,500 mg DDT (approximately up to 22 mg/kg) suspended in an oil solution. Variable sensitivity of the mouth (defined by the author as a prickle at the tip of the tongue, lower lip, and chin area) was reported in volunteers exposed to 250 and 500 mg DDT/person. Six hours after exposure to 750 or 1,000 mg DDT, disturbance of sensitivity of the lower part of the face, uncertain gait, malaise, cold moist skin, and hypersensitivity to contact were observed. Prickling of the tongue and around the mouth and nose, disturbance of equilibrium, dizziness, confusion, tremors, malaise, headache, fatigue, and severe vomiting were all observed in volunteers within 10 hours after oral exposure to 1,500 mg DDT. All volunteers exposed to DDT orally had achieved almost complete recovery within 24 hours after exposure. Similar symptoms were reported in persons after accidental or intentional ingestion of DDT (Francone et al. 1952; Garrett 1947; Hsieh 1954; Mulhens 1946).

Only two studies explicitly evaluated neurotoxicity in humans following chronic exposure. There was no correlation between DDT exposure and neurological effects in workers whose estimated exposure, based on DDA excretion data, was approximately 14–42 mg/person/day (Ortelee 1958). Occupational exposure involved all possible routes of exposure, but most of the intake is considered to be from the oral route. Inhaled dusts are poorly absorbed because of size, but they are cleared by the mucociliary mechanisms and a fair portion is then ingested. None of the subjects had any evidence of hyperexcitability, and the results of the neurological examinations were normal. No neurological effects related to DDT were noted in volunteers who ingested 3.5 or 35 mg DDT/day (0.038–0.063 or 0.36–0.61 mg/kg/day) for
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12–18 months (Hayes et al. 1956). The subjects displayed no loss of coordination and there was no indication of tremors. Other tests (over 20) were negative and showed no peripheral neuropathy or central nervous system functional deficits. Background DDT levels in food of both controls and test subjects were 0.0021–0.0038 mg DDT/kg/day.

The nervous system appears to be one of the primary targets in animals after acute, subchronic, and chronic oral exposure to DDT. Acute oral exposure to high doses of DDT has been associated with DDT-induced tremors or myoclonus (abrupt, repeated involuntary contractions of skeletal muscles), hyperexcitability, and convulsions in several species. These effects have been observed in rats after single oral gavage doses of 50–600 mg DDT/kg/day (Henderson and Wooley 1969b; Herr and Tilson 1987; Herr et al. 1985; Hietanen and Vainio 1976; Hong et al. 1986; Hrdina and Singhal 1972; Hrdina et al. 1973; Hwang and Van Woert 1978; Philips and Gilman 1946; Pranzatelli and Tkach 1992; Pratt et al. 1986; Tilson et al. 1987). Mice receiving a single oral gavage dose of 160 mg DDT/kg had tremors (Hietanen and Vainio 1976), and single doses of 200–600 mg \( p,p' \)-DDT/kg/day induced convulsions (Matin et al. 1981). In guinea pigs and hamsters similarly dosed, no tremors were observed at 160 mg DDT/kg, but hind leg paralysis occurred in guinea pigs (Hietanen and Vainio 1976).

Acute oral exposure of animals to DDT has also been associated with increases in brain biogenic amine and neurotransmitter levels. Alterations in the metabolite 5-HIAA (5-hydroxy-indoleacetic acid), the degradation product of serotonin, have been reported to correlate with DDT-induced tremors; doses at 50 mg/kg/day or greater resulted in increases in the levels of 5-HIAA in the brain (Hong et al. 1986; Hrdina et al. 1973; Hudson et al. 1985; Hwang and Van Woert 1978; Tilson et al. 1986). Alterations in the levels of other neurotransmitters have been found. The neurotransmitter changes observed are consistent with one of the putative mechanisms for DDT toxicity; DDT is thought to influence membrane ion fluxes and consequently potentiate neurotransmitter release (see Section 2.5.2). Acetylcholine and norepinephrine decreased in rats after acute exposure to 400 mg/kg DDT (Hrdina et al. 1973). Also, aspartate and glutamine were increased in brain tissue of rats (Hong et al. 1986; Hudson et al. 1985; Tilson et al. 1986).

The effects of acute DDT exposures on adult learning and motor activity are discussed in 2.2.2.6 Developmental Effects, where they are compared to similar, but more pronounced, behavioral effects resulting from perinatal exposure.
Body tremors and hunched appearance were observed in female Osborne-Mendel rats after 26 weeks of treatment in the diet with approximately 16 mg technical DDT/kg/day in a 78-week study (NCI 1978). Similar findings were reported by Rossi et al. (1977) in female Wistar rats after 9 weeks of treatment with approximately 34 mg technical DDT/kg/day in the diet. Intermediate and acute exposure to DDT resulted in changes in brain lipid metabolism that affected total brain lipids and the relative brain lipid ratios in nonhuman primates. Rhesus monkeys exhibited a decrease in total brain lipids and the relative amount of cholesterol to phospholipid after oral exposure to 10 mg technical DDT/kg/day for 100 days or a single oral dose of 150 mg/kg/day (Sanyal et al. 1986). The results were more pronounced in the intermediate group than the acute group. Decreases in the levels of brain phospholipids and cholesterol may result in altered neuronal transmission (Sanyal et al. 1986). Lipids associated with the myelin sheath were not affected by DDT. Staggering, weakness, and loss of equilibrium were observed in monkeys treated for up to 14 weeks with 50 mg p,p’-DDT/kg/day, a dose level which was also lethal (Cranmer et al. 1972a). No such manifestations of toxicity were seen with a 5 mg/kg/day dose. Hunched appearance was reported in male rats after 8 weeks of treatment with approximately 59 mg p,p’-DDE/kg/day and in male mice after 22 weeks of treatment with approximately 27 mg p,p’-DDE/kg/day in 78-week duration studies (NCI 1978).

Hyperactivity and tremors were also reported in chronic studies in mice at doses up to 8.3 mg DDT/kg/day (Kashyap et al. 1977; Turusov et al. 1973). Even after a change of diet or a decrease in dose, the tremors persisted for several weeks. No clinical signs of neurotoxicity were observed in hamsters fed diets to provide doses up to 95 mg technical DDT or p,p’-DDE/kg/day for life (Rossi et al. 1983).

The highest NOAEL values and all LOAEL values from reliable studies for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1. Developmental neurological effects are plotted in the developmental section.

### 2.2.2.5 Reproductive Effects

No association between DDT maternal blood levels and miscarriage (Leoni et al. 1989) or premature rupture of fetal membranes was found in epidemiological investigations (Ron et al. 1988).

A difference in DDE blood levels between full-term and premature infants was reported (O'Leary et al. 1970a). Women who delivered early had infants with mean DDE blood levels of 19–22.1 ppb, while
women who delivered at full-term had infants with mean DDE blood levels of 4.9–6.1 ppb. Saxena et al. (1980, 1981), Wassermann et al. (1982), and Procianoy and Schvartsman (1981) reported that DDE levels were higher in maternal blood (ranging from 10.1 to 163.8 ppb) and in placental tissue (ranging from 31.2 to 83.6 ppb) of mothers having premature infants or who had spontaneously aborted compared to mothers who delivered full-term infants. Mothers with infants born at full term had 1.2–12.6 ppb DDE in their blood and 11.8 ppb in their placental tissue.

Levels of DDD in the maternal blood of women with premature infants or spontaneously aborted fetuses ranged from 10.1 to 65.5 ppb and placental tissue levels from 10.7 to 20.6 ppb (Saxena et al. 1980, 1981; Wassermann et al. 1982). Mothers with full-term infants had blood DDD levels ranging from 3.3 to 6.9 ppb and placental tissue concentrations of 4.9 ppb. However, Wassermann et al. (1982), Saxena et al. (1983), and O'Leary et al. (1970b) stated that although results suggest an association between DDT, DDE, and DDD levels and premature birth or spontaneously aborted fetuses, the relationship was not statistically significant.

An increase in chlorinated pesticide concentrations in the blood of premature and underweight full-term newborns was reported by Grasso et al. (1973). Trebicka-Kwiatkowska et al. (1971) reported a case of intrauterine fetal death in a woman who had been occupationally exposed to DDT and DDE. The concentrations of DDT and DDE in her placenta and blood were higher than those found in women who gave birth to healthy children.

A case-control study of women with endometriosis (n=86) and a matched control group of women without the condition (n=70) found no association between plasma concentration of DDT compounds and the occurrence of endometriosis (Lebel et al. 1998). No differences were observed between cases and controls in crude geometric mean total plasma DDT (DDT plus DDE) or in geometric mean total plasma DDT adjusted for age, body mass index, and symptoms indicating a need for laparoscopy. No differences were observed in crude geometric mean \( p,p' \)-DDE or \( p,p' \)-DDT concentrations in plasma between cases and controls.

An ecologic study evaluated the relationship between several factors, including the concentration of \( p,p' \)-DDE in tree bark as a measure of DDT contamination in the environment, and birth rate among countries or pregnancy rate among states in the United States (Cocco 1997). In both multivariate regression analyses, no relationship between DDE exposure (as measured by the environmental concentration) and response was observed.
Concentration of \( p,p' \)-DDE in human milk was inversely related to duration of lactation in women of Tlahualilo, Mexico, who had lactated previously, but not among women having their first lactation (Gladen and Rogan 1995). Median lactation duration declined from 7.5 months among women with lipid-adjusted DDE concentration of 0–2.5 ppm, to 3 months among women with \( \geq 12.5 \) ppm in their milk; the difference was statistically significant. Significantly elevated crude hazard ratios (defined by the authors as estimated ratios of the hazard of weaning relative to the 0–2.5 ppm group; hazard was defined as the instantaneous probability of weaning) were observed in groups with milk DDE levels \( \geq 7.5 \) ppm; hazard ratios adjusted for various determinant factors were elevated above unity in the group with milk DDE \( \geq 12.5 \) ppm. A similar inverse relationship between milk DDE and lactation duration was seen in women in the United States (Rogan et al. 1987). In contrast, no correlation was seen between DDE concentration in maternal milk fat and birth weights, head circumference, or neonatal jaundice, but the authors indicated that higher levels of DDE (\( \geq 4 \) ppm) in maternal milk fat were associated with hyporeflexia in infants (Rogan et al. 1986).

It has long been suspected that technical grade DDT has estrogen-like properties based on findings in wildlife exposed to the pesticide (Bishop et al. 1991; Guillette et al. 1994); results from studies in laboratory animals have left little doubt (Bitman and Cecil 1970; Clement and Okey 1972; Singhal et al. 1970; Welch et al. 1969). The estrogenic activity is largely due to the \( o,p' \)-isomer of DDT, which is present as a 15–21% contaminant of technical DDT (Metcalf 1995). For example, estrogenic effects on the uterus (increased weight and glycogen content) and premature vaginal opening were observed in immature rats given diets that provided doses of 100 mg/kg \( o,p' \)-DDT from days 23–30 of life suggesting an agonistic action; \( p,p' \)-DDT did not have estrogenic activity (Clement and Okey 1972). Also, Singhal et al. (1970) showed that injection of a single dose of 100 mg \( o,p' \)-DDT/kg to ovariectomized rats mimicked estrogens in increasing uterine weight, glycogen content, and the activities of several enzymes involved in glycolysis and the hexose monophosphate shunt pathway. Much of the research in this area has been conducted in experimental animals administered the test substance parenterally or, more recently, in \textit{in vitro} systems. Representative studies are discussed in Section 2.5.2 Mechanisms of Toxicity.

No spermatotoxic effects were observed in an acute screening test in rats given a single oral gavage dose of 100 mg \( p,p' \)-DDT/kg/day or five daily doses of 50 mg/kg/day (Linder et al. 1992). In juvenile male rats dosed by oral gavage on days 4 and 5 of life with 500 mg/kg/day or from day 4 to day 23 with 200 mg DDT/kg/day, a decrease in testis weight was observed (Krause et al. 1975). After two doses, significant decreases were seen at 34 days, and after repeated lower doses, decreases were significant at
days 18, 26, and 34. Treated males were mated with healthy females on days 60 and 90. The number of fetuses and implantations was decreased 30% at the 60-day mating but not at the 90-day mating of rats dosed on days 4 and 5. For rats receiving multiple doses, the decreases were 95 and 35% after mating at days 60 and 90, respectively. In adult male rats dosed with 200 mg DDT/kg every other day (oral gavage) for 2 weeks, serum testosterone levels were decreased (statistically significant) compared to controls, but serum levels of luteinizing hormone and follicle stimulating hormone were not significantly altered (Krause 1977). In the same study, testicular levels of testosterone were decreased, although not significantly, in adult male rats treated with 100 mg DDT/kg 3 times per week for 3 weeks, and no histologic effects on spermatogenesis were seen (Krause 1977). Oral gavage dosing of male mice at 6.25 mg/kg/day of \( p,p' \)-DDT for 28 days had no effect on testis weight (Orberg and Lundburg 1974). In a dominant lethal test in male rats with a single oral gavage dose of 100 mg/kg of \( p,p' \)-DDT, a clear genotoxic response was not reported, but the proportion of mated females with dead implants was somewhat increased.

The effect of DDT on fertility was examined in male and female rats fed diets providing an intake of 0.56 mg DDT/kg/day for 60 days before mating and continuing throughout gestation (Green 1969). A 75% depression of fertility was found, but there was no effect on litter size. The F₁ pups from these dams were completely infertile when mated. Jonsson et al. (1976) reported that dietary dosing of female rats with technical grade DDT for 36 weeks caused sterility at 7.5 mg/kg/day, and this was accompanied by a decrease in serum progesterone; 3.75 mg/kg/day had no effect on fertility. When 21-day-old female rats were fed diets to provide \( o,p' \)-DDT levels of 0.1–4.0 mg/kg/day for up to 14 weeks, no effects on age of vaginal opening were seen, and after mating, there were no effects on litter size or pup weight at birth or weaning (Wrenn et al. 1971). No adverse reproductive effects were reported in rats treated with 10 mg \( p,p' \)-DDE/kg/day for 5 weeks before mating and during gestation and lactation (Kornbrust et al. 1986). Reproductive parameters examined included percent sperm positive, percent pregnant, gestation length, litter size, sex ratio of pups, and milk production and composition. Significantly decreased fertility was observed in female mice fed technical grade DDT for 60 days at a dose level of 51.4 mg/kg/day (Bernard and Gaertner 1964). Female mice exposed to 1.67 mg \( p,p' \)-DDT/kg/day for periods that included premating and gestation had decreased number of implanted ova, lengthening of the estrus cycle, decreased corpora lutea, and decreased implants (Lundberg 1973, 1974). Administration of up to approximately 3.4 mg technical DDT/kg/day in the diet to mice for 86 days, including mating, resulted in no adverse reproductive effects, but treated mice had larger litter sizes relative to controls (Loudoux et al. 1977). Treatment of male and female mice for 120 days with approximately 1.3 mg technical DDT/kg/day (30 days before mating plus 90 additional days) had no effect on fertility, fecundity, or litter
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size (Ware and Good 1967). Treatment of pregnant rabbits with $10 \text{ mg } p,p^\prime$-DDT by gavage on
days 7–9 of gestation resulted in premature deliveries and a significant increase in the number of
resorptions (Hart et al. 1971, 1972); however, no such effects were seen after treatment on gestation
days 21–23 (Hart et al. 1972). Neither fertility nor pre- or postimplantation embryonic losses were
significantly affected in female rabbits administered 3 mg technical DDT/kg (only dose level tested)
3 days/week for 12–15 weeks before artificial insemination and throughout gestation (Seiler et al. 1994).
However, this exposure regime significantly reduced ovulation rate, but did not cause treatment-related
histopathological alterations in the ovarian cortex, corpora lutea, or uterus (Lindenau et al. 1994).

In recent years, evidence has been presented that the persistent DDT metabolite, $p,p^\prime$-DDE, is an
androgen receptor antagonist; this evidence is discussed in 2.5.2 Mechanisms of Toxicity. A number of
experiments have investigated in vivo anti-androgenic effects. Kelce et al. (1995) conducted a series of
experiments in male rats administered $p,p^\prime$-DDE at different ages. Effects from prenatal plus juvenile
exposure are discussed in 2.2.2.6 Developmental Effects. Treatment of adult male rats (120 days old)
with 200 mg $p,p^\prime$-DDE/kg/day for 4 days significantly reduced androgen-dependent seminal vesicle and
ventral prostate weight relative to controls (Kelce et al. 1995). These rats had been castrated and
implanted with testosterone-containing Silastic capsules to maintain a constant serum testosterone level.
Prostates from treated rats had a 13-fold increase in androgen-repressed testosterone-repressed prostatic
message 2 (TRPM-2) messenger RNA levels and a 35% decline in androgen-induced prostate binding
subunit 3 (C3) mRNA levels relative to control rats (Kelce et al. 1995). These findings, coupled with
results from in vitro studies (Section 2.5.2) on receptor (androgen and estrogen) binding, suggested that
the antagonistic effects of DDT on the male reproductive system are mediated by $p,p^\prime$-DDE through
competitive inhibition of binding of androgens to the androgen receptor (AR) and subsequent inhibition
of transcriptional activity. In a subsequent study, Kelce et al. (1997) observed a significant reduction in
immunohistochemical staining of androgen receptor in epididymal nuclei of adult rats given 200 mg
$p,p^\prime$-DDE/kg/day for 5 days as well as a significant increase in TRPM-2 and a decrease in testosterone-
induced C3 (third subunit of prostatein or prostate specific binding protein mRNA). Kelce et al. (1997)
also reported a significantly reduced seminal vesicle and ventral prostate weight in the rats.

Reproductive studies of chronic dietary DDT exposure or multigeneration studies have not generally
indicated reproductive toxicity. However, the doses used were sufficiently low so that tremors,
convulsions, and death would not be a confounding factor. Keplinger et al. (1970) conducted a six-
generation dietary study in mice with two matings per generation; mice in all generations were mated at
4 months of age. No effects were observed at 3.2 mg/kg/day; 13 mg/kg/day caused decreased fertility
evidenced by decreased viability and lactation indices, and the 32 mg technical grade DDT/kg/day dose caused frank toxic effects and was discontinued after three generations. No adverse effects on reproduction were reported after 15 months of exposure of field mice to technical grade DDT at dietary levels providing up to 2.4 mg/kg/day (Wolfe et al. 1979). No adverse effects on reproduction were observed in rats fed up to 18.6 mg technical grade DDT/kg/day in the diet for 2 generations (Ottoboni 1969), 1.25 mg/kg/day for 3 generations (Treon et al. 1954), or 1 mg/kg/day for 11 breedings (Ottoboni 1972). Duby et al. (1971) found no reproductive effects in two successive generations of rats fed technical grade DDT (0.75 mg/kg/day), \( p,p' \)-DDT (0.6 mg/kg/day) or \( o,p' \)-DDT (0.15 mg/kg/day). A three-generation study was conducted in Beagle dogs given daily oral doses of 0, 5, or 10 mg technical grade DDT from weaning to termination (Ottoboni et al. 1977); all dogs were sacrificed by 28 months of age and all females were mated at the first estrus only. The parental generation consisted of 4 males and 7–10 females/group. In the F\(_1\) and F\(_2\) generations, 8–19 females/dose group were mated with males of the same generation. The only effect noted was a reduction in the age at first estrus in females of the F\(_2\) generation, but it is doubtful if this is related to DDT administration. A total of 650 pups were produced.

No effects were observed on length of gestation, fertility, litter size, viability, gestation, or lactation indices. In another study in dogs, Deichman et al. (1971) reported that daily administration of \( p,p' \)-DDT by capsule for 14 months at a level of 12 mg/kg/day caused subnormal reproduction in dogs. However, this was a one-generation study with several chlorinated pesticides, only one dose of DDT (without aldrin) was administered to four females, and these females were mated to males that had been fed DDT plus aldrin. In addition, the age of the dogs at initiation of study was not provided, and mating in some dogs took place up to 19 months after dosing was discontinued. No correlation between fertility and levels of DDT in adipose tissue at time of mating could be made, and no clear conclusions on the effect of DDT on reproduction can be determined.

In the 78-week chronic bioassay conducted by NCI (1978), no treatment-related adverse effects on the ovaries, uterus, mammary gland, or prostate were observed in Osborne-Mendel rats treated in the diet with up to 45 mg technical DDT/kg/day, 59 mg \( p,p' \)-DDE/kg/day, or 231 mg technical DDD/kg/day. The same findings were reported for B6C3F\(_1\) mice treated with up to 30.2 mg technical DDT/kg/day, 49 mg \( p,p' \)-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978). Reproductive function was not evaluated in this study.

The highest NOAEL values and all LOAEL values from reliable studies for reproductive effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.
2.2.2.6 Developmental Effects

DDT and its metabolites have been found in human blood, placental tissue, organs from stillborns, and umbilical cord blood following pregnancy. Levels of DDT, DDE, and DDD were higher in maternal blood and in placental tissue in mothers who gave birth to premature infants or who spontaneously aborted fetuses compared to mothers who gave birth to full-term infants (Procianoy and Schvartsman 1981; Saxena et al. 1980, 1981, 1983; Wassermann et al. 1982). However, other chemicals, such as polychlorinated biphenyls (PCBs) and other chlorinated pesticides, were also increased in the maternal blood of these subjects, and the specific contribution (if any) of DDT, DDE, or DDD could not be determined. A difference in DDE blood levels between full-term and premature infants was reported by O’Leary et al. (1970a). Women who delivered early had infants with mean DDE blood levels of 19–22.1 ppb, while women who delivered at full-term had infants with mean DDE blood levels of 4.9–6.1 ppb. No association was seen in a more recent case-control study that compared maternal serum DDE between Mount Sinai Medical Center patients who had spontaneously delivered preterm (n=20) and a group of control patients who had delivered at term (n=20), and were matched for age, race/ethnicity, and prepregnancy body mass index (Berkowitz et al. 1996). No difference in median serum \( p,p' \)-DDE (unadjusted for lipid content) was observed between cases and controls (p=0.51; Wilcoxon signed rank test). Median control serum DDE was significantly higher than serum DDE in a subgroup of cases who were preterm because of premature labor (n=8), but was no different from a subgroup of cases who were preterm because of premature rupture of membranes.

In animals, DDT produces embryotoxicity and fetotoxicity, but not teratogenicity. Estrogen-like effects on the developing reproductive system have been reported. The \( o,p' \)-isomers of DDT and DDE have greater estrogen-like effects than other isomers and when administered subcutaneously to rats in the first few days of life can seriously affect the development and maturation of the reproductive system (see 2.6 Relevance to Public Health). Developmental effects have been observed in animals after acute oral exposure to DDT during gestation or in the early perinatal development period; the seriousness of these effects is dependent on the isomeric form, the dose, and the timing of exposure. Exposure during early gestation resulted in a 25% decrease in fetal body weights and in significant decreases in fetal brain and kidney weights in the offspring of pregnant rabbits given oral gavage doses of 1 mg DDT/kg/day on gestation days 4–7 (Fabro et al. 1984). Offspring from rabbit dams orally exposed to a dose level of \$10\text{ mg } p,p'\text{-DDT/kg/day by gavage on days 7–9 of gestation showed a significant reduction in weight on day 28 (Hart et al. 1971, 1972). However, treatment late in gestation (days 21, 22, and 23) did not induce such an effect (Hart et al. 1972). Gellert and Heinrichs (1975) exposed pregnant rats orally to 28 mg...}
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o,p'-DDT, p,p'-DDT, o,p'-DDE, or o,p'-DDD/kg/day on days 15–19 of gestation. No significant effects on body weight, weight of the ovaries and pituitary, estrous cycle, or vaginal opening in the offspring were noted with the exception of a small but significant delay (2 days) in vaginal opening with the o,p'-DDD isomer. The p,p'-isomer is most prevalent in the environment, accounting for approximately 85% of the total amount of DDT, DDE, or DDD found; also, technical grade DDT contains between 65–80% p,p'-DDT, between 15–21% o,p'-isomer, and up to 4% p,p'-DDD (Metcalf 1995).

As previously mentioned in Section 2.2.2.5 Reproductive Effects, the DDT metabolite, p,p'-DDE, has been found to have antiandrogenic activity (Kelce et al. 1995, 1997). In vivo anti-androgenic effects on adult rats are discussed in that section. Kelce and co-workers showed that male pups from Long-Evans dams exposed during gestation days 14–18 to 100 mg p,p'-DDE/kg/day and then exposed indirectly to maternally stored p,p'-DDE via breast milk had significantly reduced anogenital distance at birth and retained thoracic nipples on postnatal day 13. Female rats normally have a shorter anogenital distance than males. Treatment of weanling male rats from either day 21 or 25 (specific day unclear in text) until day 57 of age with 100 mg p,p'-DDE/kg/day resulted in a statistically significant delayed onset of puberty (measured by the age of preputial separation) by 5 days. The fact that serum levels of testosterone were not reduced suggested that the antiandrogenic effects were not confounded by the reported ability of DDT-related chemicals to increase steroid metabolism. Other gestational exposure studies have confirmed these findings. For example, anogenital distance was not affected in male Sprague-Dawley rats on postnatal day 2 after treating the dams with up to 100 mg p,p'-DDE/kg on gestation days 14–18, but was significantly reduced in similarly exposed Long-Evans pups (You et al. 1998). A 10 mg/kg dose to the dams was without effect in the Long-Evans pups. Anogenital distance was not affected in female pups from either strain. Treatment of the dams with 10 mg p,p'-DDE/kg resulted in retention of thoracic nipples in Sprague-Dawley pups, but only the higher dose (100 mg/kg) had this effect in Long-Evans pups. Treatment with p,p'-DDE also resulted in an apparent reduction of androgen receptor expression in male sex organs from mainly high-dose Sprague-Dawley pups, as shown by immunochemical staining; however, there were no changes in androgen receptor steady state mRNA levels in the high-dose Sprague-Dawley rats, but mRNA were increased 2-fold in the high-dose Long-Evans rats. Exposure of the pups to p,p'-DDE during gestation and lactation had no significant effect on the onset of puberty in either strain.

A similar study in Holtzman rats exposed during gestation days 14–18 to doses between 1 and 200 mg p,p'-DDE/kg (offspring were exposed to p,p'-DDE in utero and via breast milk) found reduced anogenital distance in males on postnatal day 1 and reduced relative ventral prostate weight on postnatal day 21 at 50 mg p,p'-DDE/kg and higher, but not at 10 mg p,p'-DDE/kg (Loeffler and Peterson 1999).
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postnatal day 4, anogenital distance was reduced only at 200 mg/kg/day. Doses up to 100 mg/kg/day to the dams had no effect on the onset of puberty, but 200 mg/kg/day did significantly delay puberty in males by less than 2 days. Androgen receptor staining in the ventral prostate was also reduced on postnatal day 21 at 100 mg/kg/day (the only dose tested). Serum levels of testosterone or 3α-diol androgens were not significantly altered at any time. mRNA levels of androgen regulated genes from both ventral and dorsolateral prostate were not significantly changed in treated animals on postnatal day 21. This study also reported that at the 100 mg/kg dose level, cauda epididymal sperm number was reduced by 17% on postnatal day 63 relative to controls. No measurements of DDE body burden were made in the 200 mg/kg/day offspring postnatally, so it is difficult to determine whether effects on puberty were due to the previous gestational plus lactational exposures or directly due to the effects of DDE present near the time of puberty.

There are limited data suggesting that if mice exposed to DDT in utero and during lactation are further exposed to DDT postnatally, responses in both immunological plaque forming assays and lymphoproliferative assays are reduced (Rehana and Rao 1992). The results of this study are difficult to interpret because of experimental design issues, including the lack of a comparison unexposed group and ambiguity about whether statistical testing was done.

Administration of DDT in utero or to neonates during sensitive periods in nervous system development has caused behavioral and neurochemical changes in adult mice (Craig and Ogilvie 1974; Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996; vom Saal et al. 1995). Offspring of dams given 34.3 mg/kg/day DDT by oral gavage during gestation and lactation displayed impaired learning and decreased memory function in a maze when tested 1 and 2 months after weaning (Craig and Ogilvie 1974). However, the dose was sufficiently high in this study to cause 39% mortality in the pups before weaning.

Ten-day-old mice treated once with 0.5 mg technical DDT/kg/day demonstrated behavioral changes when tested at 4 months of age (Eriksson et al. 1990a, 1990b). The test entailed placing animals in a new cage with infrared motion detecting beams for 1 hour. Locomotion (horizontal movement), rearing (vertical movement), and total activity (vibration, tremors, grooming, movement) were scored and summed for each 20-minute period. Initially, motor activity was fairly comparable between DDT-treated mice and controls; locomotion and activity were similar, although rearing was increased. During the last 40 minutes in the box, the DDT-treated animals had significantly more locomotion, rearing, and activity than the controls. When control mice were placed in a new environment, such as the test cage, they
initially increased their activity as they explored. Eventually, this exploratory activity decreased as they become familiar with their new environment; this phenomenon is known as habituation. Thus, the authors concluded that perinatal DDT exposure interferes with habituation, which is considered a simple, nonassociative learning process. The neurobehavioral effects in the 4-month-old mice only appeared after dosing at 10 days and not after similar dosing at day 3 or 19 of age. The induction period was limited to a peak in the rate of brain development and development of muscarinic cholinergic receptors (Ericksson et al. 1992). Since this behavioral assay used motor exploration as the end point, an alternate interpretation of the observed results is that the DDT directly affected neural regulation of activity rather than learning; however, a problem with appropriate control of motor behavior would also be a functional deficit of concern. Hyperactivity has been observed in DDT-treated adult mice (Kashyap et al. 1977; Rossi 1977; Turusov et al. 1973).

One month after behavioral testing, the potassium-evoked release of acetylcholine from cortical slices was significantly increased in treated mice compared to controls. This is consistent with the well-characterized effect of DDT in slowing the closure of sodium channels and thus causing general central nervous system stimulation and neurotransmitter release. Apparently, behavioral effects seen in adult mice represented a persistent neurological change since no residual DDT from their neonatal exposure remained in the brain (Eriksson et al. 1990b). Radiolabeled DDT was found in the brain at 1 and 7 days but not at 30 days following a single oral dose of 0.5 mg DDT/kg to 10-day-old mice. The classification of this effect as developmental, rather than an immediate effect of current DDT body burden, hinges on the apparent clearance of DDT before the behavioral testing.

In parallel experiments, neurochemical changes were also observed shortly after 10-day-old mice were treated with DDT. However, all of these specific neurochemical changes did not persist into adulthood. A single low dose of DDT (0.5 mg/kg) administered orally to 10-day-old (preweaning) mice affected the muscarinic cholinergic receptors in the brain. A significant increase in the density of specific muscarinic receptors was observed in the cerebral cortex, but not the hippocampus, at 7 days postexposure, but was not evident as early as 24 hours postexposure (Eriksson and Nordberg 1986). Furthermore, a significant decrease in the percentage of muscarinic high-affinity binding sites and a corresponding increase in the percentage of muscarinic low-affinity binding sites were measured, indicating that most of the increased binding could be attributed to low affinity sites. According to the study authors, the low-affinity muscarinic binding sites are thought to correspond to the M1 receptors in the cerebral cortex, which are postulated to be associated with neuronal excitation (McKinney and Richelson 1984). The persistence of these observed neurochemical changes in muscarinic receptors in the cerebral cortex was also evaluated.
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(Eriksson et al. 1990b). The density of the muscarinic receptors in the cerebral cortex, hippocampus, and striatum of the 3-month-old NMRI mice that had been given a single dose of 0.5 mg DDT/kg at 10 days of age was determined. The study authors reported a tendency towards a decrease in the amount of specific binding in the cerebral cortex, but no significant changes in the hippocampus and striatum. No significant changes were noted in choline acetyltransferase activity in the cerebral cortex, hippocampus, or striatum. However, significant (p<0.01) decreases in cerebral cortex muscarinic receptors at 4, 5, and 7 months of age were seen in similar later studies from the same group of investigators (Eriksson et al. 1992, 1993; Johansson et al. 1995, 1996). Tests of spontaneous motor activity conducted at the ages of 5 and 7 months old revealed that mice treated perinatally at the age of 10 days with DDT still exhibited hyperactive behavior relative to controls (Johansson et al. 1995, 1996). Nicotinic cholinergic receptor density was not significantly altered in 5- or 7-month-old mice treated with DDT at the age of 10 days. In these more recent studies, Johansson et al. (1995, 1996) also compared the motor responses to bioallethrin (a type I pyrethroid insecticide) and paraoxon in mice treated with and without DDT perinatally. From the graphic presentation of the results, it appears that pretreatment with DDT altered (increase or decrease) some of the responses attributed to paraoxon alone, but the results with bioallethrin were much less clear.

Behavioral effects have also been observed in animals exposed as adults. Inhibition of nonassociative learning processes (habituation response) occurred in adult rats acutely exposed to DDT (Sobotka 1971). Open field activity was assessed in rats, and activity (crossing squares on a checkered board) was measured over a 5-minute period; the normal response is increased activity for the first 2 minutes and decreased activity in the last 2 minutes (e.g., habituation). This "habituation" response was significantly affected (continued activity) in adult rats when tested 24 hours after administration of a single dose of 25 mg/DDT/kg but not at the lower doses tested (1 and 10 mg DDT/kg). The open field test used by Sobotka was not as sensitive a test of habituation as the tests on the Eriksson studies reviewed above. No differences in problem solving, locomotion speed, or reaction to stress were found between untreated rats and rats given oral doses of DDT up to 30 mg/kg/day (Khairy 1959). However, the scores for the pattern of locomotion significantly increased with dose (Khairy 1959). These doses are approximately 50 times that administered to neonates in the Eriksson studies.

A different behavioral response, the rate of urine marking in a novel territory, was examined in a study by vom Saal et al. (1995). Pregnant mice were administered o,p'-DDT by gavage in doses ranging from approximately 0.018 to 91 mg/kg/day on gestation days 11–17. Behavioral testing of male mice was conducted at the age of 70 days. Exposure to $1.82 mg/kg/day resulted in a significant increase in the
number of urine marks deposited by the mice during a 1-hour test in a novel environment. The authors (vom Saal et al. 1995) stated that since marking a territory is a central feature of the reproductive strategy of male mice, alteration of this behavior could markedly impact the social structure of the species.

Intermediate-duration oral exposure to DDT in animals has been shown to produce developmental effects such as infertility, mortality, and slow development in offspring of exposed dams (Clement and Okey 1974; Craig and Ogilvie 1974; Deichmann and Keplinger 1966). Exposure throughout gestation and lactation is more fetotoxic in rats than exposure only in gestation. Clement and Okey (1974) exposed pregnant rats to 1.7, 16.8, or 42.1 mg \( p,p' \)-DDT/kg/day for an unspecified period before mating and during gestation and/or lactation. An increase in mortality of pups exposed perinatally via dams receiving 42.1 mg \( p,p' \)-DDT/kg/day was reported, along with a decrease in growth of the pups after exposure via nursing from dams receiving 16.8 or 42.1 mg \( p,p' \)-DDT/kg/day or 84 mg \( o,p' \)-DDT/kg/day (Clement and Okey 1974). In mice exposed from mothers receiving 34.3 mg/kg/day technical grade DDT, preweaning mortality was observed in 10% of the neonates exposed to DDT prenatally and nursed on unexposed or "foster" mothers, while 39% of the neonates exposed perinatally (during gestation and through lactation) died before weaning (Craig and Ogilvie 1974). In addition, mice exposed perinatally subsequently showed learning impairment and decreased memory function in the maze test (Craig and Ogilvie 1974).

Developmental effects, including preweaning mortality and premature puberty, were reported in animals in multigeneration studies. An increase in preweaning mortality was observed in the offspring of mice chronically exposed to 41.3 mg technical or \( p,p' \)-DDT/kg/day (Tomatis et al. 1972; Turusov et al. 1973). Del Pup et al. (1978) found a decrease in 30-day survival of neonatal mice after exposing successive generations of dams to 16.5 mg DDT/kg/day in the diet for a total of 70 weeks. Increases in abortions, stillbirths, and pup mortality were reported in mice exposed to 1.3–6.5 mg DDT/kg/day in a multigeneration study; however, most of the females in the 6.5-mg/kg group died before delivery (Shabad et al. 1973). Green (1969) reported that there was an increase in the number of resorptions in rats exposed to 0.56 mg DDT/kg/day and that no litters were produced by the second-generation animals in a multigeneration study. However, it is unclear from the study whether females were mated to exposed males or to untreated males. Treon et al. (1954) conducted a multigeneration study in which dams were fed 0.125–1.25 mg DDT/kg/day throughout gestation and lactation. No reductions in litter size were noted. Changes in preweaning mortality were reported but were not considered to be dose related. Other developmental aspects evaluated were negative. No conclusions concerning the developmental effects of DDT could be drawn from the Treon et al. study.
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In a multigeneration study, Ottoboni et al. (1977) reported an increase in the incidence of premature puberty that increased with dose and with each consecutive generation among female dogs (4–19 dogs per group) dosed with 1, 5, or 10 mg \( p,p' \)-DDT/kg/day. However, the increase was significant only in the two high-dose groups when all generations were combined. A significant increase in constricting rings of the tail was seen in the offspring of rats fed 18.6 mg DDT/kg/day through two generations (Ottoboni 1969).

The highest NOAEL values and all LOAEL values from reliable studies for developmental effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1. Based on the studies by Eriksson and Nordberg (1986) and Eriksson et al. (1990a, 1990b), an acute oral MRL of 0.0005 mg/kg/day was calculated as described in the footnote in Table 2-1 and in Section 2.6.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to DDT, DDE, or DDD alone. In animals, the results depend upon the dose, route of administration, and species sensitivity.

In a dominant lethal assay, treatment of male rats with a single dose of 100 mg \( p,p' \)-DDT/kg resulted in a statistically significant increase in the proportion of females with one or more dead implantations only in animals mated during the post-meiotic stage of spermatogenesis (Palmer et al. 1973). In a dominant lethal assay in mice, DDT was administered orally to male mice at 150 mg/kg/day for 2 days (acute), or 100 mg DDT/kg twice weekly for 10 weeks (intermediate); the final dose was given 24 hours before sequential mating began (Clark 1974). Significant increases occurred in the number of dead implants per female. Acute doses resulted in maximum sensitivity in the induction of dominant lethal effects in week 5 and chronic doses in week 2, with continued increases above control through week 6. Repeated dosing caused significant reductions in testes weight, sperm viability, and a reduction of cell numbers in all stages of spermatogenesis. With acute treatment, the meiotic stage of spermatogenesis appeared to be the most sensitive. Acute treatment produced a significantly increased frequency of chromosome breakage, univalents, and stickiness in spermatocytes.

Rats treated orally (by gavage) with DDT in single doses of 50–100 mg/kg or daily doses of 20–80 mg/kg/day for 5 days did not show a dose-related increase in percent of chromosomal aberrations over the solvent control (Legator et al. 1973). DDE, when administered in a single oral dose to male mice at the rate of 50 mg/kg, did not inhibit testicular DNA synthesis (Seiler 1977).
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Administration of up to 50 mg $p,p'$-DDT/kg by gavage to rabbits on gestation days 7–9 did not affect chromosomal number distribution or the percentage of aberrations compared with controls (Hart et al. 1972). In addition, the distribution of chromosomes in liver samples from fetuses of DDT-treated rabbits and the percentage of chromosomal aberrations in these fetuses did not differ from controls (Hart et al. 1972).

Other genotoxicity studies (in vitro) are discussed in Section 2.6.

2.2.2.8 Cancer

Studies of humans exposed to DDT have not definitively established an association between DDT exposure and the development of cancer. Some positive epidemiological evidence of an association has been reported for breast and pancreatic cancers. However, the evidence for a positive relation of breast cancer with DDT exposure is balanced by equally strong evidence that no association exists, and the pancreatic cancer studies are limited by very small numbers of cases which could lead to statistically spurious positive results. No association was found between human DDT exposure and Hodgkin’s disease, non-Hodgkin’s lymphoma, multiple myeloma, prostate and testicular cancers, or endometrial cancer. Many of these studies have several confounding factors such as exposure to multiple pesticides, inadequate follow-up times, and uncertain exposure concentrations. The human cancer epidemiology database is extensive, and the studies are presented below in the following order: breast cancer, pancreatic cancer, Hodgkin’s disease and non-Hodgkin’s lymphoma, multiple myeloma, prostate and testicular cancer, endometrial cancer, and the occurrence of any cancer.

Human Studies

Breast Cancer. Numerous epidemiological studies have investigated the association between breast cancer and levels of DDT and DDT-derived compounds in various tissues in humans. Some studies suggest a positive association (Dewailly et al. 1994; Falck et al. 1992; Gütes et al. 1998; Wasserman et al. 1976; Westin and Richter 1990; Wolff et al. 1993), while others do not support such an association (Aschengrau et al. 1998; Dorgan et al. 1999; Helzlsoer et al. 1999; Høyer et al. 1998; Hunter et al. 1997; Krieger et al. 1994; Liljegren et al. 1998; Lopez-Carrillo et al. 1997; Moysich et al. 1998; Mussalo-Rauhamaa et al. 1990; Schecter et al. 1997; Unger et al. 1984; van’t Veer et al. 1997). The root of the uncertainty appears to be the complex interactions between environmental factors such as past and current exposure patterns, physiological state with respect to menopause or body growth, dietary habits, body
burden and disposition, and concurrent exposure to other estrogenic and antiestrogenic organochlorines. In addition, numerous known determinant factors for breast cancer, such as age, breast-feeding, and familial breast cancer, and doubtless some unknown factors, potentially confound analyses. Reviews of the relation between DDT exposure and breast cancer have concluded (1) that studies showing a positive relationship were limited in several ways, including small sample size and failure to adjust analyses for known breast cancer risk factors, and (2) that the ecologic and epidemiologic evidence generally do not support the hypothesis of a causal association between breast cancer and DDT exposure (Adami et al. 1995; Ahlborg et al. 1995; Safe and Zacharewski 1997). Some investigations appear to have addressed some of these concerns by either statistically adjusting the analysis for known risk factors or focusing their analyses on subsets of breast cancer patients.

As in all epidemiological studies, the primary issue in studies of DDT and breast cancer is relating exposures to the occurrence of cancer. Nearly all of the breast cancer studies in humans have characterized DDT exposure in terms of some measurement indicative of the body burden of DDT/DDE/DDD measured in various tissues; one exception examined the relationship between occupational exposure to DDT and the occurrence of breast cancer (Aschengrau et al. 1998). There are several methods for assessing current DDT body burdens, which represent both current and past exposures. Most DDT is stored in the fat, so the most accurate method of assessing body burden is measuring levels in adipose tissue samples. Procedures for obtaining adipose tissue samples are relatively invasive, however, and unless samples are available incidentally from biopsies or surgical procedures, such samples are difficult to obtain. Alternatively, serum DDT/DDD/DDE levels can be measured; however, since DDT/DDD/DDE are fat soluble, the serum levels may vary with the fat content of the blood (McKinney et al. 1984). Variability in serum DDT/DDE/DDD that is attributable to variability in serum lipids can be accounted for by using lipid-adjusted serum DDT/DDE/DDD levels. Several studies that evaluated for an association between DDT exposure and breast cancer (Dorgan et al. 1999; Helzlouer et al. 1999; Høyer et al. 1998; Hunter et al. 1997; Lopez-Carrillo et al. 1997; Moysich et al. 1998) have adjusted blood serum levels on the basis of lipid content. The studies discussed below are varied in their methods of the assessment of DDT body burdens.

The second issue related to appropriate exposure assessment in human breast cancer studies pertains to the timing of the exposure assessment relative to the etiology of cancer. Cancer is a chronic disease and can have a latency time of 15–20 years after initiation. Theoretically, DDT could contribute to breast cancer either by being a complete carcinogen, an initiator, or a promoter. Thus, for DDT to cause or contribute to breast cancer, exposure needs to occur at a time substantially before the time of diagnosis of
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the cancer. A common methodological approach in many of the cancer studies reported below has been
to assess DDT body burdens at or shortly before the time of breast cancer diagnosis. This method is
limited by the assumption that a “snapshot” of DDT body burden obtained near the time of diagnosis
represents DDT exposures at the time of cancer initiation or early promotion, perhaps as much as 15–20
years earlier. This assumption could be in error for several reasons. First, a large amount of the DDT
body burden measured could represent more recent exposures, although in developed countries where
DDT use is banned, average exposures in food have presumably declined with time (EPA 1980a; Gartrell
et al. 1986b; Lauenstein 1995; Schmitt et al. 1990). Second, the presence of the cancer itself or other
conditions associated with the cancer might influence DDT metabolism, excretion, or the use of fat stores
and the mobilization of fat-stored DDT/DDE/DDD to the blood, and hence, the concentration of
DDT/DDE/DDD in blood, fat, and other tissues. Prospective studies provide the most appropriate data
for characterizing historical exposures and relating those exposures to the subsequent diagnosis of cancer.
The three most credible studies of DDT and breast cancer incidence (Helzlsouer et al. 1999; Høyer et al.
1998; Kreiger et al. 1994) have been prospective, using blood samples obtained a substantial number of
years prior to the diagnosis of cancer. Each of these studies concluded that DDT and/or DDE exposures,
as measured by blood burden at a point in time, were not causally associated with the occurrence of breast
cancer.

The strongest evidence of a positive association between breast cancer and exposure to DDT and DDT-
related compounds is provided in a case-control analysis nested within a prospective study in which blood
samples of New York City women attending a mammography clinic were collected between 1985 and
1991 (Wolff et al. 1993). Serum DDE (not lipid-corrected) was determined on the archived blood
samples of women who were diagnosed with breast cancer within 6 months of entering the study (n=58)
and in matched, cancer-free control women from the same cohort (n=171). Controls were matched to
case patients with respect to menopausal status, age at entry into the study, number and dates of blood
donations, and day of menstrual cycle (if premenopausal) at time of first blood drawing. Mean serum
DDE was significantly higher in case patients (11.0 ng/mL) than in control subjects (7.7 ng/mL)
(p=0.031). The adjusted odds ratio for breast cancer in the highest quintile of serum DDE was
significantly elevated (OR=3.68; 95% CI=1.01 to 13.50), using the lowest quintile as the referent group.
A significant positive trend was identified between the odds ratio for breast cancer and increasing quintile
(p=0.035). A significant positive trend was also obtained for the relation between the adjusted odds ratio
and serum DDE when serum DDE was evaluated as a continuous variable using conditional multiple
logistic regression (p=0.0037). The odds ratios were adjusted for first-degree family history of breast
cancer, lifetime months of lactation, and age at first full-term pregnancy; other potential confounders,
including age at menarche, history of benign breast disease, history of tobacco and alcohol use, and race were found not to affect the outcome in preliminary evaluations. This study supports a positive relation between serum DDE and breast cancer, in spite of a short follow-up period and a relatively small number of subjects.

Several additional studies support the Wolff et al. (1993) findings by associating DDT/DDE/DDD body burden with breast cancer. \(p,p'\)-DDE and \(p,p'\)-DDT levels in breast adipose tissue were significantly elevated in Hartford, Connecticut patients with breast cancer (n=20) in relation to age-matched controls (n=20) who had benign breast disease (Falck et al. 1992); samples were obtained from biopsy or mastectomy tissue, near the time of diagnosis in 1987. Women from Quebec City with estrogen receptor (ER)-positive breast cancer cells (n=9) had significantly higher \(p,p'\)-DDE levels in breast adipose tissue (p=0.01) and plasma (p=0.052) than in controls with benign breast disease (n=17) near the time of diagnosis during 1991–1992 (Dewailly et al. 1994); the difference was not statistically significant for women with ER-negative breast cancer cells. Wasserman et al. (1976) found that the concentrations of \(p,p'\)-DDT and \(o,o'\)-DDD in malignant breast tissue of hospitalized Brazilian women collected after diagnosis (dates not reported) were significantly greater than those found in adjacent “normal” breast tissue in the same women (p<0.01 and p<0.1, respectively). Concentrations of \(p,p'\)-DDE, \(p,p'\)-DDD, \(o,o'\)-DDT, and \(o,o'\)-DDE were also elevated in malignant breast tissue over adjacent normal tissue, but the differences were not statistically significant. A similar comparison was performed in a 1993–1994 case-control study of German women, in which the age-adjusted geometric mean concentration of \(p,p'\)-DDE in malignant breast tissue of recently mastectomized women (n=45) was found to be 62% higher (p=0.017) than the age-adjusted geometric mean concentration of \(p,p'\)-DDE in benign breast tissue in the control group (n=20); however, no statistically significant difference was found with respect to \(p,p'\)-DDT concentrations (Güttes et al. 1998).

In contrast to the above findings, Liljegren et al. (1998), found that the DDE concentration in breast tissue fat of women with malignant breast cancer (n=43) was no different from the DDE concentration in breast adipose tissue of women with benign breast disease (n=35), whether or not the study group was divided into pre- and postmenopause subgroups; samples were collected during surgical procedures in 1993-1995, after diagnosis. Odds ratio analysis of the entire study group, the postmenopausal subgroup, and the ER-positive subgroup revealed no association between breast cancer malignancy and tissue DDE concentration. Similarly, Unger et al. (1984) found that there was no difference in mean DDE levels in biopsied extractable breast fat tissue between newly diagnosed breast cancer patients and noncancer patients; the dates of biopsies were not provided.
Four prospective studies found no association between serum DDT/DDE/DDD and breast cancer incidence in developed countries using blood samples collected prior to the diagnosis of breast cancer, and in three instances (Helzlsouer et al. 1999; Høyer et al. 1998; Krieger et al. 1994), substantially prior to diagnosis. Cholesterol-adjusted plasma DDE was determined in blood samples collected during 1989–1990 in a prospective study of the health of 121,700 married nurses in the United States (Hunter et al. 1997). Historical plasma DDE was no different between women who developed breast cancer before June, 1992 (n=236) and pair-wise matched control women who did not subsequently develop breast cancer. The lack of an association was also observed within strata of menopausal status, age, age at menarche, age at birth of first child, number of children, and history of lactation. The negative findings, however, should be treated with caution because of the brief follow-up period (not more than 3 years).

A prospective nested case-control study of blood samples collected between 1964 and 1971 compared DDE concentration in blood serum of northern California women who were later diagnosed with breast cancer (n=150; 50 each of white, black, and Asian women) with serum DDE of paired control women who did not develop breast cancer in the interval at least 6 months after the blood was drawn through the end of 1990 (Krieger et al. 1994). Serum DDE was not adjusted for serum lipid content. These blood serum samples were collected prior to the U.S. ban on DDT in 1972, and the serum DDE levels were much higher than those measured in the Wolff et al. (1993) study. Serum samples were collected an average of 14 years prior to cancer diagnosis. No difference in DDE serum level was observed in the combined analysis of 150 pairs of cases and controls. When the odds ratios were calculated for data stratified according to the amount of time between the serum sample collection and the breast cancer diagnosis, the results did not change. For black women (50 pairs), serum DDE levels were higher in case patients than paired controls by an average of 5.7 ppb, although the difference was not statistically significantly higher (95% CI on the difference ranged from -3.3 to 14.8). The study also found that serum DDE was significantly higher in black and Asian women compared to white women.

A case-control study of 240 breast cancer patients and 477 controls was nested within a prospective study initiated in 1976 to investigate the fate of 7,712 women in the Copenhagen City Heart Study (Høyer et al. 1998). Odds ratios for breast cancer were not increased in upper quartiles of lipid-adjusted serum total DDT, \( p,p' \)-DDT, or \( p,p' \)-DDE, compared to the lowest quartile of lipid-adjusted serum concentrations. The analysis was adjusted to account for the following potential confounders: weight, height, number of full-term pregnancies, alcohol consumption, smoking, physical activity, menopausal status, household income, marital status, and education. Blood samples were collected in 1976, and breast cancer diagnosis occurred up to 17 years following the sample. Exclusion of women who developed breast cancer within 5 years of the sample collection left 200 cases and 400 controls.
years of serum sampling did not alter the results. It is unclear from this report what the average amount of time was between the collection of the serum sample and the diagnosis of breast cancer.

Serum DDE (both lipid-adjusted and unadjusted) was measured in blood samples collected in 1974 or 1989 in a breast cancer case-control study nested within a prospective cohort study, consisting primarily of residents of Washington County, Maryland (Helzlsouer et al. 1999). Blood samples were collected from 20,305 residents of Washington County in 1974, and from 25,080 residents in 1989. A group of 346 women who were diagnosed with breast cancer by June, 1994 after having donated blood (for a total follow-up period of up to 20 years), who were residents of Washington County at the time of donating blood, and who had no other invasive cancers comprised the case group; 346 cancer-free control women were matched for age, race, menopausal status, and date of blood donation. Neither lipid-adjusted nor unadjusted DDE concentrations were significantly elevated in women who subsequently developed breast cancer, compared to controls. Separate risk analyses were conducted for quintiles of DDE concentration in samples from 1974 and for tertile samples from 1989, and for lipid-adjusted and unadjusted serum DDE; in all analyses, odds ratios for breast cancer cases relative to controls were not significantly elevated from unity. Women who donated in both 1974 and 1989 and who were diagnosed with breast cancer after 1989 were included in both program-specific analyses.

The association between breast cancer and DDT exposure was evaluated in 105 breast cancer cases relative to 208 matched controls in a case-control study nested within a prospective breast cancer study (Dorgan et al. 1999). Breast cancer was diagnosed up to 9.5 years after blood samples were obtained (between 1977 and 1987) from a cohort of women who participated in the Columbia, Missouri Breast Cancer Serum Bank study. DDT exposure was estimated using lipid-adjusted serum levels of \( o,p' \)-DDT, \( p,p' \)-DDT, \( o,p' \)-DDE, \( p,p' \)-DDE, \( p,p' \)-DDD, and total DDT. The percent of participants with serum DDT compound levels above the assay detection limit was not elevated in cases compared to controls. Risk ratios calculated by quartile of DDT compound level were evaluated for total DDT, \( p,p' \)-DDT, and \( p,p' \)-DDE, and found not to be elevated.

The possible confounding effect of menopause status was addressed in two studies that limited the investigation to postmenopausal women. A case-control study of postmenopausal women in western New York State (154 cases; 192 controls) found no association between risk of breast cancer and current age- and lipid-corrected serum \( p,p' \)-DDE concentrations, based on an odds ratio analysis (Moysich et al. 1998). Samples were collected between 1986 and 1991, within several months after diagnosis. The analysis controlled for a variety of breast cancer determinant factors, including age, education, familial
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breast cancer, parity, quetelet index (body mass index expressed as kg/m²), age at first birth, duration of lactation, years since last pregnancy, fruit and vegetable intake, and serum lipids. Another case-control study evaluated postmenopausal women from several European countries, showing no difference in current \( p,p' \)-DDE concentration in buttocks adipose tissue between women with breast cancer (\( n=265 \)) and cancer-free women matched for age and study center (\( n=341 \)) (van’t Veer et al. 1997). The dates of tissue sampling were not reported. Both of these studies were limited by characterizing exposure after diagnosis of cancer.

Two studies evaluated hospital populations of breast cancer patients in countries where DDT has been used in the recent past for malaria control programs, and found no relationship between risk of breast cancer and serum concentrations of \( p,p' \)-DDT or metabolites. Lopez-Carrillo et al. (1997) investigated the association between current serum levels of DDE and \( p,p' \)-DDT and the occurrence of breast cancer in hospital patients in Mexico City from 1994 to 1996. Neither arithmetic mean nor geometric mean serum DDE (either wet weight or lipid weight basis) were significantly different between Mexican women with breast cancer (\( n=141 \)) and age-matched control women with no breast cancer. Arithmetic mean serum \( p,p' \)-DDT also was not different between the groups, either on a wet weight or lipid weight basis. Control women were recruited from various diagnostic areas of the hospitals, excluding oncology and gynecology; mean serum DDE was not statistically significantly different across diagnostic areas among control women. No significant effect of serum DDE on breast cancer risk was found for all subjects, or for subsets of subjects based on menopausal status, using an odds ratio analysis adjusted for age, quetelet index, breast feeding with first birth, parity, familial history of breast cancer, and time elapsed since first birth. Among northern Vietnamese women, no difference was found in 1994 plasma \( p,p' \)-DDE and \( p,p' \)-DDT concentrations between newly diagnosed breast cancer patients (\( n=21 \)) and age- and residence-matched control patients who had fibrocystic breast disease (Schecter et al. 1997). Plasma levels of DDE and DDT were not adjusted for plasma lipid content. Relative risk of breast cancer was not significantly elevated for subjects in the higher tertiles of plasma DDE, DDT, and total DDT (DDT plus molar-adjusted DDE), compared to the lowest tertile. No differences were observed between controls and cases with respect to age, age at menarche, age at first pregnancy, parity, history of lactation, and maximum attained body weight. The authors concluded that exposure to \( p,p' \)-DDT is not an important factor in the etiology of breast cancer among northern Vietnamese women, although they acknowledge that the study was limited by small sample size.

Aschengrau et al. (1998) explored the relationship between occupational exposure to estrogenic chemicals and the occurrence of breast cancer. Investigators compared probable exposure to DDT (inferred from
subjectively reported employment history and a job exposure analysis that related job type to probable xenobiotic exposure) in women from Cape Cod, Massachusetts who were diagnosed with breast cancer during 1983–1986 (n=261) with age- and race-matched controls (n=753) from Cape Cod. No relationship was found; the incidence of women who were occupationally exposed to DDT was regarded as “rare” and was not numerically reported in the study. No information was provided regarding the estimated timing of DDT exposure versus diagnosis of breast cancer.

**Pancreatic Cancer.** Pancreatic cancer was weakly associated with exposure to DDT in a nested case-control mortality study following up a cohort of 5,886 chemical manufacturing workers who were potentially exposed between 1948 and 1971 (Garabrant et al. 1992). Deaths due to pancreatic cancer occurred between 1953 and 1988. The mortality registry had been updated and periodically analyzed. An elevated mortality from pancreatic cancer was first seen in the cohort in 1987. The association between pancreatic cancer and exposure to 429 chemicals or groups of related chemicals was examined for 28 cases of pancreatic cancer and 76 matched controls. Only 16 of the 28 cases were medically verified; medical records were not available for 12 subjects whose death certificates indicated pancreatic cancer as the underlying cause of death. Only 11 of the cases had been exposed to DDT or related materials. The relative risk (RR) for exposure to DDT alone was 4.8 (6 cases, 7 controls; 95% CI=1.2–17.6) and for DDD was 4.3 (9 cases, 12 controls; 95% CI=1.5–12.4). The RR for DDT increased with greater-than-median exposure duration and more than 20 years of latency. Multivariate analyses to correct for confounding factors (e.g., cigarettes, decaffeinated coffee, antacid use) did not change the RR markedly. When exposures to other chemicals (e.g., ethylan, nitrofen, dinocap, carbon tetrachloride, dispersing agents) found associated with pancreatic cancer (i.e., RR>1) were added to the multivariate model the RR for DDT remained relatively stable, ranging from 3.1 to 5.4 (statistical significance was not reported). It was concluded that DDT was an independent risk factor for pancreatic cancer. The evidence was not strong enough to conclude that DDD was an independent risk factor. The study was limited because of the small number of pancreatic cancer cases in DDT-exposed persons and the large number of exposures. Although confounding factors and biases have been minimized, the evidence for association is weak.

An association between pancreatic cancer and historical use of DDT is weakly supported in a case-control study of hospital patients in southeastern Michigan, which provides a slightly increased, but nonsignificant odds ratio of 1.6 for pancreatic cancer (95% CI=0.8 to 3.1; cases=17, controls=23) for patients who were ever exposed to DDT, as compared to patients who had not (Fryzek et al. 1997).
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**Lymphoma.** Hodgkin’s disease and non-Hodgkin’s lymphoma were investigated in a retrospective study of 31 cases of Hodgkin’s disease, 93 cases of non-Hodgkin’s lymphoma, and 204 referents. Nonsignificant odds ratios for subjectively reported DDT exposure were 2.2 for Hodgkin’s disease (a CI was not calculated due to small numbers of exposed subjects) and 3.0 for non-Hodgkin’s lymphoma (90% CI=0.3–13) (Persson et al. 1993). Data were obtained by questionnaire from Swedish workers diagnosed between 1975 and 1984. The numbers of exposed cases and controls were too small to provide strong evidence of an association between DDT exposure and the diseases; DDT-exposed subjects included only one case of Hodgkin’s disease, four cases of non-Hodgkin’s lymphoma, and three referents.

Mean \( p,p' \)-DDE concentration in adipose tissue was 33% higher in Swedish patients newly diagnosed during 1994-1995 with non-Hodgkin’s lymphoma than in surgical controls (Hardell et al. 1996), although the difference was not statistically significant \((p=0.29)\). Small numbers of subjects (28 patients with non-Hodgkin’s lymphoma and 17 controls), however, limited the power of the statistical test to discern a significant difference.

Analysis of pooled data from three case-control studies in the United States revealed tenuous evidence of an association between DDT exposures and the occurrence of non-Hodgkin’s lymphoma among male farmers (Baris et al. 1998). Exposure was reported subjectively, and was categorized into the following three groups: DDT use on crops and animals, DDT use on animals only, and DDT use on crops only. Odds ratios and confidence intervals were obtained by logistic regression. Using a reference group of nonfarmers and pooled data for farmers from four Midwestern states, the age- and state-adjusted odds ratio for the occurrence of non-Hodgkin’s lymphoma were 1.5 (95% CI=1.1–2.1) for farmers who used DDT on crops \((n=74)\) and 1.6 (95% CI=1.1–2.3) for farmers who personally handled DDT that was applied to crops \((n=63)\). The odds ratios were lower and not statistically significantly elevated above unity for using or handling DDT applied to animals or applied to animals and crops combined. When adjusted for use of other individual pesticides or pesticide groups, when evaluated by type of non-Hodgkin’s disease, or when stratified by co-exposure to 2,4-D and organophosphate pesticides, no significant odds ratios were observed. No association was observed between estimated duration of DDT use and occurrence of non-Hodgkin’s lymphoma, adjusted for use of other pesticides.

Lipid-corrected total serum DDT (sum of \( o,p' \)-DDT, \( p,p' \)-DDT, \( o,p' \)-DDE, and \( p,p' \)-DDE) was not associated with risk for non-Hodgkin’s lymphoma in patients diagnosed with the disease between 1975 and 1989 \((n=74)\) when compared to matched, cancer-free controls \((n=147)\) in a case-control study nested within a prospective cohort study of Maryland residents that was begun in 1974 (Rothman et al. 1997).
separate evaluation for each DDT compound was not reported. The median lipid-adjusted concentration of total DDT in archived blood of patients who subsequently developed non-Hodgkin’s lymphoma (3,150 ng/g lipid) was not significantly higher than in patients who did not develop the disease (2,770 ng/g lipid) (Wilcoxon signed rank test; p=0.2). Odds ratios for non-Hodgkin’s lymphoma in serum DDT concentration quartiles, compared to the lowest quartile, were not statistically significant and ranged from 1.2 in the second quartile to 1.9 in the highest quartile.

A population case-control study of the association between subjectively reported DDT use and non-Hodgkin’s lymphoma was conducted on farmers in Iowa and Minnesota with newly diagnosed or confirmed disease and population-based controls (Cantor et al. 1992). Significantly elevated maximum likelihood estimates of odds ratios were obtained for ever having handled DDT applied to crops (OR=1.7; CI=1.2–2.6; cases=57 and controls=75) and for having handled DDT applied to crops only prior to 1965 (OR=1.8; CI=1.1–2.7; cases=45 and controls=57). Odds ratios were not significant for exposure to DDT applied as an animal insecticide. In spite of the fact that the odds ratios were adjusted using logistic analysis for vital status, age, state, smoking, family history of lymphopoeitic cancer, high-risk occupation, and high-risk exposure, causality could not be established because of exposure to multiple pesticides.

**Multiple Myeloma.** Several studies evaluated a possible association between DDT exposure and risk of multiple myeloma. Eriksson and Karlson (1992) investigated the several environmental factors that are possibly related to the occurrence of multiple myeloma in Sweden. Using univariate statistical analysis, a significantly increased relative risk of multiple myeloma of 1.75 (90% CI = 1.19–2.64) was obtained for any DDT exposure, but not for DDT exposures stratified by exposure duration. Relative risk decreased and was nonsignificant when multivariate analysis was used to correct for confounding risk factors. For a group of 20 Iowa farmers who reported that they mixed, handled, or applied DDT as a crop insecticide, a nonsignificant odds ratio for multiple myeloma of 1.7 (95% CI=0.9–3.1) was obtained using a control group of 52 nonfarmers (Brown et al. 1993). An odds ratio of 1.8 was obtained for farmers who failed to use protective equipment, although statistical significance cannot be determined since a confidence interval was not reported. A nonsignificant odds ratio of 1.1 (95% CI=0.6–1.9) for multiple myeloma was estimated for 20 farmers who mixed, handled, or applied DDT as an animal insecticide, using a control group of 84 unexposed individuals. The combined evaluation of crop DDT exposure plus animal DDT exposure was not provided.

Proportional mortality analysis was conducted on death certificates of a cohort of 590 persons who applied DDT or inspected DDT application areas, and 453 unexposed workers, in a malaria eradication
campaign in Sardinia, Italy conducted during 1946–1950 (Cocco et al. 1997a, 1997b). Based on information on annual use of DDT, its concentration in the pesticide mix, and the concentration applied to surfaces, the investigators estimated that DDT exposure concentrations ranged from 170 to 600 mg/m³ in outdoor operations. They also estimated that on average, for a man working 6 hours/day in pesticide application, the minimum indoor exposure would have been 254 g/day (exactly how this was estimated is unclear). Proportional mortality ratios (PMR) were provided for numerous types of cancer, for both DDT-exposed and unexposed groups, and the general Italian male population was used as the reference group for estimating expected mortality. For most types of cancer, the PMR was either elevated in both exposed and unexposed groups, or was not elevated in either group. For deaths due to multiple myeloma, however, the PMR was elevated (statistically significant) in exposed workers (PMRx100=341) [where a value of 100 indicates no difference between observed and expected mortality from multiple myeloma, and values above 100 indicate that the observed mortality was greater than the expected]; 95% CI=110–795; n=5), but not in unexposed workers (PMRx100=94; 95% CI=1–522; n=1). These results provided only marginal support for a positive association between occupational DDT exposure and multiple myeloma, because of the small numbers of cases. No consistent pattern of association was observed when data were categorized by estimated duration of exposure in days.

In a case-control study of workers in Italy who worked in an agricultural profession at some time, the odds ratio for multiple myeloma was significantly elevated above unity for self-reported exposure to chlorinated pesticides, including DDT (OR=1.6; 95% CI=1.1–2.4) (Nanni et al. 1998). Very similar, albeit marginally significant results were obtained for exposure specifically to DDT (OR=1.6; 95% CI=1.0–2.5). The referent group was comprised of age- and gender-matched individuals who had never worked in agriculture. A higher, but not statistically significant, odds ratio was obtained for exposure to DDT among workers whose primary occupation was agricultural (OR=2.6; 95% CI=0.9–7.8).

**Prostate and Testicular Cancer.** An ecologic study evaluated the relationships between \( p,p' \)-DDE concentration in subcutaneous fat, or \( p,p' \)-DDE in tree bark, and mortality from prostate and testicular cancers using multivariate statistical techniques (Cocco and Benichou 1998). Adipose DDE was obtained from samples collected in the EPA Human Monitoring Program in 1968 for people in 22 states, tree bark DDE data were available for 18 states representing the years 1992–1995, and age-adjusted mortality rates from prostate and testicular cancers during 1971–1994 were available by state from the National Center for Health Statistics. Numerous demographic factors were considered as possible confounders, and data were obtained from public sources. Separate analyses were conducted for whites and African Americans since mean adipose DDE in African Americans was 74% higher than in whites (p<0.001). The authors
concluded that study results do not support an association between prostate and testicular cancer mortality and DDE exposure.

**Endometrial Cancer.** No association was found between newly-diagnosed endometrial cancer and lipid-corrected blood serum concentrations of \( p,p' \)-DDT, \( o,p' \)-DDT, and \( p,p' \)-DDE, as indicated by nonsignificant relative risk values, in a multicenter case-control study of women in the United States (Sturgeon et al. 1998). In addition, simple comparisons of serum levels of DDT compounds between women who had endometrial cancer and controls showed no clear pattern. Median lipid-corrected serum \( p,p' \)-DDT was elevated above control levels (\( p=0.03 \)), lipid-corrected serum \( o,p' \)-DDT was less than controls (\( p=0.09 \)), and lipid-corrected serum \( p,p' \)-DDE did not differ between cases and controls (\( p=0.58 \)).

The mean concentration of \( ^{1} \) DDT (sum of \( p,p' \)-DDT, \( o,p' \)-DDT, \( p,p' \)-DDE, and \( p,p' \)-DDD) was significantly higher (\( p<0.001 \)) in uterine leiomyomatous tissue (0.845 ppm) obtained from 25 recent hysterectomies of 36- to 55-year-old women than in normal uterine tissue (0.103 ppm) obtained from 25 recent autopsies of women from the same age range (Saxena et al. 1987). The mean concentration of each of the individual forms was nonsignificantly elevated above control levels in the leiomyomatous tissue. Dates that tissue samples were obtained were not reported.

The occurrence of endometriosis, a benign proliferation of endometrial tissue outside the endometrial cavity, was not associated with DDT exposure as measured by lipid-adjusted plasma \( p,p' \)-DDT, \( p,p' \)-DDE, and \( ^{1} \) DDT in a study of 86 cases and 70 controls confirmed by laparoscopy in 1994 (Lebel et al. 1998). Geometric mean plasma concentrations of DDT compounds were not elevated in all cases compared to all controls, nor in subgroups of cases compared to controls matched by symptomatology (e.g., pelvic pain, infertility, and tubal fulguration).

**All Cancer.** In a prospective cancer mortality study of 919 adults from Charleston, South Carolina (Austin et al. 1989), serum levels of total DDT (DDT plus DDT molar equivalents of DDE) were estimated in 1974–1975, and 10 years later, the individuals were followed up and the cause of death was determined for the deceased. The cohort was divided into exposure tertiles based on total serum DDT; the lowest tertile was used as the reference group for calculating relative mortality rates. Adjustments were made for age, race, gender, years of education, and smoking habits. Relative risk of death, and specifically of death due to any cancer, was not significantly elevated in the high serum DDT tertile groups. No consistent positive trend in risk of cancer mortality relative to serum DDT was observed.
However, there was some evidence of a dose-response relation between serum DDT and respiratory cancer, but the point estimates were unstable and the trend was not statistically significant.

A historical prospective mortality study was conducted on 740 white male workers employed between 1935–1976 in occupations that involved exposures to DDT (Wong et al. 1984). Follow-up was conducted in 1976, and expected age- and cause-specific mortality rates were calculated from U.S. rates for white males for 5-year periods during 1935–1975. Among individuals exposed to DDT, overall mortality (all cancers), expressed as the standard mortality ratio, was not elevated over expected values. Standard mortality ratios were also not significantly elevated for individual cancers of the digestive, respiratory, urogenital, and lymphohaematopoietic systems. Several factors confound these results: individuals exposed to DDT also were potentially exposed to other chemicals, and smoking history was not included in the analysis.

Mortality and health impairments in a cohort of 2,620 pesticide workers and 1,049 controls were tracked during 1971–1977 (Morgan et al. 1980), and cancer rates were found to be significantly elevated in at least one category of exposed workers for internal cancers, leukemias, and lymphomas (evaluated together), as well as for skin cancers and all cancers. However, geometric mean total serum DDT (DDT plus DDE) measured in 1971–1973 was not significantly different between subjects who developed cancer of leukemia by the end of 1977 (n=43) and a group of subjects without the disease (n=45). Exposure to multiple pesticides was a significant confounding factor in this study.

A weak positive correlation was seen between the occurrence of any cancer and the consumption of DDT-contaminated fish (r=0.045; p=0.0001) in a cross-sectional survey of Triana, Alabama residents (Tadi-Uppala et al. 1998). Data were collected by questionnaire. The overall prevalence of cancer in the community was 6%. The data were reported in an abstract, so methodological details were not available for evaluation; a follow-up case-control study is planned.

In summary, the database of human cancer epidemiology studies is equivocal about whether DDT/DDE/DDD exposure poses an increased risk of cancer.

Animal Studies

DDT is one of the most widely studied pesticides in animals, and data are available on a number of carcinogenicity studies in several species. Intermediate exposures, in which animals were exposed to
DDT in food, caused cancer increases in mice but not in rats or hamsters. Mice that were observed for 50–105 weeks after cessation of treatment developed liver hepatomas following dietary exposure to 42.8 mg \( p,p' \)-DDT/kg/day for 15–30 weeks (Tomatis et al. 1974b). DDT did not produce increases in the tumor incidence in rats exposed to 2.5–20 mg/kg/day in the food for up to 45 weeks (Kimbrough et al. 1964; Laug et al. 1950; Numoto et al. 1985) or in hamsters fed 40 mg DDT/kg/day for 30 weeks (Tanaka et al. 1987).

Chronic exposure (>1 year) to DDT caused cancer in multiple strains of mice but not in dogs or nonhuman primates. Chronic exposure to DDT produced liver neoplasms in mice strains ([C57BL/6 × C3H/Anf]F\( _{1} \), [C57BL/6 × AKR]F\( _{1} \), BALB/c, and CF1) fed DDT at doses as low as 0.38 mg DDT/kg/day for a minimum of 78 weeks (Innes et al. 1969; Kashyap et al. 1977; Terracini et al. 1973; Thorpe and Walker 1973; Tomatis et al. 1972, 1974a; Turusov et al. 1973). An increased incidence of pulmonary adenomas was observed in mice after chronic gavage administration (Shabad et al. 1973). Malignant lymphomas and lung and liver tumors were also observed in mice treated with DDT in the food (Kashyap et al. 1977).

Some evidence exists to indicate that DDT may be carcinogenic in the rat. Rats maintained on diets containing DDT for more than 2 years or at doses higher than 25 mg DDT/kg/day developed liver tumors, primarily in female rats (Cabral et al. 1982b; Fitzhugh and Nelson 1947; Rossi et al. 1977). Liver tumors occurred in rats at doses of 19.7 mg DDT/kg/day for 2 years (Cabral 1982b). In contrast, no evidence of carcinogenicity was seen in rats receiving up to 45 mg technical DDT/kg/day for 78 weeks in the NCI (1978) bioassay. No significant increases in tumor incidence were observed in mice administered DDT at doses of 3–30 mg/kg/day (Del Pup et al. 1978; NCI 1978). Long-term exposure failed to induce statistically significant increases in tumors in monkeys at doses of 3.9–20 mg/kg/day for up to 5 years (Adamson and Sieber 1979, 1983; Durham et al. 1963); or in dogs at 80 mg/kg/day for 49 months (Lehman 1965).

Evidence of carcinogenicity of DDT in hamsters is equivocal. Rossi et al. (1983) reported an increased incidence (14% in controls, 34% in treated hamsters) of adrenal neoplasms in hamsters administered approximately 95 mg DDT/kg/day via the diet for 30 months. At lower doses, Cabral et al. (1982a) did not observe a statistically significant increase in adrenal gland tumors; however, the incidence in males was increased compared to controls in animals receiving 40 mg DDT/kg/day via the diet for 28 months. Other studies in hamsters did not indicate any carcinogenic effects of DDT; however, early deaths
occurred in one study (Agthe et al. 1970) and the duration of exposure was shorter in another (Graillot et al. 1975).

Several multigeneration studies have been conducted in mice. In these studies, exposure of the F₁ and subsequent generations to DDT was initially perinatal (i.e., in utero and through lactation) and was followed postweaning by oral exposure to DDT in the diet. In a study by Tarjan and Kemeny (1969), exposure to 0.4 mg $p,p'$-DDT/kg/day resulted in significant increases in leukemia and pulmonary carcinomas in the F₂ generation and occurred with increasing frequency with each subsequent generation of mice. Liver tumors (0.3–0.4 mg/kg/day) (Tomatis et al. 1972; Turusov et al. 1973) and pulmonary tumors (1.3 mg/kg/day) (Shabad et al. 1973) in the F₁ generation had a shorter latency period than in the parental generation, but the tumor incidence was comparable and did not increase with consecutive generations.

There are several studies of the potential carcinogenicity of DDE and DDD in rats, mice, and hamsters. DDE administered chronically in the diet produced liver tumors in male and female mice at doses of 27–43 mg/kg/day for 30–78 weeks (NCI 1978; Tomatis et al. 1974a) and in hamsters dosed with approximately 48 mg $p,p'$-DDE/kg/day for 128 weeks (Rossi et al. 1983). DDE did not induce significant increases in tumor incidence in rats exposed to DDE in the diet at doses ranging from 12 to 42 mg/kg/day for 78 weeks (NCI 1978), but doses of approximately 43 mg/kg/day for 130 weeks significantly increased the incidence of liver tumors in mice (Tomatis et al. 1974a). DDD induced liver tumors and lung adenomas in CF-1 mice at doses of approximately 43 mg/kg/day (Tomatis et al. 1974a), but it was not tumorigenic in B6C3F₁ mice in a 78-week study at doses of approximately 142 mg/kg/day (NCI 1978). In the NCI (1978) bioassay, the combined incidences of thyroid follicular cell adenoma and follicular cell carcinomas were 1/19, 16/49, and 11/49 in controls, low-dose (116 mg/kg/day), and high-dose (231 mg/kg/day) male rats, respectively. The difference between the control and low-dose group was significant according to the Fisher Exact test. However, NCI (1978) pointed out that the variation of these tumors in control male rats in the study did not permit a more conclusive interpretation of the lesion.

EPA has estimated an oral cancer potency factor ($q_{1}^{*}$) for DDT of $3.4 \times 10^{-1}$ (mg/kg/day)$^{-1}$ which was derived using the linearized multistage model (IRIS 1999a). This potency factor is derived from the geometric mean of potency factors based on the incidence of liver tumors in mice and rats as reported by Cabral et al. (1982b), Rossi et al. (1977), Terracini et al. (1973), Thorpe and Walker (1973), Tomatis and Turusov (1975), and Turusov et al. (1973). At this potency, $3.4 \times 10^{-1}$ (mg/kg/day)$^{-1}$, the lifetime average
daily doses that would result in risks of $1 \times 10^{-4}$, $1 \times 10^{-5}$, $1 \times 10^{-6}$, and $1 \times 10^{-7}$ are $2.9 \times 10^{-4}$, $2.9 \times 10^{-5}$, $2.9 \times 10^{-6}$, and $2.9 \times 10^{-7}$ mg/kg/day, respectively.

The oral cancer potency factor ($q_1^*$) for DDD is $2.4 \times 10^{-1}$ (mg/kg/day)$^{-1}$ based on the incidence of liver tumors in CF-1 mice (Tomatis et al. 1974a) and the oral $q_1^*$ for DDE is $3.4 \times 10^{-1}$ based on the geometric mean of six slope factors for liver tumors in both sexes of B6C3F1 mice (NCI 1978), CF-1 mice (Tomatis et al. 1974a), and Syrian hamsters (Rossi et al. 1983). At these potencies, the lifetime average doses that would result in risk of $1 \times 10^{-4}$, $1 \times 10^{-5}$, $1 \times 10^{-6}$, and $1 \times 10^{-7}$ are $4.2 \times 10^{-4}$, $4.2 \times 10^{-5}$, $4.2 \times 10^{-6}$, and $4.2 \times 10^{-7}$ mg/kg/day, respectively, for DDD and $2.9 \times 10^{-4}$, $2.9 \times 10^{-5}$, $2.9 \times 10^{-6}$, and $2.9 \times 10^{-7}$ mg/kg/day, respectively, for DDE.

Cancer Effect Levels (CELS) are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.3 Dermal Exposure

Occupational exposure to DDT involved multiple routes of exposure. The primary contact was probably inhalation and dermal; however, absorption of DDT from the lungs may not have been significant, and ingestion via the mucociliary apparatus of the respiratory tract is more likely. Therefore, epidemiological studies of occupational exposure are discussed under oral exposure.

2.2.3.1 Death

The dermal LD$_{50}$ of DDT in rats was reported by Ben-Dyke et al. (1970), Cameron and Burgess (1945), and Gaines (1969) to range from 2,500 to 3,000 mg DDT/kg. In guinea pigs, a single dose of 1,000 mg DDT/kg resulted in death of 50% of the animals (Cameron and Burgess 1945). The LD$_{50}$ in rabbits was 300 mg DDT/kg (Cameron and Burgess 1945) and 4,000–5,000 mg DDD/kg (Ben-Dyke et al. 1970). In the study by Cameron and Burgess (1945), the animals were dermally exposed to various doses of DDT in solvents including kerosene (1 or 10%), ethyl alcohol, acetone, or ether. It is uncertain what contribution these solvents made to the toxic effects observed; the authors stated that kerosene itself may have caused some deaths.
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2.2.3.2 Systemic Effects

No studies were located regarding gastrointestinal, musculoskeletal, or ocular effects in humans or animals after dermal exposure to DDT, DDE, or DDD.

All of the information on the systemic and neurological effects of dermal exposure to DDT in animals is derived from a study by Cameron and Burgess (1945). In this study, rabbits, guinea pigs, and rats were dermally exposed to various doses of DDT in solvents including kerosene (1 or 10%), ethyl alcohol, acetone, or ether. It is uncertain what contribution these solvents made to the toxic effects observed; the authors stated that kerosene itself may have caused some deaths. The only information reported on the method of application stated that the skin area was shaved 24 hours before application of DDT impregnated in cloth and that precautions were taken to prevent animals from licking contaminated skin. The duration of exposure was not clearly reported. In addition, the species and the number of animals exhibiting specific toxic symptoms were not clearly reported and no statistical analysis was conducted.

Respiratory Effects. No studies were located regarding respiratory effects in humans after dermal exposure to DDT, DDE, or DDD. In rats, guinea pigs, and rabbits exposed to acute dermal doses ranging from 50 to 200 mg DDT/kg, pulmonary edema and respiratory failure were reported (Cameron and Burgess 1945).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after dermal exposure to DDT, DDE, or DDD. Cameron and Burgess (1945) exposed rats, guinea pigs, and rabbits to acute dermal doses ranging from 50 to 200 mg DDT/kg and reported fat in the fibers of the heart.

Hematological Effects. No studies were located regarding hematological effects in humans after dermal exposure to DDT, DDE, or DDD. Cameron and Burgess (1945) exposed rats, guinea pigs, and rabbits to acute dermal doses ranging from 50 to 200 mg DDT/kg. A decrease in hemoglobin and leukocytosis was reported.

Hepatic Effects. No studies were located regarding hepatic effects in humans after dermal exposure to DDT, DDE, or DDD. Cameron and Burgess (1945) exposed rats, rabbits, and guinea pigs to acute dermal doses of 10, 50, or 100 mg DDT/kg and reported fatty degeneration, calcification, and necrosis in the liver.
2. HEALTH EFFECTS

Renal Effects. No studies were located regarding renal effects in humans after dermal exposure to DDT, DDE, or DDD. Cameron and Burgess (1945) exposed rats, rabbits, and guinea pigs to acute dermal doses ranging from 50 to 100 mg DDT/kg and reported fat deposits, tubular changes, calcification, and necrosis of the kidneys.

Dermal Effects. Cameron (1945) conducted a series of experiments on volunteers wearing undergarments impregnated with 1% DDT in order to determine whether this treatment would protect soldiers against body lice. Several individuals had transient dermatitis, but no other symptoms were observed. The length of exposure via this route was not specified. Cameron and Burgess (1945) exposed rats, rabbits, and guinea pigs to 10, 50, or 100 mg DDT/kg and reported inflammation, edema, and destruction of the epidermis. Guinea pigs were dosed 5 days a week for 3 weeks with 322–400 mg DDT/kg (Kar and Dikshith 1970). A decrease in skin amino acids, disruption and degeneration of the basal cell layer, and morphologic changes in the cells were reported.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to DDT, DDE, or DDD.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to DDT, DDE, or DDD. Cameron and Burgess (1945) exposed rats, rabbits, and guinea pigs to acute, dermal doses ranging from 50 to 200 mg/kg DDT and reported tremors and nervousness.

No studies were located regarding the following effects in humans or animals after dermal exposure to DDT, DDE, or DDD:

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects
2. HEALTH EFFECTS

2.2.3.7 Genotoxic Effects

*In vitro* genotoxicity studies are discussed in Section 2.6.

2.2.3.8 Cancer

No case studies or epidemiological investigations concerning the carcinogenic effects in humans after dermal exposure exclusively to DDT, DDE, or DDD were located. Occupational studies that probably involved both dermal and inhalation routes of exposure are discussed in Section 2.2.2.8.

Dermal exposure (skin painting) of mice to DDT did not result in a significant increase in tumor incidence when applied in a 5% solution in kerosene once weekly for 52 weeks (Bennison and Mostofi 1950) or at 8 mg/kg twice weekly for 80 weeks (Kashyap et al. 1977). No information on dermal exposure of rats or hamsters to DDT or dermal exposure to DDE or DDD was located.

2.3 HEALTH EFFECTS IN WILDLIFE POTENTIALLY RELEVANT TO HUMAN HEALTH

Overview

The 1972 EPA decision to ban DDT for most crop uses in the United States was significantly influenced by a large body of scientific information indicating adverse health effects in wildlife (EPA 1975). The wildlife health effects that were considered by EPA in banning DDT were severe, including lethality of DDT in birds and fish and DDE-induced reproductive effects in birds, particularly eggshell thinning (EPA 1975). Wildlife may be regarded as sentinels for human health (NRC 1991). Although it is difficult to draw firm conclusions about human health from the toxicity observed in sentinel wildlife species in the environment, these observations have motivated more precise experiments with known doses of DDT, DDD, and DDE in both wildlife species and more traditional laboratory animal models, as well as identifying key health end points for epidemiological investigation. Wildlife field observations have also stimulated investigation of reproductive effects in mammalian models more directly relevant to humans and *in vitro* and mechanism of action studies that have resulted in the identification of some DDT isomers and metabolites as androgen antagonists and estrogen agonists. There have been a number of intriguing mechanistic studies of DDT isomers and metabolites in fish that relate to reproductive and developmental effects (Das and Thomas 1999; Faulk et al. 1999; Khan and Thomas 1998; Loomis and Thomas 1999; Sperry and Thomas 1999; Thomas 1999); these are discussed in Section 2.5.2, Mechanisms of Toxicity. Environmental monitoring studies have shown that DDT, DDE, and DDD are also highly persistent in...
2. HEALTH EFFECTS

the environment (see Section 5.3, Environmental Fate), and therefore, continue to present a potential health hazard both to humans and wildlife. It should not be forgotten that wildlife is part of the same broad ecological web as humans, and thus, toxic effects on wildlife ultimately affect the quality of human life as well.

Field observations of health effects in wildlife have strongly influenced the design of experimental studies. A high degree of causal uncertainty usually exists in field studies because wildlife species are frequently co-exposed to many other toxicants, such as other organochlorine pesticides and heavy metals, and are subjected to a variety of other uncontrolled and unknown stresses that may affect their health and confound an analysis of causation of a particular effect.

The purpose of this section is to provide a qualitative synopsis of health effects in terrestrial wildlife to address the potential concern that effects observed in wildlife that are attributable to DDT/DDE/DDD exposure may also occur in humans. The organization of Section 2.3, Health Effects in Wildlife Potentially Relevant to Human Health, closely parallels that of Section 2.2, Discussion of Health Effects by Route of Exposure, to facilitate weight-of-evidence evaluations that may use both human health and wildlife toxicological effects data. The primary focus of this section is on experimental studies with known doses of DDT isomers and metabolites, but key observations from ecological field studies of wildlife have also been highlighted. These ecological field studies include observations of reproductive developmental effects in alligators living in contaminated Lake Apopka. No case reports of lethality in wildlife populations from exposure during DDT application were included because the exposure scenario is no longer relevant since the banning of DDT in 1972.

Where statistical significance of an observed effect was evaluated in a wildlife experimental study, statistical significance (p < 0.05) was indicated in the text of this section using the term “significant”; if the term “significant” was not used in describing an observed effect, then no statistical evaluation is implied. This convention for this section is in contrast to the convention used in Section 2.2, Discussion of Health Effects by Route of Exposure, in which observed effects that are discussed in the text are usually assumed to be significant unless otherwise specified. Unfortunately, many experimental studies in wildlife used a small number of animals, making meaningful statistical tests of significance difficult. Study designs for testing toxicity in more traditional laboratory animals have generally included larger samples sizes, facilitating tests of significance.

Experimental wildlife health effects information concerning DDT/DDE/DDD exposures was located for approximately 40 terrestrial species and on numerous end points. A large proportion of the information, however, is represented by a relatively small number of species and end points. The most heavily studied
taxonomic group was birds, and among birds, the Mallard/white Pekin duck (*Anas platyrhyncus*), Japanese quail (*Coturnix coturnix japonica*), domestic fowl, and ringed turtle dove (*Streptopelia risoria*) had the greatest representation. The most commonly reported end points were lethality, and neurological and reproductive end points. Of particular interest are those effects that were observed consistently across species and in spite of variability in exposure scenarios. The significant health effects most consistently reported were lethality (several taxa), hepatic (liver enzyme induction and liver damage in birds), endocrine (estrogenic effects in several taxa, and reduced thyroid weight and altered thyroid activity in birds), neurological (tremors in several taxa), reproductive (oviposition delay and eggshell thinning in birds), and developmental (reduced chick survival in birds).

A hazard identification table (Table 2-2) is provided so the reader may quickly scan the wildlife database for species or toxicological end points that are of particular interest. The table is divided into the following four sections based on species taxonomy: Wild mammals, reptiles, and amphibians; Birds—raptors, wading birds, water birds; Birds—gallinaceous birds; and Birds—passerines and nonpasserine ground birds. The organization of effect categories within each section of the table parallels that of the text so that more detailed information for particular table entries may be readily located. The specific toxicological effects reflected in the table under each effect category may vary between sections of the table, since specific end points may have been evaluated in certain species but not in others. Not every study mentioned in the text was reported in the table. Some studies that reported ambiguous results with respect to certain toxicological end points are included in the text, but no corresponding entry was made in Table 2-2 for the ambiguous results. Not every significant effect reported in the text received a unique entry in Table 2-2. Effects reported in different studies that would receive the same coding for a given species were all represented by a single entry in the table. Effects that were observed at high exposure levels but not at low exposure levels were entered once in the table as an observed effect. The individual isomers of DDT, DDE, and DDD, as well as technical grades and unspecified mixtures, received unique codes in the table so that the reader may readily focus on compounds of particular interest. Since Table 2-2 is intended for hazard identification, parenteral exposures were included, as well as oral, inhalation, and dermal routes that are more directly relevant to human environmental exposures. In contrast, the LSE tables in the previous section included only inhalation, oral, and dermal exposures.

Table 2-2 is intended to be a visual aid to illustrate the wildlife database; it is not intended to be a stand-alone document. The reader should refer to the text for more detailed experimental design information and for information concerning the statistical significance of the observed effects.
Table 2.2. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife

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<thead>
<tr>
<th>Adverse biological effect</th>
<th>Short-tailed shrew</th>
<th>Free-tailed bats</th>
<th>Big brown bat</th>
<th>Pipistrelle bat</th>
<th>Common frog</th>
<th>Bull frog</th>
<th>Common toad</th>
<th>Smooth newt</th>
<th>African clawed frog</th>
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**TABLE KEY:**

NO = evaluated, but not observed;  
O = observed  
$A = acute$;  
$I = intermediate$;  
$C = chronic$  
$1 = p,p'-DDT$;  
$2 = o,p'-DDT$;  
$3 = technical grade DDT$;  
$4 = unspecified DDT$;  
$5 = p,p'-DDE$;  
$6 = o,p'-DDE$;  
$7 = unspecified DDE$;  
$8 = p,p'-DDD$;  
$9 = o,p'-DDD$;  
$10 = technical grade DDD$;  
$11 = unspecified DDD$;  
$12 = DDT/DDE/DDD mixture$
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<th>Freetail bats</th>
<th>Big brown bat</th>
<th>Pipistrelle bat</th>
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**TABLE KEY:**
- NO = evaluated, but not observed;
- O = observed

**Subscript (Exposure Duration):**
- A = acute;
- I = intermediate;
- C = chronic

**Superscript (Chemical Identity):**
- 1 = p,p'-DDT;
- 2 = o,p'-DDT;
- 3 = technical grade DDT;
- 4 = unspecified DDT;
- 5 = p,p'-DDE;
- 6 = o,p'-DDE;
- 7 = unspecified DDE;
- 8 = p,p'-DDD;
- 9 = o,p'-DDD;
- 10 = technical grade DDD;
- 11 = unspecified DDD;
- 12 = DDT/DDE/DDD mixture
Table 2-2. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (continued)

<table>
<thead>
<tr>
<th>Adverse biological effect</th>
<th>Bald eagle</th>
<th>White pelican</th>
<th>American kestrel</th>
<th>Double-crested cormorant</th>
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<th>Clapper Rail</th>
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**TABLE KEY:**
- NO = evaluated, but not observed;
- O = observed

**Subscript (Exposure Duration):**
- A = acute;
- I = intermediate;
- C = chronic

**Superscript (Chemical Identity):**
- 1 = p,p'-DDT;
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- 7 = unspecified DDE;
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- 9 = o,p'-DDD;
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- 12 = DDT/DDE/DDD mixture
Table 2-2. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (continued)

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<th>Adverse biological effect</th>
<th>Bald eagle</th>
<th>White pelican</th>
<th>American kestrel</th>
<th>Double-crested cormorant</th>
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TABLE KEY:
NO = evaluated, but not observed;
O = observed

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A = acute; I = intermediate; C = chronic

Superscript (Chemical Identity):
1 = p,p'-DDT; 2 = o,p'-DDT; 3 = technical grade DDT; 4 = unspecified DDT; 5 = p,p'-DDE; 6 = o,p'-DDE; 7 = unspecified DDE; 8 = p,p'-DDD; 9 = o,p'-DDD; 10 = technical grade DDDD; 11 = unspecified DDDD; 12 = DDT/DDE/DDD mixture
Table 2-2. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (continued)

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**TABLE KEY:**

NO = evaluated, but not observed; O = observed

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A = acute;  
I = intermediate;  
C = chronic

**Superscript (Chemical Identity):**

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Table 2-2. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (continued)

Birds: raptors, wading birds, water birds (continued)

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Genotoxic

Cancer

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**TABLE KEY:**

- NO = evaluated, but not observed;
- O = observed

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<table>
<thead>
<tr>
<th>Adverse Biological Effect</th>
<th>Bobwhite quail</th>
<th>Japanese quail</th>
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<th>Crowned Guinea fowl</th>
<th>Domestic fowl</th>
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</table>

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Systemic Effects

Respiratory

Cardiovascular
- pulse rate
- ventricular beat amplitude
- heart weight
- heart muscle tone

Gastrointestinal

Hematological hematocrit

Musculoskeletal
- soft skull
- calcium uptake in bone

Hepatic
- liver weight
- plasma aspartate aminotransferase
- vitamin A storage
- hypertrophy
- microsomal hormone metabolism

Renal
- kidney weight

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TABLE KEY:
NO = evaluated, but not observed;
O = observed

Subscript (Exposure Duration):
A = acute;
I = intermediate;
C = chronic

Superscript (Chemical Identity):
1 = p,p'-DDT;
2 = o,p'-DDT;
3 = technical grade DDT;
4 = unspecified DDT;
5 = p,p'-DDD;
6 = o,p'-DDD;
7 = unspecified DDE;
8 = p,p'-DDD;
9 = o,p'-DDD;
10 = technical grade DDD;
11 = unspecified DDD;
12 = DDT/DDE/DDD mixture
Table 2-2. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (continued)

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<th>Blue jay</th>
<th>Cardinal</th>
<th>Ringed turtle dove</th>
<th>Rock dove</th>
<th>Pigeons (homing and white king)</th>
<th>Bengalese finch</th>
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**TABLE KEY:**
NO = evaluated, but not observed; O = observed

**Subscript (Exposure Duration):**
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**Superscript (Chemical Identity):**
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- 3 = technical grade DDT;
- 4 = unspecified DDT;
- 5 = p,p'-DDE;
- 6 = o,p'-DDE;
- 7 = unspecified DDE;
- 8 = p,p'-DDD;
- 9 = o,p'-DDD;
- 10 = technical grade DDD;
- 11 = unspecified DDD;
- 12 = DDT/DDE/DDD mixture
2. Health Effects

2.3.1 Death

Based on the following analysis, the order of susceptibility to DDT-induced mortality appears to be amphibians > mammals > birds. Animals on restricted diets, such as migrating or nesting animals, are generally more sensitive to DDT-induced lethality than animals fed on nutritionally sufficient diets.

Mammals. Studies of DDT lethality in mammals are limited to bats and shrews, and generally attribute the cause of death to accumulation of DDT/DDE/DDD in the brain. In pipistrelle bats (*pipistrellus*), no mortality occurred after single oral doses of \( p,p' \)-DDT below 45 mg/kg body weight for up to 31 days postdosing, but 100% mortality occurred within 28 days in groups administered single doses of \$95\ mg/kg body weight; the estimated LD\(_{50}\) was 63 mg/kg body weight (Jefferies 1972). A single oral dose of technical grade DDT at 20 mg/kg body weight caused some mortality in big brown bats (*Eptesicus fuscus*), while \$40\ mg/kg body weight was 100% lethal (Luckens and Davis 1964). For 40 days, free-tailed bats (*Tadarida brasiliensis*) were fed mealworms that were raised in wheat bran containing 100 ppm \( p,p' \)-DDE; the treated bats lost body weight quicker and died sooner than an untreated control group during a postexposure starvation period (Clark and Kroll 1977). Among the 17 treated bats, a strong negative relationship was seen between \( p,p' \)-DDE residue in the brain and percent lipid in the carcass, suggesting that \( p,p' \)-DDE mobilized from fat will accumulate in the brain (Clark and Kroll 1977). Based on a review of the experimental literature and DDT/DDE/DDD residues in dead wild bats, Clark (1981) estimated that the minimum lethal concentrations are 12 ppm (w/w) DDT in the brain of the little brown bat (*Myotis lucifugus*), and 460 and 540 ppm DDE in the free-tailed bat and the little brown bat, respectively. The combined effect of starvation and exercise on the disposition of existing DDE body burden was evaluated in wild-captured free-tailed bats (Geluso et al. 1976). Median brain DDE in the starved-sedentary group was increased by a factor of 12.7 in young bats to 53.8 in older bats relative to the unstarved group, and median brain DDE in the starved-exercised group was increased by a factor of 43.2 in young bats to 123.1 in older bats over levels in the unstarved group, suggesting that bats may be particularly vulnerable to DDE-induced mortality during migration.

Dietary LC\(_{50}\) values in short-tailed shrews (*Blarina brevicauda*) for 14-day \( p,p' \)-DDT exposures ranged from 651 to 1,160 mg/kg diet when DDT was dissolved in oil prior to mixing in the diet, and ranged from 839 to 2,550 mg/kg diet when DDT was added as the powder (Blus 1978). The concentration of DDT in the brains of shrews that died was highly variable, and DDE residues were relatively low, suggesting that accumulation in the brain had little effect on mortality in shrews.
Amphibians. Lethality information in adult amphibians is limited to studies in the common frog (*Rana temporaria*) and the bullfrog (*Rana catesbeiana*). No mortality was seen in adult common frogs dosed twice weekly for 8 weeks with DDT (isomeric composition not specified) at 0.6 mg/kg, but in treated frogs that were not fed, 50% mortality was seen by the end of the exposure period (Harri et al. 1979). The LD$_{50}$ in the adult common frog 20 days after a single oral administration of DDT (unspecified isomer) in gelatin capsules at unreported dose levels was estimated to be 7.6 mg/kg body weight; LD$_{50}$ values at 3 and 4 days after the single oral administration were approximately 85 and 25 mg/kg, respectively (Harri et al. 1979). Mortality was seen in common frog tadpoles immersed for 1 hour in 1 or 10 ppm *p,p*-DDT, but not in 0.1 ppm (Cooke 1970a). In the adult bullfrog, a 14-day oral LD$_{50}$ of >2,000 mg/kg body weight was reported following a single oral administration of *p,p*-DDT in gelatin capsules at unreported dose levels (U.S. Fish and Wildlife Service 1984).

Birds. Historically, observations of high mortality in local wild bird populations occurred coincidentally with application of DDT for pest control (EPA 1975). At the site of DDT application, local bird populations were acutely exposed by inhalation of airborne DDT, by ingestion of DDT residues on insects and other invertebrates such as earthworms, and by direct ingestion of DDT while preening. Several authors have postulated that high mortality may occur during times of stress, such as during nesting or during migration, when energy from fat stores is mobilized (EPA 1975). As fat stores are depleted, fat-stored and newly absorbed DDT could distribute to the brain; as in mammals, accumulation of high levels in the brain of birds is hypothesized to be lethal (EPA 1975). Since DDT was banned, the primary route of exposure to DDT compounds in wild bird populations has been in the diet through the food chain. Available experimental data on bird lethality indicate that DDT/DDE/DDD have moderate to low toxicity in birds after ingestion in the diet or from gavage administration (WHO 1989).

Acute LD$_{50}$ values of orally administered DDT (unspecified isomeric composition) in 2-month-old Japanese quail (*Coturnix coturnix japonica*), *p,p*-DDT in 4-month-old pheasant (*Phasianus colchicus*), technical grade DDT in 6-month-old California quail (*Callipepia californica*), DDT (unspecified isomeric composition) in 3-month-old Mallard ducks (*Anas platyrhyncus*), DDT (unspecified isomeric composition) in the rock dove (*Columba livia*), and *p,p*-DDT in the adult sandhill crane (*Grus canadensis*) ranged from 595 mg/kg body weight in 6-month-old male California quail to >4,000 mg/kg body weight in male and female rock doves (U.S. Fish and Wildlife Service 1984). Dietary LC$_{50}$ values for DDT (unspecified isomeric composition) ingestion ranged from 311 to 1,869 mg/kg diet after 5-day exposures in immature bobwhite quail (*Colinus virginianus*), Japanese quail, Mallard duck, and pheasant (U.S. Fish and Wildlife Service 1965, 1975). A dietary LC$_{50}$ of 1,612 mg/kg diet for *p,p*-DDT after a
2. HEALTH EFFECTS

5-day exposure was reported in 10-week-old clapper rails (Rallus longirostris) (Van Veltzen and Kreitzer 1975). Dietary LC$_{50}$ values for technical grade DDT after 5-day exposures in immature bobwhite quail, cardinal (Richmondena cardinalis), house sparrow (Passer domesticus), and blue jay (Cyanocitta cristata) ranged from 415 to 1,610 mg/kg diet (Hill et al. 1971). Dietary LC$_{50}$ values for $p,p'$-DDT after 10-day exposures in immature Mallard ducks ranged from 1,202 to 1,622 mg/kg, and in adult Mallard ducks was 1,419 mg/kg (Friend and Trainer 1974a). The dietary LC$_{50}$ values for DDT (unspecified isomeric composition) after acute (<10 days) exposure in immature bobwhite quail, pheasants, and Mallard ducks ranged from 500 to 1,000 mg/kg diet and in adult bobwhite and pheasants, ranged from 1,000 to 2,500 mg/kg diet; after intermediate (<100 days) exposure, LC$_{50}$ values in immature birds ranged from 100 to 400 mg/kg diet and in adult birds (including Mallards) from >100 to 1,000 mg/kg diet (U.S. Fish and Wildlife Service 1963). In the red-winged blackbird (Agelaius phoeniceus), dietary LC$_{50}$ values after acute (<10 days) and intermediate (<30 days) exposures to DDT (unspecified isomeric composition) were 1,000 and 500 mg/kg diet, respectively (U.S. Fish and Wildlife Service 1963). Dietary LC$_{50}$ values for ingestion of $p,p'$-DDE (isomeric composition not specified) ranged from 825 to 3,570 mg/kg diet after 5-day exposures in immature bobwhite quail, Japanese quail, Mallard duck, and pheasant (U.S. Fish and Wildlife Service 1975). Acute (exposure duration not specified) oral LD$_{50}$ values for DDD (unspecified isomeric composition) were 386, >700, and >2,000 mg/kg body weight in 3- to 4-month-old pheasants, 6-month-old California quail, and 3-month-old Mallard ducks (U.S. Fish and Wildlife Service 1984). Dietary LC$_{50}$ values for technical grade DDD ranged from 445 to 4,810 mg/kg diet after 5-day exposures in immature bobwhite quail, Japanese quail, pheasant, and Mallard ducks (U.S. Fish and Wildlife Service 1975).

Time to death in adult and immature bald eagles (Haliaetus leucocephalus) was inversely related to dietary technical grade DDT level in the feed; birds fed 4,000 ppm died within 23 days, while birds at lower exposure levels survived for up to 112 days (Chura and Stewart 1967). All three bald eagles (adult and immature) fed 4,000 ppm technical grade DDT in the diet died after at least 15 days of exposure, and one of two eagles fed 160 ppm technical DDT in the diet died after at least 76 days of exposure (Chura and Stewart 1967; Locke et al. 1966). Groups of 10–30 Mallard ducks (5-day-old, 30-day-old, and adult ducks) were fed $p,p'$-DDT at 250–2,000 ppm for 10 days in a diet specially formulated to provide adequate nutrition, but minimize fat formation (Friend and Trainer 1974a); onset and mean time to mortality occurred earlier in younger ducks compared to older ducks, although mortality was seen in all age groups. Survival times up to 49 and 29 days were seen in house sparrows fed 200 and 300 ppm DDT (unspecified isomer), respectively, in chick starter mash (Bernard 1963). DDT (isomeric composition not specified) provided in drinking water (12% solution) or as residue in earthworms sprayed twice daily with
2. HEALTH EFFECTS

a 12% solution (DDT residue concentration in earthworms was not reported) caused 100% mortality in wild-captured adult house sparrows within 17 days of the initial exposure (Boykins 1967).

Liver DDE was 128 and 253 ppm in two male kestrels that died compared to a mean level of 24 ppm in surviving males, and brain DDE residues were 212 and 301 ppm in the two birds that died compared to a mean level of 15 ppm in surviving males (Porter and Wiemeyer, 1972). DDT and DDE residue levels in the brains of ducks that died were between 6 and 17 times the levels seen in ducks that survived to 10 days postexposure in groups of 10–30 Mallard ducks (5-day-old, 30-day-old, and adult ducks) provided with \( p,p' \)-DDT at 250–2,000 ppm for 10 days in a diet specially formulated to provide adequate nutrition, but minimize fat formation (Friend and Trainer 1974a); DDT residue levels were generally higher in the younger ducks than in older ducks. In contrast, DDE levels in the brains of cowbirds (\( Molothrus ater \)) that survived 8–12 days of dietary exposure to 500 ppm \( p,p' \)-DDT were higher than brain DDE levels in birds that died during exposure, suggesting that brain DDE was not the principle factor inducing mortality in cowbirds (Stickel et al. 1966).

Observations of mortality were reported in several other studies. Mortality was observed in 2/12 male kestrels (\( Falco sparverius \)), one adult and one yearling, exposed for at least 14 months on diets containing 2.8 ppm \( p,p' \)-DDE (Porter and Wiemeyer 1972). There was no significant increase in mortality rate in barn owls (\( Tyto alba \)) fed 3 ppm DDE (isomeric composition not reported) in the diet for 2 years compared with controls (Mendenhall et al. 1983); however, two DDE-treated females died when they were unable to lay eggs that were “virtually shell-less.” Mortality occurred in 6–29% of female pheasants (\( Phasianus colchicus \)) and 33–100% of male pheasants fed $100 \text{ ppm} \text{ technical grade DDT}$ for at least 22 days; no deaths occurred in birds fed 10 ppm for up to 101 days (Azevedo et al. 1965). Survival of Japanese quail administered up to 50 ppm DDT (unspecified isomeric composition) was reportedly comparable to control group survival throughout a 3-generation reproductive toxicity assay (Shellenberger 1978). \( o,p' \)- and \( p,p' \)-DDT increased pentobarbital-induced mortality rates in Japanese quail when administered in the diet at 100 ppm for 2–14 days prior to a single intramuscular injection of pentobarbital (Bitman et al. 1971). Mortality in Japanese quail (\( Coturnix coturnix japonica \)) was significantly exposure-related in birds fed diets containing between 700 and 1,600 ppm \( p,p' \)-DDT for 20 days; factors that affected weight, such as restricted diet, sex, strain, and breeding condition, also affected susceptibility to DDT intoxication—heavier birds were less susceptible than lighter, more stressed birds (Gish and Chura 1970). No effect on hen mortality was seen in laying bobwhite quail (\( Colinus virginianus \)) administered up to 20 mg/bird of DDT (unspecified isomeric composition) every other day during a 4-week exposure period (Wilson et al. 1973). \( p,p' \)-DDT provided in the diet caused
mortality in Bengalese finches (*Lonchura striata*) at 84 ppm (within 46 days) and 168 ppm (within 35 days), but not at #12 ppm (Jefferies and Walker 1966).

### 2.3.2 Systemic Effects

**Respiratory Effects.** No experimental studies were located regarding respiratory effects in wild mammals, reptiles, or amphibians from exposure to DDT/DDE/DDD.

*Birds.* No gross lung lesions were observed in 6-week-old pheasant chicks (*Phasianus colchicus*) fed 100 ppm technical grade DDT for up to 101 days or 500 ppm for up to 23 days (Azevedo et al. 1965).

**Cardiovascular Effects.** No experimental studies were located regarding cardiovascular effects in wild mammals, reptiles, or amphibians from exposure to DDT/DDE/DDD.

No cardiovascular effects were observed in birds after dietary exposures to DDT/DDE/DDD, but capsular bolus administration of DDT or DDE resulted in changes in heart morphology and function that may be interpreted to be secondary to thyroid effects. Cardiovascular lesions were limited to a single observation of poor heart muscular tone at relatively high intermediate duration exposures.

*Birds.* Heart weights were not significantly affected in white pelicans (*Pelecanus erythrorhynchos*) exposed by daily oral administrations of a combination of 20 mg *p,p*-DDT, 15 mg *p,p*-DDE, and 15 mg *p,p*-DDD for 10 weeks (Greichus et al. 1975); doses were injected into the first fish fed to the birds each day. Heart weights were not significantly decreased in double-crested cormorants (*Phalacrocorax auritus*) fed diets containing up to 25 ppm of total DDT/DDE/DDD for 9 weeks (Greichus and Hannon 1973). Heart weight was increased in homing pigeons (*Columba livia*) administered 3 mg/kg/day of *p,p*-DDT by capsule for 8 weeks, but heart weights showed exposure-related decreases at doses of 6–54 mg/kg/day, with an overall significant decreasing trend in heart weight with dose (Jefferies et al. 1971). A significant dose-related decreasing trend in heart weight was also seen in pigeons administered daily doses of 18–72 mg/kg/day of *p,p*-DDE by capsule for 8 weeks (Jefferies and French 1972). A dose-related increase in relative heart weight was observed in Bengalese finches (*Lonchura striata*) fed up to 0.3 mg/kg/day of *p,p*-DDT for at least 15 weeks (Jefferies 1969). Jefferies (1969) suggested that the significant increasing trend in heart weight with dose observed in Bengalese finches at low doses was due to DDT-induced hyperthyroidism. In a later study in pigeons, Jefferies et al. (1971) refined the hypothesis, suggesting a biphasic heart response to changes in thyroid activity with increasing dose.
They postulated that increased heart weight in homing pigeons at low, intermediate-duration oral exposures was due to a hyperthyroid condition, while a dose-related decrease in heart weights at higher oral doses in pigeons occurred due to hypothyroidism. The hypothesis of a hyper-hypothyroidism continuum with increasing dose was supported by observations (discussed below) that pulse rate and ventricular S-wave amplitude peaked at low doses in homing pigeons, with a dose-related decline of both parameters at higher dose levels. Further data supporting the hypothesis of biphasic thyroid activity in pigeons is provided in an observation of biphasic metabolic rate (Jeffries and French 1971), increased thyroid weights with decreased thyroidal colloid (Jeffries and French 1969, 1971), and increased adrenal weights (Jeffries et al. 1971). These effects are discussed further below in respective subsections of Section 2.3.2.3, Systemic Effects.

Pulse rate was increased above controls at all dose levels tested in the homing pigeon fed \( p,p' \)-DDT by capsule for 3 or 6 weeks; pulse rate peaked at 18% above controls at 3 mg/kg/day, and showed a decreasing trend with dose level at 6–36 mg/kg/day (Jeffries et al. 1971). Bengalese finches showed an exposure-related increase in pulse rate at oral doses of \( p,p' \)-DDT up to 11.7 mg/kg/day (Jeffries et al. 1971).

The amplitude of the ventricular beat in homing pigeons peaked at 3 mg/kg/day after 3- or 6-week oral exposures and showed a significant exposure-related decrease at exposure levels up to 36 mg/kg/day (Jeffries et al. 1971). In Bengalese finches, there was no clear effect on the amplitude of the ventricular beat at oral dose levels up to 11.7 mg/kg/day for up to 6 weeks of exposure (Jeffries et al. 1971).

No gross heart lesions were observed in 6-week-old pheasant chicks (Phasianus colchicus) fed 100 ppm technical grade DDT for up to 101 days or 500 ppm for up to 23 days (Azevedo et al. 1965). Hearts in two homing pigeons receiving daily doses of \$36 mg/kg/day \( p,p' \)-DDE (but not at \#18 mg/kg/day) for 8 weeks were “flaccid, with thin musculature” (Jeffries and French 1972).

**Gastrointestinal Effects.** No experimental studies were located regarding gastrointestinal effects in wildlife from exposure to DDT/DDE/DDD.

**Hematological Effects.** No experimental studies were located regarding hematological effects in wild mammals, reptiles, or amphibians from exposure to DDT/DDE/DDD. In experimental studies in birds, hematological effects were observed inconsistently.
Hematological effects were inconsistently observed in birds after oral and subcutaneous exposures to DDT compounds. Bird hematology appeared to be more sensitive to gavage exposure than to dietary exposure. Relatively high, acute gavage exposure in crowned guinea hens resulted in decreased hemoglobin, erythrocyte count, and hematocrit, while no effect on hemoglobin content or hematocrit were observed in Japanese quail and cormorants exposed in the diet for an intermediate duration. Alternative hypotheses explaining the decreases in red blood cell indices after bolus doses include a direct disruption of erythrocyte membranes by lipophilic DDT, a reduced erythrocyte viability from nuclear metabolic interference, an inhibition of erythrocyte proliferation in hematopoietic tissue, or an estrogenic inhibitory effect on red blood cells (Fourie and Hattingh 1979). Intermediate-duration dietary exposures in bobwhite quail and ringed turtle doves resulted in increased and decreased hematocrits, respectively. Except for decreased red blood cell count in cockerels (young male chickens; young roosters; domestic fowl), parenteral exposures in domestic fowl showed no effects in hematological parameters.

*Birds.* Blood hemoglobin was not significantly affected in double-crested cormorants (*Phalacrocorax auritus*) fed diets containing up to 25 ppm of total DDT/DDE/DDD for 9 weeks (Greichus and Hannon 1973). Hemoglobin was significantly decreased in crowned guinea fowl (*Numida meleagris*) after an assumed daily gavage dose of 75 mg/kg body weight (exposure units were ambiguously reported) of technical grade DDT on 5 consecutive days (Fourie and Hattingh, 1979), while a 12-week dietary exposure to up to 100 ppm *p,p’*-DDE did not significantly affect hemoglobin concentration in Japanese quail (*Coturnix coturnix japonica*) (Dieter 1974). No effect on hemoglobin level was seen in chickens administered daily subcutaneous injections of DDT (unspecified isomeric composition) for up to 81 days for a cumulative dose of 2–3 g/chicken (Burlington and Lindeman 1952).

Erythrocyte count was significantly decreased in crowned guinea fowl after an assumed daily gavage dose of 75 mg/kg body weight (exposure units were ambiguously reported) of technical grade DDT on 5 consecutive days (Fourie and Hattingh, 1979). No effect on erythrocyte count was seen in chickens administered daily subcutaneous injections of DDT (unspecified isomeric composition) for up to 81 days for a cumulative dose of 2–3 g/chicken (Burlington and Lindeman 1952). Erythrocyte count was reduced compared to controls by an average of 17.8% in White Leghorn cockerels injected with DDT (unspecified isomer) subcutaneously for between 60 and 89 days at dose levels that increased from 15 to 300 mg/kg/day during the exposure period (Burlington and Lindeman 1950).

Hematocrit was not significantly affected in double-crested cormorants fed diets containing up to 25 ppm of total DDT/DDE/DDD for 9 weeks (Greichus and Hannon 1973). Hematocrit was significantly
decayed in crowned guinea fowl (*Numida meleagris*) after an assumed daily gavage dose of 75 mg/kg body weight (exposure units were ambiguously reported) of technical grade DDT on 5 consecutive days (Fourie and Hattingh 1979). A 12-week dietary exposure to up to 100 ppm *p,p'*-DDE did not significantly affect hematocrit in Japanese quail (Dieter 1974). Hematocrit was unaffected compared to controls in White Leghorn cockerels injected with DDT (unspecified isomer) subcutaneously for between 60 and 89 days at dose levels that increased from 15 to 300 mg/kg/day during the exposure period (Burlington and Lindeman 1950). Hematocrit was significantly increased in bobwhite quail (*Colinus virginianus*) fed diets containing from 10 (lowest level tested) to 150 ppm technical grade DDT for several months (Lustick et al. 1972; Peterle et al. 1973). The increased hematocrit in bobwhite quail was hypothesized to be a compensatory increase in relative red blood cell volume related to increased metabolic oxygen demand caused by a DDT-induced increase in thyroxin secretion by the thyroid; the study confirmed increased uptake of *I*\(^{131}\) by the thyroid in DDT-exposed birds, indicating increased thyroid activity (Lustick et al. 1972; Peterle et al. 1973). Significantly decreased hematocrit was seen in ringed turtle doves (*Streptopelia risoria*) fed a diet containing 200 ppm (but not at \#20 ppm) of DDE (unspecified isomeric composition) for 8 weeks (Heinz et al. 1980). The decrease in hematocrit observed in ringed turtle doves occurred only at a dietary exposure level of DDE greater than those used to administer DDT in the bobwhite quail study.

**Musculoskeletal Effects.** No experimental studies were located regarding musculoskeletal effects in wild mammals, reptiles, or amphibians from exposure to DDT/DDE/DDD.

**Birds.** No gross skeletal muscle lesions were observed in 6-week-old pheasant chicks (*Phasianus colchicus*) fed 100 ppm technical grade DDT for up to 101 days or 500 ppm for up to 23 days (Azevedo et al. 1965).

Calcium uptake in bone (which is mediated by estradiol) was significantly reduced (compared to controls) at 8 days postmating in ringed turtle doves (*Streptopelia risoria*) fed diets containing 10 ppm *p,p'*-DDT for 3 weeks prior to mating, but not in birds allowed to complete their clutch (Peakall 1970). “Extremely soft skulls” were observed in homing pigeons (*Columba livia*) that died within 35 days of oral exposure to 72 mg/kg/day of *p,p'*-DDE in capsules (Jefferies and French 1972).
Hepatic Effects. No experimental studies were located regarding hepatic effects in reptiles or amphibians from exposure to DDT/DDE/DDD.

DDT and DDE consistently induced hepatic microsomal enzyme activity in six species of birds after oral exposures; mixed results were obtained in five studies in Japanese quail. Five of the studies showing enzyme induction indicated that the increased hepatic enzyme activity significantly accelerated the breakdown of steroid hormones, including progesterone and estrogen in females and testosterone in males, potentially affecting hormone balance. No effect on liver weights was observed in birds orally administered DDT alone, but significantly increased liver weights were seen in three species fed DDE alone, probably due to hepatic enzymatic induction. Decreased liver weights were observed in two piscivorous species after oral exposure to a mixture of DDT/DDE/DDD; the authors did not speculate on the cause of the decrease in liver weights. Increased activity of liver enzymes in the blood was consistently observed in three species, indicating liver cell damage (which causes the enzymes to leak out from the cells), and microscopic lesions of the liver were observed in two species. With few exceptions, liver effects are a consistent, albeit nonspecific, indicator of DDT/DDE/DDD toxicity in birds, and induction of liver-mediated metabolism may affect steroid hormone balance.

Mammals. Short-tailed shrews showed liver weights that were not significantly different from controls after consuming an earthworm diet containing an average of 16.6 ppm DDT for 3 weeks (unspecified isomeric composition) (Braham and Neal 1974).

Birds. The hepatic microsomal mixed function oxidase system was significantly induced in puffins administered approximately 6 mg DDE (unspecified isomer)/bird for 16–21 days before sacrifice by decapitation (Bend et al. 1977). Hepatic microsomal ethylmorphine N-demethylase activity was significantly increased in kestrels (Falco sparverious) fed diets containing 10 ppm DDE (unspecified isomeric composition) for 5 years (Gillett et al. 1970). No effect on hepatic microsomal protein, but significantly increased hepatic P-450 activity, were seen in domestic chicken hens orally administered 40 mg/hen of technical grade DDT for 5 days (Chen et al. 1994).

Japanese quail (Coturnix coturnix japonica) showed increased pentobarbital-induced sleeping time when fed each of o,p' - and p,p' -isomers of DDT, DDE, and DDD separately at 100 ppm in the diet for up to 14 days (Bitman et al. 1971), indirectly suggesting that the DDT compounds inhibited the hepatic microsomal enzymes that metabolize pentobarbital. Gillett et al. (1970) reported significantly decreased hepatic microsomal epoxidase activity in Japanese quail fed up to 100 ppm DDT (unspecified isomeric
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composition) for 27 weeks. Another study provided some evidence that 28-day dietary exposure to 50 ppm of \( p,p' \)-DDT, DDE, and DDD altered (causing both increases and decreases) hepatic enzymatic activity in Japanese quail (Bunyan et al. 1970), while yet another study indicated increased hepatic microsomal P-450 levels without a significant change in microsomal protein content in Japanese quail fed diets of up to 100 ppm \( p,p' \)-DDE for 21 days (Bunyan and Page 1973; Bunyan et al. 1972). Liver oxidative enzyme activity was not affected in female Japanese quail fed diets containing up to 30 ppm technical grade DDT for 107 days (Kenney et al. 1972).

Metabolism of 17\( \beta \)-estradiol was significantly increased in the hepatic microsomal fraction obtained from domestic fowl hens fed diets containing 300–1,200 ppm technical grade DDT for 7 to 21 days (Britton 1975). Hepatic microsomal extracts from female bobwhite quail (Colinus virginianus) fed a diet containing 5 ppm technical grade DDT for 30–70 days produced a significantly greater conversion of \(^{14}C\)-labelled progesterone to metabolites \textit{in vitro} than microsomal extracts from untreated female quail; microsomal enzyme extracts from DDT-treated male quail did not produce a significant increase in mean testosterone conversion \textit{in vitro} (Lustick et al. 1972; Peakall 1967; Peterle et al. 1973). Metabolism of both testosterone and progesterone was significantly increased over control levels in liver microsomal fractions obtained from male and female White King pigeons, respectively, after a 1-week dietary exposure to 10 ppm \( p,p' \)-DDT (Peakall 1967). Similarly, estradiol metabolism was significantly increased in liver microsomal fractions obtained from ringed turtle doves (Streptopelia risoria) fed 10 ppm of technical grade DDT in the diet for 3 weeks (Peakall 1969). Hepatic enzyme metabolism of estradiol was significantly increased at 8 days postmating in ringed turtle doves fed diets containing 10 ppm \( p,p' \)-DDT for 3 weeks prior to mating, but not in birds allowed to complete their clutch (Peakall 1969, 1970).

Relative liver weights were significantly depressed in white pelicans (Pelecanus erythrorhynchos) administered a combination of 20 mg \( p,p' \)-DDT, 15 mg \( p,p' \)-DDD, and 15 mg \( p,p' \)-DDE for 10 weeks (Grechius et al. 1975). Liver weights were significantly decreased in double-crested cormorants (Phalacrocorax auritus) fed diets containing $5 ppm of total DDT/DDE/DDD for 9 weeks (Grechius and Hannon 1973). Liver weights and yield of microsomal protein were not significantly affected in puffins administered approximately 6 mg DDE (unspecified isomer)/bird for 16–21 days before sacrifice by decapitation (Bend et al. 1977). In Japanese quail, relative liver weights were significantly increased after 12 weeks on a diet containing $25 ppm \( p,p' \)-DDE (Dieter 1974). In other studies with Japanese quail, liver weights were not significantly affected by nine oral administrations of 10 mg \( o,p' \)-DDT over 3 weeks (Cooke 1970b) or by dietary exposure to up to 100 ppm of the \( p,p' \)-isomers of DDT, DDE, and
DDT, DDE, and DDD

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DDD for 28 days (Bunyan et al. 1970, 1972). Liver weight and microsomal protein were not significantly different from controls in Japanese quail fed diets containing up to 100 ppm DDT (unspecified isomeric composition) for 27 weeks (Gillett et al. 1970). Significantly increased relative liver weights were seen compared to controls in bobwhite quail fed diets containing 50–150 ppm technical grade DDT for 30–70 days (Lustick et al. 1972). No consistent effect on chicken liver weights was seen in birds fed between 400 and 800 ppm $p,p'$-DDT in the feed for 2–6 weeks (Glick 1974). No significant effects on liver weights or hepatic microsomal protein levels were seen in domestic fowl hens orally administered 40 mg/hen of technical grade DDT for 5 days (Chen et al. 1994). No effect on liver weights was seen in redstarts (*Phoenicurus phoenicurus*) administered a cumulative oral dose of 126 µg $p,p'$-DDT administered in equal daily doses over a 12-day period (Karlsson et al. 1974). Significantly increased liver weights were seen in ringed turtle doves fed diets containing $20$ ppm DDE (unspecified isomeric composition) for 8 weeks (Heinz et al. 1980). A significant dose-related increase in liver weight was seen in homing pigeons (*Columba livia*) administered daily doses of $p,p'$-DDE for 8 weeks (Jefferies and French 1972) or $p,p'$-DDT for 42 days (Jefferies and French 1969) by capsule at between 18 and 72 mg/kg/day.

Plasma liver enzyme activities (creatine kinase, aspartate aminotransferase, cholinesterase, fructose-diphosphate aldose, and lactate dehydrogenase) were significantly increased in Japanese quail, suggesting liver damage at exposure levels of $5$ ppm $p,p'$-DDE in the diet for 12 weeks (Dieter 1974). Crowned guinea fowl (*Numida meleagris*) showed significantly increased hepatic enzyme activities in blood collected after 5 days of oral exposure to approximately 75 mg/kg technical grade DDT (dose was ambiguously reported) (Fourie and Hattingh 1979). Significantly increased plasma aspartate aminotransferase was seen in ringed turtle doves fed diets containing 200 ppm (but not 20 ppm) of DDE (unspecified isomeric composition) for 8 weeks (Heinz et al. 1980).

Centrilobular liver degeneration was seen in 6-day-old chickens within 2 days of a single intraperitoneal injection with 0.25 mmol $o,p'$-DDD, and increased in severity over the next several days (Jönsson et al. 1994). No gross liver lesions were observed in 6-week-old pheasant chicks (*Phasianus colchicus*) fed 100 ppm technical grade DDT for up to 101 days or 500 ppm for up to 23 days (Azevedo et al. 1965). Dose-related “marked” liver hypertrophy was observed in homing pigeons orally administered capsules containing $p,p'$-DDT at doses ranging from 3 to 54 mg/kg/day over a 17-week period (Jefferies and French 1971).
Daily oral exposure of homing pigeons to \( p,p' \)-DDT in capsules (\$36 \text{mg/kg/day}) for up to 8 weeks resulted in a significant decrease in hepatic vitamin A storage (Jefferies and French 1971) (vitamin A is a fat-soluble compound that is essential for normal night vision, health of epithelial cells, and normal growth of bones and teeth, and is stored in the liver). The authors suggested that the reduced liver vitamin A was related to DDT-induced hypothyroidism, as evidenced also by reduced body temperature and oxygen consumption. In contrast, a lower dose of DDT (3 \text{mg/kg/day}), which caused hyperthyroidism, significantly increased hepatic vitamin A storage. Liver vitamin A was significantly increased in white pelicans administered a combination of 20 \text{mg} \( p,p' \)-DDT, 15 \text{mg} \( p,p' \)-DDD, and 15 \text{mg} \( p,p' \)-DDE injected into the first fish fed to the birds each day over a 10-week period (Greichus et al. 1975). Liver carotene (a vitamin A precursor converted to vitamin A in the liver) was not significantly different from controls (Greichus et al. 1975). Liver vitamin A content was significantly decreased in double-crested cormorants fed diets containing \$5 \text{ppm of total DDT/DDE/DDD} for 9 weeks (Greichus and Hannon 1973). In this case, liver carotene levels were also not significantly affected. Thyroid status was not evaluated in the studies of Greichus and coworkers.

Liver glycogen was marginally (not significantly) decreased and liver lipid levels were significantly increased in bobwhite quail fed diets containing 100 \text{ppm technical grade DDT} for 10 weeks (Haynes 1972).

Serum lipid was not significantly affected in Japanese quail either by four consecutive daily intramuscular injections with 5 \text{mg} \( o,p' \)-DDT or by nine oral administrations of 10 \text{mg/bird of} \( o,p' \)-DDT over 3 weeks (Cooke 1970b). Crowned guinea fowl showed significantly increased serum cholesterol compared to pre-exposure levels after a 5-day oral exposure to approximately 75 \text{mg/kg/day technical grade DDT} (Fourie and Hattingh 1979).

Significantly depressed serum protein was observed in white pelicans (\textit{Pelecanus erythrorhynchos}) administered daily oral doses of a combination of 20 \text{mg} \( p,p' \)-DDT, 15 \text{mg} \( p,p' \)-DDD, and 15 \text{mg} \( p,p' \)-DDE for 10 weeks (Greichus et al. 1975). Blood total protein was not significantly affected in double-crested cormorants fed diets containing up to 25 \text{ppm of total DDT/DDE/DDD} for 9 weeks (Greichus and Hannon 1973). Plasma protein was not significantly affected in crowned guinea fowl after an assumed daily gavage dose of 75 \text{mg/kg body weight} (exposure units were ambiguously reported) of technical grade DDT on 5 consecutive days (Fourie and Hattingh 1979). No effects on plasma protein level was seen in cockerels administered daily subcutaneous injections of DDT (unspecified isomeric...
composition) for up to 81 days starting on the 8th day posthatch; daily dose was unreported, but cumulative dose was 2–3 g/cockerel (Burlington and Lindeman 1952). No effects on fibrinogen level or prothrombin time were seen in blood of cockerels administered daily subcutaneous injections of DDT (unspecified isomeric composition) for up to 81 days for a cumulative dose of 2–3 g/cockerel (Burlington and Lindeman 1952). Prothrombin is formed and stored in the liver; in the presence of thromboplastin and calcium, it is converted into thrombin, which, in turn, converts fibrinogen to fibrin for blood coagulation.

Renal Effects. No experimental studies were located regarding renal effects in wild mammals, reptiles, or amphibians from exposure to DDT/DDE/DDD.

Birds. No renal effects were observed in experimental studies in birds. Kidney weights were not significantly affected in white pelicans (Pelecanus erythrorhynchos) exposed by daily oral administrations of a combination of 20 mg \( p,p' \)-DDT, 15 mg \( p,p' \)-DDD, and 15 mg \( p,p' \)-DDE for 10 weeks (Greichus et al. 1975). No effect on kidney weights was seen in redstarts (Phoenicurus phoenicurus) administered a cumulative oral dose of 126 µg \( p,p' \)-DDT administered in equal daily doses over a 12-day period (Karlsson et al. 1974).

No gross kidney lesions were observed in 6-week-old pheasant chicks (Phasianus colchicus) fed 100 ppm technical grade DDT for up to 101 days, or 500 ppm for up to 23 days (Azevedo et al. 1965).

Endocrine Effects. No experimental studies were located regarding endocrine effects in wild mammals from exposure to DDT/DDE/DDD.

Thyroid weights in birds were consistently elevated in six studies of dietary or capsular DDT exposures. Thyroid function in birds appeared to be biphasic after dietary exposure, showing decreased \( \text{I}^{131} \) uptake or no change in two studies at \( \#25 \) ppm DDT, and increased \( \text{I}^{131} \) uptake in four studies at \( \$100 \) ppm. The opposite pattern appears to have occurred in birds administered bolus doses of DDT in capsules, with hyperthyroidism occurring at relatively low bolus doses and hypothyroidism at high doses. The incidence of lesions in thyroid tissue increased with increasing dosage; thus, the hypothyroidism observed at high bolus oral doses may be due to degenerative changes in the thyroid. Similar degeneration may not occur at high dietary concentrations because dietary exposure occurs relatively gradually over time and may not result in blood DDT levels high enough to damage thyroid tissue. Gross adrenal morphology was unaffected by oral exposure to DDT, but histological examination showed changes in the cortico-
medullary ratio in birds fed DDT in the diet and degenerative changes in adrenals of birds exposed parenterally. Adrenal function has not been directly evaluated in wildlife species. Estrogenic changes have been reported in birds, reptiles, and amphibians after parenteral exposure to o,p'-DDT, and reduced phallus size and altered sex ratio at hatching have been reported in reptiles exposed in ovo to DDE. See Section 2.5.2, Mechanisms of Toxicity, for further discussion of estrogenicity of DDT/DDE/DDD in laboratory animals and in vitro.

Reptiles. Significantly elevated plasma vitellogenin, suggesting estrogenic activity, was induced in adult male red-eared turtles (Trachemys scripta) intraperitoneally injected with o,p'-DDT at either 1 or 250 µg/g/day for 7 days. The amounts of vitellogenin produced were significantly lower than those seen in turtles injected with 1 µg/g/day 17β-estradiol (Palmer and Palmer 1995). Vitellogenin is a protein precursor of egg proteins that is produced in the liver of oviparous and ovoviviparous species and is found in measurable quantities in blood; production is stimulated by estrogens in the blood that are produced in the ovary; thus, vitellogenin is normally absent in the blood of males (Hadley 1984).

Amphibians. Plasma vitellogenin was significantly increased in adult male African clawed frogs (Xenopus laevis) intraperitoneally injected with o,p'-DDT at either 1 or 250 µg/g/day for 7 days (Palmer and Palmer 1995), suggesting estrogenic activity. However, the amounts of plasma vitellogenin induced were significantly lower than those seen in frogs injected with 1 µg/g/day 17β-estradiol (Palmer and Palmer 1995).

Birds. Thyroid weights were significantly increased in an exposure-related manner in juvenile male Mallards (Anas platyrhyncus) fed technical grade DDT at 2.5–250 ppm in the diet for 30 days (Peterle et al. 1973). Thyroid glands were significantly enlarged in bobwhite quail (Colinus virginianus) fed technical grade DDT in the diet at 500 ppm (but not at #50 ppm) for at least 3 months (Hurst et al. 1974). Bobwhite quail fed on diets containing 100 ppm (but not 10 ppm) technical grade DDT for at least 13 weeks showed significantly increased thyroid weights relative to controls (Lustick et al. 1972). Significantly increased relative thyroid weight was seen in bobwhite quail held for 1 week at -18 EC after being fed 100 ppm technical grade DDT for several months, but not in controls or birds fed 10 ppm (Peterle et al. 1973). A significant treatment-related increase in relative thyroid weight was seen in homing pigeons (Columba livia) fed p,p'-DDT or p,p'-DDE in capsules every other day over a 42- to 56-day period at 18–72 mg/kg/day (Jefferies and French 1969, 1972). Another experiment by Jefferies and French (1971) confirmed the finding of increased thyroid weight in homing pigeons in response to daily oral exposure to p,p'-DDT (3–36 mg/kg/day) for up to 8 weeks.
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Uptake of I$^{131}$ into the thyroid was decreased (not significantly) in juvenile male Mallards (*Anas platyrhyncus*) fed 2.5 or 25 ppm technical grade DDT in the diet for 30 days, and a significantly increased uptake of I$^{131}$ into the thyroid was seen in birds at 250 ppm DDT (Peterle et al. 1973). Thyroid uptake of I$^{131}$ was significantly increased in bobwhite quail fed 500 ppm technical grade DDT in the diet for 1–3 months, but not after 4 months of treatment (Hurst et al. 1974). Bobwhite quail fed diets containing 100 ppm (but not 10 ppm) technical grade DDT for at least 13 weeks showed significantly increased thyroid activity as measured by I$^{131}$ uptake relative to controls (Lustick et al. 1972). In another experiment, significantly increased I$^{131}$ uptake into the thyroid was seen in bobwhite quail held for 1 week at -18°C after being fed 100 ppm technical grade DDT for several months, but not in controls or birds fed 10 ppm (Peterle et al. 1973). Jefferies and French (1971) found that body temperature and oxygen consumption were decreased in a dose-related manner in homing pigeons (*Columba livia*) in response to daily oral exposure to *p,p'-DDT* in capsules (3–36 mg/kg/day) for up to 8 weeks, and that significantly increased hepatic vitamin A storage (suggesting hyperthyroidism) was seen in the low-dose group, while significantly decreased hepatic vitamin A storage (suggesting hypothyroidism) was seen in the high-dose group; the authors noted that hypothyroidism has been associated with eggshell thinning in birds.

The incidence of hyperplasia of the thyroid follicular epithelium was increased in treated birds, and follicular colloid was decreased, in homing pigeons fed 18–72 mg/kg/day of *p,p'-DDT* or *p,p'-DDE* in capsules every other day over a 42- to 56-day period (Jefferies and French 1969, 1972). Another experiment by Jefferies and French (1971) confirmed the finding of hyperplasia and decreased follicular colloid in homing pigeons in response to daily oral exposure to *p,p'-DDT* (3–36 mg/kg/day) for up to 8 weeks.

Adrenal weight was unaffected in juvenile male Mallards fed technical grade DDT at 2.5–250 ppm in the diet for 30 days (Peterle et al. 1973). Adrenal weights were not significantly affected in domestic chickens by a 6-week dietary exposure to *p,p'-DDT* at 400 or 800 ppm in the feed (Glick 1974). Adrenal gland weight was not significantly affected in bobwhite quail fed technical grade DDT in the diet at 500 ppm (but not at #50 ppm) for at least 3 months (Hurst et al. 1974). Adrenal weights were not significantly affected in bobwhite quail fed diets containing up to 150 ppm technical grade DDT for up to 242 days (Lehman et al. 1974). No significant effect was seen on adrenal weight in bobwhite quail at exposure levels up to 150 ppm of technical grade DDT in the diet for several months (Peterle et al. 1973). A significant dose-related increase in adrenal weights was observed in homing pigeons fed *p,p'-DDT* in the diet at estimated dose rates of up to 54 mg/kg/day for 8 weeks (Jefferies et al. 1971) and in homing pigeons administered *p,p'-DDE* in capsules at 18–72 mg/kg/day for 8 weeks (Jefferies and French 1972).
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Adrenal cortico-medullary ratio was unaffected in juvenile male Mallards fed technical grade DDT at 2.5–250 ppm in the diet for 30 days (Peterle et al. 1973). An exposure-related increase in adrenal cortical-medullary ratio was observed in bobwhite quail at exposure levels up to 150 ppm of technical grade DDT in the diet for several months (Peterle et al. 1973); the authors speculated that this alteration of the cortico-medullary ratio may induce a reduced production and release of adrenaline compared to levels of corticosteroids. In bobwhite quail fed diets containing up to 150 ppm technical grade DDT for up to 242 days, there was a significant exposure-related increase in the cortico-medullary ratio of adrenal gland (Lehman et al. 1974). Focal vacuolation and pycnotic nuclei were seen in adrenal interrenal cells of 6-day-old chickens within 1 week of a single intraperitoneal injection with 0.25 mmol $o,p'$-DDD (Jönsson et al. 1994).

Plasma corticosterone levels were unaffected in juvenile male Mallards (*Anas platyrhyncus*) fed technical grade DDT at 2.5–250 ppm in the diet for 30 days (Peterle et al. 1973).

No studies were located that directly evaluated for effects to the pancreas; however, a few studies measured blood sugar levels. Crowned guinea fowl showed significantly decreased serum blood sugar compared to pre-exposure levels after a 5-day oral exposure to approximately 75 mg/kg/day technical grade DDT (Fourie and Hattingh 1979). No effect on blood sugar level was seen in cockerels administered daily subcutaneous injections of DDT (unspecified isomeric composition) for up to 81 days starting on the 8th day posthatch; daily dose was unreported, but cumulative dose was 2–3 g/chicken (Burlington and Lindeman 1952).

**Dermal Effects.** No experimental studies were located regarding dermal effects in wildlife from exposures to DDT/DDE/DDD.

**Ocular Effects.** No experimental studies were located regarding ocular effects in wildlife from exposures to DDT/DDE/DDD.

**Body Weight Effects.** No experimental studies were located regarding body weight effects in reptiles from exposure to DDT/DDE/DDD.

Body weight loss or reduced body weight gain were observed in mammalian, avian, and amphibian species in response to DDT/DDE/DDD exposures. Birds were most intensively studied, and among birds, raptors, passerines, and nonpasserine ground birds were more sensitive to DDT/DDE/DDD exposures.
with respect to body weight changes than gallinaceous birds. Body weight loss has been associated with hyperthyroidism, and weight gain has been associated with hypothyroidism (Jefferies 1969); see further discussion of DDT-induced thyroid effects under Endocrine, above. No clear patterns in body weight changes were evident regarding relative sensitivities based on particular DDT compound or route of exposure.

**Mammals.** Free-tailed bats (*Tadarida brasiliensis*) fed diets containing 107 ppm DDE (unspecified isomeric composition) showed significantly decreased body weight gain compared to controls after a 40-day exposure period (Clark and Kroll 1977). Body weights were generally not significantly affected in short-tailed shrews (*Blarina brevicauda*) fed DDT (unspecified isomeric composition) in the diet for 7, 14, or 17 days (Blus 1978); exposure levels were not reported, but were sufficiently high to calculate $LC_{50}$ levels of 651 mg/kg diet. Another study in short-tailed shrews also reported body weights comparable to controls after consuming an earthworm diet containing an average of 16.6 ppm DDT for 3 weeks (unspecified isomeric composition) (Braham and Neal 1974).

**Amphibians.** Body weight loss was significantly exposure-related in tadpoles of the common frog (*Rana temporaria*) exposed for 1 hour to 0.01–10 ppm $p,p'$-DDT in the water column (Cooke 1970a).

**Birds.** Body weights were not significantly affected in white pelicans (*Pelecanus erythrorhynchos*) by daily oral administrations of a combination of 20 mg $p,p'$-DDT, 15 mg $p,p'$-DDE, and 15 mg $p,p'$-DDD for 10 weeks (Greichus et al. 1975); doses were injected into the first fish fed to the birds each day. American kestrels (*Falco sparverius*) that died after exposure to 2.8 ppm $p,p'$-DDE in the diet for 14–18 months lost between 30 and 35% of their body weight; kestrels that survived the chronic dietary exposure lost an average of 16% of their body weight (Porter and Wiemeyer 1972). Bald eagles (*Haliaetus leucocephalus*) experienced weight loss of up to 49% after 10–16 weeks on diets containing 10–4,000 ppm technical grade DDT (Chura and Stewart 1967).

Body weights of Mallard ducklings (*Anas platyrhynchos*) were not significantly affected by a 10-day oral exposure to $p,p'$-DDT at up to 2,000 ppm in the diet (Friend and Trainer 1974a), but in apparent contradiction, body weight gain was “suppressed” in Mallard ducklings fed DDT (unspecified composition) at 500–900 ppm in the diet for 10 days (Friend and Trainer 1974b).

Body weights of adult female Japanese quail (*Coturnix coturnix japonica*), but not males, were significantly decreased after daily intramuscular injections of 5 mg $o,p'$-DDT for 4 days (Cooke 1970b);
male body weights were also unaffected by nine oral administrations of 10 mg DDT over a 3-week period. In another study in Japanese quail, body weights were not significantly affected by dietary exposure to up to 100 ppm \( p,p' \)-DDE and \( p,p' \)-DDT for 21 days (Bunyan and Page 1973; Bunyan et al. 1972). Growth of Japanese quail as measured by body weight was comparable to control group growth throughout a 3-generation reproductive toxicity assay in which birds were administered up to 50 ppm DDT (unspecified isomeric composition) in the diet (Shellenberger 1978).

Bobwhite quail (\textit{Colinus virginianus}) lost between 2 and 24% of body weight after 5 days of feeding on diets containing $400$ ppm technical grade DDT (Hill et al. 1971); wild quail lost appreciably more weight than farm-raised birds at the same exposure levels. No effect on hen body weight was seen in laying bobwhite quail orally administered up to 20 mg/bird of DDT (unspecified isomeric composition) by capsule every other day during a 4-week exposure period (Wilson et al. 1973).

Chicken body weights were not significantly affected by 6-week dietary exposure to 400 or 800 ppm (Glick 1974) or by \#81 days of daily subcutaneous injections of DDT (isomeric composition unspecified) for a cumulative dose of 2–3 grams (Burlington and Lindeman 1952). However, a more recent study found a slight but significant loss of body weight, accompanied by a significant reduction in food consumption, in hens orally administered 40 mg/hen of technical grade DDT for 5 days (Chen et al. 1994). No effect on body weight was observed in chicken hens fed \( p,p' \)-DDT at \#200 ppm in the diet for 12 weeks (Davison and Sell 1972).

Pheasant (\textit{Phasianus colchicus}) adult females fed diets containing 400 ppm DDT (unspecified isomeric composition) for at least 10 weeks lost weight, but females fed 100 ppm DDT gained weight (Genelly and Rudd 1956).

Nonsignificant body weight loss was seen in ringed turtle doves (\textit{Streptopelia risoria}) fed \( p,p' \)-DDE at 10 or 50 ppm in the diet for 63 days (Haegel and Hudson 1977). No significant change in body weight was seen in ringed turtle doves fed diets containing up to 200 ppm DDE (unspecified isomeric composition) for 8 weeks (Heinz et al. 1980). Homing pigeons (\textit{Columba livia}) that died after several weeks of oral exposure to \( p,p' \)-DDE at $36$ mg/kg/day by capsule showed an average weight loss of approximately 33% of their original weights, and birds that survived 8 weeks of exposure had lost an average of 2% of body weight; controls showed no change in body weight (Jefferies and French 1972).
House sparrows (*Passer domesticus*) fed diets containing 320–700 ppm technical grade DDT for 5 days lost between 10 and 12% of their body weight on the average (Hill et al. 1971). Body fat content and body weight gain were significantly decreased in an exposure-related manner in white-throated sparrows (*Zonotrichia albicollis*) fed diets containing 5–25 ppm technical grade DDT for 31 days prior to the beginning of the migratory season (Mahoney 1975); birds fed *p,p*-DDE at 5 or 25 ppm in the diet for 6 weeks showed no significant alteration in body weight gain or body fat indices. No effect on body weight was seen in redstarts (*Phoenicurus phoenicurus*) administered a cumulative oral dose of 126 µg *p,p*-DDT administered in equal daily doses over a 12-day period (Karlsson et al. 1974).

Metabolic Effects. No experimental studies were located regarding metabolic effects in reptiles or amphibians from exposure to DDT/DDE/DDD. Metabolic rate was increased in mammals and birds receiving relatively low oral bolus (capsular) doses of DDT, and decreased at relatively high bolus doses. Blood calcium was consistently unaffected by DDT/DDE/DDD treatment in birds after dietary or parenteral exposures; no effect on blood calcium was seen in seven studies using six bird species after acute or intermediate durations. Altered blood calcium was seen only after relatively high, intermediate duration oral bolus (capsular) exposure in one bird species. Two studies in birds reported increased blood pCO2 after acute oral exposures, although the significance of this is uncertain.

Mammals. Metabolic rate as measured by O2 consumption rate was significantly increased compared to controls in short-tailed shrews (*Blarina brevicauda*) fed an earthworm diet containing an average of 16.6 ppm DDT (unspecified isomeric concentration) for 1 week, but not after 2 or 3 weeks of exposure; treated shrews that were starved after exposure also showed an increase in metabolic rate compared to a control group that showed reduced metabolic rate in response to starvation (Braham and Neal 1974).

Birds. Bobwhite quail (*Colinus virginianus*) fed on diets containing 10–150 ppm technical grade DDT for at least 6 weeks showed increased (not statistically significant) metabolic rate compared to controls as measured by oxygen consumption at all ambient temperature levels tested between 5 and 40 °C, except at thermal neutrality at 30 °C, at which oxygen consumption was comparable to controls (Lustick et al. 1972; Peterle et al. 1973). In low-temperature stressed quail, shivering occurred in many birds but was most pronounced in birds that died after being fed DDT, while at the highest temperatures tested, several DDT-treated birds collapsed while none of the controls collapsed; the authors surmised that dietary DDT may have reduced the upper critical temperature of the thermoneutral zone from 40 to 35 °C (Lustick et al. 1972; Peterle et al. 1973). It is possible that the increased severity of “shivering” observed in stressed quail that eventually died may actually have been DDT-induced neurotoxicity (i.e., tremors), since similar
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responses that have been attributed to neurotoxicity have been observed in several other studies of energy-stressed birds (Section 2.3.2.5, Neurological/Behavioral effects). After 11 weeks consuming \( p,p' \)-DDT in capsules at 3 mg/kg/day, homing pigeons (Columba livia) showed significantly increased oxygen consumption (with a significant increasing time-trend), but at 36 mg/kg/day for 11 weeks, there was a significant decrease in oxygen consumption (with a significant decreasing time trend) (Jefferies and French 1971). Jefferies and French (1971) found that body temperature significantly decreased over time in homing pigeons in response to daily oral exposure to \( p,p' \)-DDT in capsules at 36 mg/kg/day or higher for up to 8 weeks.

Blood calcium was not significantly affected in double-crested cormorants (Phalacrocorax auritus) fed diets containing \#25 ppm total DDT/DDE/DDD for 9 weeks (Greichus and Hannon 1973). Serum calcium was not significantly affected in white pelicans (Pelecanus erythrorhynchos) exposed by daily oral administrations of a combination of 20 mg \( p,p' \)-DDT, 15 mg \( p,p' \)-DDE, and 15 mg \( p,p' \)-DDD for 10 weeks (Greichus et al. 1975); doses were injected into the first fish fed to the birds each day. Blood calcium levels during egg laying was not significantly affected in Pekin ducks (domesticated Mallards; Anas platyrhynchos) fed diets containing 250 ppm DDE (unspecified isomeric composition) for 10 days; no other exposure levels were tested (Peakall et al. 1975). Decreased serum calcium was seen in laying bobwhite quail (Colinus virginianus) administered 20 mg/bird of DDT (unspecified isomeric composition) by capsule every other day during a 4-week exposure period, but not at 10 mg DDT/bird (Wilson et al. 1973). Serum calcium was not significantly affected in Japanese quail (Coturnix coturnix japonica) exposed by four consecutive daily intramuscular injections with 5 mg \( o,p' \)-DDT or by nine oral administrations of 10 mg/bird of \( o,p' \)-DDT over 3 weeks (Cooke 1970b). No effect on plasma calcium levels was seen in cockerels administered daily subcutaneous injections of DDT (unspecified isomeric composition) for up to 81 days starting on the 8th day posthatch; daily dose was unreported, but cumulative dose was 2–3 g/cockerel (Burlington and Lindeman 1952). No significant effect on plasma calcium was seen in hens fed 40 mg/hen of technical DDT for 5 days (Chen et al. 1994). Blood calcium during egg laying was not significantly affected in ringed turtle doves (Streptopelia risoria) by a 3-week dietary exposure to 100 ppm DDE (unspecified isomeric composition); no other exposure levels were tested (Peakall et al. 1975).

Blood pCO\(_2\) (partial pressure of CO\(_2\) in blood in units of mm Hg) was significantly increased in adult male Japanese quail (Coturnix coturnix japonica) fed diets containing $10 ppm technical grade DDT (but not at 3 ppm) for 2 weeks, but at 6 weeks, there was a significant increase only at 10 ppm and not at higher exposure levels; there was no consistent effect in females (Kenney et al. 1972). Significantly
increased blood pCO₂, but no significant effect on pO₂ and blood pH, was also seen in crowned guinea fowl (*Numida meleagris*) compared to pre-exposure levels after a 5-day oral gavage exposure to approximately 75 mg/kg/day technical grade DDT (Fourie and Hattingh 1979).

Significantly depressed serum potassium levels were observed in white pelicans (*Pelecanus erythrorhynchos*) administered daily oral doses of a combination of 20 mg *p*,*p*-DDT, 15 mg *p*,*p*-DDD, and 15 mg *p*,*p*-DDE for 10 weeks (Greichus et al. 1975); no significant effects were seen in serum inorganic phosphorus, uric acid, magnesium, or sodium. Blood sodium, urea nitrogen, and phosphorus were not significantly affected in double-crested cormorants fed diets containing up to 25 ppm of total DDT/DDE/DDD for 9 weeks (Greichus and Hannon 1973). Plasma osmolality and plasma sodium were significantly increased in white Pekin ducks fed 100 ppm DDE in the diet for a total of 15 days; plasma potassium was not significantly affected (Miller et al. 1976). Crowned guinea fowl showed significantly decreased serum potassium and urea nitrogen compared to pre-exposure levels after a 5-day gavage exposure to approximately 75 mg/kg/day technical grade DDT (Fourie and Hattingh 1979); no significant effect was seen on blood sodium or osmolarity. No effect on plasma phosphorous level was seen in cockerels administered daily subcutaneous injections of DDT (unspecified isomeric composition) for up to 81 days starting on the 8th day posthatch; daily dose was unreported, but cumulative dose was 2–3 g/chicken (Burlington and Lindeman 1952). Significantly decreased plasma sodium was seen in ringed turtle doves fed diets containing 200 ppm (but not at 20 ppm) of DDE (unspecified isomeric composition) for 8 weeks; no significant effect on plasma potassium was seen (Heinz et al. 1980).

**Other Systemic Effects.** No experimental studies were located regarding other systemic effects in wild mammals, reptiles, or amphibians from exposure to DDT/DDE/DDD.

**Birds.** Nasal gland (“salt gland”) secretion rate was not significantly affected in white Pekin ducks (domesticated Mallards; *Anas platyrhynchos*) fed 50 ppm DDE (unspecified isomeric composition) in the diet for a total of 7 days (Miller et al. 1976). In Mallards maintained on fresh water (but not in those maintained on saltwater), nasal gland secretion rate was significantly depressed when challenged with intravenous saltwater injections after up to 9 days of feeding on diets containing $10$ ppm DDE (unspecified isomeric composition) (Friend et al. 1973).

No significant changes compared to controls were seen in lactic, malic, α-glycero-phosphate, or glucose-6-phosphate dehydrogenase activities in extracts of homogenated liver, brain, breast muscle, and kidney
tissue from redstarts (*Phoenicurus phoenicurus*) administered a cumulative oral dose of 126 µg *p,p*-DDT administered in equal daily doses over a 12-day period (Karlsson et al. 1974).

### 2.3.3 Immunological and Lymphoreticular Effects

No experimental studies were located regarding immunological or lymphoreticular effects in wild mammals, reptiles, or amphibians from exposure to DDT/DDE/DDD. Spleen weights were unaffected in several bird species. Immunological function in chickens was impaired after dietary exposure to DDT, but not in Mallards after similar exposures.

**Birds.** Spleen weight was not significantly affected in white pelicans (*Pelecanus erythrorhynchos*) administered a combination of 20 mg *p,p*-DDT, 15 mg *p,p*-DDD, and 15 mg *p,p*-DDE per day for 10 weeks (Greichus et al. 1975). Double-crested cormorants (*Phalacrocorax auritus*) fed diets containing up to 25 ppm of total DDT/DDE/DDD for 9 weeks showed no significant change in spleen weight (Greichus and Hannon 1973). Spleen and bursa weights were not significantly affected in chickens fed diets containing 500 ppm of *p,p*-DDT for 5 weeks (Glick 1974).

Serum immunoglobulin levels were not significantly affected in white pelicans exposed by daily oral administrations of a combination of 20 mg *p,p*-DDT, 15 mg *p,p*-DDD, and 15 mg *p,p*-DDE for 10 weeks (Greichus et al. 1975). The antibody titre in response to bovine serum albumin (BSA) injections was significantly decreased in domestic fowl chicks fed diets containing 400 ppm of *p,p*-DDT (but not at 200 ppm) for 5 weeks and then had food withheld for 4 days prior to injection with BSA (but not in birds that did not have food withheld); serum IgG and IgM were depressed at exposure levels of $200$ ppm for 4 weeks (Glick 1974). Plaque formation in response to sheep red blood cell challenge and an index of phagocytic activity were not significantly changed relative to controls in domestic fowl chicks fed diets containing 500 ppm of *p,p*-DDT for 5 weeks (Glick 1974). A 10-day dietary exposure to up to 900 ppm of *p,p*-DDT in the feed did not significantly affect hepatitis-induced mortality or incidence liver lesions in Mallard ducks (*Anas platyrhynchos*) (Friend and Trainer 1974b).

“Severe dissolution” of bursal follicles and vacuolation with loss of medullary cells was observed in the bursae of domestic fowl chicks fed diets containing 500 ppm of *p,p*-DDT for 5 weeks (Glick 1974).
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2.3.4 Neurological/Behavioral Effects

No experimental studies were located regarding neurological or behavioral effects in reptiles from exposure to DDT/DDE/DDD.

Neurological effects (tremors, convulsions, hyperactivity, and behavioral changes) were observed in mammalian wildlife, amphibians, and birds experimentally exposed to DDT or DDE, particularly after administration of lethal doses or after administration of lower doses when food intake was restricted. The most commonly reported neurological effect was tremors. Studies generally did not offer explanations as to the possible mechanisms that caused tremors, although it is not unreasonable to assume a mechanism similar to that seen in laboratory animals (see Section 2.5.2, Mechanisms of Toxicity). Diets were experimentally restricted in several studies to simulate the health effects of DDT/DDE/DDD mobilized from fat during periods of energetic stress in the wild such as may occur, for example, during periods of nesting, migration, or thermal or other stress. Reviews (EPA 1975; WHO 1989) have postulated that during periods of energy stress, DDT mobilized from fat is redistributed to the brain (presumably because of the high lipid content in brain tissue) where it induces neurological effects and death. A study in bats (Clark and Kroll 1977) demonstrated that DDT residues in the brain increase substantially when the diet was restricted. Although a direct action on the central nervous system in wildlife has not been confirmed by observations of brain lesions, one study in birds did show significant decreases in brain neurotransmitter levels that were associated with increased brain DDE residue levels after sublethal dietary exposures (Heinz et al. 1980). Alterations in neurotransmitter levels may explain changes in bird behavior that were observed in several species. However, most available data suggest that wildlife species may not be sensitive sentinels of neurological effects in humans because the most prominent neurological effects in wildlife occurred primarily at lethal exposure levels or in energy-stressed animals at lower exposure levels.

Mammals. Tremors, convulsions, and hyperactivity ("running fits") were observed in 16 of 40 short-tailed shrews (Blarina brevicauda) that died after consuming p,p'-DDT in the diet ad libitum for 14 days at unreported concentrations (the range of concentrations was sufficient to identify an LC₅₀ of 1,784 ppm) (Blus 1978). Prolonged tremors were seen in free-tailed bats (Tadarida brasiliensis) fed diets containing 107 ppm DDE (unspecified isomeric composition) for 40 days and subsequently starved; tremors were observed only during starvation in treated bats but not in control bats (Clark and Kroll 1977). Tremors were seen in big brown bats (Eptesicus fuscus) within 2.5 hours of a single oral dose of technical grade DDT at 800 mg/kg, and were seen up to 14 days postdosing in virtually all bats administered DDT at
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doses ranging from 20 to 800 mg/kg (Luckens and Davis 1964). Pipistrelle bats also showed tremors the day before dying from a single oral exposure to >45 mg/kg of \( p,p' \)-DDT (Jefferies 1972).

Amphibians. Common frog (\textit{Rana temporaria}) tadpoles showed uncoordinated movement and signs of hyperactivity after 1 hour of exposure to as low as 0.1 ppm \( p,p' \)-DDT (but not at 0.01 ppm) (Cooke 1970b), and transient uncoordinated hyperactivity when exposed to 0.001 ppm \( p,p' \)-DDT for as few as 5 days (Cooke 1973a). Similar neurological symptoms were seen in common frog tadpoles exposed as eggs to DDT for only 24–48 hours (Cooke 1972). Tadpoles of common frogs, common toads (\textit{Bufo bufo}), and smooth newts (\textit{Triturus vulgaris}) showed hyperactivity and abnormal movement when exposed to DDT (unspecified isomeric composition) for 24–48 hours during metamorphosis (Cooke 1972). Adult common frogs showed hyperactivity, tremors, lack of muscular coordination, and weakness several days after a single lethal oral dose of DDT (isomer not reported) at an unreported dose level; adult frogs who did not die within 10 days of the exposure recovered fully, and did not show further signs of neurotoxicity (Harri et al. 1979). Adult common frogs administered DDT (unspecified isomeric composition) in 16 twice-weekly oral doses of 0.6 mg/kg/dose in gelatin capsules showed similar signs of neurotoxicity and eventually died, but only when food was withheld at the time of exposure; frogs that were fed at the time of dosing did not show any signs of toxicity (Harri et al. 1979).

Birds. Brain weight was not significantly affected in white pelicans (\textit{Pelecanus erythrorhynchos}) that consumed a diet of fish containing an unreported dose of a mixture of \( p,p' \)-DDT (40%), \( p,p' \)-DDE (30%), and \( p,p' \)-DDD (30%) for 10 weeks, and then subjected to a restricted diet for 2 weeks (Greichus et al., 1975). Double-crested cormorants (\textit{Phalacrocorax auritus}) fed diets containing up to 25 ppm of total DDT/DDE/DDD for 9 weeks showed no significant change in brain weight (Greichus and Hannon 1973). No effect on brain weights was seen in redstarts (\textit{Phoenicurus phoenicurus}) administered a cumulative oral dose of 126 µg \( p,p' \)-DDT administered in equal daily doses over a 12-day period (Karlsson et al. 1974).

No gross brain lesions were observed in 6-week-old pheasant chicks (\textit{Phasianus colchicus}) fed 100 ppm technical grade DDT for up to 101 days or 500 ppm for up to 23 days (Azevedo et al. 1965).

Brain dopamine levels were significantly decreased in ringed turtle doves after 8-week dietary exposures of 20 and 200 ppm DDE (unspecified isomeric composition), but not when fed 2 ppm, and brain norepinephrine was significantly decreased at 200 ppm, but not at 2 or 20 ppm (Heinz et al. 1980).
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significant negative correlation was seen between neurotransmitter levels and DDE residues in the brain (Heinz et al. 1980).

Bald eagles (Haliaetus leucocephalus) showed tremors before dying from consuming diets containing technical grade DDT at 160 ppm or greater for 15 to 112 days, but tremors were not observed in eagles that did not die after consuming 10 ppm diets for up 120 days (Chura and Stewart 1967). Tremors were also seen in two out of three bald eagles before dying after administration of 4,000 ppm technical grade DDT in the diet for at least 15 days (Locke et al. 1966). An adult and an immature male American kestrel (Falco sparverius) fed diets containing 2.8 ppm p,p'-DDE exhibited tremors prior to death during exposures that ranged from 14 to 16 months in duration (Porter and Wiemeyer, 1972). Double-crested cormorants (Phalacrocorax auritus) fed diets containing ≥25 ppm total DDT/DDE/DDD for 9 weeks showed tremors and convulsions prior to death (Greichus and Hannon 1973).

Pheasants exhibited trembling before death from consuming 100 ppm technical grade DDT in the diet for at least 22 days (Azevedo et al. 1965). Bobwhite quail (Colinus virginianus) showed “slight” tremors during a 5-day dietary exposure to 800 ppm technical grade DDT in the feed; more severe neurotoxic signs, including convulsions, were seen in quail fed 1,600 ppm (Hill et al. 1971). Premortality tremors were seen in Japanese quail fed diets containing ≥700 ppm (lowest level tested) of p,p'-DDT for up to 20 days (Gish and Chura 1970). Japanese quail (Coturnix coturnix japonica) provided with an earthworm diet containing 298 ppm DDT (unspecified isomeric composition) for up to 5 days exhibited tremors before dying (Boykins, 1967), but showed no tremors or convulsions after consuming ≥100 ppm p,p'-DDE in a dry diet of mash for 12 weeks (Dieter, 1974). Pharol D-1 quail fed 40 ppm p,p'-DDT for 12 weeks showed tremors, but did not die (Davison et al. 1976).

House sparrows, cardinals (Richmondena cardinalis), and blue jays (Cyanocitta cristata) each showed tremors after consuming technical grade DDT at concentrations in the diet ranging from 320 to 910 ppm for 5 days (Hill et al. 1971). Tremors were seen in house sparrows (Passer domesticus) provided with drinking water containing 12% DDT (unspecified isomeric composition) or earthworm diets containing at least 86 ppm DDT for 6 or fewer days (Boykins 1967). “Severe” tremors were observed prior to the death of cowbirds (Molothrus ater) fed diets containing 500 ppm of p,p'-DDT for at most 12 days (Stickel et al. 1966). Trembling accompanied by significantly decreased body temperature and oxygen consumption was seen in homing pigeons (Columba livia) orally administered p,p'-DDT at 36 mg/kg/day for 12 weeks and then 54 mg/kg/day for 6 weeks (Jefferies and French 1971). Trembling was observed in
pigeons that died after oral exposure to \( p,p' \)-DDE at $36\ \text{mg/kg/day} \) by capsule for up to 56 days (Jefferies and French 1972).

Ataxia was observed in 8 chickens fed diets containing 1,600 ppm of \( p,p' \)-DDT for <2 to 4 weeks before dying, but no effects were seen at 800 ppm (Glick, 1974). Uncoordinated movement was seen in pheasants that died after consuming 100 ppm technical grade DDT in the diet for at least 22 days (Azevedo et al. 1965). Bobwhite quail (\( Colinus virginianus \)) showed “slight” balance disturbances during a 5-day dietary exposure to $800\ \text{ppm} \) technical grade DDT (Hill et al. 1971). Balance disturbances were seen in house sparrows, cardinals (\( Richmondena cardinalis \)), and blue jays (\( Cyanocitta cristata \)) after consuming technical grade DDT at concentrations in the diet ranging from 320 to 910 ppm for 5 days (Hill et al. 1971).

Predatory response time and attack rate were not significantly affected in American kestrels fed diets containing 6 ppm \( p,p' \)-DDE for 4 months, both in comparison to pretreatment rates and compared to controls (Rudolph et al. 1983). Mallard peck order was apparently not affected by consuming 2.5–250 ppm technical grade DDT in the diet for at least 29 days (Peterle et al. 1973). The onset of nocturnal restlessness indicative of normal migratory behavior (Zugunruhe) appeared to be delayed for 1 week in white-throated sparrows (\( Zonotrichia albicollis \)) fed 5–25 ppm technical grade DDT in the diet for 31 days prior to the migratory season and for approximately 2 weeks during the initial phases of the migratory season (followed by a 14-week observation period on untreated diet); the behavior was abnormally increased toward the end of the migratory season after exposure had ceased (Mahoney 1975). A similar late migratory season increase in nocturnal restlessness was seen in white-throated sparrows fed 5–25 ppm DDE (unspecified isomeric composition) in the diet for 31 days prior to the migratory season and for approximately 2 weeks during the initial phases of the migratory season (Mahony 1975).

Significantly decreased courting behavior was seen in ringed turtle doves fed \( p,p' \)-DDE at 10 or 50 ppm in the diet for 63 days (Haegele and Hudson 1977). Courtship behavior in ringed turtle doves (\( Streptopelia risoria \)) was not significantly affected by a 3-week pre-pairing dietary exposure to 100 ppm \( p,p' \)-DDE, but when birds had also been on a 10% food reduction, courtship behavior was “practically eliminated”; a significant interaction between DDE exposure and restricted diet was apparent, because the reduction in courting behavior was not as pronounced in birds on the restricted diet that had not been exposed previously to DDE (Keith and Mitchell 1993). Decreased nest attendance by parental birds was reported in ringed turtle doves fed diets ad libitum containing 100 ppm \( p,p' \)-DDE for a 3-week period prior to pairing for mating (Keith and Mitchell 1993); decrease in chick survival appeared to be related to nest attendance, and the authors hypothesized that losses in young birds were related to decreased food
intake by the chicks. No significant effect on locomotor activity pattern was reported in redstarts (*Phoenicurus phoenicurus*) administered a cumulative oral dose of 126 µg *p,p’*-DDT administered in equal daily doses over a 12-day period (Karlsson et al. 1974).

### 2.3.5 Reproductive Effects

No experimental studies were located regarding reproductive effects in reptiles and amphibians from exposure to DDT/DDE/DDD. Little information is available concerning reproductive effects from DDT/DDE/DDD exposures in wild mammals. In birds, the well-publicized decline in wild raptor populations, including the bald eagle, during the 1950s and 1960s was attributed partly to reproductive impairment, particularly eggshell thinning (see Section 2.3.2.7, Eggshell Thinning in Birds). Egg production, fertility, and hatchability were largely unaffected in numerous studies in a variety of bird species. However, increased embryolethality, decreased egg size, delayed oviposition after mating, and increased testicular effects were observed with some regularity among experimental studies in birds. Several authors speculated that the effects were due to DDT-induced hormonal imbalances, and in fact, blood hormone levels (estrogen, luteinizing hormone) were altered in three of four studies in birds consuming either DDT or DDE in the diet. While the mechanisms of toxicity for these effects have not been thoroughly investigated in wildlife, and thus the direct relevance to human health is uncertain, the consistency of certain reproductive effects suggests that wildlife species may be appropriate sentinels for reproductive toxicity of DDT/DDE/DDD in humans.

**Mammals.** Short-tailed shrews showed testis weights that were not significantly different from controls after consuming an earthworm diet containing an average of 16.6 ppm DDT for 3 weeks (unspecified isomeric composition) (Braham and Neal 1974).

**Birds.** Ovary weight and oviduct weight were not significantly affected in adult female Japanese quail (*Coturnix coturnix japonica*) administered *o,p’*-DDT by intramuscular injection at 5 mg/bird on each of 4 consecutive days (Cooke 1970b). Ovary weights were significantly reduced in an exposure-related manner in Japanese quail fed diets containing between 700 and 1,600 ppm *p,p’*-DDT for 20 days (Gish and Chura 1970); the effect was more pronounced in treatment groups with relatively lower body weights. Increases in oviduct weight and uterine glycogen content were observed in chickens and Japanese quail administered 50 mg/bird of *o,p’*-DDT (but not in birds administered *p,p’*-DDT) by intraperitoneal injection on 3 consecutive days; the increases were comparable to those seen in birds injected 3 times with 0.5 mg 17β-estradiol (Bitman et al. 1968). Ovary and oviduct weights were
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significantly decreased in ringed turtle doves fed diets containing 100 ppm \( p,p' \)-DDE for a 3-week period prior to pairing for mating (Keith and Mitchell 1993).

Latency time between first pairing and first oviposition was significantly increased compared to controls in Mallard hens fed diets containing 10 ppm DDE (isomeric composition not reported) for 2 months prior to pairing and through the breeding season (Vangilder and Peterle 1980). Delayed oviposition after initial pairing (compared to controls), attributed by the authors to delayed ovulation, was observed in Japanese quail fed diets containing either 100 ppm \( p,p' \)-DDT or 100 ppm \( p,p' \)-DDE (the only exposure levels tested) for up to 74 days (Cecil et al. 1971). The incidence of delayed oviposition was significantly increased in a dose-related manner in Bengalese finches (\textit{Lonchura striata}) after dietary exposure to \( p,p' \)-DDT at up to 0.3 mg/bird/day (dose levels were not reported) for at least 15 weeks (Jefferies 1967, 1969). Jefferies (1967) hypothesized that the proximal cause of the delay in oviposition in Bengalese finches was delayed ovulation because of underdeveloped ovaries; he further postulated that DDT may have induced an estrogen-like inhibition of FSH and LH secretion by the pituitary thus, follicle stimulating hormone (FSH) and luteinizing hormone (LH) stimulation of ovary development may have been inhibited. An exposure-related significant increase (compared to controls) in median latency period between pairing for mating and the first oviposition was seen in ringed turtle doves (\textit{Streptopelia risoria}) fed diets containing 10 and 40 ppm \( p,p' \)-DDE for approximately 90 days (Richie and Peterle 1979); in doves fed 40 ppm, there was also a delay and a nonsignificant suppression in peak serum LH levels after pairing, compared to controls (Richie and Peterle 1979), although the authors did not believe the findings established a clear causal relationship. Significantly delayed oviposition, associated with significantly reduced blood estradiol (compared to controls) and significantly increased hepatic enzyme metabolism of estradiol at 8 days postmating (but not in birds after completing their clutch), was observed in ringed turtle doves fed diets containing 10 ppm \( p,p' \)-DDT for 3 weeks prior to mating (Peakall 1970).

Egg production was not significantly affected in American kestrels (\textit{Falco sparverius}) fed diets containing unreported levels (reportedly calculated to be “just short” of the lethal level) of DDT (unspecified isomeric composition) for at least a full year that encompassed two breeding seasons, nor was an effect seen in first-year young that were fed DDT at the parental dietary levels and bred in the second breeding season of the study (Porter and Wiemeyer 1969). Interestingly, mean egg production was significantly increased in two consecutive breeding seasons in barn owls fed diets containing 3 ppm DDE (unspecified isomer) for several months prior to the first breeding season and for almost 2 years before the second (Mendenhall et al. 1983). The reasons for this were compensatory egg production that
occurred in the DDE-fed owls, which replaced eggs that were lost due to breakage, and re-nesting that occurred among owls that lost their entire clutches.

Egg production per hen was not significantly affected in Mallards fed #40 ppm \( p,p'-\text{DDT}, p,p'-\text{DDE}, \) or technical grade DDD in the diet either for several weeks or over 1 year (Heath et al. 1969). Egg production was not significantly affected in Mallards (\textit{Anas platyrhynchos}) exposed to 40 ppm \( p,p'-\text{DDE} \) in the diet for 1–4 months (Risebrough and Anderson 1975) or 10 ppm DDE (isomeric composition not reported) for 2 months prior to pairing and through the breeding season (Vangilder and Peterle 1980). Egg production and embryonation (the production of an embryo within the egg) were not significantly affected in black duck (\textit{Anas rubripes}) clutches that were laid after approximately 5 months of exposure to 10 or 30 ppm (the only levels tested) \( p,p'-\text{DDE} \) in the diet (Longcore et al. 1971).

Egg production was significantly decreased in Japanese quail fed technical grade DDT in the diet at 10–100 ppm (but not at 3 ppm) for up to 95 days (Kenney et al. 1972). However, egg production was not significantly affected in Japanese quail fed up to 200 ppm \( p,p'-\text{DDE} \) for 13 weeks or up to 40 ppm \( p,p'-\text{DDT} \) for 16 weeks, or in Pharol D-1 quail fed diets containing up to 40 ppm \( p,p'-\text{DDT} \) for 12 weeks (Davison et al. 1976). Egg production was significantly decreased in Japanese quail that were on restricted diets for approximately 10 days prior to dietary exposure to \$700 \text{ ppm} \) (lowest level tested) of \( p,p'-\text{DDT} \) for 20 days, but not consistently in birds fed normal quantities of food prior to exposure (Gish and Chura 1970). Egg production was not significantly affected in chickens or in Japanese quail by dietary exposure to up to 100 ppm of DDT/DDE/DDD (a commercial mix of DDT compounds) for up to 10 weeks (Scott et al. 1975). There was no consistent effect on egg production in three consecutive generations of Japanese quail fed diets containing up to 50 ppm DDT (isomeric composition not specified) for their lifetime (Shellenberger 1978). Significantly reduced first-month egg production was observed in Japanese quail fed diets containing 100 ppm \( p,p'-\text{DDE} \) for up to 74 days, but not in those fed 100 ppm \( p,p'-\text{DDT} \) (the only exposure levels tested); egg production during 3 subsequent months was not significantly different from control levels in both treatment groups (Cecil et al. 1971). Chickens fed \( p,p'-\text{DDT} \) at up to 200 ppm in the diet for 12 weeks showed no significant changes relative to controls in egg production (eggs/bird; eggs/clutch) (Davison and Sell 1972). No significant effect on egg production was observed in chickens orally administered 40 mg technical grade DDT/chicken on 5 days (Chen et al. 1994). No effect on egg production was seen in laying bobwhite quail (\textit{Colinus virginianus}) orally administered up to 20 mg/bird of DDT (unspecified isomeric composition) by capsule every other day during a 4-week exposure period (Wilson et al. 1973). Pheasant (\textit{Phasianus colchicus}) egg production was not significantly affected by exposure to up to 500 ppm technical grade DDT in the diet for at least
21 days prior to egg-laying until either the beginning of egg-laying or through egg-laying (Azevedo et al. 1965).

Egg production was significantly reduced by an average of 13.5% in ringed turtled doves fed diets containing 40 ppm of \( p,p' \)-DDE for 126 days (Haegle and Hudson 1973). Clutch size was unaffected in Bengalese finches by dietary exposure to \( p,p' \)-DDT at estimated dose levels of up to 0.3 mg/bird/day for at least 15 weeks (Jefferies 1969).

Egg weight and lipid content were reportedly not significantly affected compared with controls in barn owls (\textit{Tyto alba}) fed 3 ppm DDE (isomeric composition not reported) in the diet for up to 2 years that encompassed two breeding seasons (Mendenhall et al. 1983). Egg weights were not significantly affected in chickens fed \( p,p' \)-DDT at up to 200 ppm in the diet for 12 weeks relative to controls (Davison and Sell 1972). Decreased mean egg weight was observed in eggs of bobwhite quail hens orally administered 20 mg/bird of DDT (unspecified isomeric composition) by capsule every other day during a 4-week exposure period, but not in birds administered 10 mg/bird (Wilson et al. 1973). Egg size was significantly decreased in a dose-related manner in Bengalese finches after dietary exposure to \( p,p' \)-DDT at up to 0.3 mg/bird/day (dose levels were not reported) for at least 15 weeks (Jefferies 1969). Significantly reduced mean egg weight was observed in ringed turtle doves (\textit{Streptopelia risoria}) fed diets containing 10 ppm \( p,p' \)-DDT for 3 weeks prior to mating (Peakall 1970).

Egg fertility was not significantly affected in American kestrels fed diets containing unreported levels (reportedly calculated to be “just short” of the lethal level) of DDT (unspecified isomeric composition) for at least a full year that encompassed two breeding seasons, nor was an effect seen in first-year young that were fed DDT at the parental dietary levels and bred in the second breeding season of the study (Porter and Wiemeyer 1969). However, among parental groups of kestrels, significantly decreased egg hatchability was observed in at least one of the two breeding seasons (Porter and Wiemeyer 1969), and among yearling breeders, significantly decreased egg hatchability was observed in DDT-treated groups compared to untreated controls (Porter and Wiemeyer 1969). Egg hatchability was significantly decreased compared to controls in Mallard hens fed diets containing 10 ppm DDE (isomeric composition not reported) for 2 months prior to pairing and through the breeding season (Vangilder and Peterle 1980). Hatchability and fertility of pheasant eggs were not significantly affected by exposure to up to 500 ppm technical grade DDT in the diet for at least 2 days prior to egg-laying until either the beginning of egg-laying or through egg-laying (Azevedo et al. 1965). Egg hatchability was not significantly affected in chickens or in Japanese quail exposed to #100 ppm of DDT/DDE/DDD (a commercial mix of DDT

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compounds) in the diet for up to 10 weeks (Scott et al. 1975). There was no consistent effect on egg fertility or hatchability in three consecutive generations of Japanese quail fed diets containing up to 50 ppm DDT (isomeric composition not specified) for their lifetime (Shellenberger 1978). Egg hatchability was not significantly affected in Japanese quail fed 200 ppm technical grade DDT in the diet for either the first or second week of the laying period (Jones and Summers 1968). Decreased fertility and hatchability were observed in eggs of bobwhite quail hens orally administered 20 mg/bird of DDT (unspecified isomeric composition) by capsule every other day during a 4-week exposure period, but not in birds administered 10 mg/bird (Wilson et al. 1973). Egg hatchability was reduced, but not significantly, in ringed turtled doves fed diets containing 40 ppm of \( p,p' \)-DDE for 126 days (Haegele and Hudson 1973).

Compared to controls, significantly increased embryolethality was observed in the eggs of yearling kestrels fed diets, since fledging, containing unreported levels of DDT (unspecified isomer) (Porter and Wiemeyer 1969). Embryonic survival was significantly decreased late in the incubation period in Mallard ducks fed $10 \text{ ppm } p,p' \text{-DDE}$ for 2–3 weeks or for over 1 year; no significant effect on embryolethality was seen in ducks fed \( p,p' \)-DDT or technical grade DDD for over 1 year (Heath et al. 1969). Embryolethality in intact eggs was significantly increased in black duck (\emph{Anas rubripes}) clutches that were laid after approximately 5 months of exposure to 10 or 30 ppm (the only levels tested) \( p,p' \)-DDE in the diet (Longcore et al. 1971).

Overall reproductive performance score (a composite index accounting for egg production, egg hatchability, and fledging rate) was significantly decreased (primarily from a decrease in fledging rate, i.e., chick survival) compared with untreated controls in ringed turtle doves fed diets \emph{ad libitum} containing 100 ppm \( p,p' \)-DDE for a 3-week period prior to pairing for mating; egg production was eliminated in birds that were fed DDE and were provided 10–30\% less food than controls that were fed \emph{ad libitum} (Keith and Mitchell 1993). See Section 2.3.8 Developmental for further discussion of fledgling survival. In another study, although egg production, egg fertility, and egg hatchability in pheasants fed diets containing up to 400 ppm DDT (unspecified isomeric composition) for at least 3 weeks were not significantly different from controls, the cumulative effect of the nonsignificant changes (reported as relative reproductive success rate-recruitment rate of chicks to 13 days of age) was markedly decreased in an exposure-related manner (Genelly and Rudd 1956).

Testis weight was not significantly affected in adult male Japanese quail orally administered 9 doses of 10 mg \( o,p' \)-DDT/bird over 3 weeks (Cooke 1970b). Testis weights were significantly reduced in an
exposure-related manner in male Japanese quail fed diets containing between 700 and 1,600 ppm p,p'-DDT for 20 days (Gish and Chura 1970); the effect was more pronounced in treatment groups with relatively lower body weights. Testis size and secondary sex characteristics were markedly reduced compared to controls in White Leghorn cockerels injected subcutaneously for 60–89 days at DDT (unspecified isomer) dose levels that increased from 15 to 300 mg/kg/day during the exposure period (Burlington and Lindeman 1950). Testis weights and secondary sex characteristics were also “strikingly” decreased in cockerels orally administered (unspecified administration technique) DDT (unspecified isomer) at 6.25–50 mg/kg/day for 47 weeks (George and Sunararaj 1995); relative testis weight was decreased up to 20% of control testis weights. Testis weights were not significantly affected in Bengalese finches exposed to \#0.3 mg/bird/day p,p'-DDT for at least 15 weeks (Jefferies 1969). Testis weights were unaffected in ringed turtle doves fed diets containing 100 ppm p,p'-DDE for a 3-week period prior to pairing for mating (Keith and Mitchell 1993).

No effect on spermatogenesis was observed in testes of bald eagles (Haliaetus leucocephalus) fed a diet containing 10 ppm technical grade DDT for 60–120 days (Locke et al. 1966). Semen volume, percentage of live sperm, sperm motility, and sperm concentration were decreased and semen cholesterol concentration was increased in a dose-related manner in White Leghorn cockerels administered oral doses (unspecified administration technique) of DDT (unspecified isomeric composition) ranging from 6.25 to 50 mg/kg/day for 47 weeks (George and Sundararaj 1995); effects persisted for 21 weeks following cessation of exposure.

“Marked” testicular degeneration was seen in one of three bald eagles fed 4,000 ppm technical grade DDT in the diet for 15 days; the other two birds died after 15 and 23 days of exposure (Locke et al. 1966). Testicular degeneration was seen in one eagle fed 160 ppm technical grade DDT for 112 days, but not in another eagle that died after 76 days at the same exposure level (Locke et al. 1966). No gross gonad lesions were observed in 6-week-old chicks of pheasants fed 100 ppm technical grade DDT for up to 101 days, or 500 ppm for up to 23 days (Azevedo et al. 1965). Testes of cockerels orally administered 50 mg/kg/day (but not at lower doses) of DDT (unspecified isomeric composition) for 47 weeks showed a variety of microscopic pathologies that persisted after cessation of exposure, most notably testicular atrophy, and including “markedly” irregular seminiferous tubule size and shape, desquamation of spermatogonia, and pyknosis of germ cells (George and Sundararaj 1995).

Plasma 17β-estradiol concentration was significantly decreased in chickens after a 5-day oral exposure to technical grade DDT at 40 mg/hen/day (Chen et al. 1994). Blood estradiol was significantly reduced...
(compared to controls) at 8 days postmating in ringed turtle doves (*Streptopelia risoria*) fed diets containing 10 ppm *p,p'*-DDT for 3 weeks prior to mating, but not in birds allowed to complete their clutch (Peakall 1970). In ringed turtle doves fed 40 ppm *p,p'*-DDE for 90 days (but not in those fed 10 ppm), there was a delay and a nonsignificant suppression in peak serum LH levels after pairing for mating, compared to controls (Richie and Peterle 1979); a concurrent delay in oviposition was observed. Since LH is a glycoprotein gonadotropin that stimulates corpora lutea formation and ovulation in females (Hadley 1984), the delay and transient suppression of peak LH levels after mating could have caused the delay in oviposition by delaying ovulation, although Richie and Peterle (1979) did not believe that the evidence indicated a clear cause and effect association.

### 2.3.6 Eggshell Thinning in Birds

Eggshell thinning in birds reached widespread public awareness in the 1960s and 1970s largely because of field observations of eggshell thinning in high-profile raptors like the bald eagle, peregrine falcon, and osprey, and the association of these observations with abrupt population declines. Field observations and experimental studies established a scientific link between DDT/DDE/DDD exposure, particularly DDE, and avian eggshell thinning, which weighed significantly in the decision to ban most domestic crop uses of DDT in the 1970s (EPA 1975). A large body of literature was developed during the 1960s and 1970s regarding the effects of DDT/DDE/DDD on eggshell integrity in birds; experimental findings on eggshell thinning are provided below. In general, raptors, waterfowl, passerines, and nonpasserine ground birds were more susceptible to eggshell thinning than domestic fowl and other gallinaceous birds, and DDE appears to have been a more potent inducer of eggshell thinning than DDT (Cooke 1973b; EPA 1975; Lundholm 1997; WHO 1989). Further, reproductive disturbances associated with DDT/DDE/DDD exposure continue to be reported in North American populations of predatory birds and/or birds that migrate to regions such as South America where DDT is still used (Lundholm 1997).

There is some question, however, as to the relevance of avian eggshell thinning to human health. Birds possess a shell gland—a specialized segment of the oviduct—that has no anatomical or physiological counterpart in humans. The function of the shell gland is to lay down calcite (*CaCO_3* - calcium carbonate) onto the developing avian egg to form the eggshell (EPA 1975). Reduced total calcium deposition as calcite, rather than reduced percent calcium in the eggshell, has been hypothesized to be the proximal cause of avian eggshell thinning (Davison 1978). Mechanisms of action that involve a direct action of DDT/DDE/DDD on the shell gland itself probably have no human relevance, but mechanisms of action that involve intermediate effects, such as reduced blood calcium, may have relevance to human
health. Possible mechanisms of eggshell thinning in birds have been extensively studied and reviewed (Cooke 1973b; EPA 1975; Lundholm 1997; Peakall et al. 1975; WHO 1989). Early experimental work focused the eggshell thinning mechanism debate on calcium metabolism as opposed to carbonate availability (EPA 1975).

An early review (Peakall et al. 1975) summarized two sets of hypotheses based on a discussion by Cooke (1973c) concerning possible mechanisms of reduced calcium deposition by the shell gland on the developing egg. One set of hypotheses (including effects to the thyroid, parathyroid, and adrenals, as well as hypotheses involving estrogen mimicry) suggested that the calcium supply to the eggshell gland was reduced, and involved an expected intermediate effect of decreased blood calcium. However, available data indicate that blood calcium level in birds was generally not sensitive to DDT/DDE/DDD exposures even in species in which eggshell thinning has been observed (Lundholm 1997; Peakall et al. 1975; see Section 2.3.3, Systemic Effects - Metabolic, above). The alternative set of hypotheses suggested that the functionality of the shell gland itself in laying down the calcium-based shell was impaired in spite of an adequate supply of calcium. Shortly after the DDT ban, a leading hypothesis for DDE-induced eggshell thinning was an inhibition of calcium ATP-ase in the shell gland; calcium ATP-ase is believed to act as a pump to produce active transport of Ca\(^{2+}\) from blood in shell gland mucosal capillaries into the lumen of the shell gland (EPA 1975; Lundholm 1997). More recent work in ducks suggests that DDE does not directly inhibit calcium ATP-ase, but rather inhibits a signal for activating the calcium pump (Lundholm 1997). An estrogenic regulation of eggshell gland calcium secretion by DDT/DDE/DDD does not appear to be a tenable hypothesis (Lundholm 1997). A principle alternative hypothesis for DDE-induced eggshell thinning involves an inhibition by \(p,p'\)-DDE (but not by \(o,p'\)-DDE or DDT or DDD isomers) of prostaglandin synthesis in the shell gland mucosa (Lundholm 1997). Lundholm (1997) postulated that shell gland prostaglandin E\(_2\) acts as a signal for calcium ATP-ase transport of Ca\(^{2+}\) (coupled to bicarbonate transport) during eggshell formation, and summarized experimental work that demonstrated a direct inhibition of prostaglandin synthetase by \(p,p'\)-DDE.

There is still some question as to the primary mechanism of eggshell thinning, and reviewers have suggested that mechanisms of eggshell thinning may differ between bird species or differ with environmental conditions or physiological state for a given species. The following experimental results illustrate the potentially wide-spread occurrence of eggshell thinning in wild bird populations.

Barn owls (\textit{Tyto alba}) showed a substantial increase in egg breakage during incubation associated with significantly thinned eggshells during two breeding seasons (60–82% breakage in 3 ppm DDE-fed owls...
versus 3–5% in controls) encompassed within a 2-year exposure period; mean number of eggs hatched and mean number of young fledged per mated pair were significantly decreased in DDE-treated owls (isomeric composition of DDE not specified), but this was likely due to the increased egg fragility (Mendenhall et al. 1983). Among parental and yearling groups of breeding American kestrels, significantly increased egg disappearance (presumably from breakage or egg-eating by parental birds) and significantly decreased eggshell thickness were seen in at least one of two consecutive breeding seasons after kestrels were fed unreported levels of DDT (unspecified isomer) in the diet for at least 1 year that encompassed the two breeding seasons (Porter and Wiemeyer 1969).

Mallard ducks (*Anas platyrhynchus*) fed 25 ppm *p,p*′-DDT in the diet (but not at #10 ppm) or $10 \text{ ppm } p,p′-\text{DDE}$ for either 2–3 weeks or for over 1 year showed a significant increase in percent eggs cracked and a decrease in eggshell thickness; no eggshell effects were seen in ducks fed technical grade DDD for over 1 year (Heath et al. 1969). Egg breakage, due to significantly decreased eggshell thickness, was increased compared to untreated controls in Mallards (*Anas platyrhynchus*) after dietary exposure to 40 ppm *p,p*′-DDE for 1–4 months (Risebrough and Anderson 1975). Eggshell thickness was significantly decreased compared to controls in Mallard hens fed diets containing 10 ppm DDE (isomeric composition not reported) for 2 months prior to pairing and through the breeding season (Vangilder and Peterle 1980). Percent of eggs that cracked during incubation and eggshell thinning were significantly increased in black duck (*Anas rubripes*) clutches that were laid after approximately 5 months of exposure to 10 or 30 ppm (the only levels tested) *p,p*′-DDE in the diet (Longcore et al. 1971).

Japanese quail (*Coturnix coturnix japonica*) showed significantly decreased eggshell weight after being fed technical grade DDT in the diet at $10 \text{ ppm for up to 95 days}$ (Kenney et al. 1972). However, neither eggshell weight nor eggshell thickness were significantly affected in Japanese quail fed up to 200 ppm *p,p*′-DDE for 13 weeks or up to 40 ppm *p,p*′-DDT for 16 weeks, or in Pharol D-1 quail fed diets containing up to 40 ppm *p,p*′-DDT for 12 weeks (Davison et al. 1976). Breaking strengths of eggshells was not significantly affected in chickens or in Japanese quail by dietary exposure to up to 100 ppm of DDT/DDE/DDD (a commercial mix of DDT compounds) for up to 10 weeks (Scott et al. 1975). A nonsignificant increase in egg breakage and significantly decreased eggshell calcium were observed in Japanese quail fed 100 ppm *p,p*′-DDT for up to 74 days, but not in those fed 100 ppm *p,p*′-DDE; eggshell thickness and eggshell weight were not significantly affected in both exposure groups (Cecil et al. 1971). Chickens fed *p,p*′-DDT at up to 200 ppm in the diet for 12 weeks showed no significant changes relative to controls in eggshell weights, eggshell calcium, and eggshell thickness (Davison and Sell 1972). Decreased eggshell thickness and shell membrane thickness, along with decreased serum calcium, were
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observed in eggs of bobwhite quail hens (Colinus virginianus) orally administered 20 mg/bird of DDT (unspecified isomer) by capsule every other day during a 4-week exposure period; no changes were seen in birds administered 10 mg/bird every other day for 4 weeks (Wilson et al. 1973). No significant effect on eggshell thickness was seen in chickens orally administered daily doses of 40 mg technical grade DDT/bird for 5 days (Chen et al. 1994).

Ringed turtle doves (Streptopelia risoria) fed diets containing 40 ppm p,p'-DDE for 126 days showed significantly reduced eggshell thickness by an average of 10% compared to controls (Haegele and Hudson 1973). Significantly reduced deposition of calcium in eggs (as measured by $^{45}$Ca incorporation) was observed in ringed turtle doves fed diets containing 10 ppm p,p'-DDT for 3 weeks prior to mating; breeding females were orally administered $^{45}$Ca on the day before pairing for mating (Peakall 1970). Peakall (1970) observed a significant decrease in eggshell weights associated with significantly reduced oviduct carbonic anhydrase (which is involved in the secretion of calcareous eggshell) activity in ringed turtle doves injected intraperitoneally with 150 mg/kg p,p'-DDE within 1 day of laying the first egg of the clutch; since exposure occurred at the end of egg development, the authors concluded that DDE interfered directly with eggshell formation at the oviduct, rather than indirectly by affecting blood estradiol. Eggshells were respectively 35 and 20% thinner than controls in ringed turtle doves after a 3-week dietary exposure to 100 ppm DDE (unspecified isomeric composition) and in Pekin ducks (domesticated Mallards: Anas platyrhyncus) fed diets containing 250 ppm DDE for 10 days; no other exposure levels were tested (Peakall et al. 1975).

2.3.7 Developmental Effects

No experimental studies were located regarding developmental effects in wild mammals from exposure to DDT/DDE/DDD.

Little information is available concerning developmental effects in amphibians, but effects in reptile and bird populations have received considerable attention. Studies of alligator populations at Lake Apopka in Florida, where a pesticide spill occurred in 1980, have reported various effects that may ultimately affect reproduction in the population, including reduced clutch viability (Woodward et al. 1993), altered steroidogenesis (Guillette et al. 1995), abnormal ovarian morphology and plasma 17β-estradiol levels in female alligators (Guillette et al. 1994), and reductions of phallus size and serum testosterone in male alligators (Guillette et al. 1994, 1995, 1996, 1997, 1999), compared to alligators at control lakes where environmental concentrations of pesticides including DDT/DDE/DDD were relatively low. The
purported estrogenicity of DDT and other contaminants was hypothesized to have induced hormonal imbalance in Lake Apopka alligators, causing the observed effects. Since the alligators were exposed to a complex mixture of environmental contaminants at Lake Apopka, the contribution of DDT/DDE/DDD to the observed effects is uncertain. However, findings in an experimental study of in ovo DDE exposures in alligators (Matter et al. 1998) support the hypothesis that certain DDT-related compounds induce estrogenic effects in reptiles, potentially ultimately affecting reproduction in the population.

In birds, the most consistently reported developmental effect was a reduction in early posthatch survival in chicks after oral exposures to DDT or DDE in maternal birds. Reduced chick survival was observed in six bird species after acute to chronic experimental exposures, regardless of whether all of the maternal exposure occurred only prior to pairing for mating, only after mating (e.g., only during the hatching phase of reproduction), or both. While the mechanism of DDT-induced reduced chick survival has not been thoroughly studied, investigators have hypothesized that increased body burden of DDT in chicks may cause direct toxicity, or that reduction in parental care-giving among treated birds may result in chick malnutrition and poor survival. Other developmental effects in birds included a decreased ability to thermoregulate and behavioral alterations in chicks of treated parental birds, and reduced testicular development in chicks directly administered DDT. Wildlife species may be appropriate sentinels of developmental effects in humans because certain effects, particularly reduced early survival in young, occurred consistently across several species under various exposure conditions.

Reptiles. Production of vitellogenin (suggestive of estrogenic activity) was not induced in 21-day-old American alligators (Alligator mississippiensis) exposed in ovo during gonadal differentiation (at male-producing incubation temperatures) with p,p'-DDE and o,p'-DDE painted onto the outer surface of the eggshell at exposure levels ranging from 0.1 to 10 µg DDE/kg of egg (Matter et al. 1998). Vitellogenin is a protein precursor of egg proteins that is produced in the liver of oviparous and ovoviviparous species and is normally found in the blood of these animals in measurable quantities; production of vitellogenin is stimulated by estrogens in the blood that are produced in the ovary; thus, it is normally absent in the blood of males (Hadley 1984). However, a significant decrease in percent male hatchlings and significantly decreased clitoral and penis sizes compared to controls were seen in 21-day-old alligators pooled from groups exposed in ovo to $1 \mu g \ p,p'\text{-DDE/kg of egg}$ painted onto the eggshell; no significant effects were seen in alligators pooled from groups exposed to $0.3 \mu g \ p,p'\text{-DDE/kg of egg}$ in ovo (Matter et al. 1998). Treatment of alligator eggs with o,p'-DDE during gonadal differentiation led to a significant decrease in percent male hatchlings in the low exposure group ($0.3 \text{ ppm}$), but not in the high exposure group ($1 \text{ ppm}$); nonsignificant decreases in clitoral/penis size were also seen in low exposure (but not in
high-exposure animals) that were exposed in ovo to o,p'-DDE (Matter et al. 1998). The lack of a dose-response for these effects after o,p'-DDE exposures in this study calls into question the biological significance of the results observed in the low exposure group.

Amphibians. Common frog (Rana temporaria) tadpole metamorphosis was significantly delayed compared to controls in tadpoles exposed for 28 days to 0.001 ppm p,p'-DDT in the surrounding water, but not in tadpoles exposed to 0.0001 ppm; abnormal spinal development was seen in 3/8 and 3/10 tadpoles in the low and high exposure groups, respectively, but not in controls (Cooke 1973a). Similar significantly delayed development was seen in common frog tadpoles exposed as eggs to 0.5 ppm DDT (unspecified isomeric composition) in the water column for only 24–48 hours (Cooke 1972). Altered facial features were observed in tadpoles of common frogs within 48 hours of a 1-hour exposure to $1 ppm p,p'$-DDT; metamorphosis also appeared to be delayed (Cooke 1970a).

Birds. Significantly decreased early chick survival was observed compared to untreated controls among chicks of yearling kestrels fed unreported levels of DDT (unspecified isomer) in the diet since they were fledged the previous year (Porter and Wiemeyer 1969). Survival to 14 days posthatch was significantly decreased (approximately 35% decrease from control survival rate) in Mallard ducklings (Anas platyrhynchus) hatched from hens fed 25 ppm p,p'-DDT in the diet (but not at #10 ppm) for either 2–3 weeks or for over 1 year; no effect on posthatch survival was seen in ducklings of hens fed p,p'-DDE or technical grade DDD for over 1 year (Heath et al. 1969). Duckling survival was significantly decreased in black duck (Anas rubripes) clutches that were laid after approximately 5 months of exposure to 10 or 30 ppm (the only levels tested) p,p'-DDE in the diet (Longcore et al. 1971). Pheasant chick (Phasianus colchicus) survival was significantly decreased in an exposure-related manner in groups fed 100 (lowest level tested) and 400 ppm DDT (isomeric composition not reported) for at least 3 weeks (Genelly and Rudd 1956). Chick survival was significantly depressed during the first 7 days posthatch in pheasants fed diets containing 500 ppm technical grade DDT (but not at 10–100 ppm) from at least 21 days prior to egg-laying until either the beginning of egg-laying or through egg-laying (Azevedo et al. 1965). Survival of Japanese quail (Coturnix coturnix japonica) chicks was significantly reduced compared to controls in groups fed 200 ppm technical grade DDT in the diet for either the first or second week of the laying period; egg hatchability was reportedly not significantly affected by DDT treatment, but 79% of chick mortality occurred within 3 days of hatching (Jones and Summers 1968); the authors concluded that lethal levels of DDT were transferred to the egg and accumulated in the developing chicks during incubation. Survival of Japanese quail, including chicks, was comparable to control group survival throughout a 3-generation reproductive toxicity assay in which birds were administered up to
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50 ppm DDT (unspecified isomeric composition) in the diet (Shellenberger 1978). Fledging rate (i.e., chick survival) was decreased to 85% (compared to 100% in controls) in ringed turtle doves (*Streptopelia risoria*) fed diets *ad libitum* containing 100 ppm *p,p*-DDE for a 3-week period prior to pairing for mating (Keith and Mitchell 1993); the decrease in chick survival was related to decreased nest attendance by parental birds, and the authors hypothesized that losses in young birds were related to decreased food intake by the chicks. No association between posthatch parental nest attendance and decreased survival in chicks was observed during the first 21 days posthatch in another study in ringed turtle doves at a lower exposure level. Survival during the first 21 days posthatch was significantly reduced compared to controls (by a factor of 2) in chicks of ringed turtle doves fed diets containing 40 ppm of *p,p*-DDE for 126 days (Haegele and Hudson 1973).

Growth, as measured by body weight and foot pad length was reportedly not significantly affected in nestling red-tailed hawks (*Buteo jamaicensis*) fed technical grade DDT at 20 mg/kg body weight every 4th day during an exposure period lasting up to 80 days (Seidensticker 1968). Growth of Japanese quail, as measured by body weight, was comparable to control group growth during a 3-generation reproductive toxicity assay in which birds were administered up to 50 ppm DDT (unspecified isomeric composition) in the diet throughout the study (Shellenberger 1978). No effect on chick weight was seen in bobwhite quail (*Colinus virginianus*) administered up to 20 mg/bird of DDT (unspecified isomeric composition) every other day during a 4-week exposure period (Wilson et al. 1973).

Failure to thermoregulate under cooling thermal stress (measured by cloacal temperature) was seen in a greater proportion (50%) of Mallard ducklings (*Anas platyrhyncus*) of hens fed diets containing 10 ppm DDE (unspecified isomeric composition) for 2 months prebreeding and through the breeding season than in ducklings of control hens (30%) (Vangilder and Peterle 1980). Among ducklings that did thermoregulate during cooling thermal stress, there was significantly greater body weight loss and significantly decreased survival time compared to control ducklings that did thermoregulate (Vangilder and Peterle 1980).

Testis development was “markedly retarded” and development of secondary sex characteristics was inhibited in cockerels administered daily subcutaneous injections of DDT (unspecified isomeric composition) for up to 81 days starting on the 8th day posthatch; daily dose was unreported, but cumulative dose was 2–3 g/cockerel (Burlington and Lindeman 1952). Similar results were seen in another subcutaneous administration study in cockerels administered DDT (unspecified isomer) at dose
levels that increased from 15 to 300 mg/kg/day over a 60- to 89-day exposure period (Burlington and Lindeman 1950).

No effect on plumage development was seen in nestling red-tailed hawks (*Buteo jamaicensis*) fed technical grade DDT at 20 mg/kg body weight every 4th day during an exposure period lasting up to 80 days (Seidensticker 1968).

Behavioral changes were observed in Mallard ducklings of hens that were fed 3 ppm *p,p'-DDE* in the diet for at least 3 months compared to controls; effects included significant hyper-responsiveness in a maternal approach stimulus test and significant under-responsiveness in a noise avoidance test (Heinz 1976).

### 2.3.8 Genotoxic Effects

No experimental studies were located regarding genotoxic effects in wildlife from exposures to DDT/DDE/DDD.

### 2.3.9 Cancer

No experimental studies were located regarding carcinogenic effects in wildlife from exposures to DDT/DDE/DDD.

### 2.4 TOXICOKINETICS

**Overview.**

Although oral exposure is considered the most significant route of entry in humans, DDT, DDE, and DDD are absorbed following inhalation, oral, and dermal exposures. Oral exposure to DDT, DDE, and DDD results in preferential absorption by the intestinal lymphatic system. Some absorption into the portal blood also occurs. Limited data exist regarding the rate and extent of DDT absorption in humans. DDT, DDE, and DDD are readily distributed in the lymph and blood to all body tissues and ultimately stored in proportion to the lipid content of the tissue, regardless of the route of exposure. Metabolism of DDT in humans appears similar to that seen in rats, mice, and hamsters, except that not all intermediate metabolites detected in animals have been identified in humans. Excretion of DDT in the form of its metabolites (e.g., DDA and its conjugates) is largely via the urine, regardless of route of exposure, but
DDT excretion may occur via feces, semen, and breast milk. Some experiments have suggested that fecal excretion may be the major route of elimination at high doses; however, this has not been confirmed by later investigations.

2.4.1 Absorption

2.4.1.1 Inhalation Exposure

Absorption of DDT by the lung is considered to be a minor route of entry. It is assumed that the large particle size of DDT (crystalline) prevents it from entering the deeper, smaller spaces of the lung, and that it is deposited on the upper respiratory tract mucosa and then eventually swallowed because of the action of the mucociliary apparatus (Hayes 1982). Some crystalline DDT, however, could be small enough to pass through the tracheal-bronchial passages. In occupational settings, human exposure has occurred by a mixture of routes, including inhalation with subsequent oral ingestion, and dermal absorption. Evidence of DDT absorption was indicated by the appearance of DDA (a DDT metabolite) in the urine (Laws et al. 1967; Ortelee 1958) and the presence of DDT in adipose tissue (Laws et al. 1967) and plasma or serum (Morgan et al. 1980; Rabello et al. 1975). However, no studies were located that quantify the rate or extent of absorption of DDT, DDE, or DDD in humans after inhalation exposure. No studies were located regarding the absorption of DDT, DDE, or DDD after inhalation exposure in animals.

2.4.1.2 Oral Exposure

Absorption following ingestion of DDT, DDE, and DDD is evident in humans both from measurements of serum and adipose tissue concentrations of these chemicals and from measurements of DDA in the urine (Hayes et al. 1971; Morgan and Roan 1971, 1974). Indirect evidence of absorption is provided in the development of toxicity following accidental or intentional (suicidal) ingestion of DDT (Hsieh 1954). In subjects chronically exposed to oral doses of DDT up to 20 mg/day (approximately 0.3 mg/kg/day), DDT appeared in the serum and reached peak serum concentrations 3 hours after ingestion (Morgan and Roan 1971). Serum levels remained elevated but returned to near pre-dose values 24 hours after each dose.

Gastrointestinal absorption can be inferred in animals. The presence of urinary metabolites in mice, rats, and hamsters (Fawcett et al. 1987; Gold and Brunk 1982, 1983, 1984), the presence of DDT and its metabolites in bile collections (Jensen et al. 1957), and the induction of tumors and other toxic effects in
animals after oral administration of DDT, DDE, or DDD provide evidence of gastrointestinal absorption. In animals, absorption of orally administered DDT is enhanced when it is dissolved in digestible oils (Keller and Yeary 1980). Approximately 70–90% of the administered dose is absorbed by rats after oral exposure to DDT in vegetable oils (Keller and Yeary 1980; Rothe et al. 1957). DDT is absorbed 1.5–10 times more effectively in laboratory animals when given in digestible oils than when dissolved in nonabsorbable solvents (Hayes 1982).

Gastrointestinal absorption by way of the intestinal lymphatic system plays a major role in the uptake of DDT in animals (Noguchi et al. 1985; Pocock and Vost 1974; Sieber 1976; Turner and Shanks 1980). For example, Sieber (1976) showed that 12–24% of the administered dose was recovered in the 24-hour lymph after intraduodenal administration of $^{14}$C-isomers to thoracic duct-cannulated rats, and most of the radioactivity was attributed to parent compounds. Other studies indicate that little DDT is absorbed from the gastrointestinal tract directly into the blood (Palin et al. 1982; Rothe et al. 1957).

2.4.1.3 Dermal Exposure

Dermal absorption of DDT in humans and animals is considered to be limited, but can be inferred by observation of toxicity after dermal application of DDT. Acute toxicity studies in several species demonstrate that toxicity, expressed as an LD$_{50}$, is less when DDT is applied dermally than when given by gavage or by injection, which reflects the difference in the amount of DDT absorbed by the dermal route. The data indicate that DDT is 4 times more toxic when given by intraperitoneal injection than when administered orally and 40 times more potent when given by intraperitoneal injection than when administered by the dermal route (Hayes 1982). Absorption of DDT from soil applied to the abdomen of monkeys, as extrapolated from urinary excretion data, was 3.3% of the applied dose in 24 hours (Wester et al. 1990).

2.4.2 Distribution

The distribution and storage of DDT in humans and animals has been extensively studied. DDT and its metabolites, DDE and DDD, are lipid-soluble compounds. Once absorbed, they are readily distributed via the lymph and blood to all body tissues and are stored in these tissues generally in proportion to organ tissue lipid content (Morgan and Roan 1971).
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Hayes et al. (1971) and Morgan and Roan (1971, 1974) evaluated the distribution of orally administered DDT, DDE, or DDD in volunteers. Morgan and Roan (1971, 1974) and Roan et al. (1971) measured the concentration of DDT, DDE, DDD, and DDA in blood, fat, and urine after oral dosing. The administered doses ranged from 5 to 20 mg DDT/kg/day for up to 6 months; the ratio of concentration of DDT stored in adipose tissue to that present in blood was estimated to be 280:1.

DDT uptake into tissues is a function of the blood flow, lipid content of that tissue, and the partition coefficient for DDT between the blood and lipids in specific organs. The ratio of DDT concentrations in adipose tissue to blood may remain relatively constant; however, the amount of DDT from past exposure cannot be determined from present blood levels only. DDT, DDE, and DDD have been reported to be distributed to and retained in the adipose tissue of humans (Morgan and Roan 1971). The affinity for storage in adipose tissue is related to each chemical's lipophilicity and increases in the order $p,p'$-DDD $> o,p'$-DDT $> p,p'$-DDT $> p,p'$-DDE (Morgan and Roan 1971).

DDT and DDE selectively partition into fatty tissue and into human breast milk which has a higher fat content than cow’s milk. Takei et al. (1983) reported concentrations from the 1969–1970 U.S. national human milk study. The $p,p'$-isomer of DDT and DDE was found in 100% of the samples tested, with mean concentrations of 0.19 and 1.9 ppm (lipid-basis), respectively. However, variance in levels of DDT and its metabolites may be influenced by such factors as number of children nursed, diet, and cigarette smoking (Bouwman et al. 1990; Bradt and Herrenkohl 1976). A steady decrease in the levels of DDT and its metabolites in human milk has been reported as a result of decreased intake of DDT. In Finland, samples taken between 1973 and 1982 indicate a reduction of more than 50% in total DDT concentration in human milk (Wickstrom et al. 1983). Using data from the United States and Canada, Smith (1999) estimated that since 1975, there has been an 11–21% decline in average DDT in breast milk. Table 5-4 shows levels of DDT and related compounds in breast milk from some recent studies.

The distribution of $p,p'$-DDT in newborn rats from dams administered $p,p'$-DDT in the diet before mating and throughout gestation was evaluated before and after suckling had occurred (Woolley and Talens 1971). In newborn rats sacrificed 0–1 hours after birth, before suckling had occurred, levels of $p,p'$-DDT were noted in the brain, liver, kidneys, and stomach. These results demonstrate that DDT readily passes through the placental barrier to enter tissues of the developing fetus. In newborn rats sacrificed after suckling, the tissue levels were relatively higher than levels in newborns before suckling. This could be attributed in part to the higher levels of DDT in the maternal milk, compared to DDT levels in maternal plasma (Woolley and Talens 1971). Recently, You et al. (1999) studied the transplacental and lactational deposition of DDT and its metabolites in rats.
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transfer of \( p,p' \)-DDE in rats. Pregnant rats were administered 10 or 100 mg \( p,p' \)-DDE/kg/day on gestation days (Gd) 14–18. In dams killed on day 15, the concentration of \( p,p' \)-DDE in the placenta was about 3-fold higher than in fetal tissues; similar observations were made in rats killed on Gd 17. Using a cross-fostering scheme, the authors found that lactational transfer provided the pups with a \( p,p' \)-DDE tissue burden far greater than that provided through placental transfer. For example, 10-day-old pups exposed only \textit{in utero} to the low-dose had no detectable \( p,p' \)-DDE in blood, liver, or brain (only samples collected); \( p,p' \)-DDE could be detected only in the liver of high-dose pups. In contrast, in pups exposed only via dam’s milk or through combined gestational and lactational exposure, \( p,p' \)-DDE was detected at much higher concentrations in the samples in the order of liver > brain > blood, and no significant differences were seen between the two groups. In 78-day-old rats, \( p,p' \)-DDE was detected only in fat in the three exposure groups, and rats exposed only \textit{in utero} had at least two orders of magnitude less \( p,p' \)-DDE in fat than the other two groups. In dams, at the end of nursing, \( p,p' \)-DDE levels in tissues and plasma were approximately 1/3 those at the end of gestation, suggesting that a large portion of the \( p,p' \)-DDE in storage sites was mobilized during lactation. See Section 2.4.5 for a description of physiologically based pharmacokinetic (PBPK) models developed by You et al. (1999) to describe transplacental and lactational transfer of \( p,p' \)-DDE.

The time course of distribution of DDT (evaluated as \( o,p' \)- and \( p,p' \)-isomers) in reproductive tissues of female rabbits was examined by Seiler et al. (1994). The rabbits were administered the test material by gavage 3 days/week for 12–15 weeks before artificial insemination and throughout gestation. The authors examined DDT residues in oviductal and uterine luminal fluid, cleavage stage embryos (day 1 postcoitum), blastocytes (day 6 postcoitum), and in fetuses, exocoelic fluid and placenta (day 11 postcoitum). No demonstrable residues were detected in cleavage stage embryos and tubal flushings. Relative to controls, DDT residues were significantly increased in blastocytes (14-fold), uterine fluid (7-fold), fetuses (40-fold), and exocoelic fluid (700-fold). The higher concentration of DDT residues found in fetuses relative to blastocytes suggested that transplacental passage may be more easily accomplished than passage into blastocytes via uterine secretions.

Mühlebach et al. (1991) examined the kinetics of distribution of \( p,p' \)-DDE in rats after a single intravenous dose of 5 mg/kg of the radiolabeled material. Peak concentrations of DDE were observed before 1 hour in the liver and muscle, at 3 hours in the skin, and between 1 and 4 days in adipose tissue. Between 4 and 14 days after exposure, the tissue/blood concentration ratio was about 6 for liver and muscle, 35 for skin, and 400 for adipose tissue. The results also showed that the distribution kinetics of
DDT, DDE, and DDD

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DDE was characterized by a redistribution from blood to liver and muscle, to skin, and ultimately to adipose tissue, and this process appeared to take about 1 day.

2.4.3 Metabolism

The metabolism of DDT, DDE, and DDD has been studied in humans and a variety of other mammalian species. The metabolism in rats, mice, and hamsters is similar to that in humans; however, not all of the intermediary metabolites identified in animals have been identified in humans. It has been proposed by a number of investigators that in mammals, the major urinary metabolite of DDT, 2,2-\(\text{bis}(\text{p}-\text{chlorophenyl})\) acetic acid (DDA), is produced by a sequence involving reductive dechlorination, dehydrochlorination, reduction, hydroxylation, and oxidation of the aliphatic portion of the molecule (Gingell 1976; Peterson and Robison 1964). In this proposed pathway (Model I: see Figure 2-2a), DDT is initially metabolized in the liver to two intermediary metabolites, DDE (Mattson et al. 1953; Pearce et al. 1952) and DDD (Klein et al. 1964). In rats, DDE is slowly converted in the liver to 1-chloro-2,2-\(\text{bis}(\text{p}-\text{chlorophenyl})\)ethene (DDMU), and then to DDA in the kidney by way of 1,1-\(\text{bis}(\text{p}-\text{chlorophenyl})\)ethene (DDNU) (Datta 1970; Datta and Nelson 1970). DDD is rapidly detoxified by way of DDMU to 1-chloro-2,2-\(\text{bis}(\text{p}-\text{chlorophenyl})\)ethane (DDMS) and then to DDNU (Datta 1970). Metabolism of DDMS to DDNU occurs in both the liver and kidney, but the kidney is the primary site (Datta 1970). DDNU is then further metabolized, primarily in the kidney, to 2,2-\(\text{bis}(\text{p}-\text{chlorophenyl})\)ethanol (DDOH) then to 2,2-\(\text{bis}(\text{p}-\text{chlorophenyl})\)ethanal (DDCHO) (Suggs et al. 1970), which is further oxidized to DDA (Peterson and Robison 1964).

Other evidence in mice and hamsters suggests an alternative metabolic scheme (Gold and Brunk 1982, 1983) (Model II: see Figure 2-2b). In these studies, one dose of radioactively-labeled DDT or DDD was administered by gavage, and urine was collected for 72 hours for analysis. The principal urinary metabolites were DDA and its conjugates. Few metabolite intermediates on the Model I pathway were isolated in the urine of DDT- or DDD-treated animals; however, if DDMU, a Model I pathway intermediate, was administered, downstream Model I metabolites were found in greater quantities. Based on this and the fact that deuterium labeling studies (Gold and Brunk 1984) indicate that removal of the alpha hydrogen from DDD is a rate limiting step in DDA formation, Gold et al. (1981) hypothesized that DDD is hydroxylated at the chlorinated 1-ethane side-chain carbon to yield 2,2-\(\text{bis}(\text{p}-\text{chlorophenyl})\)acetyl chloride (DDA-Cl), which in turn can be hydrolyzed to the major urinary metabolite, DDA. Epoxidation of DDMU, a minor metabolite of DDD in Model II (note that in Model I it is not minor), yields DDMU-epoxide (Gold et al. 1981). The major (Model II) urinary metabolite DDA-Cl, which is an electrophile
Figure 2-2a. Model I Metabolic Scheme for DDT*

*Adapted from Peterson and Robinson 1964
**Figure 2-2b. Model II Metabolic Scheme for DDT**

*Derived from Gold and Brunk 1982*
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capable of acylating nucleophilic cellular molecules, and the minor DDMU-epoxide metabolite may contribute to the known tumorigenicity of DDT and DDD via the formation of covalent DDA adducts in the mouse. Urinary metabolites were similar in both female Swiss mice and female Golden Syrian hamsters (Gold and Brunk 1982, 1983, 1984). The metabolic disposition of DDT, DDD, and DDMU in the hamster is similar to that of the mouse and proceeds by the same oxidative metabolic pathways in both species (Gold and Brunk 1983). Therefore, it is unlikely that the observed differences in species sensitivity to the DDT-induced tumorigenicity in the mouse and the resistance to tumor production from DDT exposure in the hamster are due to differences in the production of the DDMU-epoxide or DDA-Cl. However, there was a species difference in the metabolic conversion of DDT to DDE. DDE was detected at much higher levels in the urine of mice after both acute and chronic studies than in hamsters (Gingell 1976; Gold and Brunk 1983). The data indicate that the hamster was less efficient than the mouse in the conversion of DDT to DDE. Fawcett et al. (1987) evaluated the metabolism of radiolabeled DDT, DDE, DDD, and DDMU in male Wistar rats. These results suggested that the metabolism of DDT to DDA proceeding via the acid chloride (DDA-Cl), as had also been found in the mouse and hamster (Gold and Brunk 1982, 1983, 1984).

Several investigators have isolated DDT metabolites from human urine, serum, and adipose tissue. The DDT metabolites in humans are the same as some of those produced in animals and it can be inferred that the metabolic pathways in humans and animals are similar. In humans, ingested DDT undergoes reductive dechlorination to DDD, which is further degraded and readily excreted as DDA (Roan et al. 1971). DDT is also converted by dehydrodechlorination to DDE, although at a much slower rate than the DDT-to-DDD pathway (Morgan and Roan 1971). Morgan and Roan (1971) concluded that the conversion of DDT to DDE occurs with considerable latency and that the extent of the conversion was estimated to be less than 20% over the course of the 3-year study. Further metabolism of DDE is apparently slow, and DDE is retained in adipose tissue (Hayes et al. 1971; Morgan and Roan 1971). According to Roan et al. (1971) and Morgan and Roan (1971), oral administration of DDT or DDD to volunteers resulted in an increased urinary excretion of DDA, but no increase in excretion of DDA above predose values was noted after oral ingestion of DDE. According to the study authors, the data indicate that DDD, not DDE, is the precursor for DDA in humans and that little if any DDE is further converted to DDA.

After Phase I metabolism (reactions involving oxidation, reduction, and hydrolysis), many of the DDT metabolites ultimately are excreted in the conjugated form. Conjugates have been reported to include
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glycine, bile acid conjugates, serine, aspartic acid, and glucuronic acid (Gingell 1975; Pinto et al. 1965; Reif and Sinsheimer 1975).

DDT induces microsomal mixed function oxidases that are involved in the catabolism of both xenobiotics and many endogenous hormones. DDT has also been shown to induce its own metabolism in rats (Morello 1965) and hamsters (Gingell and Wallcave 1974). DDE and DDD have also caused the induction of hepatic cytochrome P-450 microsomal enzymes (Pasha 1981). DDT, DDE, and DDD were each found to be phenobarbital-type cytochrome P-450 inducers in male F344 rats, causing induction of hepatic CYP2B and less of CYP3A, but not CYP1A proteins (Nims et al. 1998). Limited induction of CYP1A1-associated enzyme activity was observed. DDT and DDE appeared to have similar inducing potencies, whereas the potency of DDD was within one order of magnitude lower than the other two compounds. Nims et al. (1998) further demonstrated that CYP2B induction resulting from DDT administration was due to the combined inductive effects of DDT, DDE, and DDD, and not exclusively to the DDE generated metabolically.

The metabolism of DDT can also produce methylsulfonyl metabolites which are potent toxicants, particularly in the adrenal gland, after metabolic activation. Methylsulfonyl metabolites of DDT (specifically 3- and 2-methylsulfonyl-DDE) were first identified in seal blubber from the Baltic Sea (Jensen and Jansson 1976); they have later been found in several species of animals (Bergman et al. 1994) and in humans (Weistrand and Noren 1997). Methylsulfonyl-DDE is formed as follows: products of the reaction between arene oxides, formed in phase I metabolism, and glutathione are degraded and excreted in the bile into the large intestine where they undergo cleavage by a microbial C-S lyase (Bakke et al. 1982; Preston et al. 1984). The thiols formed are methylated, reabsorbed, and the sulfur is further oxidized to the corresponding methylsulfones, which are distributed by the blood (Haraguchi et al. 1989). Further information regarding the toxicity of this metabolite is presented in Section 2.6 under Endocrine Effects.

2.4.4 Elimination and Excretion

Excretion of DDT has been studied in humans and a variety of animals. The major route of excretion of absorbed DDT in humans appears to be in the urine, but some excretion also occurs by way of feces (via biliary excretion) (Jensen et al. 1957) and breast milk (Takei et al. 1983). Results of studies with mice, rats, and hamsters indicate that the metabolites of DDT and small amounts of unmetabolized DDT are excreted primarily in the urine and feces (Gold and Brunk 1982, 1983, 1984).
The biological half-lives for the elimination of these compounds are ranked as follows: DDE>DDT>DDD. This relationship is based on the chemical stability of each compound in the body, efficiency of excretory mechanisms, and possibly transport in and out of fat depots (Morgan and Roan 1971). The excretion of DDT was investigated in volunteers who ingested DDT. Hayes et al. (1971) reported that, in subjects receiving 35 mg/day (approximately 0.5 mg/kg) for up to 18 months, urinary excretion of DDA increased rapidly for the first few days and a steady state level of approximately 13–16% of the daily dose was reached and remained stable for 56 weeks. However, although the rate of excretion of DDA was relatively constant in each individual, there were marked differences observed between men receiving the same dose. Urinary excretion of DDA fell rapidly after cessation of dosing. It appears that a steady state for storage was reached within 12–18 months of daily dosing, after which humans were apparently able to eliminate the entire daily dose of 35 mg/day. Although no excretion of DDT metabolites was detected in the feces, the authors stated that there were probably DDT metabolites in the feces which were organic unextractable polar conjugates (Hayes et al. 1971). Since only 5.7 mg/day of all DDT isomers were found in the urine at steady state, it was postulated that other routes of excretion, such as biliary transport, may be involved. This was shown by Paschal et al. (1974). Roan et al. (1971) reported that increased urinary excretion of DDA is detectable within 24 hours of ingestion of DDT (5, 10, or 20 mg/day), DDD (5 mg/day), or DDA (5 mg/day). DDA excretion returns to predose levels within 2–3 days of dose termination for DDA, but continues significantly above predose levels for over 4 months after termination of DDD or DDT doses. Ingestion of DDE (5 mg/day) failed to produce any increase in DDA excretion.

DDT excretion in the feces may be a major route of excretion at high doses of DDT. DDT and DDT-related metabolites have been identified in the feces of humans receiving 35 mg/day (Hayes et al. 1956); however, this result has not been confirmed by later investigations (Hayes et al. 1971). According to Jensen et al. (1957), biliary excretion is the major source of DDT metabolites found in the feces of rats, as demonstrated in bile-cannulated rats given an intravenous injection of DDT. Following intravenous administration of DDT in rats, bile cannulation results indicated that enterohepatic circulation was occurring for conjugated DDA, a DDT metabolite (Gingell 1975; Pinto 1965).

Analysis of urine from humans occupationally exposed to DDT showed the presence of DDA (Laws et al. 1967; Ortelee 1958; Ramachandran et al. 1984). By comparing the urinary excretion of DDA with that of volunteers given known doses of DDT, the average occupational exposure can be estimated (WHO 1979). The observations by Laws et al. (1967) and Ortelee (1958) indicate that the urinary excretion of DDA is correlated with the level of exposure to DDT. The concentration of DDA in the urine in occupationally
exposed workers was reported to be greater than that observed in the general population, while DDE excretion was reported to be only slightly higher than in the general population. It is of interest that monkeys fed DDT stored DDE in their fat (not DDT) and when feeding ceased, it was rapidly lost, probably by urinary excretion (Durham et al. 1963).

Parameters of elimination of DDE and DDE-derived radioactivity in rats were estimated by Mühlebach et al. (1991) after administration of a single intravenous dose. Over a 14-day period following dosing, 34% of the administered dose was excreted in the feces and 1% in the urine. In the feces, 10% of the excreted radioactivity represented unchanged DDE, whereas no unchanged DDE could be detected in the urine. No hexane-extractable lipophilic metabolites were found in the feces. The average total DDE recovered in tissues and excreta was 90%. The total body burden half-life was 120 days.

2.4.5 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 et al. 1987; Andersen and Krishnan 1994). 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 parametrization, (3) model simulation, and (4) model validation (Krishnan and
Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-3 shows a conceptualized representation of a PBPK model.

Models of the pharmacokinetics of \( p,p' \)-DDE, a principle metabolite of DDT, have been proposed by You et al. (1999). The You et al. (1999) models are PBPK models of \( p,p' \)-DDE uptake and disposition in pregnant and lactating/nursing rats. The models are based on experimental studies in which pregnant Sprague-Dawley rats were administered gavage doses of \( p,p' \)-DDE, and the kinetics of \( p,p' \)-DDE tissue levels in the dams, fetuses, and pups were measured. The models provide an approach to estimating tissue doses in fetuses and pups associated with maternal exposures to \( p,p' \)-DDE and can be used to explore dose-response relationships for the developmental effects of \( p,p' \)-DDE in the Sprague-Dawley rat.

**Description of the model.** Figures 2-4 and 2-5 show conceptualized representations of the gestation model and the lactation/nursing models, respectively. Parameters used in the models are shown in Tables 2-3 and 2-4. The gestation model simulates the absorption of an oral dose of \( p,p' \)-DDE from the
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Figure 2-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance

Source: adapted from Krishnan et al. 1994

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.
Figure 2-4. Diagrammatic Representation of the PBPK Model for Gestation*. Terms are Defined in Table 2-3 and Table 2-4.

N = number of concepti

*Adapted from You et al. 1999
Figure 2-5. Diagrammatic Representation of the PBPK Model for the Lactating Dam and Nursing Pup*. Terms are Defined in Table 2-3 and Table 2-4.

N = number of pups

Portal and lymphatic absorption routes for dams are not shown (see Figure 2-4).

*Adapted from You et al. 1999
2. HEALTH EFFECTS

Table 2-3. Tissue:Blood Partition Coefficients and Pharmacokinetic Constants for Modeling DDE Disposition in the Pregnant Rat\textsuperscript{a}

<table>
<thead>
<tr>
<th>Tissue:blood partition coefficients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>7</td>
</tr>
<tr>
<td>Fat</td>
<td>450</td>
</tr>
<tr>
<td>Poorly-perfused tissues</td>
<td>12</td>
</tr>
<tr>
<td>Well-perfused tissues</td>
<td>6</td>
</tr>
<tr>
<td>Kidney</td>
<td>6</td>
</tr>
<tr>
<td>Uterus</td>
<td>6</td>
</tr>
<tr>
<td>Placenta</td>
<td>2</td>
</tr>
<tr>
<td>Mammary gland</td>
<td>12</td>
</tr>
</tbody>
</table>

Pharmacokinetic constants

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_{AD}$ (L/day) Portal absorption rate constant</td>
<td>24</td>
</tr>
<tr>
<td>$K_{LY}$ (L/day) Lymphatic absorption rate constant</td>
<td>74</td>
</tr>
<tr>
<td>$K_{FX}$ (L/day) Fecal excretion rate constant</td>
<td>230</td>
</tr>
<tr>
<td>$K_{b}$ (L/day) Biliary excretion rate constant</td>
<td>1.2</td>
</tr>
<tr>
<td>PA\textsubscript{F} (L/day) Fat diffusion coefficient</td>
<td>5</td>
</tr>
<tr>
<td>PA\textsubscript{1} (L/day) Placenta-to-embryo/fetus diffusion coefficient</td>
<td>1.6</td>
</tr>
<tr>
<td>PA\textsubscript{2} (L/day) Embryo/fetus-to-placenta diffusion coefficient</td>
<td>1.9</td>
</tr>
<tr>
<td>$K_{12}/K_{21}$ Diffusion to deep fat</td>
<td>1.0/0.1</td>
</tr>
<tr>
<td>$T_{de1}$ (day) Delay in time</td>
<td>0.1</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Adapted from You et al. 1999
## Table 2-4. Physiological Constants Used in the PBPK Model for the Lactating Dam and the Nursing Pup$^a$

<table>
<thead>
<tr>
<th></th>
<th>Dam</th>
<th>Pup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg) (BW)</td>
<td>0.290–0.340</td>
<td>0.0061–0.58</td>
</tr>
<tr>
<td>Tissue volumes (% of body weight)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver, $V_L$</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Well-perfused tissues, $V_{WP}$</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Poorly-perfused tissues, $V_{PP}$</td>
<td>76-$V_{MT}$</td>
<td>76</td>
</tr>
<tr>
<td>Fat, $V_F$</td>
<td>7</td>
<td>0.0199*pBW+1.664</td>
</tr>
<tr>
<td>Mammary tissue, $V_{MT}$</td>
<td>4.4–9.6</td>
<td></td>
</tr>
<tr>
<td>Milk, $V_{milk}$</td>
<td>0.002L</td>
<td></td>
</tr>
<tr>
<td>Cardiac output (L/h)</td>
<td>14*pBW$^{0.75}$</td>
<td>18*pBW$^{0.74}$</td>
</tr>
<tr>
<td>Blood flows (% of cardiac output)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver, $Q_L$</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Well-perfused tissues, $Q_{WP}$</td>
<td>41-$Q_{MT}$</td>
<td>49</td>
</tr>
<tr>
<td>Poorly perfused tissues, $Q_{PP}$</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Fat, $Q_F$</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Mammary tissue, $Q_{MT}$</td>
<td>9–15</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Adapted from You et al. 1999
gastrointestinal tract through a hepatic portal pathway to the liver and a lymph pathway to blood plasma. The latter pathway was included to simulate the absorption of lipophilic compounds that are administered in lipid vehicles (e.g., corn oil). Plasma \( p,p' \)-DDE is assumed to exchange with maternal fat, kidney, liver, mammary tissue, and other richly-perfused and poorly-perfused maternal tissues; and with the embryo/fetus and placenta (yolk sac and chorioallantoic). The lactating/nursing model simulates transfer of \( p,p' \)-DDE from the dam to the nursing pup from mammary milk, followed by exchanges with pup fat, kidney, and other richly-perfused and poorly-perfused tissues in the pups.

All exchanges with blood plasma, in both models, are simulated as flow-limited processes, with the exception of the following. Exchanges between maternal fat and a deep fat compartment are assumed to be diffusion-limited and are represented with first order rate constants. Exchanges between the embryo/fetus and placenta are modeled as diffusion-limited processes and are represented with diffusion coefficients (L/day). Parameters used in the model were either taken from the literature, estimated by using the SIMUSOLV simulation program, or set by visually inspecting the fit of the data.

Elimination pathways in the maternal model include metabolism, transfer from mammary tissue to maternal milk (in the lactation model), and fecal excretion from the gastrointestinal tract, including transfer from bile to the gastrointestinal tract. A fecal pathway from liver (presumably through bile and the gastrointestinal tract) is included in the pup model.

**Validation of the model.** The models have been calibrated with data from experimental studies. Pregnant Sprague-Dawley rats were administered gavage doses of 0, 10, or 100 mg \( p,p' \)-DDE on Gd 14–18. A subset of the dams were killed 4 hours after each dosing, and tissue levels of \( p,p' \)-DDE were measured in the dams, placenta, and fetuses. A subset of pups in each dose group was cross-fostered to assess \( p,p' \)-DDE transfer to tissues from maternal milk. The gestational model was calibrated by adjusting variables to achieve agreement between estimated and observed concentrations of \( p,p' \)-DDE in maternal and pup plasma, liver, and fat, and in placenta and fetal tissue. The lactation/nursing model was calibrated with data on \( p,p' \)-DDE concentrations in pup blood, liver, and fat. Reasonable agreement was achieved between model output and observations.

**Risk assessment.** The models provide an approach to estimating tissue doses in fetuses and pups associated with maternal gavage doses of \( p,p' \)-DDE to pregnant Sprague-Dawley rats. This information can be used to interpret the results of developmental toxicity bioassays of \( p,p' \)-DDE in terms of maternal, fetal, and pup tissue dose-response relationships.
Target tissues. Output from the You models that are described in You et al. (1999) are estimates of the \( p,p' \)-DDE concentrations in maternal and pup blood and plasma, liver, and fat, and in placenta and embryo/fetus. Estimates of \( p,p' \)-DDE concentrations in other tissues may also be feasible, although they are not described in model evaluations thus far reported (You et al. 1999).

Species extrapolation. The models have been calibrated to predict \( p,p' \)-DDE pharmacokinetics in pregnant and lactating/nursing Sprague-Dawley rats. Extrapolation to other physiological states (e.g., immature rats, nonpregnant adults, senescent rats), other rat strains, or other species would require modification to the models to account for different tissue masses, blood flows, and possibly other kinetic variables.

Interroute extrapolation. The models are calibrated to simulate the pharmacokinetics of \( p,p' \)-DDE when it is administered by gavage doses in corn oil or in a similar lipid vehicle. The gestation model includes a lymphatic absorption pathway from the gastrointestinal tract that is intended to simulate the absorption kinetics of \( p,p' \)-DDE dissolved in a lipophilic vehicle. The kinetics would be expected to be different for aqueous vehicles. Therefore, the output of the models cannot be extrapolated to other types of vehicles or to other exposure pathways (e.g., dietary, drinking water) or routes (e.g., dermal, inhalation) without re-evaluation and possibly recalibration and modification of the models.

2.5 MECHANISMS OF ACTION

2.5.1 Pharmacokinetic Mechanisms

DDT, DDE, and DDD are efficiently absorbed, distributed, and stored because of their high lipophilicity. There are not thought to be specific transport or distribution mechanisms for DDT, DDE, or DDD other than their affinity for other hydrophobic fats. These chemicals are absorbed in the stomach and, to a larger extent, in the intestine. Sieber (1976) studied lymphatic absorption of DDT and related compounds in rats and found these compounds to be preferentially absorbed via the intestinal lymphatic system with some absorption into blood. Pocock and Vost (1974) and Sieber et al. (1974) reported that most DDT absorbed into lymph is carried in the lipid core of chylomicrons. Once absorbed into the lymphatic system, DDT is carried throughout the body and incorporated into fatty tissues. In addition to facilitating the absorption of these compounds from the gastrointestinal tract, the lipophilicity of DDT, DDE, and DDD enables them to cross the blood-brain barrier readily without a specific transporter. Uptake into
tissues is a function of the blood flow, lipid content of the specific tissue, and the partition coefficient for DDT between the blood and lipids in specific tissues.

One study in humans suggests that DDT is primarily transported in the blood bound to protein. In occupationally exposed workers, Morgan et al. (1972) found that less than 18% of \( p,p' \)-DDT and \( p,p' \)-DDE in human blood is carried in erythrocytes. Less than 1% of all DDT-related compounds is carried by the chylomicrons in plasma of normal fat content. Instead, DDT-related compounds are carried by proteins and are undetectable in plasma from which protein has been precipitated. Following ultracentrifugation, \( p,p' \)-DDT and \( p,p' \)-DDE are found in relation to lipoproteins of various densities, but mainly in the triglyceride-rich, low density, and very low density lipoproteins. Results from electrophoresis experiments showed that plasma albumin, and secondarily the smaller globulins are the principal plasma constituents associated with blood-borne \( p,p' \)-DDT and \( p,p' \)-DDE.

Extensive information regarding the metabolism of DDT and DDT-related compounds was presented in Section 2.4.3. DDT and DDT-related compounds are metabolized primarily in the liver and kidney, but important activation reactions also occur in other tissues such as the lung and adrenal glands. The metabolism of DDT can be considered both a detoxification reaction as well as an activation reaction. For effects associated with the parent compound, such as neurotoxicity, metabolism means detoxification. For other toxicities, such as anti-androgenicity and adrenal effects, biotransformation of DDT may be an activation process. In general, the metabolism of DDT in animals is similar to that in humans; however, there are also differences between species, and within species, there are differences between tissues. DDT, DDE, and DDD induce CYP2B-associated activities in rat liver, which makes them phenobarbital-type cytochrome P-450 inducers. Studies in humans have shown that the major route of excretion of absorbed DDT is the urine and that DDA is the main urinary metabolite.

2.5.2 Mechanisms of Toxicity

Mechanisms for the major effects of DDT are discussed in this section. In animals, these adverse effects include neurotoxicity, hepatotoxicity, metabolic effects, reproductive effects, and cancer.

**Neurological Effects.** DDT acts on the central nervous system by interfering with the movement of ions through neuronal membranes. There appear to be at least four mechanisms by which DDT affects ion movement, all possibly functioning simultaneously. DDT both delays the closing of the sodium ion channel and prevents the full opening of the potassium gates (Ecobichon 1995; Narahashi and Haas
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DDT has been shown to target a specific neuronal adenosine triphosphatase (ATPase) thought to be involved in the control of the rate of sodium, potassium, and calcium fluxes through the nerve membrane (Matsumura and Patil 1969). This ATPase plays a vital role in neuronal repolarization. In addition, it has been suggested that DDT inhibits the ability to transport calcium ions in nerves possibly by binding with a hydrophobic site on calmodulin and secondarily effecting a Ca/Mg ATPase; however, this mechanism has not been confirmed (Matsumura 1985). Calcium ions are essential to the release of neurotransmitters. These actions combine to effectively maintain the depolarization of the nerve membrane, potentiating the release of transmitters and leading to central nervous system excitation manifested as hyperexcitability, tremors, and convulsions, along with secondary effects from convulsions, such as tachycardia, metabolic acidosis, and hyperthermia.

The action of DDT as a central nervous system stimulant may also be related to a deficiency of brain serotonin (Hwang and Van Woert 1978). Much research has focused on changes in levels of biogenic amines and amino acids resulting from DDT exposure. It is possible that some of these changes could be a result of the effects of DDT on membrane ion transport and consequent neurotransmitter release. Several researchers have reported increased levels of 5-HIAA, 3-methoxy-4-hydroxyphenylglycol (MHPG), aspartate, and glutamate in the brains of rats exposed to DDT (Hong et al. 1986; Hudson et al. 1985; Pratt et al. 1985). 5-HIAA and MHPG are metabolites of the biogenic amines serotonin and norepinephrine, respectively, which act as inhibitors in the central nervous system. The increases in levels of 5-HIAA and MHPG indicate increased breakdown of these inhibitory neurotransmitters. Both aspartate and glutamate function as excitatory amino acids. The overall effect of increased levels of aspartate and glutamate is the induction of a state of increased excitability in the neurons of the central nervous system. This leads to hyperexcitability in the exposed animal and contributes to tremors and convulsions, which have been observed following DDT exposure. Serotonin, in addition to being active in the inhibition of neurons, plays an important role in the regulation of body temperature. It has been suggested that the increased turnover of serotonin in DDT-exposed organisms may be responsible for DDT-induced hyperthermia (Hudson et al. 1985). Other data suggest that DDT-induced hyperthermia may be due to heat generated by muscular movement during tremors or convulsions (Herr et al. 1986).

**Reproductive and Developmental Effects.** DDT intake, particularly during sexual differentiation, can adversely affect the reproductive system of male animals. Such effects have been attributed to DDT and related compounds acting in any of the following manners or in any combination of them: (1) mimicking endogenous hormones, (2) antagonizing endogenous hormones, (3) altering the pattern of synthesis or metabolism of hormones, and (4) modifying hormone receptor levels. DDT is
primarily suspected of influencing reproduction and development through its interaction with steroid hormones receptors for estrogens and androgens.

Estrogens and androgens are very lipid soluble and thus they diffuse easily through the cell membrane into the cytosol, where empty steroid receptors are located. In the classical model for steroid hormone action, once a steroid receptor binds a steroid, it dissociates from its molecular chaperones, and is translocated to the nucleus. In the nucleus, the hormone-receptor complex binds to hormone response elements in the enhancers, silencers, or promoters upstream of the genes controlled by the steroid in question. The hormone-receptor complex acts as a transcription factor to either stimulate or repress transcription of RNA from the steroid responsive gene. This RNA is spliced to form mRNA which directs the synthesis of proteins that cause the characteristic responses to the steroid hormone. Some ancillary models for immediate action of steroid hormones have recently been proposed and involve either cross-talk interactions with, or possibly direct binding to, other hormone and growth factor cell surface receptors, and cell surface receptor mediated uptake of serum carrier proteins bound to steroid hormones (Chen and Farese 1999). It was long thought that estrogen mediated its effects by binding to a single receptor, estrogen receptor α (ERα). Recently, however, a second estrogen receptor, ERβ, has been discovered (Kuiper et al. 1996; Mosselman et al. 1996). None of the studies examining the difference in estrogen receptor binding affinity for DDT isomers and metabolites differentiated between ERα and ERβ. It has not been fully established what effects are mediated by each estrogen receptor. However, there appears to be tissue-specific distribution of the two receptors (Kuiper et al. 1997), which may allow for tissue-specific effects by estrogens. In tissues where both receptors are expressed, ligand binding to the receptors results in heterodimer formation (an ERα receptor pairs up with an ERβ receptor) (Cowley et al. 1997; Pace et al. 1997; Pettersson et al. 1997), which may result in different patterns of gene regulation than seen with homodimeric pairing (an ERα with an ERα or an ERβ with an ERβ). Additionally, each different estrogenic compound might act as an estrogen agonist at one receptor type and an estrogen antagonist at the other receptor type.

Results from numerous studies using a wide range of experimental approaches suggest that binding to the estrogen receptor and subsequent events are the predominant mechanism by which estrogenic effects are expressed. Tests for estrogenicity fall into two general categories, in vivo and in vitro (Zacharewski 1998). Examples of the former include the uterotrophic (increase in uterine wet weight) and vaginal cell cornification assays. In vitro assays include (i) measuring the activities of enzymes involved in steroid synthesis, (ii) competitive ligand binding assays using binding globulins and receptors, (iii) cell proliferation assays, and (iv) gene expression assays in mammalian cells and yeast. If possible, both in
vivo and in vitro tests should be conducted since, for instance, in vitro assays can give false positives if the chemical is not absorbed or distributed to the target tissue or is rapidly metabolized. Conversely, false negatives may arise from the lack of an activation system in the in vitro system; other factors may play a role too. Also, both in vivo and in vitro tests are available for assessing androgenic effects such as measurement of anogenital distance in new born male rodents and androgen receptor binding assays in prostate cytosol, respectively. Some representative studies that examined mechanistic aspects of estrogenicity and antiandrogenicity of DDT and related compounds are briefly summarized below. Bulger and Kupfer (1983) reviewed the literature and references to most of the earlier studies on estrogenic effects can be found therein.

\[ p,p'-DDT \text{ (200 mg/kg twice) and } o,p'-DDD \text{ (200 mg/kg up to 5 times) administered intraperitoneally to rats had almost no estrogenic activity for initiating implantation, in contrast with responses observed after administration of } o,p'-DDE \text{ (200 mg/kg once) and } o,p'-DDT \text{ (200 mg/kg once) (Johnson et al. 1992). The latter two chemicals not only initiated implantation but also maintained pregnancy when administered repeatedly. } p,p'^{-}DDT \text{ was as efficient as } o,p'^{-}DDT \text{ in a uterine response assay in rats in vitro, but exhibited low estrogenic activity in vivo (Galand et al. 1987). Welch et al. (1969) reported an estrogenic activity ranking of } o,p'^{-}DDT > \text{ technical DDT} > p,p'^{-}DDT \text{ in immature female rats treated intraperitoneally. Singhal et al. (1970) showed that } o,p'^{-}DDT \text{ (100 mg/kg) was much more effective in increasing uterine weight in young rats than } p,p'^{-}DDT \text{ after a single intramuscular injection. Shelby et al. (1996) examined the estrogenicity of } o,p'^{-}DDT \text{ in three different assays; (1) competitive binding with the mouse uterine receptor, (2) transcriptional activation in HeLa cells transfected with plasmids containing an estrogen receptor and an estrogen response element linked to a reporter gene, and (3) the uterotropism assay in mouse. The first two assays are in vitro assays, whereas the third one was carried out by injecting immature mice subcutaneously with } o,p'^{-}DDT \text{ on three consecutive days and determining uterine weight on the fourth day. } o,p'^{-}DDT \text{ gave positive estrogenic responses in the three assays, but with a potency that was several orders of magnitude weaker than 17\beta\text{-estradiol and diethylstilbestrol (DES). } o,p'^{-}DDT, o,p'^{-}DDD, \text{ and } p,p'^{-}DDT \text{ were full estrogenic agonists in the in vitro E-screen test, } p,p'^{-}DDE \text{ and } p,p'^{-}DDD \text{ were partial agonists and technical DDT was a full agonist (Soto et al. 1997). The E-screen test uses breast cancer estrogen-sensitive MCF-7 cells, and the rationale of the assay is that a human serum-borne molecule specifically inhibits the proliferation of human estrogen-sensitive cells, and estrogens induce proliferation by neutralizing this inhibitory effect. 10^7 \text{ times more } o,p'^{-}DDT, o,p'^{-}DDD, p,p'^{-}DDT, p,p'^{-}DDE, p,p'^{-}DDD, \text{ and technical DDT was needed to produce maximal cell yields than 17\beta\text{-estradiol. } p,p'^{-}DDE \text{ also showed partial antagonistic effects on MCF-7 cell proliferation (Soto et al. 1998).} \]
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Gaido et al. (1997) used a yeast system to express the estrogen receptor, a reporter gene regulated by two estrogen receptor response elements, and a yeast gene that is supposed to enhance steroid receptor mediated gene transcription. \(\text{o,p}^-\text{DDT} \text{ and } \text{o,p}^-\text{DDD} \) appeared to stimulate estrogen receptor responsive genes at very high doses, but a complete curve of expression versus dose was not done for these two chemicals. The authors extrapolated EC\(_{50}\) (effective concentration for 50% maximal response) values for \(\text{o,p}^-\text{DDT} \text{ and } \text{o,p}^-\text{DDD} \) assuming that these chemicals would have been as effective as estradiol in inducing reporter gene expression if a complete dose response experiment had been done. The calculated EC\(_{50}\) values were 1.8 mM for \(\text{o,p}^-\text{DDT} \) (8x10\(^6\) less potent than estradiol) and 3.32 mM for \(\text{o,p}^-\text{DDD} \) (15x10\(^7\) less potent than estradiol) compared to an actual estradiol EC\(_{50}\) of 2.25 nM. \(\text{o,p}^-\text{DDE} \) produced little apparent response. Sohoni and Sumpter (1998) investigated the ability of \(\text{o,p}^-\text{DDT} \) and \(\text{p,p}^-\text{DDE} \) to induce estrogen receptor regulated gene expression in yeast expressing the human estrogen receptor and a secreted reporter gene controlled by an estrogen response element. A complete dose-response curve was generated for \(\text{o,p}^-\text{DDT} \) and it was found to be about 10\(^5\) less potent than 17\(\beta\)-estradiol in inducing estrogen regulated gene transcription. There was little response to \(\text{p,p}^-\text{DDE} \) even at concentrations as high as 0.5 mM.

Several investigators have demonstrated that \(\text{o,p}^-\text{DDT} \) can compete with estradiol for binding to the estrogen receptor. An IC\(_{50}\) is the concentration at which 50% of the maximal inhibition of binding to the labeled standard (in this case, estradiol) is achieved. Danzo (1997) showed that \(\text{o,p}^-\text{DDE} \) (IC\(_{50}=40 \mu\text{M}\)) competed with 17\(\beta\)-estradiol (IC\(_{50}=2.7 \text{nM}\)) for binding to the estrogen receptor in rabbit uterine extracts and \(\text{p,p}^-\text{DDT} \) and \(\text{p,p}^-\text{DDE} \) were much less effective competitors. Kelce et al. (1995) showed in uterine extracts from immature rats that \(\text{o,p}^-\text{DDE} \) (IC\(_{50}=5 \mu\text{M}\)) competed with 17\(\beta\)-estradiol (IC\(_{50}=0.8 \text{nM}\)) for estrogen receptor binding and that \(\text{p,p}^-\text{DDT} \), \(\text{p,p}^-\text{DDE} \), and \(\text{p,p}^-\text{DDD} \) were relatively ineffective competitors (IC\(_{50}>1,000 \mu\text{M}\)). The observations of the lack estrogenicity of the \(\text{p,p}^-\) isomers were consistent with results from earlier in vivo studies (Bitman and Cecil 1970; Gellert et al. 1972; Nelson 1974).

Kelce et al. (1995) characterized the binding of \(\text{p,p}^-\text{DDT} \), \(\text{p,p}^-\text{DDE} \), \(\text{o,p}^-\text{DDT} \), and \(\text{p,p}^-\text{DDD} \) to the androgen and estrogen receptors in vitro in uterine cytosolic extracts from immature rats and in rat ventral prostate cytosol, respectively. In competitive androgen receptor binding assays using a radiolabeled synthetic androgen (R1881), the four chemicals showed dose-dependent competitive inhibition. \(\text{p,p}^-\text{DDE} \) was the greatest competitor with an inhibition constant (K\(_i\)) of 3.5 \(\mu\text{M}\), which was similar to that of DES and about 30 times weaker than 17\(\beta\)-estradiol. The other three isomers were 12–20-fold less effective than \(\text{p,p}^-\text{DDE} \). Based on IC\(_{50}\) values for displacement of the synthetic androgen from the
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androgen receptor or 17β-estradiol from the estrogen receptor, \(o,p'-\text{DDT}\) was 20-fold more effective as a competitor of estrogen binding to the estrogen receptor than androgen binding to the androgen receptor. \(p,p'-\text{DDT}, p,p'-\text{DDD},\) and \(p,p'-\text{DDE}\) bound the androgen receptor 14, 11, and 200 times more effectively than the estrogen receptor, respectively. A control experiment was done to demonstrate that the anti-androgenic effects of the DDT isomers were not due to their ability to inhibit the conversion of testosterone by 5α-reductase to 5α-dihydrotestosterone and 5α-androstan-3α-17β-diol. In microsomes isolated from the adult rat caput and corpus epididymis, the four DDT isomers were all 20-fold less effective in inhibiting this reaction than DES or 17β-estradiol. Danzo (1997) also confirmed that \(p,p'-\text{DDE}\) (IC\(_{50}\) = 6.8 µM) could compete with dihydrotestosterone (IC\(_{50}\) = 1.1 nM) for binding to androgen receptors in rat prostate cytosol. In contrast to Kelce, Danzo found that \(o,p'-\text{DDT}\) and \(p,p'-\text{DDT}\) were only slightly less effective than \(p,p'-\text{DDE}\) in competing with dihydrotestosterone for androgen receptor binding.

The binding experiments described above cannot distinguish between an agonist and an antagonist as both might bind equally well to the androgen receptor. \(p,p'-\text{DDE}\)’s action as an androgen receptor antagonist has been demonstrated by its ability to inhibit the androgen receptor from either appropriately inducing or repressing transcription from androgen responsive genes containing androgen receptor binding sites in their regulatory sequences. Kelce et al. (1995) transiently transvected monkey kidney cells with an androgen receptor expression vector and a reporter gene containing the MMTV promoter which contains binding sites for the androgen receptor. In a 5-hour expression assay, both 0.2 µM \(p,p'-\text{DDE}\) and 1 µM hydroxyflutamide were able to inhibit 5α-dihydrotestosterone (0.1 nM) induced transcription by about 50%. In contrast, in lysates of rat ventral prostate, the androgen antagonist hydroxyflutamide was 10 times more effective than \(p,p'-\text{DDE}\) in inhibiting binding to the androgen receptor. In the transient tranvection assay, levels of 5α-dihydrotestosterone were not measured in the wells, so there was no control for whether the DDE could have affected its metabolism. \(p,p'-\text{DDT}\) and \(o,p'-\text{DDT}\) also showed some ability to inhibit the transcription of androgen responsive genes in this assay. Kelce et al. (1997) performed an in vivo experiment on castrated adult male rats which were maintained on a constant dose of testosterone from implanted Silastic capsules; this experiment was designed to eliminate possible variations in testosterone levels from feedback at the hypothalamus or pituitary. After 5 days gavage with 200 mg/kg/day of \(p,p'-\text{DDE}\), northern blots of mRNA isolated from the prostate showed significant increases in steady state levels for mRNA for testosterone repressed prostatic message and decreases in testosterone induced C3 (third subunit of prostatic specific binding protein). The \(p,p'-\text{DDE}\) did not affect testosterone metabolism in these animals. Kelce et al. (1995) suggested that their
findings raised the possibility that the androgen receptor, rather than the estrogen receptor, is the site of hormonal blockade by persistent environmental pollutants such as \( p,p' \)-DDE.

Other investigators have confirmed Kelce’s results showing the anti-androgenic effects of \( p,p' \)-DDE on androgen receptor regulated genes. Maness et al. (1998) investigated how isomers of DDT, DDE, and DDD inhibited androgen receptor regulated gene expression \textit{in vitro} in HEPG2 human hepatoma cells transiently transvected with the human androgen receptor and a reporter gene linked to an androgen responsive promoter. These cells were exposed for 24 hours to a maximally inducing dose (0.1 µM) of dihydrotestosterone and various doses of either \( p,p' \)-DDT, \( p,p' \)-DDE, \( p,p' \)-DDD, \( o,p' \)-DDT, \( o,p' \)-DDE, or \( o,p' \)-DDD. Details of the data were not presented, but from the graphical presentation of the data, both isomers of DDT, DDE, and DDD appear to be equipotent (IC\(_{50}\) 1–10 µM) in inhibiting dihydrotestosterone induced gene transcription. The authors state that \( p,p' \)-DDE was the most potent inhibitor (IC\(_{50}=1.86 \)µM), but no evidence of statistical significance is discussed. No sampling of the cells or media was done to determine whether DDT isomers might have been affecting the metabolism of dihydrotestosterone in these experiments on liver cells.

Sohoni and Sumpter (1998) investigated anti-androgenic effects in yeast expressing the human androgen receptor plus a secreted reporter gene controlled by androgen response elements. Both \( o,p' \)-DDT and \( p,p' \)-DDE were approximately equipotent in inhibiting dihydrotestosterone (DHT) responsive gene expression. Both were about as effective as the anti-androgen flutamide. From graphs, they appeared to have IC\(_{50}\) values on the order of 10 µM from 4-day incubations with a submaximally inducing dose of DHT (1.25 nM) and DDT or DDE; however, the authors felt that explicit calculations of IC\(_{50}\) values were inappropriate, because if incubation times were extended to 5 or 6 days, DHT seemed to partially overcome the inhibition by \( p,p' \)-DDE (\( o,p' \)-DDT was not tested in these tests). Again, no sampling of yeast media was done to determine if the DDT or DDE was affecting metabolism of DHT.

Collectively, the results of these studies suggest that DDT-related compounds might have estrogenic or anti-androgenic activities if sufficient doses are used. The androgen antagonist mechanism demonstrated in these studies would explain a number of reproductive and developmental effects seen in male rats of various ages exposed to \( p,p' \)-DDE. These include reduced anogenital distance and retention of thoracic nipples in pups exposed during gestation and lactation (Kelce et al. 1995; Loeffler and Peterson 1999; You et al. 1998;); delayed puberty in rats exposed either during juvenile development (Kelce et al. 1995) or gestation and lactation (Loeffler and Peterson 1999), and reduced accessory sex organ weights in
exposed adult males (Kelce et al. 1995, 1997). The experimental details of these studies are discussed extensively in Section 2.2.2.5 Reproductive Effects and Section 2.2.2.6 Developmental Effects.

DDT and metabolites apparently also exhibit estrogen or androgen receptor-independent effects as shown for example in a study by Juberg and Loch-Caruso (1992) in which the estrogenic \( o,p'\)-DDT increased contractions of rat uterus strips \textit{ex vivo}, but \(17\beta\)-estradiol did not. The estrogen antagonist, tamoxifen, failed to block the stimulatory effect of \( o,p'\)-DDT. Furthermore, the nonestrogenic DDT analogue, \( p,p'\)-DDD, significantly stimulated uterine contraction. The authors also demonstrated that the increase in contractility was not due to release of prostaglandin E2 (PGE\(_2\)) from the uterine strips since PGE\(_2\) levels in the muscle bath showed no significant differences between control and DDT-treated strips. A more recent study from the same group directly showed that \( p,p'\)-DDD causes a dramatic increase in intracellular free calcium in rat myometrial smooth muscle cells (Juberg et al. 1995). This increase resulted primarily from an increase in calcium influx from the extracellular medium and release from intracellular calcium stores. The elevation in intracellular calcium is consistent with an increase in uterine contractility.

**Mechanistic Studies of DDT in Fish.** There have been a number of intriguing mechanistic studies of DDT isomers and metabolites in fish that relate to reproductive and developmental effects. Two subtypes of nuclear androgen receptors have been identified in both kelp bass and Atlantic croaker; one subtype is expressed in the brain and the other in ovarian tissue (Sperry and Thomas 1999). The brain receptor subtype seems more similar to mammalian androgen receptors in binding characteristics; the ovarian receptor is unique to teleost fish. Both \( p,p'\) and \( o,p'\) isomers of DDT, DDD, and DDE can displace dihydrotestosterone from the ovarian androgen receptor subtype. Analogous to ER\(\alpha\) and ER\(\beta\) in humans, there are also different estrogen receptor subtypes in Atlantic croaker fish; two slightly different estrogen receptors have been identified in the testis and liver of these fish (Loomis and Thomas 1999). \( o,p'\)-DDT, as well as \( o,p'\)-DDE and \( o,p'\)-DDD, can bind to both of these receptors with low affinity relative to estradiol; binding of these isomers was somewhat better to the testicular receptor than to the hepatic receptor. There has been one report in Atlantic croaker that \( o,p'\)-DDD can competitively inhibit binding of maturation-inducing steroid to its plasma membrane receptor (Das and Thomas 1999; Thomas 1999). Similar to estrogen, \( o,p'\)-DDT can stimulate gonadotropin release in Atlantic croaker (Khan and Thomas 1998). Another report reveals that \( o,p'\)-DDT impairs survival related behavior in larval offspring of exposed Atlantic croaker (Faulk et al. 1999).
### Metabolic Effects.

DDT and DDT-analogues were found to be phenobarbital-type (CYP2B and to a lesser extent CYP3B) inducers in rat liver (Nims et al. 1998). Since some of these isozymes metabolize endogenous steroids and other hormones, it is possible DDT could increase the turnover or change serum levels of endogenous macromolecules metabolized by these P-450 isozymes. This would be consistent with the increases in microsomal catabolism of cortisol observed in DDT-exposed humans. These subjects excreted significantly increased amounts of the cortisol metabolite 17-hydroxycortisone in their urine (Nhachi and Loewenson 1989; Poland et al. 1970). Thus, hormonal homeostasis could be indirectly affected and effects would be seen on several systems including the reproductive system.

### Hepatic Effects.

Hepatic effects in animals associated with DDT, DDE, and DDD exposure include increased liver weights, hypertrophy, hyperplasia, microsomal enzyme and cytochrome P-450 induction (CYP2B, phenobarbital-type induction), cell necrosis, and increased levels of SGPT (ALT) and SGOT (AST) enzymes released from damaged liver cells. DDT and its metabolites have been reported to disrupt the ultrastructure of mitochondrial membranes (Byczkowski 1977). This disruption may result in cell damage and some cell death. Consequently, the liver could begin cell regeneration to compensate for this loss of cells. This regenerative process often leads to hyperplasia and hypertrophy, which combine to increase the weight of the liver, and may contribute to the promotion of liver tumors (Fitzhugh and Nelson 1947; Schulte-Hermann 1974).

### Cancer.

Although the evidence regarding the carcinogenicity of DDT in humans is inconclusive, DDT and related compounds have been shown to be carcinogenic in some laboratory animals. Several mechanisms have been proposed: direct mutagenicity through formation of covalent DNA adducts; promotion of pre-existing abnormal cells; or cytotoxicity leading to hyperplasia and promotional tumor development. These mechanisms may not be mutually exclusive. DDMU epoxide and DDA-Cl are two electrophiles that potentially can be produced during DDT metabolism. These could form covalent adducts with DNA, and thereby contribute to the cytotoxicity as well as the carcinogenicity of DDT. DDMU epoxide is a minor side-product by both of the predominant models (I and II) for DDT biotransformation. DDA-Cl is a major DDT metabolite in the Model II catabolism scheme (Gold and Brunk 1983). Electrophiles, as a class, are frequently mutagenic. Consistent with this hypothesis, DDMU-epoxide has been found to be mutagenic in the *S. typhimurium* Ames assay (Gold and Brunk 1983). DDA-Cl is not known to have been similarly assayed, so there is no direct biological evidence of its mutagenicity. There are apparently species differences in carcinogenicity of DDT. In the hamster and mouse, metabolism of DDT, DDD, and DDMU is similar (Gold and Brunk 1983). Therefore, it is unlikely that the observed differences in response between the mouse and hamster are due to relative
differences in the production of DDMU-epoxide or DDA-Cl. There is a species difference in the conversion of DDT to DDE in that the hamster was less efficient than the mouse in the conversion of DDT to DDE (Gingell 1976; Gold and Brunk 1983).

A possible mechanism of carcinogenicity may be a phenobarbital-like promotion of pre-existing abnormal cells that develop into types of tumors commonly seen in aging rats (Williams and Weisburger 1991). DDT has demonstrated promoting activity in several initiation-promotion assays (see Section 2.10). Mechanisms by which DDT promotes tumors may include direct liver injury leading to cell death and cell regeneration that could subsequently result in excess cell proliferation, hyperplasia, and tumor development (Schulte-Herman 1974); inhibition of apoptosis, which is programmed cell death characterized by DNA fragmentation (Wright et al. 1994); and reduction of gap junctional intercellular communication (GJIC) (Ren et al. 1998). DDT reduced DNA fragmentation in seven different cell types with chemical- or UV-induced apoptosis (Wright et al. 1994), supporting the hypothesis that DDT promotes tumors in part by inhibiting the death of initiated cells. Another possible mechanism of carcinogenicity may be hormonal promotion of initiated cells via estrogenic action. The estrogenic activity of DDT isomers is discussed above under the subheading Reproductive and Developmental Effects.

A tumor promoter may reduce GJIC by reducing gap junction channel permeability, gap junction number, or connexin expression (Ren et al. 1998), by increasing Ca\(^{2+}\) concentration in the cell (Adenuga et al. 1992), or by disrupting gap junction plaque stability by producing reactive oxygen radicals that affect plasma membrane fluidity (Jansen and Jongen 1996). The effects of a specific tumor promoter are frequently cell- or connexin-specific. DDT has induced GJIC inhibition \textit{in vitro} in rat liver epithelial cells (Guan and Ruch 1996; Ruch et al. 1994), primary hepatocytes (Budunova et al. 1993), Syrian hamster embryo cells (Rivedal et al. 1994; Roseng et al. 1994), mouse skin cells (Jansen and Jongen 1996), human breast cells (Kang et al. 1996), and human urothelial cells (Morimoto 1996), and \textit{in vivo} in rat liver cells (Tateno et al. 1994). Mechanisms and determinant factors of DDT-induced GJIC inhibition have been investigated extensively.

Using several combinations of cell lines and connexin types, Ren et al. (1998) showed that DDT-induced GJIC inhibition was more consistent with a cell type-dependent mechanism of GJIC inhibition than a connexin-dependent mechanism.
In “normal” human breast epithelial cells that did not express the estrogen receptor, GJIC inhibition was strongly DDT dose-dependent after a 90-minute in vitro exposure to $25 \mu \text{M}$ (Kang et al. 1996). Levels of phosphorylated connexin43 were significantly reduced in cells with DDT-induced GJIC inhibition, suggesting that intercellular communication in human breast tissue may be modulated by dephosphorylation of the connexin proteins. The same levels of DDT did not alter steady-state levels of connexin43 mRNA, suggesting that DDT alters connexin43 proteins after translation, rather than during transcription (Kang et al. 1996). Human urothelial cell lines were susceptible to DDT-induced GJIC inhibition at DDT concentrations that were not cytotoxic for up to 7 days (Morimoto 1996). For 48-hour exposures, the degree of inhibition was not dose-dependent, but dose dependence was evident in 96-hour exposures.

Jansen and Jongen (1996) investigated whether tumor stage affected the degree of DDT-induced GJIC inhibition in mouse skin cells by conducting parallel fluorescent dye transfer assays in primary mouse keratinocytes, DMBA-initiated mouse epidermal 3PC cells, and mouse skin carcinoma-derived CA3/7 cells. The investigators found that the order of GJIC percent inhibition in cell types was primary keratinocytes > initiated 3PC cells > carcinoma-derived cells, where percent inhibition of GJIC was measured by comparison to cell type-specific controls. DDT-induced GJIC inhibition in the 3PC initiated cell line was both dose- and time-dependent within a 90-minute exposure. GJIC inhibition by DDT was also dose-dependent in liver cells of rats orally administered DDT in vivo for 2 weeks (Tateno et al. 1994). The number and size of immunostained connexin32 spots were reduced in liver cells of rats administered $25 \text{mg/kg/day}$, while the area of dye spread was significantly reduced only at 50 mg/kg/day. The time course of GJIC inhibition showed significantly reduced area of dye spread after 1, 2, and 4 weeks of exposure, with recovery to control levels at 6 weeks.

As mentioned in Section 2.2.2.8, numerous studies have examined the role of environmental estrogens, DDT and related compounds among them, as possible contributors to the increased incidence of breast cancer. Several mechanisms for DDT-induced increased breast cancer risk have been proposed including: (1) by binding to the ER, which induces a series of biochemical reactions ultimately resulting in protein synthesis and cell proliferation in estrogen-sensitive tissues including the breast; (2) by shifting the balance of endogenous 17β-estradiol metabolites in favor of the genotoxic 16α-hydroxyestrone, at the expense of the nongenotoxic 2-hydroxyestrone; and (3) by mimicking epidermal growth factor in human mammary epithelial cells, thus stimulating cell proliferation.
In addition to the studies that characterized the binding of DDT to the estrogen receptor already mentioned in the discussion of reproductive effects, many additional similar studies have specifically used breast cancer cells to demonstrate the involvement of the estrogen receptor in breast cancer cell proliferation (Dees et al. 1996, 1997a, 1997b; Shekhar et al. 1997; Zava et al. 1997). These and other studies clearly demonstrated that DDT analogues increase cell proliferation in human breast cancer cells by an ER-mediated mechanism that can be blocked by antiestrogens, and that their estrogenic potencies are several orders of magnitude lower than that of 17β-estradiol.

Another mechanism by which DDT compounds may increase cancer risk is by increasing the production of genotoxic metabolites from the breakdown of 17β-estradiol, at the expense of producing nongenotoxic metabolites. Two 17β-estradiol metabolites that have been studied extensively are 16α-hydroxyestrone (16α-OHE1) and 2-hydroxysterone (2-OHE1), which are formed via two mutually exclusive metabolic pathways. 16α-OHE1 binds covalently to the estrogen receptor in human breast cancer cells (Swaneck and Fishman 1988), and has induced genetic and proliferative changes in mouse mammary epithelial cells (Telang et al. 1992). 2-OHE1, in contrast, inhibited both basal and estradiol-induced growth of MCF-7 human breast cancer cells, acting as an anticarcinogen (Schneider et al. 1984). Several studies addressed the hypothesis that the balance of the two metabolites, expressed as the ratio 16α-OHE1/2-OHE1, may be predictive of xenoestrogen-induced mammary cancer in humans; as the ratio of 16α-OHE1/2-OHE1 increases, so does the risk of breast cancer.

The ratio of estradiol metabolites 16α-OHE1/2-OHE1 was increased over controls in cultures of ER-positive MCF-7 human breast cancer cells by o,p'-DDT, o,p'-DDE, and p,p'-DDE (Bradlow et al. 1995). McDougal and Safe (1998) also found that the 16α-OHE1 / 2-OHE1 ratio in a MCF-7 human cancer cell assay was elevated when the cells were exposed to o,p'-DDE, and E2 2-hydroxylation was reduced compared to controls in cells exposed to o,p'-DDE and o,p'-DDT; however, the ratio did not consistently predict known mammary carcinogens in the same assay. In ER-negative MCF-10 and MDA-MB-231 cell lines, on the other hand, neither o,p'-DDE nor o,p'-DDT induced significant changes in either C2- or 16α-hydroxylation of estradiol (Bradlow et al. 1997), suggesting an estrogenic mechanistic pathway. In the MCF-7 cell line, C2-hydroxylation was reduced to 67% of the control level by o,p'-DDT, but addition of the antiestrogen indole-3-carbinol blocked the effect, again suggesting that the effect is ER-mediated.

The 16α-OHE1/2-OHE1 ratio hypothesis is controversial, however. Epidemiology studies of the association of 16α-OHE1 with breast cancer have provided mixed results (Safe 1998). In addition,
although 16α-OHE1 induced cell proliferation, a closely related compound, 16α-OHE2, did not (Schneider et al. 1984, as cited in Safe 1998). Also, while 2-OHE1 inhibited cell growth, the isomer 2-OHE2 enhanced cell proliferation in MCF-7 human breast cancer cells (Schneider et al. 1984, as cited in Safe 1998). Safe (1998) did not elaborate on the relative metabolic production of the different isomers.

A third mechanism by which DDT compounds may increase the risk of breast cancer is by producing proliferative changes in ER-negative breast cells via a nonestrogenic pathway by mimicking epithelial growth factor (EGF). *p,p’*-DDT stimulated two growth factor receptors associated with malignant breast lesions and increased STATS-mediated gene expression, ultimately increasing proliferation of untransformed ER-negative MCF-10A human breast epithelial cells (Shen and Novak 1997a). The study results indicated that *p,p’*-DDT may modulate breast cell proliferation by multiple mechanisms not regulated by the ER, while the *o,p’*-isomer was inactive in this test system.

When endogenous growth factors bind to growth factor receptors that are receptor tyrosine kinases, a chain of biochemical reactions is initiated that leads to transcription of genes involved in cellular proliferation and differentiation (Shen and Novak 1997b). *p,p’*-DDT mimicked EGF in human mammary epithelial cells by increasing EGF receptor tyrosine kinase activity at 0.01 and 0.1 µM concentrations, but appeared to impede the activity at 1 and 10 µM concentrations (Shen and Novak 1997b).

### 2.5.3 Animal-to-Human Extrapolations

In humans and animals, acute high doses of DDT primarily affect the nervous system. However, it is uncertain whether effects on other systems and/or organs seen in animals exposed to lower doses for prolonged periods of time would also manifest in humans exposed under similar exposure conditions. In general, the metabolism of DDT in animals is similar to that in humans; however, there are also differences between species, and within species, differences between tissues. Comparisons of elimination rates of DDT from fat showed that the process is faster in rats followed by dogs and monkeys and slowest in humans (Morgan and Roan 1974). Rats eliminate DDT 10 to 100 times faster than humans. Morgan and Roan (1974) suggested that the differences in elimination rats could be due to differences in liver metabolism, gut bacterial metabolism, enterohepatic recirculation, or factors related to the accessibility of plasma-transported pesticide to the excretory cells of the liver. For specific effects, such as adrenal gland toxicity, *in vivo* and *in vitro* susceptibility to *o,p’*-DDD and 3-methylsulfonyl-*p,p’*-DDE varied among animal species (Brandt et al. 1992), and human adrenals *in vitro* showed potentially different susceptibility than animal glands *in vitro*. This is most likely due to differences in metabolism and
covalent binding activities. Thus far, the endocrine-disrupting activity of DDT and analogues observed in experimental animals and in wildlife has not been observed in humans exposed to DDT.

2.6 RELEVANCE TO PUBLIC HEALTH

Overview.

DDT is probably one of the best known and most widely studied pesticides. It was used extensively during World War II to control lice and other insects by application directly to humans. Numerous studies have been conducted in a variety of animal species. The human data are somewhat more limited.

Studies of workers in DDT-manufacturing plants or spray applicators who had occupational exposure to DDT over an extended period provide information on the possible adverse effects on human health. Studies of mortality have been conducted in several occupational cohorts. Occupational exposure to DDT involved multiple routes of exposure. The primary contact was probably inhalation and dermal; however, absorption of DDT from the lungs may not have been significant, and ingestion via the mucociliary apparatus of the upper respiratory tract is probable. Therefore, occupational exposures to DDT would most likely result in exposure by the oral route. There are no experimental studies in animals by the inhalation route with which to compare observed human effects. Some of the central nervous system effects observed in animals by the oral route have also been identified in humans exposed occupationally or through voluntary or accidental ingestion of DDT. These effects include cold moist skin, hypersensitivity to contact, tremors, and convulsions. Signs and symptoms of poisoning in humans and animals resulting from exposure to relatively high doses of DDT include paresthesia of the tongue, lips, and face; hyperexcitability to stimuli; dizziness; disturbed equilibrium; tremor; perspiration, headache, nausea, vomiting, confusion, and tonic and clonic convulsions. Symptoms appear several hours after exposure, and in animals exposed to lethal doses, death occurs within 24–72 hours.

The central nervous system is a major target organ in humans and animals. Studies in animals suggest that the liver and the reproductive system could also potentially be target organs in humans (see Section 2.2). In animals, liver effects, ranging from increased enzyme levels to necrosis and tumors, and neurological effects, including myoclonus, appear to be the primary effects associated with DDT and DDE exposure. Reproductive effects, which include decreased fertility, abortions, and stillbirths, have also been reported in animals. Adrenal toxicity, advancing to necrosis, appears to be the primary effect associated with high dosage oral acute- or intermediate-duration exposure to DDD in animals.
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DDT and its degradation products have been found in many air, water, and soil samples. However, levels in most air and water samples are low, and exposure through these pathways is minimal. A more important exposure pathway is from the DDT and DDE that remain in the soil and may be transferred to crops grown in this soil. Since DDT, DDE, and DDD can bioaccumulate, consumption of fish from contaminated waterways may also be an important exposure pathway. Levels of DDT in food are low (estimated dietary intake of 2.2 µg/day in 1981); no health effects would be expected from ingestion of DDT alone at these levels. However, DDT, DDE, and DDD accumulate in adipose tissue. \( p,p' \)-DDT and \( p,p' \)-DDE, but not \( p,p' \)-DDD, were found in breast milk at levels up to 1.7 and 11 ppm, respectively (Takei et al. 1983). There have been no reports of adverse health effects in infants from DDT exposure via ingestion of breast milk. Adverse effects in animals exposed during lactation have been observed. It should be noted that breast milk often contains other pesticides and industrial pollutants in addition to DDT and its metabolites.

Issues relevant to children are explicitly discussed in Section 2.8 Children’s Susceptibility and Section 5.6 Exposures of Children.

**Minimal Risk Levels for DDT, DDE, and DDD.**

*Inhalation MRLs*

No MRLs were derived for inhalation exposure since adequate experimental data were not available by this route of exposure.

*Oral MRLs*

A chronic oral MRL of 0.0005 mg/kg/day was derived for DDT.

This MRL is based on a LOAEL of 0.5 mg/kg/day for neurodevelopmental effects in mice reported in a series of studies from the same group of investigators (Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996). An uncertainty factor of 1000 was used (10 for use of a LOAEL, 10 for animal to human extrapolation, and 10 to account for intrahuman variation).

The most significant finding was the presence of altered motor behavior in adult mice treated with DDT perinatally. Groups of 10-day-old male NMRI mice were treated by gavage with a single dose of
0 (vehicle control) or 0.5 mg DDT/kg in a fat emulsion vehicle by gavage (Eriksson et al. 1990a). At the age of 4 months, the mice were subjected to behavioral tests of spontaneous activity (locomotion, rearing, and total activity). Tests were conducted for 1 hour, and scores were summed for three 20-minute periods. During the last 40 minutes of testing, the treated mice showed significantly more activity than untreated controls. This was interpreted as disruption of a simple, nonassociative learning process, (i.e., habituation), or a retardation in adjustment to a new environment. These same results were reported in a later paper (Eriksson et al. 1990b) in which the authors also reported results of neurochemical evaluations conducted 2–3 weeks after behavioral testing. They measured muscarinic acetylcholine (MACH) receptors density and choline acetyltransferase (ChAT) activity in the cerebral cortex and hippocampus (MACH also in striatum) and also measured K⁺-stimulated ACh release from cerebral cortex slices. In addition, five 10-day-old mice were administered 0.5 mg ¹⁴C-DDT and the radioactivity in the brain was assayed 24 hours, 7 days, or 1 month after dosing. The results showed that K⁺-evoked ACh release in treated mice was significantly increased relative to controls, ChAT activity was not changed in the cerebral cortex or hippocampus, and the density of MACH was not significantly changed in the hippocampus or striatum, but a decreasing trend was seen in the cerebral cortex. DDT-derived radioactivity could be detected until day 7 after dosing, but none could be detected 1 month after dosing.

Previous studies have shown a significant increase in density of MACH in the cerebral cortex of 10-day-old mice 7 days after dosing, but not at 1 day postexposure compared to controls (Eriksson and Nordberg 1986). No increased binding was noted in the hippocampus either 1 or 7 days posttreatment. This was further investigated by evaluating the proportion of high- and low-affinity binding sites and affinity constants of the muscarinic receptors. A significant increase in the percentage of low-affinity binding sites accompanied by a significant decrease in high-affinity binding sites was measured in the cerebral cortex 7 days postexposure. No significant changes in affinity constants were noted. According to the authors, these low-affinity binding sites correspond to the M₁ receptor in the cerebral cortex, which are thought to be associated with neuronal excitation. No changes were observed in the sodium-dependent choline uptake system in the cerebral cortex 7 days postexposure.

In a follow-up study, Eriksson et al. (1992) treated 3-, 10-, and 19-day-old mice, and conducted behavioral testing and neurochemical evaluations at 4 months of age. As previously published, mice treated at 10-days-old exhibited hyperactivity relative to controls and also had a significant decrease in the density of MACH in the cerebral cortex. No such changes were seen in mice treated at 3 or 19 days old. The authors suggested that the changes in MACH density and behavior might be the consequence of early interference with muscarinic cholinergic transmission specifically around the age of 10 days.
subsequent studies by the same group, mice were tested at 5 and 7 months old (Eriksson et al. 1993; Johansson et al. 1995). At both time points, mice treated with DDT perinatally showed increased spontaneous motor activity relative to controls, and decreased density of MACh in the cerebral cortex. No changes were seen regarding percentages of high- or low-affinity muscarinic binding sites in the cerebral cortex. Mice in these studies were also treated orally with the type I pyrethroid insecticide, bioallethrin, and tested for motor activity at 5 months old (Eriksson et al. 1993) and 7 months old (Johansson et al. 1995). In general, mice treated with DDT at the age of 10 days and later with bioallethrin showed increased motor behavior relative to those treated with bioallethrin alone, suggesting a DDT-induced increased susceptibility to bioallethrin. Mice treated first with DDT and later on with bioallethrin showed increased difficulties in learning a skill, such as the swim maze test, compared with untreated mice, mice treated with DDT alone, or mice treated with bioallethrin alone (Johansson et al. 1995). In yet another study from this group, paraoxon replaced bioallethrin, and the mice were tested at 5 and 7 months-old (Johansson et al. 1996). In addition, acetylcholinesterase activity was measured in cerebral cortex of 5-month-old mice and MACh and nicotinic cholinergic receptors in the cortex of 7-month-old mice. Relevant new findings include that: (1) DDT did not significantly alter acetylcholinesterase activity; (2) DDT did not alter the effects of paraoxon on acetylcholinesterase activity (decreased); (3) DDT altered (increased or decreased) some of motor responses due to paraoxon alone at 7 months but not at 5 months; (4) none of the treatments altered performance in the swim maze test; and (5) none of the treatments altered the density of nicotinic cholinergic receptors in the cortex.

In this series of studies, two responses seem to be consistent from study to study in mice treated with DDT perinatally and tested as adults, a decrease in the density of muscarinic cholinergic receptors in the cerebral cortex and increased spontaneous motor activity. Whether or not there is a causal relationship is not clear. DDT also altered some motor responses induced by other pesticides, but a pattern was not always clear. The investigators interpreted the latter findings as DDT inducing changes early in the brain that translated into increased susceptibility to other pesticides later in life. The DDT-induced increase in spontaneous motor activity at the dose of 0.5 mg/kg is considered a less serious LOAEL.

An intermediate oral MRL of 0.0005 mg/kg/day was derived for DDT.

This MRL is based on a NOAEL of 0.05-0.09 mg/kg/day for liver effects in Osborne-Mendel rats administered technical DDT in the diet at dosage levels of 0, 1, 5, 10, or 50 ppm for 15–27 weeks (Laug et al. 1950). In this dietary study, the amount of DDT added to the food was measured, but the actual food consumption and body weights of the rats were not measured. The calculated value for the NOAEL
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ranges from 0.05 to 0.09 mg/kg/day depending on the food consumption values used to calculate the actual dose of DDT consumed. Details about the dose calculation are discussed in Appendix A. The approximate doses provided in the diet in this study were: 0.05–0.09, 0.25–0.5, 0.5–0.9, and 2.5–4.6 mg/kg/day. An uncertainty factor of 100 was used (10 for interspecies extrapolation and 10 for human variability).

This study was essentially designed to examine whether DDT accumulates in adipose tissue and to what extent, how age and dose level affect accumulation, and how rapidly it is eliminated. Seventy-seven rats were used for microscopic evaluation of only the liver and kidney. This was based on findings from a previous study from the same group (Fitzhugh and Nelson 1947, see below) in which higher dietary levels of DDT had been used. Based on the previous findings, only the liver was expected to show microscopic changes. Although not explicitly stated, it is assumed that morphologic evaluations were conducted at the times when DDT levels in fat were determined (after 15, 19, 23, and 27 weeks of treatment).

There were no morphologic alterations in the kidneys. Liver alterations were noticed at the 5 ppm (0.25–0.5 mg/kg/day) dietary level of DDT and higher, but not at 1 ppm (0.05–0.09 mg/kg/day). Liver changes consisted of hepatic cell enlargement, especially in central lobules, increased cytoplasmic oxyphilia with sometimes a semihyaline appearance, and more peripheral location of the basophilic cytoplasmic granules. Necrosis was not observed. The severity of the effects was dose-related, and males tended to show more hepatic cell changes than females. Changes seen at the 5 ppm level (0.25–0.5 mg/kg/day) were considered by the authors as "minimal".

In the Fitzhugh and Nelson (1947) study, 16 female Osborne-Mendel rats were fed a diet containing 1,000 ppm technical DDT (approximately 96 mg/kg/day) for 12 weeks. Sacrifices were conducted at cessation of dosing and at various intervals after a DDT-free period. Liver changes were similar to those seen in the Laug et al. (1950) study, although of increased severity, and were still present in rats killed after 2 weeks in a DDT-free diet. Minimal liver changes were apparent after 4–6 weeks of recovery, and complete recovery was seen after 8 weeks. Hepatic effects ranging from increased liver weight to cellular necrosis have been reported in animals after chronic exposure to DDT in the diet.

An oral MRL for chronic-duration exposure was not derived because of the inadequacy of the available data on liver effects in animals to describe the dose-response relationship at low dose levels. The liver appears to be the most sensitive target of DDT for chronic duration exposures. In a brief communication, Fitzhugh (1948) stated that histopathological lesions occurred in the liver of rats fed 10 ppm DDT in the diet for 2 years, but no experimental details were given, so the quality of the study cannot be evaluated. This dietary level was the lowest level tested in the study, but was
still higher than the lowest level resulting in hepatic effects in the Laug et al. 1950 study used for derivation of the intermediate duration MRL.

No acute-, intermediate-, or chronic-duration dermal MRLs were derived for DDT because of the lack of an appropriate methodology for the development of dermal MRLs.

**Death.** Although there are no documented, unequivocal reports of a fatal human poisoning occurring exclusively from ingestion of pure DDT, ingestion of DDT dissolves in kerosene by a child was fatal (Hill and Robinson 1945). The patient exhibited the typical neurotoxic symptoms of DDT intoxication observed in animals (tremors and convulsions). Mortality studies have been conducted with several occupational cohorts (Austin et al. 1989; Morgan et al. 1980; Wong et al. 1984). This exposure to DDT involved primarily skin contact and inhalation of DDT particulates. However, absorption of DDT from the lungs may not have been significant, and dermal absorption is limited, so that ingestion due to mucous trapping and mucociliary transport in the upper respiratory tract is most likely. No increase in mortality rate was identified in any of these studies.

The acute toxicity (LD$_{50}$) of DDT has been studied in several animal species following oral, dermal, and injection exposure. Death has been observed in 50% of animals following oral exposure to 113–800 mg DDT/kg (Bathe et al. 1976; Cameron and Burgess 1945; Gaines 1969; Kashyap et al. 1977), 400–4,000 mg DDD/kg (Ben-Dyke et al. 1970; Tomatis et al. 1974a), and 810–846 mg DDE/kg (Tomatis et al. 1974a). The LD$_{50}$ for dermal exposure to DDT ranged from 2,500 to 3,000 mg/kg (Ben-Dyke et al. 1970; Cameron and Burgess 1945; Gaines 1969). Intraperitoneal and subcutaneous injection of DDT has resulted in LD$_{50}$ values ranging from 9.1 to 333 mg/kg and from 250 to 1,500 mg/kg, respectively (Bathe et al. 1976; Cameron 1945; Cameron and Burgess 1945; Okey and Page 1974). LD$_{50}$ values following subcutaneous injection of DDT are much higher than those reported following oral exposure and lower than those following dermal exposure. No LD$_{50}$ values were located for injection exposure to DDE or DDD.
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Systemic Effects.

Respiratory Effects. Moderate irritation to the upper respiratory tract has been reported in volunteers exposed to DDT-containing aerosols (Neal et al. 1944). However, the irritations may have been caused by the vehicles used to dissolve DDT and disperse the aerosols. Oral exposure of rats to DDT did not result in adverse effects on the respiratory system (Deichmann et al. 1967; NCI 1978). However, after intraperitoneal exposure to 12.5 mg DDT/kg/day, guinea pigs exhibited a decrease in lung mast cells and histamine levels (Ashari and Gabliks 1973).

Cardiovascular Effects. Tachycardia occurred in an individual after accidental ingestion of an estimated dose of 16.3 mg DDT/kg (Hsieh 1954). Cardiovascular effects, which were not observed in any oral or dermal animal studies, were reported in several species after intravenous exposure. Ventricular fibrillation, which resulted in respiratory failure and death, was reported to have occurred in some cats, rabbits, monkeys, and dogs exposed intravenously to DDT at doses ranging from 25 to 75 mg/kg/day (Philips and Gilman 1946).

Hematological Effects. Several studies provided some information regarding hematological effects in humans after exposure to DDT (Hayes et al. 1956; Laws et al. 1967; Morgan and Lin 1978; Ortelee 1958) or DDE (Dunstan et al. 1996; Morgan and Lin 1978). Exposure levels were estimated in two of these studies and were reported to be between 0.038 and 0.61 mg/kg/day. Overall, these studies did not provide any conclusive evidence of adverse hematological effects in the groups examined. Limited data in animals were consistent with the findings in humans.

Hepatic Effects. Correlations between DDT serum levels and the presence of the liver enzymes SGOT (AST), SGPT (ALT), LDH, and alkaline phosphatase in the serum have been reported in an epidemiological study of workers exposed to multiple pesticides. However, there is no evidence as to whether the liver injury this reflects is irreversible (Laws et al. 1973; Morgan and Lin 1978). DDT does stimulate production of liver enzymes in both humans and animals, in particular the mixed function oxidase (MFO) enzymes, (Kolmodin et al. 1969; Pasha 1981; Street and Chadwick 1967). The consequences of induction of MFO enzymes include altered metabolism of drugs, xenobiotics, and steroid hormones. The impact of induction of MFO enzymes is uncertain, and in the absence of other hepatic effects, such induction alone is not considered an adverse effect.
In animals, the liver appears to be one of the primary targets of DDT toxicity. The severity of injury to the liver increases progressively with dose. With acute oral exposure, adverse liver effects can include increased liver weight and elevated serum levels of liver enzymes (Agarwal et al. 1978; de Waziers and Azais 1987; Pasha 1981). Subchronic and chronic oral exposure to DDT resulted in hepatic cell hypertrophy, histopathologic alterations, necrosis, and hyperplasia (Cranmer et al. 1972a; Fitzhugh and Nelson 1947; Graillot et al. 1975; Jonsson et al. 1981; Orberg and Lundberg 1974). The oral MRL for intermediate-duration exposure was based on the study by Laug et al. (1950), in which minimal hepatocellular hypertrophy and cytoplasmic eosinophilia were seen after 15 weeks feeding of DDT at a dosage of approximately 0.25-0.5 mg/kg/day; the NOAEL was approximately 0.05-0.09 mg/kg/day.

Acute studies in which animals were exposed to DDT by injection demonstrated many of the same effects seen in animals exposed by the oral and dermal routes. Rats and mice exposed to DDT intraperitoneally at doses ranging from 100 to 200 mg DDT/kg/day exhibited an increase in hepatic microsomal enzyme levels or an increase in liver weights (Chhabra and Fouts 1973; Nigg et al. 1974; Parkki et al. 1977). An increase of hepatic microsomal enzyme activities was also observed in rats exposed intratracheally to 50 mg DDT/kg/day for 3 days (Narayan et al. 1985a, 1985b). A recent study found that DDT, DDE, and DDD induced CYP2B-associated enzyme activities in liver from rats treated with the chemicals in the diet for 14 days (Nims et al. 1998). Treatment also resulted in considerable induction of CYP2B protein, lesser induction of CYP3A protein, and almost no induction of CYP1A protein. Limited induction of CYP1A-associated enzymes was observed. Based on these observations, DDT and analogues have been classified as phenobarbital-type cytochrome P-450 inducers in the rat. DDT and DDE appeared to have similar inducing potencies, whereas the potency of DDD was within one order of magnitude lower than the other two compounds. Nims et al. (1998) further demonstrated that CYP2B induction resulting from DDT administration was due to the combined inductive effects of DDT, DDE, and DDD, and not exclusively to the DDE generated metabolically.

**Endocrine Effects.** The adrenal gland consists of: the adrenal medulla, which secretes norepinephrine and epinephrine, and the adrenal cortex, which is composed of three zones. These zones are: (1) the zona glomerulosa, producing mineralocorticoids involved in controlling electrolyte homeostasis, (2) the zona fasciculata, the primary source of glucocorticoids involved in controlling carbohydrate metabolism and stress responses, and downregulating some immune responses, and (3) the zona reticularis, the primary adrenal source of very small quantities of sex steroids (Ross and Reith 1985).
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As previously mentioned in Section 2.2.2.4, \( o,p' \)-DDD has been used for four decades in the treatment of adrenocortical carcinoma and Cushing’s disease in humans (Bergenstal et al. 1960; Wooten and King 1993). The therapeutic action is based on the induction of selective necrosis of the zona fasciculata and zona reticularis of the adrenal cortex; this was first observed in dogs given DDD orally in early studies by Nelson and Woodard (1949). Studies have shown a high correlation between adrenocorticolytic activity and metabolic activation by adrenocortical mitochondria. Dog adrenal mitochondria had significantly greater metabolism of \( o,p' \)-DDD and covalent binding activities than did adrenal mitochondria from rabbits, rats, or guinea pigs (Martz and Straw 1980). Levels of metabolism and covalent binding measured in human adrenal mitochondria were intermediate between levels measured in dogs and rabbits and those measured in rats and guinea pigs (Martz and Straw 1980). A more recent study with dog adrenal cortical homogenates showed that the majority of the \( ^{14} \text{C-} o,p' \)-DDD-derived radioactivity was covalently bound to proteins, and that no radioactivity was associated with DNA (Cai et al. 1995). The rank order of species regarding metabolism and protein binding was cow > dog > rat adrenal homogenates > human normal adrenal or tumor homogenates. According to Cai et al. (1995), their results are consistent with an acyl chloride being the reactive intermediate formed from the dichloromethyl moiety of \( o,p' \)-DDD.

As previously mentioned in Section 2.4.3 Metabolism, methylsulfonyl metabolites of DDT (3-MeSO_2-DDE and 2-MeSO_2-DDE; all studies have been conducted with the \( p,p' \)-isomers, and therefore, the chlorine position is not specified in the abbreviation) have been identified in humans and animals (Haraguchi et al. 1989; Noren et al. 1996; Weistrand and Noren 1997). 3-MeSO_2-DDE is a potent toxicant in the adrenal cortex, particularly of mice, and possibly in humans after local activation by cytochrome P-450. For example, whole body autoradiography of \( ^{14} \text{C-labeled} \) 3-MeSO_2-DDE in female mice injected with the test material intravenously showed heavy accumulation of radioactivity confined to the zona fasciculata of the adrenal cortex (Lund et al. 1988). Morphological evaluation of the adrenals showed extensive vacuolation and necrosis of the zona fasciculata 1 to 12 days after a single dose of 25 mg/kg; degenerative changes were seen at 12.5 mg/kg. Studies in vitro showed a dose- and time-dependent covalent irreversible binding to protein and formation of water soluble metabolites (Lund et al. 1988). This was blocked by the cytochrome P-450 inhibitor, metyrapone, and the addition of reduced glutathione decreased binding. A subsequent study in mice administered 3-MeSO_2-DDE intraperitoneally identified mitochondria in the zona fasciculata as the primary targets for 3-MeSO_2-DDE-induced toxicity (Jönsson et al. 1991). Disorganization and disappearance of central cristae were observed as soon as 6 hours after a dose of 3 mg/kg. Higher doses showed mitochondrial vacuolization, followed by disappearance of mitochondria or cellular necrosis. Jönsson et al. (1991) further suggested that of the two
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cytochrome P-450s expressed predominantly in the adrenal cortex, P-45011β and P-450SCC, the former (which converts 11-deoxycorticosterone to cortisone) is involved in the metabolic activation of 3-MeSO₂-DDE in mice. P-450SCC is also expressed in the ovary and testes, but no binding or toxicity was seen in these organs. Lund and Lund (1995) later provided direct evidence for an involvement of adrenocortical mitochondrial P-450s in the bioactivation of 3-MeSO₂-DDE. Intraperitoneal administration of radioactive 3-MeSO₂-DDE to pregnant or lactating mice resulted in specific accumulation and binding of 3-MeSO₂-DDE-derived radioactivity in the zona fasciculata of adrenals from 16- to 18-day-old fetuses or suckling pups, showing ready transplacental passage of the metabolite and transfer via maternal milk (Jönsson et al. 1992). The results also suggested that cytochrome P-45011β was involved in the activation of 3-MeSO₂-DDE in the fetal adrenal cortex. Quantitative measurements showed that 7 days after dosing, the amount of radioactive label of the pups adrenals was 2 and 3.6 times higher than maternal adrenals at 1.5 and 25 mg/kg dose levels, respectively, suggesting that mother’s milk may be an important route of exposure of 3-MeSO₂-DDE in DDT-exposed animals. A later study showed that P-45011β seems to be expressed during gestation days 10–12 in the adrenal cortex in the mouse fetus (Jönsson et al. 1995). 3-MeSO₂-DDE was also found to reduce the capacity of pups and maternal adrenals to secrete corticosterone (Jönsson 1994) by a mechanism possibly involving competitive inhibition of adrenocortical CYP11B1 (Johansson et al. 1998). Human adrenal glands in vitro were found also to bioactivate 3-MeSO₂-DDE to a metabolite that bound irreversibly to mitochondria (Jönsson and Lund 1994). Binding was inhibited by metyrapone indicating the involvement of cytochrome P-450, but the specific isozyme was not elucidated.

Comparative studies by Brandt et al. (1992) showed that adrenal cortical cytochrome P-450 from mink and otter metabolically activate and bind both p,p'-DDD and o,p'-DDD, whereas 3-MeSO₂-DDE is not activated by these species in vitro. Both isomers induced necrosis and focal bleeding in the zona fascicularis/zona reticularis in vivo in mink. Adrenals from chickens also activated and covalently bound 3-MeSO₂-DDE and o,p'-DDD in vitro, and both compounds were adrenotoxic in vivo.

**Immunological and Lymphoreticular Effects.** Because immunotoxicological evaluation of DDT in humans is limited to a single study with only three volunteers and a study of 23 Swedish fish-consumers, the evidence is inconclusive. In the study with volunteers, antibody titers specific for certain bacterial antigens were elevated when DDT was given orally preceded by the antigen given by injection, however, the levels may not have been outside the normal range of values for exposure to the antigen alone (Shiplov et al. 1972). In the Swedish study, the concentration of p,p'-DDT in the plasma of 12 of the subjects was significantly negatively correlated with both the proportion and absolute numbers of NK
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cells, and plasma DDT was significantly elevated in fish consumers compared to nonconsumers of fish (Svensson et al. 1994). Immunological effects have been reported in animals following oral exposure; interpretation of these studies should consider the complexity of the immunological system. These effects include increases in gamma globulin and serum immunoglobulin and decreased cell-mediated immunity (Banerjee et al. 1996; Street and Sharma 1975). Guinea pigs immunized with diphtheria toxoid followed by intraperitoneal injections of 20 mg DDT/kg/day exhibited a decrease in anaphylactic shock upon challenge with DDT compared to untreated controls (Gabliks et al. 1973). According to the authors, this effect may be related to alterations in the histamine-mediated mechanism of anaphylaxis. Leprosy bacterial growth in mouse foot pad was increased in mice inoculated with the bacterium and subsequently fed DDT at $10.7 \text{ mg/kg/day}$ for 24 weeks (Banerjee et al. 1997a). The immunotoxicity of DDT administered in the diet at $5.7 \text{ mg/kg/day}$ for 4 weeks was enhanced by decreased dietary protein in rats (Banerjee et al. 1995). Increased physical/emotional stress in mice enhanced the immunotoxicity of DDT fed to mice at 20.3 mg/kg/day for 4 weeks (Banerjee et al. 1997b). A comparison of the immunotoxicity of orally administered DDT, DDE, and DDD in rats revealed no clear pattern of relative toxicity (Banerjee et al. 1996). While effects on immune competence in humans have not been fully characterized, immune responses observed in animals may be indicative of effects in humans subjected to long-term, low-level exposure to DDT.

**Neurological Effects.** Human case studies indicate that the central nervous system is one of the primary target organ systems for DDT toxicity following oral exposure at high doses (Hayes 1982). Clinical symptoms include hyperexcitability, tremors, and convulsions. Experimental data in animals exposed to DDT by the oral and injection routes (intraperitoneal, intravenous, subcutaneous) confirm the effects observed in humans of DDT on the nervous system. Tremors, hyperexcitability, or convulsions were observed following acute and chronic exposure in rats and mice. Doses at which these effects occurred were lower in the chronic studies than in the acute studies.

Alterations in muscarinic receptors (Eriksson and Nordberg 1986) and in levels of neurotransmitters and biogenic amines observed in animals indicate that subclinical neurochemical changes could also occur in humans exposed to DDT (Herr et al. 1986; Hong et al. 1986; Hudson et al. 1985). Changes in neurotransmitter levels in the brain have also been seen following intraperitoneal and intramuscular injections of DDT (Hrdina et al. 1972; Uppal et al. 1983).

Behavioral deficits in learning processes have been described in adult mice exposed perinatally (Craig and Ogilvie 1974) or as neonates (Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996).
These studies suggest that exposure of the developing fetus or newborn to DDT during the critical stages in nervous system development may cause developmental neurotoxicity manifested later in life. Behavioral neurotoxicity has been described in rats treated with DDT as adults (Sobotka 1971); however, administered doses of at least 50 times that given to neonates were required to produce learning deficits.

No studies were located regarding neurological effects after oral exposure to DDE or DDD. However, neurological responses after intraperitoneal injections of DDD have been reported. Guinea pigs exposed intraperitoneally to 300 mg DDD/kg/day for 14 days exhibited tremors (Jensen et al. 1957).

**Reproductive Effects.** No available studies indicate that DDT has an adverse effect on human reproduction. Certain data suggest a positive relationship between levels of maternal blood DDE and preterm delivery (O’Leary et al. 1970a), while other data indicate no difference between total DDT or DDE in the blood of women who had miscarried (Leoni et al. 1989) or delivered preterm (Berkowitz et al. 1996) and levels in women whose pregnancy had gone full term. Also, no positive correlation was found between blood levels of DDT, DDE, or DDD and premature rupture of the fetal membranes when these levels were compared to levels in women whose membranes did not rupture prematurely (Berkowitz et al. 1996; Ron et al. 1988). No associations were seen between plasma DDT or DDE and the occurrence of endometriosis (Lebel et al. 1998). However, measurements of DDT levels in blood are reflective of current body burdens, but may not be reflective of past exposure.

*p,p’*-DDT as well as *o,p’*-DDT can have adverse effects on reproduction after short term or longer term exposure of rats. Acute oral exposure to 100–500 mg DDT/kg/day has been associated with decreased male fertility (Krause et al. 1975). Longer-term exposure of male and female rodents to lower doses of DDT (0.56–39 mg/kg/day) has also resulted in decreased fertility, stillbirths, and increased fetal mortality (Deichmann et al. 1971; Green 1969; Jonsson et al. 1976). Similar effects were reported in studies where DDT was administered by injection (Gellert et al. 1972; Kihlstrom et al. 1975; Nigam et al. 1977).

A DDT metabolite, *p,p’*-DDE, was recently shown to have anti-androgenic activity when administered to rats during pregnancy (Kelce et al. 1995; Loeffler and Peterson 1999; You et al. 1998) or after birth (Kelce et al. 1995, 1997). The mechanism of DDT-mediated anti-androgenicity and results from representative studies *in vitro* are discussed in Section 2.5.2.
While DDT intake by adult rodents can adversely affect reproductive performance, in general, mature animals must receive high doses before fertility is impaired (Ottoboni 1969). However, exposure of the developing fetus to lower doses resulted in reproductive effects later in life.

\( o,p' \)-DDT has also been shown to be estrogenic in animals after oral and intraperitoneal administration. This estrogenic activity is evidenced by a uterotrophic effect, increases in uterine wet weight, and increases in concentrations of RNA or DNA and/or carbohydrates in uterine tissue. For example, oral doses ranging from 50 to 100 mg \( o,p' \)-DDT/kg/day have been reported to elicit estrogenic activity in rats (Bitman and Cecil 1970; Clement and Okey 1972). Estrogenic activity has also been demonstrated for other isomers in injection studies. Welch et al. (1969) reported an estrogenic activity ranking of \( o,p' \)-DDT > technical DDT > \( p,p' \)-DDT in immature female rats treated intraperitoneally. Singhal et al. (1970) showed that \( o,p' \)-DDT was much more effective in increasing uterine weight in young rats than \( p,p' \)-DDT after a single intramuscular injection. The \( p,p' \)-isomer is the most prevalent in the environment, accounting for approximately 85% of the total amount of DDT, DDE, or DDD found; the \( o,p' \)-isomer constitutes most of the remaining 15% of each chemical. The mechanism of DDT-mediated estrogenicity as well as results from mechanistic studies \textit{in vitro} are discussed in Section 2.5.2.

Safe (1995) conducted a mass/potency balance exercise to assess the impact of environmental estrogens as causative agents of adverse health effects, primarily reproductive disturbances and breast cancer. Besides environmental estrogens (xenoestrogens), humans are exposed to several structural classes of naturally occurring estrogens including plant bioflavonoids and various mycotoxins. The estrogenic activities of these substances has been investigated \textit{in vivo} and \textit{in vitro} cell systems and in ER binding assays; most elicit multiple estrogenic responses. Also, a number of foodstuffs contain 17\( \beta \)-estradiol and estrone. At the same time, several different structural classes of chemicals present in the human diet show antiestrogenic activity, including 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) and related halogenated aromatics. Polynuclear aromatic hydrocarbons (PAH), found in cooked foods, and indole-3-carbinol (IC), a major component of cruciferous vegetables, have also shown antiestrogenic properties. From published data, Safe (1995) estimated a dietary estrogen equivalent level of 0.0000025 \( \mu \)g/day from estrogenic pesticides and of 102 \( \mu \)g/day from bioflavonoids. Studies from the literature also suggested that the estrogenic potencies of bioflavonoids relative to 17\( \beta \)-estradiol are 0.001–0.0001, whereas for pesticides, the estrogenic potency is about 0.000001. Therefore, the estrogen equivalent from dietary intake of flavonoids was 4x10\(^7\) times higher than that from estrogenic pesticides. A similar exercise with the antiestrogenic compounds led to the conclusion that the sum of antiestrogen toxic equivalents are orders of magnitude higher than the estimated dietary intakes of estrogenic pesticide equivalents. These
conclusions are not necessarily contradictory to the recommendation that intake of pesticides should continue to be monitored and kept to a minimum for the protection of developing organisms, but rather point out the multiple sources of potentially endocrine-active substances.

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Developmental Effects. No studies were located regarding developmental toxicity after DDT exposure in humans. Some studies have shown an association between DDT, DDE, or DDD levels in the blood and premature births and spontaneous abortion; however, PCBs and other chlorinated pesticides were also found to be elevated in these blood samples (Procianoy and Schvartsman 1981; Saxena et al. 1980, 1981, 1983; Wassermann et al. 1982). A more recent study found no association between serum DDE levels and preterm delivery in a group of Mount Sinai Medical Center patients (Berkowitz et al. 1996).

In animals, DDT produces embryotoxicity and fetotoxicity, but not teratogenicity. Acute oral exposure of animals to DDT resulted in decreased fetal body and organ weights, increases in resorptions, and an increased incidence of prematurity (Fabro et al. 1984; Hart et al. 1971, 1972). Intermediate or chronic oral exposure to DDT resulted in mortality, slowed development, and premature puberty (Clement and Okey 1974; Craig and Ogilvie 1974; Naishtein and Leibovich 1971; Ottoboni et al. 1977; Tomatis et al. 1972; Turusov et al. 1973).

Estrogen-like effects on the developing reproductive system have been reported. Developmental effects have been observed in animals after acute oral exposure to DDT during gestation or in the early perinatal development period; the seriousness of these effects depends on the isomeric form, the dose, and the timing of exposure. For example, oral exposure of rabbits to $10 \text{ mg} \ p,p' \text{-DDT/kg}$ during gestation days 7–9 resulted in reduced body weight in the offspring on day 28, but no such effect was seen when the dams were exposed on gestation days 21–23 (Hart et al. 1971, 1972). Gellert and Heinrichs (1975) evaluated 4 DDT isomers by administering them orally to pregnant rats (approximately 28 mg/kg) on days 15–19 of gestation and reported no significant effects on body weight, weight of the ovaries and pituitary, estrous cycle, or vaginal opening in the offspring with the exception of a small but significant delay (2 days) in vaginal opening with the $o,p' \text{-DDD}$ isomer. $o,p' \text{-DDD}$ was also the only isomer to induce persistent vaginal estrous and anovulation in female rats treated subcutaneously as neonate (1 mg/pup on days 2–4 of life) (Gellert and Heinrichs 1975). In female neonates injected subcutaneously with $o,p' \text{-DDT}$ ($3.3 \text{ mg/kg/day}$), there were significant alterations in the estrous cycle (persistent vaginal estrus), decreases in ovary weight, and decreases in corpora lutea when these animals were evaluated as
adults (Gellert et al. 1974). These effects reflect the estrogenic activity of o,p'-DDT on the developing reproductive system.

There is also evidence suggesting that exposure during gestation and lactation results in more severe effects in the offspring than exposure in utero only. A 10% preweaning mortality rate was reported in mice born to dams exposed to technical DDT during gestation and nursed by untreated females, compared to 39% mortality among pups with continued exposure via mother’s milk (Craig and Ogilvie 1974).

Recent studies have found the DDT metabolite, p,p'-DDE, to have anti-androgenic effects when administered to rats at relatively high doses. Kelce et al. (1995) showed that pups from dams exposed during gestation days 14–18 to 100 mg p,p'-DDE/kg/day and then exposed indirectly to maternally stored p,p'-DDE via breast milk had significantly reduced anogenital distance at birth and retained thoracic nipples on postnatal day 13. Treatment of weanling male rats from either day 21 or 25 until day 57 of age with 100 mg p,p'-DDE/kg/day resulted in a statistically significant delayed onset of puberty (measured by the age of preputial separation) by 5 days. The fact that serum levels of testosterone were not reduced suggested that the antiandrogenic effects were not due to a DDE-induced increase in steroid metabolism. Other gestational exposure studies have confirmed these findings and have pointed out strain differences in sensitivity. For example, anogenital distance was not affected in male Sprague-Dawley rats on postnatal day 2 after treating the dams with up to 100 mg p,p'-DDE/kg on gestation days 14–18, but was significantly reduced in similarly exposed Long-Evans pups (You et al. 1998). Treatment of the dams with 10 mg p,p'-DDE/kg resulted in retention of thoracic nipples in Sprague-Dawley pups, but only the higher dose (100 mg/kg) had this effect in Long-Evans pups. Treatment with p,p'-DDE also resulted in an apparent reduction of AR expression in male sex organs from mainly high-dose Sprague-Dawley pups, as shown by immunochemical staining; however, there were no changes in androgen receptor steady state mRNA levels in the high-dose Sprague-Dawley rats, but androgen receptor mRNA were increased 2-fold in the high-dose Long-Evans rats. A similar study in Holtzman rats exposed during gestation days 14–18 to doses between 1 and 200 mg p,p'-DDE/kg (offspring were exposed to p,p'-DDE in utero and via breast milk) found reduced anogenital distance in males on postnatal day 1 and reduced relative ventral prostate weight on postnatal day 21 at 50 mg p,p'-DDE/kg, but not at 10 mg p,p'-DDE/kg (Loeffler and Peterson 1999). Doses up to 100 mg/kg/day to the dams had no effect on onset of puberty, but 200 mg/kg/day did significantly delay puberty in males by less than 2 days. Androgen receptor staining in the ventral prostate was also reduced on postnatal 21. Serum levels of testosterone or 3α-diol androgens were not significantly altered at any time. This study also reported that at the 100 mg/kg dose level, cauda epididymal sperm number was reduced by 17% on postnatal day 63 relative to controls. No
measurements of DDE body burden were made in the 200 mg/kg/day offspring postnatally, so it is difficult to determine whether effects on puberty were due to the previous gestational plus lactational exposures or directly due to the effects of DDE present near the time of puberty.

Administration of DDT \textit{in utero} or to neonates during sensitive periods in nervous system development has caused behavioral and neurochemical changes in adult mice (Craig and Ogilvie 1974; Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996; vom Saal et al. 1995). Offspring of dams given 34.3 mg/kg/day DDT by oral gavage during gestation and lactation displayed impaired learning and decreased memory function in a maze when tested 1 and 2 months after weaning (Craig and Ogilvie 1974). However, the dose was sufficiently high in this study to cause 39% mortality in the pups before weaning. In the series of experiments conducted by Eriksson and co-workers, exposure of 10-day-old mice to a single relatively low dose of 0.5 mg of technical DDT/kg resulted in altered motor behavior at the age of 4–5 months and in alterations in neurotransmitter receptors in the brain. The findings from the Eriksson’s studies served as the basis for derivation of an acute oral MRL for DDT.

Developmental effects, including preweaning mortality and premature puberty, were reported in animals in multigeneration studies. An increase in preweaning mortality was observed in the offspring of mice chronically exposed to 41.3 mg technical or \textit{p,p}'-DDT/kg/day (Tomatis et al. 1972; Turusov et al. 1973). Del Pup et al. (1978) found a decrease in 30-day survival of neonatal mice after exposing successive generations of dams to 16.5 mg DDT/kg/day in the diet for a total of 70 weeks. Increases in abortions, stillbirths, and pup mortality were reported in mice exposed to 1.3–6.5 mg DDT/kg/day in a multi-generation study; however, most of the females in the 6.5-mg/kg group died before delivery (Shabad et al. 1973).

Given the widespread nature of DDT in the environment and the potential for placental transfer, exposure \textit{in utero} or during the sensitive postnatal period by way of nursing could occur, since DDT and DDE are consistently found in human breast milk.

\textbf{Genotoxic Effects.} DDT, DDE, and DDD have been tested in several genotoxicity studies. Tables 2-5 and 2-6 report the results of \textit{in vivo} and \textit{in vitro} studies, respectively. Results following \textit{in vivo} and \textit{in vitro} exposure to DDT are similar (Table 2-5). Chromosomal aberrations have been reported in \textit{in vivo} studies. Blood cultures of men occupationally exposed to several pesticides, including DDT, exhibited an increase in chromatid lesions (Yoder et al. 1973). Rabello et al. (1975) reported
Table 2-5. Genotoxicity of DDT, DDE, and DDD *In Vivo*

<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>End point</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammalian cells:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human (plasma)</td>
<td>Chromosomal aberrations</td>
<td>+</td>
<td>Rabello et al. 1975</td>
</tr>
<tr>
<td>Human (plasma)</td>
<td>Chromosomal aberrations</td>
<td>+</td>
<td>Yoder et al. 1973</td>
</tr>
<tr>
<td>Human (lymphocytes)</td>
<td>Chromosomal aberrations</td>
<td>+</td>
<td>Rupa et al. 1991</td>
</tr>
<tr>
<td>Mouse</td>
<td>Chromosomal aberrations</td>
<td>+</td>
<td>Clark 1974</td>
</tr>
<tr>
<td>Rat</td>
<td>Chromosomal aberrations</td>
<td>–</td>
<td>Legator et al. 1973; Palmer et al. 1973</td>
</tr>
<tr>
<td>Rabbit (fetus’ liver)</td>
<td>Chromosomal aberrations</td>
<td>–</td>
<td>Hart et al. 1972</td>
</tr>
<tr>
<td>Mouse (bone marrow)</td>
<td>Chromosomal aberrations</td>
<td>+</td>
<td>Johnson and Jalal 1973; Larsen and Jalal 1974</td>
</tr>
<tr>
<td>Mouse</td>
<td>Dominant lethal</td>
<td>+</td>
<td>Clark 1974</td>
</tr>
<tr>
<td>Rat (testes)</td>
<td>Dominant lethal</td>
<td>+</td>
<td>Krause et al. 1975</td>
</tr>
<tr>
<td>Rat</td>
<td>Dominant lethal</td>
<td>(+)</td>
<td>Palmer et al. 1973</td>
</tr>
<tr>
<td>Mouse (inhibition of testicular synthesis)</td>
<td>DNA synthesis</td>
<td>– (DDE)</td>
<td>Seiler 1977</td>
</tr>
<tr>
<td>Rat (liver)</td>
<td>DNA lesions</td>
<td>+</td>
<td>Hilpert et al. 1983</td>
</tr>
<tr>
<td>Host-mediated assays:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Serratia marcescens</em></td>
<td>Gene mutation</td>
<td>– (DDT, DDE)</td>
<td>Buselmaier et al. 1973</td>
</tr>
<tr>
<td>(Mouse hosted-mediated)</td>
<td></td>
<td>+ (DDD)</td>
<td></td>
</tr>
<tr>
<td><em>Neurospora crassa</em></td>
<td>Gene mutation</td>
<td>–</td>
<td>Clark 1974</td>
</tr>
<tr>
<td>Invertebrate systems:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Drosophila melanogaster</em></td>
<td>Dominant lethal</td>
<td>+</td>
<td>Clark 1974</td>
</tr>
</tbody>
</table>

− = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid
### Table 2-6. Genotoxicity of DDT, DDE, and DDD In Vitro

<table>
<thead>
<tr>
<th>Species (test system)</th>
<th>End point</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prokaryotic organisms:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Salmonella typhimurium</em> (TA1535, TA1537, TA98, TA100)</td>
<td>Gene mutation</td>
<td>–</td>
<td>McCann et al. 1975</td>
</tr>
<tr>
<td><em>Escherichia coli</em> (Pol-A)</td>
<td>Gene mutation</td>
<td>–</td>
<td>Fluck et al. 1976</td>
</tr>
<tr>
<td><em>E. coli</em> (Back mutation)</td>
<td>Gene mutation</td>
<td>–</td>
<td>Fahrig 1974</td>
</tr>
<tr>
<td><em>Escherichia marcescens</em> (glucose prototrophy)</td>
<td>Gene mutation</td>
<td>–</td>
<td>Fahrig 1974</td>
</tr>
<tr>
<td><em>Bacillus subtilis</em> (rec-assay)</td>
<td>DNA damage</td>
<td>–</td>
<td>Shirasu et al. 1976</td>
</tr>
<tr>
<td><em>E. coli</em> (col E1 plasmid DNA)</td>
<td>DNA damage</td>
<td>–</td>
<td>Griffin and Hill 1978</td>
</tr>
<tr>
<td><em>E. coli</em> (DNA cell binding assay)</td>
<td>DNA damage</td>
<td>–</td>
<td>Kubinski et al. 1981</td>
</tr>
<tr>
<td><strong>Fungal and plant cells:</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><em>Neurospora crassa</em></td>
<td>Recessive lethal</td>
<td>–</td>
<td>Clark 1974</td>
</tr>
<tr>
<td><em>Saccharomyces cerevisiae</em></td>
<td>Mitotic gene conversion</td>
<td>–</td>
<td>Fahrig 1974</td>
</tr>
<tr>
<td><strong>Mammalian cells:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human (lymphocytes [structural])</td>
<td>Chromosomal aberrations</td>
<td>(+)</td>
<td>Lessa et al. 1976</td>
</tr>
<tr>
<td>Chinese hamster V79 cells</td>
<td>Chromosomal aberrations</td>
<td>+ (DDE)</td>
<td>Kelly-Garverit and Legator 1973</td>
</tr>
<tr>
<td>Chinese hamster (B14F28 cells [chromosomal damage])</td>
<td>Chromosomal aberrations</td>
<td>+</td>
<td>Mahr and Miltenburger 1976</td>
</tr>
<tr>
<td>Kangaroo rat (cells)</td>
<td>Chromosomal aberrations</td>
<td>+</td>
<td>Palmer et al. 1972</td>
</tr>
<tr>
<td>Chinese hamster (V79 cells [6-thioguanine resistant mutation])</td>
<td>Gene mutation</td>
<td>–</td>
<td>Tsushimoto et al. 1983</td>
</tr>
<tr>
<td>Mouse (L51784 lymphoma cells)</td>
<td>Gene mutation</td>
<td>+</td>
<td>Amacher and Zelljadt 1984</td>
</tr>
<tr>
<td>Rat (liver epithelial cell)</td>
<td>Gene mutation</td>
<td>–</td>
<td>Telang et al. 1981</td>
</tr>
<tr>
<td>Human SV-40 (unscheduled DNA synthesis)</td>
<td>DNA damage</td>
<td>–</td>
<td>Ahmed et al. 1977</td>
</tr>
<tr>
<td>Mouse (hepatocytes-UDS)</td>
<td>DNA damage</td>
<td>–</td>
<td>Probst et al. 1981</td>
</tr>
<tr>
<td>Rat (hepatocytes-UDS)</td>
<td>DNA damage</td>
<td>–</td>
<td>Probst and Hill 1980</td>
</tr>
<tr>
<td>Hamster (hepatocytes-UDS)</td>
<td>DNA damage</td>
<td>–</td>
<td>Maslansky and Williams 1981</td>
</tr>
</tbody>
</table>

= negative result; + = positive result; (+) = weakly positive; DNA = deoxyribonucleic acid
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chromosomal aberrations in workers occupationally exposed to DDT. When all workers were considered, regardless of direct or indirect exposure, a significant increase in the incidence of chromosomal damage was reported. In pesticide sprayers who were exposed to DDT as well as seven other pesticides, increased frequencies of sister chromatid exchanges and chromosomal aberrations in peripheral lymphocytes were reported, compared to controls (Rupa et al. 1988). Human lymphocytes exposed \textit{in vitro} to concentrations between 0.06 and 15.7 µg technical DDT/mL exhibited a significant increase of chromosomal structural aberrations only at certain intermediate concentrations (Lessa et al. 1976). These studies suggest that DDT at high exposures, in certain populations, may cause chromosomal damage in humans. Increases in sister chromatid exchanges, the proliferation rate index, and the mitotic index were also reported in pesticide sprayers exposed to DDT along with several other pesticides (Rupa et al. 1989).

As shown in Table 2-6, DDT and related compounds were, for the most part, non-mutagenic in prokaryotic organisms and did not induce DNA damage under the conditions tested. However, chromosomal damage was observed in some nonhuman test systems following \textit{in vitro} and \textit{in vivo} exposure to DDT, DDE, or DDD (Table 2-6). Mahr and Miltenburger (1976) reported chromosomal damage in the B14F28 Chinese hamster cell line after exposure to DDT, DDE, or DDD. Palmer et al. (1972) also observed these same results in kangaroo rat cells (\textit{Potorous tridactylis}) \textit{in vitro} after exposure to DDT, DDE, or DDD. Kelly-Garvert and Legator (1973) reported a significant increase in chromosomal aberrations in Chinese hamster V79 cells after exposure to DDE, but not DDT. BALB/C mice exposed \textit{in vivo} to DDT exhibited chromosomal aberrations of the bone marrow (Johnson and Jalal 1973; Larsen and Jalal 1974). \textit{In vivo} studies also have reported other genotoxic effects of DDT. Clark (1974) reported an increase in dominant lethality in early spermatid and spermatocyte stages in mice exposed to DDT at high doses. Similar results were reported in rats by Palmer et al. (1973). This suggests that DDT may have an effect on spermatogenesis or fertility in humans, but this effect may not occur at exposure levels encountered in the environment.

\textbf{Cancer.} The evidence for carcinogenicity of DDT compounds in humans is inconclusive, in spite of extensive epidemiological work. During the 1970s, observations of the bioaccumulative and persistent properties and animal carcinogenicity of DDT compounds prompted numerous epidemiologic studies with the goal of determining whether exposure to DDT compounds was related to cancer in humans. The primary route of exposure to DDT compounds in humans is probably ingestion in food, particularly in countries where the use of DDT was historically heavy, but has been subsequently banned. Repeated, relatively high oral, inhalation, and dermal exposures may occur occupationally in individuals who are...
directly involved in manufacturing, handling, mixing, or applying the pesticide, or in individuals who live in areas where the pesticide is applied.

Several studies have evaluated the risk for various cancers in individuals who may have had relatively high exposures, including agricultural and pest control workers (Baris et al. 1998; Brown et al. 1993; Cantor et al. 1992; Cocco et al. 1997a, 1997b; Morgan and Lin 1978), chemical manufacturing workers (Garabrant et al. 1992), and residents of countries where DDT is currently used (Lopez-Carrillo et al. 1997; Schecter et al. 1997). Collectively, the high-exposure studies have found no consistent evidence of an association between exposure to DDT and cancer occurrence. Most of these studies have confounding factors, commonly encountered in epidemiological studies, such as exposure to multiple pesticides, inadequate follow-up times, and uncertain exposure concentrations. Well-conducted prospective studies have evaluated groups of cancer patients using measurements indicative of body burden to characterize past DDT exposure and have generally found no association (Høyer et al. 1998; Hunter et al. 1997; Krieger et al. 1994), with a few notable exceptions (Wolff et al. 1993).

The primary issue in studies of DDT and cancer is relating exposures to the occurrence of cancer. Nearly all of the breast cancer studies in humans have characterized DDT exposure in terms of concentrations of DDT/DDE/DDD measured in various tissues, which represent both current and past exposures. The epidemiological studies varied in their method for assessing DDT body burden. Because DDT is lipid-soluble, measurement of adipose DDT most accurately reflects DDT body burden, followed by lipid-adjusted blood serum samples, and unadjusted serum, plasma, and whole blood levels. The second issue related to appropriate exposure assessment in human breast cancer studies pertains to the timing of the exposure assessment relative to the etiology of cancer. Cancer is a chronic disease and can have a latency time of 15–20 years after initiation. For DDT to cause or contribute to breast cancer, exposure could be required to occur at a time substantially before the time of diagnosis of the cancer. Studies that assess DDT body burdens at or shortly before the time of breast cancer diagnosis are limited by the assumption that a “snapshot” of DDT body burden obtained near the time of diagnosis is supposed to represent DDT exposures at the time of cancer initiation or early promotion, perhaps as much as 15–20 years earlier. This assumption could be in error because a large amount of the measured DDT body burden could represent exposures that occurred after contracting cancer, and the cancer itself might influence DDT disposition.

The possible link to breast cancer has received particular attention due to several case-control studies that suggested a connection between DDT levels in the body and the occurrence of cancer (Dewailly et al.
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1994; Falck et al. 1992; Güttes et al. 1998; Wasserman et al. 1976; Wolff et al. 1993). \( o,p' \)-DDT was estrogenic, and \( p,p' \)-DDT and \( p,p' \)-DDE were weakly estrogenic in various \textit{in vitro} assays (see Section 2.5), and certain estrogens have been linked to breast cancer (Adami et al. 1995). Investigators have hypothesized that DDT compounds could promote cell proliferation by mimicking \( 17\beta \)-estradiol at the estrogen receptor (see Section 2.5.2). Reviews of the role of organochlorines in the etiology of breast cancer have generally concluded that the epidemiological studies that show a positive association were limited in several ways, including small sample sizes, failure to account for other breast cancer risk factors, and failure to account for probable co-exposure to other organochlorines (Adami et al. 1995; Ahlborg et al. 1995; Safe and Zacharewski 1997). Adami et al. (1995) pointed out that certain organochlorines, such as DDT compounds, act as estrogens while others are antiestrogenic, and that the body burdens of these organochlorines are likely to be intercorrelated. Further, since DDT compounds are relatively weak estrogens and exposure is generally very low in countries where DDT use is banned, the contribution of DDT compounds to total estrogens in the bloodstream of women is likely to be negligible. Thus, even if DDT compounds are carcinogenic in humans, the link to cancer may not always be evident due to their relatively low contribution to total estrogens or co-exposure to antagonistic organochlorines, and most epidemiological studies will not identify an association. The same arguments could be applied to cancer types other than breast cancer. Ardies and Dees (1998) have hypothesized, however, that DDT exposure may play a significant role in breast cancer development during periods of rapid growth in premenarche childhood and during periods of breast development, when the body is more sensitive to estrogenic compounds. See Section 2.5.2 for a discussion on possible mechanisms of breast cancer and Section 2.6 (Reproductive Effects) for a discussion on estrogenic-antiestrogenic balance.

DDT, DDE, and DDD have been shown to be carcinogenic in animal studies. Chronic exposure (81 weeks to life) at doses as low as 0.26 mg DDT/kg/day produced liver tumors, primarily hepatomas, in four strains of mice (Innes et al. 1969; Thorpe and Walker 1973; Tomatis et al. 1972). In mice, pulmonary adenomas occurred at doses ranging from 1.3 to 32.5 mg DDT/kg/day (Kashyap et al. 1977; Shabad et al. 1973) and malignant lymphomas occurred after exposure to 16.5 mg DDT/kg/day for 80 weeks (Kashyap et al. 1977). Liver-cell tumors have also been reported in rats dosed with 19.7–34 mg DDT/kg/day for 120 weeks to life (Cabral et al. 1982b; Rossi et al. 1977). \( p,p' \)-DDE has been found to cause an increase in the incidence of hepatocellular carcinomas in both sexes of B6C3F1 mice dosed at approximately 27 mg/kg/day for 18 months (NCI 1978); and it caused an increase in liver neoplastic nodules in hamsters at doses of approximately 95 mg/kg/day for up to 128 weeks (Rossi et al. 1983). \( p,p' \)-DDD caused a slight increase in thyroid tumors in male but not female rats, and it was not carcinogenic in either sex of B6C3F1 mice (NCI 1978). Over 25 animal carcinogenicity studies were
available for review. DDT has been shown to promote the carcinogenicity of other substances (Diwan et al. 1994; Kitagawa et al. 1984; Nishizumi 1979; Peraino et al. 1975; Preat et al. 1986; Rojanapo et al. 1993). On the other hand, some studies have observed an inhibitory action of DDT on the carcinogenicity of other chemicals (Rojanapo et al. 1993; Silinskas and Okey 1975). A proposed mechanism of promotion is discussed in Section 2.5.2.

EPA has determined that DDT, DDE, and DDD are probable human carcinogens (B2). The Department of Health and Human Services has determined that DDT may reasonable be anticipated to be a human carcinogen. The International Agency for Research on Cancer (IARC) had determined that DDT, DDE, and DDD are probable human carcinogens (2B).

2.7 ENDOCRINE DISRUPTION

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, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Numerous reviews have been written regarding the endocrine disrupting capabilities of DDT and related compounds (Bulger and Kupfer 1983; Chapin et al. 1996; Colborn et al. 1993; Crisp et al. 1998; Gillesby and Zacharewski 1998; Golden et al. 1998; Gray et al. 1997; and many others). Much of the historical information summarized below, particularly the early data, has been extracted from these reviews. The
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focus of this section is on effects in humans and in animal species traditionally used in laboratory experiments; information on endocrine effects, as well as other health effects, on wildlife is presented in Section 2.3 Health Effects in Wildlife Potentially Relevant to Human Health.

It has been known for several decades that DDT and related compounds have weak estrogenic action in experimental animals and wildlife, but there is insufficient information to show that these chemicals have estrogenic action in humans. Estrogen influences the growth, differentiation, and functioning of many target tissues, including male and female reproductive systems such as mammary gland, uterus, vagina, ovary, testes, epididymis, and prostate. Several studies in humans have examined possible associations between body burdens of DDT and analogues and the incidence of alterations in these systems and tissues. No association could be shown between the incidence of endometriosis and plasma concentrations of DDT (DDT plus DDE) in a case-control study by Lebel et al. (1998). A number of other studies reported that levels of DDT, DDE, and DDD were higher in maternal blood and in placental tissue in mothers who gave birth to premature infants or who spontaneously aborted fetuses compared to mothers who gave birth to full-term infants (Procianoy and Schwartsman 1981; Saxena et al. 1980, 1981, 1983; Wassermann et al. 1982). However, other endocrine-disrupting chemicals, such as PCBs and other chlorinated pesticides, were also increased in the maternal blood of these subjects, and the specific contribution of DDT, DDE, or DDD could not be determined. In contrast, a similar study did not show the same association between serum DDE levels and preterm delivery (Berkowitz et al. 1996). With regard to cancers of the reproductive tissues, no association was found between risk of endometrial cancer and lipid-corrected blood serum concentrations of \( p,p' \)-DDT, \( o,p' \)-DDT, and \( p,p' \)-DDE in a multicenter case-control study of women in the United States (Sturgeon et al. 1998). Also, there was no association found between \( p,p' \)-DDE concentration in subcutaneous fat and incidence of prostate and testicular cancer mortality (Cocco and Benichou 1998). The issue of breast cancer has received special attention following reports of high levels of organochlorine compounds in breast cancer patients; however, most reviews of this issue have concluded that (1) studies showing a positive relationship were limited in several ways, including small sample size and failure to adjust analyses for known breast cancer risk factors, and (2) the current ecologic and epidemiologic evidence does not support the hypothesis of a causal association between breast cancer and DDT exposure (Adami et al. 1995; Ahlborg et al. 1995; Safe 1995; Safe and Zacharewski 1997). Details of the individual studies about breast, endometrial, testicular, and prostate cancer are presented in Section 2.2.2.8 Cancer.

Early studies in experimental animals administered the chemicals orally or by parenteral routes, whereas in recent years, much research has focused on elucidating the mechanisms of action involved using in...
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vitro test systems. Such tests can be used to assay for estrogeic, anti-estrogenic, androgenic, and anti-androgenic activity. In general, results from in vivo and in vitro studies indicate that DDT and analogues have much lower estrogenic potency than the endogenous hormone, 17β-estradiol. Experiments conducted by Gellert et al. (1972) showed that young rats administered 5 mg o,p′-DDT/kg/day for 27 days had delayed vaginal opening and increased uterine and ovarian weights. In another study, using the uterine glycogen response assay, Bitman and Cecil (1970) observed that o,p′-DDT was the most potent among several isomers. o,p′-DDT and o,p′-DDE were approximately 2,500 and 40,000 times less potent than the synthetic estrogen, DES, respectively; o,p′-DDD was inactive. In yet another study, the lowest dose of o,p′-DDT needed to produce estrogenic effects in the immature rat uterus was about 1x10^5 times greater than that of DES (Clement and Okey 1972). An in vivo assay with rats and mink showed that o,p′-DDT had uterotropic activity, whereas p,p′-DDT had only slight activity, and the activity of technical DDT was dependent on the level of o,p′-DDT that it contained (Duby et al. 1971). However, no reproductive effects were observed in two successive generations of rats fed technical DDT, p,p′-DDT, or o,p′-DDT (Duby et al. 1971). Many other in vivo studies have shown the estrogenic potential of DDT and related analogues (Gellert and Heinrichs 1975; Gellert et al. 1974; Heinrichs et al. 1971; Welch et al. 1969).

More recent in vitro experiments have examined binding of DDT, DDE, and DDD isomers to estrogen and androgen receptors and subsequent steroid regulated gene transcription. The experimental details of these studies are discussed in Section 2.5.2, Mechanisms of Toxicity: Reproductive and Developmental Effects. Although the results have varied somewhat between different investigators, in general, o,p′-DDT and o,p′-DDE appear to act as very weak estrogen agonists, while p,p′-DDE can function as an androgen antagonist. In particular, p,p′-DDE functions as an antagonist after it has bound to the androgen receptor (Kelce et al. 1995). This androgen antagonism or anti-androgenic activity can explain a number of reproductive and developmental effects seen in male rats of various ages exposed to p,p′-DDE. These effects include reduced anogenital distance and retention of thoracic nipples in pups exposed during gestation and lactation (Kelce et al. 1995; Loeffler and Peterson 1999; You et al. 1998); delayed puberty in rats exposed either during juvenile development (Kelce et al. 1995) or at very high doses during gestation and lactation (Loeffler and Peterson 1999); and reduced accessory sex organ weights in exposed adult males (Kelce et al. 1995, 1997). The experimental details of those studies are discussed extensively in Section 2.2.2.5, Reproductive Effects and Section 2.2.2.6, Developmental Effects.

The results of these and other studies suggest that DDT analogues can produce both agonistic and antagonistic responses by interfering with the binding of endogenous androgens and estrogens to their
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The amount of naturally occurring estrogens ingested daily through a normal diet may be far greater than the daily intake of estrogenic pesticides (Safe 1995). In addition, many experiments (Danzo 1997; Gaido et al. 1997; Kelce et al. 1995; Shelby et al. 1996; Soto et al. 1997) show that DDT isomers and metabolites have orders of magnitude less estrogenic activity than 17β-estradiol. This does not imply a lack of related risk, since estrogenic pesticides such as DDT and analogues bioconcentrate in the food chain and accumulate in the body. Moreover, key endocrine processes can be profoundly affected by exposure to extremely small amounts of active chemicals during critical windows of embryonic, fetal, and neonatal development. As for anti-androgenic effects, Kelce et al. (1995) stated that the concentration of p,p'-DDE required to inhibit androgen receptor transcriptional activity in cell culture (64 ppb) is less than levels that accumulate from the environment such as in eggs of demasculinized male alligators in Florida’s Lake Apopka (5,800 ppb) and in humans in areas where DDT remains in use or is present in contaminated ecosystems.

The adrenal gland may also be the target of some DDT isomers and metabolites. The metabolism of DDT can produce methylsulfonyl metabolites, such as methylsulfonyl-DDE, which are potent adrenal toxicants (Bakke et al. 1982; Brandt et al. 1992; Preston et al. 1984). o,p’-DDD is used therapeutically to treat adrenocortical carcinomas in humans. Furthermore, in some wild birds, but not others, adrenal weights or cortico-medullary ratios were affected by p,p’-DDT, p,p’-DDE, or technical grade DDT (Hurst et al. 1974; Jefferies and French 1972; Jefferies et al. 1971; Lehman et al. 1974; Peterleef et al. 1973). Adrenal toxicity is discussed more extensively in Section 2.6, Relevance to Public Health: Endocrine Effects.

2.8 CHILDREN’S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and in vitro models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children’s unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6 Exposures of Children.
Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while 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).
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No studies were located that specifically addressed effects of exposure to DDT in children, with the exception of a report by Hill and Robinson (1945) that described the case of a 1-year-old child who ingested 1 ounce of 5% DDT in kerosene that led to coughing, vomiting, tremors, convulsions, and eventually, death. The contribution of the kerosene solvent to the DDT toxicity was not clear. Data in adults are derived mostly from cases of accidental and/or intentional acute exposure (ingestion) of large amounts of DDT and from controlled studies in volunteers. Information from these studies indicate that the primary target of DDT toxicity is the nervous system. The effects are manifested as hyperexcitability, tremors, and convulsions (Francone et al. 1952; Garrett 1947; Hayes 1982; Hsieh 1954). It is reasonable to assume that the same effects would be seen in children similarly exposed. Additional information is derived from early occupational studies with limitations including lack of precise exposure data and presence of other compounds. Some of the long-term exposure reports provided suggestive evidence of adverse liver effects (Hayes 1956; Morgan and Lin 1978). None of these exposure scenarios appear likely for children in the United States at the present time.

Results from a few animal studies suggest that young and older animals exhibit different susceptibility to DDT toxicity, at least regarding neurotoxicity in response to relatively high doses of DDT. For example, the LD$_{50}$ values for DDT in newborn, preweanling, weanling, and adult rats were $4,000$, $438$, $355$, and $195$ mg/kg, respectively (Lu et al. 1965). However, when one-quarter of the daily LD$_{50}$ dose was administered daily for 4 days to preweanling and adult rats, both groups had similar 4-day LD$_{50}$ values. Lu et al. (1965) suggested that the elimination mechanisms in the preweanling rats is less developed than in the adult rats, thus making them more susceptible to repeated small doses. In another study, 10-day-old rats were more resistant to the acute lethal toxicity of purified $p,p'$-DDT than 60-day-old rats (Henderson and Woolley 1970). In both groups, respiratory failure was the cause of death; however, the time course of DDT poisoning in the young rats was prolonged considerably as compared to the adults. Furthermore, the immature rats did not exhibit seizures nor the hyperthermia that preceded death in the older animals. The decreased sensitivity of the younger rats was attributed to an incomplete development of the neural pathways involved in seizure activity and in thermoregulation. The relevance of these findings to human health is unknown.

A decrease in testis weight was observed in juvenile male rats dosed by oral gavage on days 4 and 5 of life with 500 mg/kg/day or from day 4 to day 23 with 200 mg DDT/kg/day (Krause et al. 1975). After two doses, significant decreases were seen at 34 days, and after repeated lower doses, decreases were significant at days 18, 26, and 34. Treated males were mated with healthy females on days 60 and 90. The number of fetuses and implantations was decreased 30% at the 60-day mating but not at the 90-day
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mating of rats dosed on days 4 and 5. For rats receiving multiple doses, the decreases were 95% and 35% after mating at days 60 and 90, respectively. In adult male rats dosed with 200 mg DDT/kg every other day (oral gavage) for 2 weeks, serum testosterone levels were decreased compared to controls (Krause 1977). In adult male rats treated with 100 mg DDT/kg 3 times per week for 3 weeks testicular testosterone was marginally decreased, but no histological alterations were observed (Krause 1977). Treatment of weanling rats from either day 21 or 25 until day 57 of age with 100 mg \( p,p' \)-DDE/kg/day did not significantly alter serum levels of testosterone, but this treatment significantly delayed onset of puberty (see below) and was likely due to the anti-androgenic effects of DDE (Kelce et al. 1995).

Studies that examined the association between developmental effects in humans and serum levels of DDT, DDE, or DDD provided no conclusive evidence for such an association (Berkowitz et al. 1996; Procianoy and Schvartsman 1981; Saxena et al. 1980, 1981, 1983; Wasserman et al. 1982). DDT has not been shown to be a structural teratogen in animals, but embryotoxicity and fetotoxicity have been reported in the absence of maternal toxicity (Clement and Okey 1974; Fabro et al. 1984; Hart et al. 1971, 1972). Developmental effects, including preweanling mortality and premature puberty, have been reported in animals in multigeneration studies (Del Pup et al. 1978; Green 1969; Ottoboni et al. 1969, 1977; Tomatis et al. 1972, Turusov et al. 1973). DDT has shown estrogenic properties in animals administered the pesticide orally or parenterally (Bitman and Cecil 1970; Clement and Okey 1972; Fabro et al. 1984; Gellert et al. 1972, 1974; Singhal et al. 1970). In female neonates injected subcutaneously with \( o,p' \)-DDT or \( o,p' \)-DDD, there were significant alterations in the estrous cycle, decreases in ovary weight, and decreases in corpora lutea when the animals were evaluated as adults (Gellert et al. 1972, 1974). In general, the estrogenic potency of DDT is orders of magnitude lower than that of estradiol.

\( p,p' \)-DDE, a persistent metabolite of DDT, was an androgen receptor antagonist in male rats exposed \textit{in utero}, and also as juveniles (Kelce et al. 1995, 1997; Loeffler and Peterson 1999; You et al. 1998). Kelce and co-workers showed that pups from dams exposed during gestation days 14–18 to 100 mg \( p,p' \)-DDE/kg/day and then exposed indirectly to maternally stored \( p,p' \)-DDE via breast milk had significantly reduced anogenital distance at birth and retained thoracic nipples on postnatal day 13. Treatment of weanling male rats from either day 21 or 25 (specific day unclear in text) until day 57 of age with 100 mg \( p,p' \)-DDE/kg/day resulted in a statistically significant delayed onset of puberty (measured by the age of preputial separation) by 5 days. You et al. (1998) reported that anogenital distance was not affected in male Sprague-Dawley rats on postnatal day 2 after treating the dams with up to 100 mg \( p,p' \)-DDE/kg on gestation days 14–18, but was significantly reduced in similarly exposed Long-Evans pups. A 10 mg/kg dose to the dams was without effect in the Long-Evans pups. Anogenital distance was
not affected in female pups from either strain. Treatment of the dams with 10 mg \( p,p' \)-DDE/kg resulted in retention of thoracic nipples in Sprague-Dawley pups, but only the higher dose (100 mg/kg) had this effect in Long-Evans pups. Treatment with \( p,p' \)-DDE also resulted in an apparent reduction of androgen receptor expression in male sex organs from mainly high-dose Sprague-Dawley pups, as shown by immunochemical staining; however, there were no changes in androgen receptor steady state mRNA levels in the high-dose Sprague-Dawley rats, but androgen receptor mRNA were increased 2-fold in the high-dose Long-Evans rats. Exposure of the pups to \( p,p' \)-DDE during gestation and lactation had no significant effect on the onset of puberty. A similar study in Holtzman rats exposed during gestation days 14–18 to doses between 1 and 200 mg \( p,p' \)-DDE/kg (offspring were exposed to \( p,p' \)-DDE in utero and via breast milk) found reduced anogenital distance in males on postnatal day 1 and reduced relative ventral prostate weight on postnatal day 21 at 50 mg \( p,p' \)-DDE/kg, but not at 10 mg \( p,p' \)-DDE/kg (Loeffler and Peterson 1999). Doses up to 100 mg/kg/day to the dams had no effect on onset of puberty, but 200 mg/kg/day did significantly delay puberty in males by less than 2 days. Androgen receptor staining in the ventral prostate was also reduced on postnatal 21. Serum levels of testosterone or 3α-diol androgens were not significantly altered at any time. This study also reported that at the 100 mg/kg dose level, cauda epididymal sperm number was reduced by 17% on postnatal day 63 relative to controls. No measurement of DDE body burden were made in the 200 mg/kg/day offspring postnatally, so it is difficult to determine whether effects on puberty were due to the previous gestational plus lactational exposures or directly due to the effects of DDE present near the time of puberty. More details about these studies can be found in Section 2.2.2.6, Developmental Effects. Kelce et al. (1995) also showed that treatment of adult male rats with 200 mg \( p,p' \)-DDE/kg for 4 days significantly reduced androgen-dependent seminal vesicle and ventral prostate weight relative to controls.

There are limited data suggesting that if mice exposed to DDT in utero and during lactation are further exposed to DDT postnatally, responses in both immunological plaque forming assays and lymphoproliferative assays are reduced (Rehana and Rao 1992). The results of this study are difficult to interpret because of experimental design issues, including the lack of a comparison unexposed group and ambiguity about whether statistical testing was done.

Behavioral deficits in learning processes have also been described in adult mice exposed to DDT perinatally (Craig and Ogilvie 1974) or as neonates (Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996); this end point is the basis of an acute oral MRL, which is discussed in detail in Section 2.6, Relevance to Public Health. These studies suggest that exposure of the developing fetus or newborn to DDT during critical stages in nervous system development can cause developmental toxicity.
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manifested later in life. Eriksson et al. (1990a, 1990b) pointed out that the dose levels that caused behavioral alterations in mice are comparable to those levels to which human neonates might be exposed in areas where DDT is still being used. Behavioral neurotoxicity has been described in rats treated with DDT as adults (Sobotka 1971), but only at doses at least 50 times those that produced learning deficits in neonates.

There is no information regarding transgenerational effects associated with DDT exposure in humans, despite some limited evidence of genotoxicity in humans. Chromosomal aberrations have been reported in blood cells from subjects occupationally exposed to DDT (Rabello et al. 1975; Rupa et al. 1988; Yoder et al. 1973) and in human lymphocytes exposed in vitro to DDT (Lessa et al. 1976). These occupational exposures, however, also included exposure to many other pesticides. Two studies, one in rats (Palmer et al. 1973) and one in mice (Clark 1974), reported an increase in dominant lethality after exposure to high doses of DDT (Clark 1974). A study in rabbits administered 50 mg \( p,p' \)-DDT/kg by gavage on Gd 7–9 found no significant alterations in the distribution of chromosomes in liver samples from fetuses or in the percentage of chromosomal aberrations relative to controls (Hart et al. 1972).

There is no information regarding the pharmacokinetics of DDT in children or regarding the nutritional factors that may influence the absorption of DDT. Analysis of urine samples from humans exposed to DDT suggest the involvement of both phase I and phase II metabolic enzymes in the biotransformation and elimination of DDT and metabolites. The specific P-450 isoenzymes involved in phase I metabolism and the particular phase II conjugating enzymes are not known with certainty, so no conclusions can be drawn based on general differences in isozyme activities between adults and children. It is not known whether the metabolism of DDT in children might be different than in adults. DDT and DDT-related compounds, particularly DDE, accumulate in fatty tissues and have been found in human milk (Dewailly et al. 1996; Scheele et al. 1995; Smith 1999; Torres-Arreola et al. 1999), placenta (Gladen and Rogan 1995; Prociunoy and Schvartsman 1981; Wassermann et al. 1982), and in most organs from stillborn infants (Curley et al. 1969). Although, there is no direct evidence of adverse health outcomes in human infants exposed in such a manner, mobilization of adipose fat for lactation might provide an increased amount of DDT to a breast-feeding infant. Levels of DDT and related compounds in human tissues from recent studies are presented in Table 5-4. Studies in animals have demonstrated placental transfer of DDT and DDE to fetuses and also to newborns via mother’s milk (Fang et al. 1977; Seiler et al. 1994; Wooley and Talens 1971; You et al. 1999). The results of these studies indicate that the amounts of chemical transferred via mother’s milk are much greater than the amounts that reach the fetus through the placenta. PBPK models for the transplacental and lactational transfer of \( p,p' \)-DDE in rats were proposed by You et
al. (1999). The models provide an approach to estimating tissue doses in fetuses and pups associated with maternal exposures to \( p,p' \)-DDE, and can be used to explore dose-response relationships for the developmental effects of \( p,p' \)-DDE in the rat. In a study in rabbits administered DDT by gavage before artificial insemination and throughout gestation, Seiler et al. (1994) found higher concentrations of DDT residues in fetuses (day 11 postcoitum) than in blastocytes (day 6 postcoitum), suggesting that transplacental passage may be more easily accomplished than passage into blastocytes via uterine secretions.

Intraperitoneal administration of the DDT metabolite, 3-MeSO\(_2\)-DDE, to pregnant or lactating mice resulted in specific accumulation and binding of 3-MeSO\(_2\)-DDE-derived radioactivity in the *zona fasciculata* of adrenals from 16- to 18-day-old fetuses or suckling pups, showing ready transplacental passage of the metabolite and transfer via maternal milk (Jönsson et al. 1992). The results also suggested that cytochrome P-45011\(\beta\) was involved in the activation of 3-MeSO\(_2\)-DDE in the fetal adrenal cortex. Quantitative measurements showed that 7 days after dosing, the labeling of the pups adrenals was 2 and 3.6 times higher than maternal adrenals at 1.5 and 25 mg/kg dose levels, respectively, suggesting that mother’s milk may be an important route of exposure of 3-MeSO\(_2\)-DDE in DDT-exposed animals. A later study showed that P-45011\(\beta\) seems to be expressed during Gd 10–12 in the adrenal cortex in the mouse fetus (Jönsson et al. 1995). 3-MeSO\(_2\)-DDE was also found to reduce the capacity of pups and maternal adrenals to secrete corticosterone (Jönsson 1994) by a mechanism possibly involving competitive inhibition of adrenocortical CYP11B1 (Johansson et al. 1998).

There are no biomarkers of exposure or effect for DDT or DDT-related compounds that have been validated in children or in adults exposed as children. There are no biomarkers in adults that identify previous childhood exposure. No studies were located regarding interactions of DDT with other chemicals in children or adults. No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to DDT or DDT-related compounds, reducing body burden, or interfering with the mechanism of action for toxic effects. In addition, no data were located regarding whether methods for reducing toxic effects in adults might be contraindicated in children.

### 2.9 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).
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Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 or 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 DDT, DDE, and DDD are discussed in Section 2.9.1.

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 DDT, DDE, and DDD are discussed in Section 2.9.2.

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 2.11, Populations That Are Unusually Susceptible.
2.9.1 Biomarkers Used to Identify or Quantify Exposure to DDT, DDE, and DDD

In general, biomarkers of exposure to DDT can be classified as specific, such as DDT itself and its metabolites, and nonspecific, such as changes in endogenous chemicals that might indicate exposure to DDT, but also to other unrelated chemicals as well. DDT, DDE, and DDD have been detected and measured in adipose tissue, blood, serum, urine, feces, semen, and breast milk using several analytical techniques (see Chapter 6). Metabolites of DDT have also been measured in body fluids. The major urinary metabolite identified in humans is DDA (Gingell 1976), while the \( p,p' \)-isomers of DDT and DDE have been detected in breast milk (Takei et al. 1983). Nair and Pillai (1992) detected \( o,p' \)-DDE, \( p,p' \)-DDE, \( o,p' \)-DDT, \( p,p' \)-DDT, and \( p,p' \)-DDD in human adipose tissue and breast milk, and \( o,p' \)-DDE \( p,p' \)-DDE, \( p,p' \)-DDD, and \( p,p' \)-DDT in whole blood. DDT metabolites identified in whole blood include \( p,p' \)-DDE, \( p,p' \)-DDD, and \( o,p' \)-DDT (Agarwal et al. 1976). Smith (1999) compiled values for DDT in human milk from 130 published studies since 1951 and observed that population means have declined in much of the world from 5,000–10,000 ppb (lipid-based) to around 1,000 ppb currently in many areas. Using a set of 13 studies from the United States and Canada, Smith (1999) estimated that since 1975, there has been an 11–21% decline in average DDT concentrations in breast milk. He also estimated a half-life of 4.2–5.6 years for DDT on a population basis. Levels of DDT in breast milk from some recent studies are presented in Table 5-4. Because DDT/DDE/DDD are fat soluble, they tend to concentrate in the fat portion of the specific biological medium (i.e., milk, serum, etc.) and therefore, their levels in the biological medium may vary with the fat content of that medium. This variability in the amount of DDT/DDE/DDD in the various media, is often accounted for by using lipid-adjusted measurements.

However, there are no quantitative data available that allow correlation of DDT/DDD/DDE levels in human tissue or fluids and exposure to particular levels of environmental contamination. Studies of pesticide production workers reported that blood levels of these compounds are generally higher in persons exposed in the workplace. Since the biological half-lives for elimination of these compounds are ranked as follows: DDE > DDT > DDD, detection of higher ratios of DDD or DDT to DDE is believed to indicate more recent exposure while lower ratios are believed to correlate with long-term exposure and storage capacity (Morgan and Roan 1971). There is a direct correlation between DDT and DDE levels in blood and adipose tissue (Hayes et al. 1971; Morgan and Roan 1971). Concentrations of DDT in adipose tissue are approximately 280 times higher than those of blood (Anderson 1985). However, because DDT and DDE are extensively stored in fatty tissue and slowly released from storage sites, there is no correlation between levels in tissues and the time course of exposure in short time spans. Analysis of residue levels of \( p,p' \)-DDT in skin lipids collected by wiping the skin with cotton and purifying lipids by
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gel permeation chromatography has been investigated by Sasaki et al. (1991b) as a noninvasive method for monitoring DDT burdens in pesticide-exposed persons; a correlation was found between skin levels and adipose tissue levels; however, these results reflect both body burden and dermal exposure. Levels of DDT (total DDT) in adipose tissue from the U.S. population have been continuously declining over the last decades from about 8 ppm (lipid adjusted) in 1970 to about 2 ppm in 1983 (Kutz et al. 1991). A review by Kutz et al. (1991) also lists levels of DDT, DDE, and DDD in samples of adipose tissue collected during the 1960s through the 1980s from populations around the world. Table 5-4 presents additional information on DDT levels in blood and adipose tissue from some recent studies.

Changes in plasma concentrations of endogenous chemicals that might be consistent with DDT exposure include increased vitamin A plasma levels, which have been shown to increase with increasing plasma levels of DDE in humans (Nhachi and Kasilo 1990). In rats, DDT administration (oral gavage of 40 mg/kg) decreased hepatic vitamin A storage (deWaziers and Azais 1987). Increased levels of urinary 17-hydroxycortisone have also been reported as indicators of DDT exposure in humans (Nhachi and Loewenson 1989; Poland et al. 1970). This is consistent with DDT induction of hepatic P-450 enzymes increasing the catabolism of cortisol to 17-hydroxycortisol (see Section 2.4.3). A potential biomarker of exposure, which has been identified from studies in laboratory animals, is an increase in GGTP. In rats, after acute oral exposure to DDT, serum levels of GGTP doubled and remained elevated for 48 hours (Garcia and Mourelle 1984). However, none of these potential biomarkers are specific to DDT, DDE, or DDD exposure, and not all the body compartments in which these changes occur are accessible for sampling in living humans.

2.9.2 Biomarkers Used to Characterize Effects Caused by DDT, DDE, and DDD

The primary target organs for DDT, DDE, and DDD toxicity include the nervous system, the reproductive system, and the liver. No biomarkers of effect specific for DDT, DDE, or DDD exposure alone were identified in the literature. Tremors and convulsions have been observed in both humans and laboratory animals after DDT exposure (Hsieh 1954; Hwang and Van Woert 1978; Matin et al. 1981). Exposure to DDT has been shown to induce hepatic microsomal enzymes in both humans and laboratory animals (Kolmodin et al. 1969; Morgan and Lin 1978; Pasha 1981; Street and Chadwick 1967). However, these biomarkers of effect are not specific for DDT, DDE, or DDD exposure, and not all the body compartments in which these changes occur are accessible for sampling in living humans.
For more general information on biomarkers of effect for the immune, renal, and hepatic systems, see CDC/ATSDR Subcommittee Report on Biological Indicators of Organ Damage (CDC/ATSDR 1990), and for biomarkers of effect for the neurological system, see the Office of Technology Assessment report (OTA 1990). For more information on the health effects after exposure to DDT, DDE, and DDD see Section 2.2.

2.10 INTERACTIONS WITH OTHER CHEMICALS

This section discusses the potential for DDT to act synergistically and/or antagonistically with other chemicals to cause physiological harm. DDT may have broad effects by changing the metabolism of other chemicals, both xenobiotics and endogenous macromolecules. DDT induces microsomal mixed function oxidases that are involved in the catabolism of both xenobiotics and many endogenous hormones, such as cortisol. DDE has also caused the induction of hepatic enzymes (Conney 1971), including cytochrome P-450 microsomal enzymes (Pasha 1981). Its effects on the latter are discussed in Section 2.4.3. In most cases, this biotransformation results in compounds that are less toxic than the parent compound and more readily excreted from the body. For some chemicals, this metabolism results in the production of metabolites that are more toxic than the parent compound and that may be carcinogenic. One interaction of concern is the enhanced conversion of other chemicals to active, carcinogenic forms mediated by microsomal enzymes induced by DDT. Several investigations indicate that DDT administered to animals along with a known carcinogen may result in either increase or decrease in tumor production relative to the carcinogen tested without DDT. A study by Walker et al. (1972) suggested that the liver enlargement was greater and the time to palpability of liver masses was earlier in mice fed dieldrin and DDT than those fed either pesticide separately. A potentiation of carcinogenic activity of dieldrin was suggested but not conclusively shown. DDT alone is thought to produce hepatic tumors both through the formation of DNA adducts and through promotional mechanisms involving cytotoxicity and compensatory cell proliferation (see Section 2.5.2). It is possible that DDT could also promote the formation of hepatic tumors initiated by other carcinogens.

DDT is reported to promote the tumorigenic effects of several known carcinogens, such as 3-methyl-(4-dimethylamine)-azobenzene (Kitagawa et al. 1984), 2-acetylaminofluorene (2-AAF) (Peraino et al. 1975), diethyl-nitrosamine (DEN) (Diwan et al. 1994; Nishizumi 1979), and carbon tetrachloride (CCl₄) (Preat et al. 1986) when given after the putative carcinogen. The promoting effect of DDT in rats is reported to act in a dose-dependent fashion, with DDT decreasing the latency period of tumor development and increasing the incidence and yield of hepatic tumors, mainly hepatocellular carcinomas.
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DDT acted as a hepatocellular tumor promoter in D2B6F1 mice when administered in the diet at 300 ppm (53 mg/kg/day) for 53 weeks, beginning 2 weeks following initiation with an intraperitoneal injection of N-nitrosodiethylamine (Diwan et al. 1994). The incidence of mice with tumors was 22/22 in the DDT-treated group, compared to 12/30 in the group receiving only N-nitrosodiethylamine; the difference was statistically significant.

Pretreatment of animals with DDT was also reported to decrease the tumorigenic effects of some previously determined carcinogens. For example, pretreatment of rats with DDT significantly lowered the incidence of mammary tumors per rat after treatment with 7,12-dimethylbenz[a]anthracene (DMBA), versus DMBA-treated controls (Silinskas and Okey 1975). The authors suggested that DDT may inhibit DMBA-induced mammary tumors by stimulating hepatic metabolism and accelerating the excretion of DMBA, so that less carcinogen is available to peripheral tissues. Other studies also have reported the DDT induction of hepatic microsomal enzymes, which reduced the carcinogenicity of azo dyes and similar carcinogens (Williams and Weisburger 1991).

Similarly, the hepatocarcinogenicity of aflatoxic B1 in mice was inhibited by pretreatment with DDT and by co-treatment with DDT when given throughout aflatoxin B1 dosing (Rojanapo et al. 1988, 1993). However, DDT acted as a hepatocarcinogenic promoter to aflatoxin B1 initiation when a 14-week DDT administration followed an 8-week aflatoxic B1 treatment, or when the DDT administration began halfway through aflatoxin B1 treatment (Rojanapo et al. 1988, 1993). Also, in groups receiving both aflatoxic B1 and DDT, in any order, absolute and relative liver weights were significantly increased over both the vehicle control and the group receiving just aflatoxin B1; treatment with aflatoxin B1 alone increased liver weights, while treatment with DDT alone did not (Rojanapo et al. 1993). The proposed mechanisms of tumor promotion are discussed in Section 2.5.2.

The effects of DDT on the nervous system are altered when DDT is given in combination with certain neurologically-active pharmacological agents. Some pharmacological agents (hydantoin, phenobarbital), prevent some or all of the neurological effects seen in animals treated with DDT (see Section 2.2.2.4), while other agents (trihexyphenidyl, haloperidol, propranolol) enhance DDT-induced neurotoxicity (Herr et al. 1985; Hong et al. 1986; Matin et al. 1981). One of the effects of DDT is to hold sodium channels open, which probably contributes to DDT-induced neurological effects (tremors and hyperexcitability). Studies by Rubin et al. (1993) have shown that DDT analogues and metabolites as well as several pyrethroids modify radioligand binding of batrachotoxinin to sodium channels in mouse brain synaptosomes. DDT and pyrethroids do not by themselves stimulate Na⁺ uptake, but they enhance

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activator-dependent uptake. DDT is more efficacious than the pyrethroids tested. Eriksson et al. (1993) have shown that the pyrethroid bioallethrin and DDT can interact in vivo in rats.

2.11 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to DDT, DDE, and DDD than will most persons exposed to the same level of DDT, DDE, and DDD in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of DDT, DDE, and DDD, or compromised function of organs affected by DDT, DDE, and DDD. Populations who are at greater risk due to their unusually high exposure to DDT, DDE, and DDD are discussed in Section 5.7, Populations With Potentially High Exposures.

No data are available on human differences in susceptibility to DDT, DDE, or DDD. Groups who might be particularly susceptible to the toxic effects of DDT are individuals with diseases of the nervous system or liver. Persons with nervous system disorders in which normal function is altered due to physiological changes, such as changes in neurotransmitter balance or impaired neuronal conduction, might be more susceptible to DDT neurotoxicity. Persons with diseases of the liver might be more sensitive to the hepatotoxic effects of DDT since normal repair function may already be compromised.

The susceptibility of children is discussed in detail in Section 2.8, Children’s Susceptibility.

2.12 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to DDT, DDE, and DDD. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to DDT, DDE, and DDD. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

Most of the strategies discussed in the following sections apply to high-dose exposures. The balance between the benefits and detriments of mitigation for low-dose chronic exposures might differ from those for high-dose exposures. Methods to reduce toxic effects should not be applied indiscriminately to all individuals exposed to DDT, DDE, or DDD; good clinical judgement should be used.
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2.12.1 Reducing Peak Absorption Following Exposure

A number of strategies have been suggested to minimize absorption from the gastrointestinal tract. Ipecac-induced emesis has been suggested unless there is a risk of lung aspiration due to unconsciousness or convulsions (HSDB 1999a, 1999b, 1999c, 1999d). Gastric lavage with mannitol may also be useful for limiting absorption, particularly when emesis is contraindicated (Dreisbach 1983). Since activated charcoal can absorb DDT, it has also been commonly used as a method for reducing intestinal uptake (Dreisbach 1983). Another method of reducing absorption is the use of a cathartic, and in practice, activated charcoal is frequently given in a slurry of one of the saline cathartics (Dreisbach 1983; HSDB 1999a, 1999b, 1999c, 1999d). Vegetable oils should not be used as cathartics because they have been shown to promote the absorption of DDT, DDE, and DDD in animals (Keller and Yeary 1980). At this point, it is unknown whether there are any specific binding or reactive agents which might prevent absorption, but this might be a strategy for future research.

Dermal absorption of DDT, DDE, and DDD is less efficient than absorption by the oral route. After dermal or ocular exposure, absorption may be reduced by decontaminating the exposed area; the generally used method is washing (HSDB 1999a, 1999b, 1999c, 1999d).

2.12.2 Reducing Body Burden

In humans, DDT and its metabolites distribute in the general circulation, but are eventually selectively concentrated in adipose tissue where they are retained for long periods of time. After the pesticide is sequestered in adipose tissue, common methods to reduce body burden such as dialysis, exchange transfusion, and hemoperfusion are probably ineffective because only small amounts are present in the blood. However, the interval immediately after absorption may be a window of opportunity for removing the xenobiotic from the circulation before it partitions into adipose tissue. Potential strategies which might be investigated include hemodialysis and hemoperfusion (Klaassen 1990).

Absorbed DDT is primarily excreted in the urine (mostly as conjugated DDA), with minor amounts excreted in feces (via biliary excretion), semen, and breast milk. There are several potential strategies for enhancing fecal DDT excretion which might be worth investigation. Studies of DDT excretion in laboratory rats indicated that oral administration of sodium muconate resulted in fecal excretion of injected DDT that was 22 times greater during the first day than in animals that had not received sodium muconate. The trans, trans muconate isomer was given by oral gavage (75 mg/kg) 2 hours after
intraperitoneal injection of \(^{14}\)C-\(p,p'\)-DDT (6.7 mg/kg). Over the first 10 days following sodium muconate treatment, fecal excretion was 2.34 times greater in rats receiving sodium muconate compared to rats that did not receive this treatment (Boileau et al. 1985). Ten days posttreatment, the experimental rats had significantly lower DDT in abdominal fat, liver, and brain showing effective reduction of body burden (Boileau 1985). The mechanism of \(\text{trans, trans}\) muconate in enhancing fecal excretion is unknown. Therefore, it is possible that administration of sodium muconate to humans could result in greater fecal excretion. Muconate may only be effective in acute poisonings, and it has not been shown if a similar effect in rats occurs after acute oral exposure to DDT.

Fecal metabolites have been measured, and at least in one case compared with biliary excretion straight from the bile duct (see Section 2.4.4). If significant enterohepatic circulation could be demonstrated, then methods to interfere might be effective in accelerating the excretion of DDT metabolites. There are several possible strategies for reducing intestinal resorption of metabolites excreted in the bile; the simplest is repeat doses of activated charcoal (Levy 1982). Another strategy which has been effective with other lipophilic xenobiotics has been the oral administration of the anion exchange resin, cholestyramine (Boylan 1978). Daily administration of mineral oil, a cathartic, in the diet of monkeys beginning 7 days after a single oral dose of DDT resulted in a reduction of DDT in adipose tissue and greater elimination in feces (Rozman et al. 1983). However, saline cathartics are the preferred alternative in humans.

### 2.12.3 Interfering with the Mechanism of Action for Toxic Effects

DDT, DDE, and DDD are stimulants which can cause tremors and convulsions by several postulated mechanisms (Section 2.5.2). The most well accepted mechanism is interference with membrane ion fluxes which leads to prolonged neuron depolarization. Other contributory mechanisms which may be secondary to inferences with ion fluxes may include decreases in brain serotonin and increases in levels of aspartate and glutamate. A number of drugs can alleviate this type of central nervous system excitation on experimental animals. These include the anticonvulsant barbiturate phenobarbital, the sedative-antianxiety drug diazepam, and the anticonvulsant phenytoin (Herr et al. 1985; HSDB 1999a, 1999b, 1999c, 1999d; Matin et al. 1981; Tilson et al. 1987). A reduction in the serotonergic activity in the brain has also been postulated to be responsible for the neurotoxic syndrome of myoclonus associated with DDT. Agents that enhance the action of serotonin, such as \(L-5\)-hydroxytryptophan, a serotonin precursor; chlorimipramine, a serotonin uptake blocker; and phenoxybenzomine or trazodone, two \(\alpha\)-receptor blockers, can reduce the neurotoxic effects (myoclonus) of DDT in mice (Hwang and Van Woert 1978).
Caution should be used in extrapolating from animal therapeutics to human applicability. Myoclonus in the rat induced by \textit{p,p'}-DDT has been studied by Pratt et al. (1986), and from electrophysiological and pharmacological analysis it was concluded that the rat was not a good model for studying 5-hydroxytryptamine-sensitive myoclonus in humans.

The reproductive system in animals is another sensitive target organ for DDT toxicity. There are no medically proven-methods for reducing DDT, DDD, and DDE reproductive toxicity by interfering with the mechanism of action in this organ.

Mitigation strategies developed in the future for other lipophilic pesticides should be investigated for their applicability to DDT, DDE, and DDD.

\textbf{2.13 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 DDT, DDE, and DDD is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of DDT, DDE, and DDD.

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.

\textbf{2.13.1 Existing Information on Health Effects of DDT, DDE, and DDD}

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to DDT are summarized in Figure 2-6. The purpose of this figure is to illustrate the existing information concerning the health effects of DDT, DDE, and DDD. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply
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**Figure 2-6. Existing Information on Health Effects of DDT, DDE, and DDD**

![Diagram showing health effects of DDT, DDE, and DDD for human and animal exposure through inhalation, oral, and dermal routes. The diagram includes categories such as death, acute, intermediate, chronic, immunological, lymphatic, neurologic, reproductive, developmental, genotoxic, and cancer. The diagram uses symbols to indicate the presence of existing studies.]

- Existing Studies
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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 (ATSDR 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.

2.13.2 Identification of Data Needs

**Acute-Duration Exposure.** With acute oral exposure to high doses, the nervous system appears to be the major target in both humans and animals. Acute oral exposure has been associated with tremors or convulsions in humans (Hsieh 1954; Velbinger 1947a, 1947b) and animals (Hong et al. 1986; Matin et al. 1981). An acute MRL has been determined based on effects observed following acute oral exposure to DDT on developmental neurotoxicity from exposure of mice during the lactation period (Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996). Studies of single oral or injection exposures of rats, guinea pigs, and mice have provided information on lethal and nonlethal levels of DDT. Further acute oral exposure studies during critical windows of embryonic, fetal, or neonatal development may be very informative.

Information on health effects following acute inhalation of DDT, DDE, or DDD in humans (Neal et al. 1944) or dermal exposure in animals (Cameron and Burgess 1945) was limited. Because of the lack of inhalation data in animals, an acute inhalation MRL could not be derived. Exposure via inhalation at the ambient levels in air (Whitmore et al. 1994) is thought to be insignificant compared with dietary uptake (see Section 5.5, General Population and Occupational Exposure). Also, in the atmosphere, about 50% of DDT is adsorbed to particulate matter and 50% exists in the vapor phase (Bidleman 1988); it is likely that particulate-absorbed DDT will be deposited in the upper respiratory tract and swallowed after mucociliary transport upward (Hayes 1982).

**Intermediate-Duration.** Intermediate-duration exposures in humans and animals have been reported. In most human studies, the exact duration and level of exposure cannot be quantified because the information is derived from case reports or epidemiological studies that do not adequately characterize exposure. Studies on volunteers have been performed in the past that provide useful information. The animal studies describe predominantly neurological, hepatic, immunological, and reproductive/developmental end points. Little or no information on respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, or dermal/ocular effects in animals exists. An intermediate oral MRL
was calculated for DDT, based on cytoplasmic eosinophilia and cellular hypertrophy of hepatocytes in
rats. The immunological studies on DDT are not considered to be adequate for MRL development. The
1992 study reported by Rehana and Rao has several deficiencies in reporting that don't allow adequate
data interpretation. The animal data indicate that the liver is the major target organ following
intermediate or chronic oral exposure, but there is only limited evidence that liver function has been
impaired in humans occupationally exposed. However, the data are limited. The importance of subtle
biochemical changes in humans, such as the induction of microsomal enzymes in the liver and decreases
in biogenic amines in the nervous system, is not known with certainty. This information would be helpful
in evaluating the toxic effects of DDT, DDE, and DDD following intermediate exposure. Levels in
environmental media are not expected to be high enough to result in high inhalation or dermal exposures.

**Chronic-Duration Exposure and Cancer.** Studies have been conducted in animals in which oral
exposure was for a chronic duration. Reproductive, neurological, and hepatic effects have been observed
in animals following chronic oral exposure (Deichmann et al. 1967, 1971; Durham et al. 1963; NCI 1978;
Rossi et al. 1977). No chronic-duration toxicity studies in which animals were exposed dermally or by
inhalation were located. However, the inhalation and dermal routes are considered minor routes of entry
with regard to absorption. Inhaled DDT is largely deposited in the upper respiratory tract and then
swallowed (Hayes 1982). Pharmacokinetic data using lung dosimetry models would provide useful
information as to the contribution of the inhalation route to total intake; however, direct absorption in the
lung is probably minimal. An oral MRL for chronic-duration exposure was not derived since the most
sensitive noncancer (hepatic) effects were observed at doses higher than the doses at which the most
sensitive acute- and intermediate-duration effects occurred. This dietary level was the lowest level tested
in the study.

Although the epidemiological evidence is insufficient to establish conclusively that DDT is a human
carcinogen, the Department of Health and Human Services (DHHS) has determined that DDT may
reasonably be anticipated to be a human carcinogen (NTP 1999). Cancer end points that have been
investigated in humans include respiratory system, pancreatic, endometrial, breast, prostate, and testicular
cancers, Hodgkin’s and non-Hodgkin’s lymphomas, and multiple myeloma. Study designs ranged in
complexity from simple pair-wise comparisons to complex, stratified multivariate analyses. Nearly all of
the human studies evaluated the carcinogenicity of either \( p,p' \)-DDT or \( p,p' \)-DDE.

Animals data provide sufficient evidence of carcinogenicity via oral exposure. On this basis, EPA has
concluded that DDT, DDE, and DDD are probable human carcinogens; IARC has concluded that they are
possible human carcinogens. DDT has been shown to be carcinogenic in a number of mouse studies (Innes et al. 1969; Kashyap et al. 1977; Thorpe and Walker 1973) and in rat studies (Cabral et al. 1982b; Rossi et al. 1977). However, some other rat studies were negative, as were those in hamsters, as well as one study in monkeys (Durham et al. 1963). Information on the mechanism of action for cancer induction by DDT in these susceptible species and on whether or not species-specific biomarkers exist would be helpful. For example, mice and hamsters metabolize DDT by similar metabolic pathways. Therefore, it is unlikely that the species difference is due to differences in the production of DDMU-epoxide or DDA-Cl (Gold and Brunk 1983). However, the hamster is less effective in the conversion of DDT to DDE (Gingell 1976; Gold and Brunk 1983). DDE has been shown to cause liver tumors in hamsters (Rossi et al. 1983). DDT has been shown to promote the carcinogenicity of other substances (Diwan et al. 1994; Kitagawa et al. 1984; Nishizumi 1979; Peraino et al. 1975; Preat et al. 1986; Rojanapo et al. 1993). On the other hand, some studies have observed an inhibitory action of DDT on the carcinogenicity of other chemicals (Rojanapo et al. 1993; Silinskas and Okey 1975). Virtually no information was located regarding the carcinogenicity of DDT by the inhalation and dermal routes of exposure.

**Genotoxicity.** Genotoxicity studies in human systems strongly suggest that DDT may cause chromosomal damage (Lessa et al. 1976; Rupa et al. 1988). *In vivo* and *in vitro* studies in animals lend support to this conclusion (Johnson and Jalal 1973; Kelly-Garvert and Legator 1973; Larsen and Jalal 1974; Mahr and Miltenberger 1976). Assays in animals also report increases in dominant lethality in rats (Palmer et al. 1973) and mice (Clark 1974) exposed to DDT at high doses. It is unknown whether similar types of effects occur in humans.

**Reproductive Toxicity.** There is no evidence that DDT and analogues adversely affect reproductive function in humans. The only reproductive information available in animals was with exposure to DDT and DDE by the oral or injection routes. Acute exposure to DDT by the oral route in animals has been associated with reproductive effects, including a decrease in fertility in male rats (Krause et al. 1975). Reproductive effects observed in animals following DDT exposures of intermediate duration are similar to those effects observed with excess estrogen, including infertility (Green 1969; Jonsson et al. 1976), and decreases in implanted ova (Lundberg 1973). Adult male rats showed a decrease in seminal vesicle and ventral prostate weight after short-term treatment with \( p,p' \)-DDE, which is thought to be due to the anti-androgenic effects of \( p,p' \)-DDE (Kelce et al. 1995). One study *in vitro* showed that all DDT/DDE/DDD isomers can exhibit some degree of anti-androgenicity (Maness et al. 1998), but it is not known whether isomers other than \( p,p' \)-DDE have anti-androgenic properties *in vivo*. Also, it would be useful to
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determine whether the persistent DDT metabolite, 3-MeSO₂-DDE, functions as an androgen antagonist in both \textit{in vitro} binding assays and gene expression assays, and how its potency compares to that of DDE itself.

Multigeneration studies have been conducted in rats (Duby et al. 1971; Green 1969; Ottoboni 1969, 1972; Treon et al. 1954), mice (Keplinger 1970), and dogs (Deichman et al. 1971; Ottoboni et al. 1977). The infertility observed in the Green (1969) study at the very low dose (0.56 mg/kg/day) raises potential concerns about human reproductive effects. However, Keplinger (1970) saw no effect at 3.2 mg/kg/day, although there was a decrease in fertility (as defined by decreased viability through the lactation period) at 32 mg/kg/day. No effects on fertility were seen in 2 or 3 generations of rats exposed to 1.25 mg/kg/day (Treon et al. 1954; Ottoboni 1969) or 0.75 mg/kg/day of technical grade DDT (Duby et al. 1971), nor in 3 generations of beagles exposed to 10 mg/kg/day (Ottoboni et al. 1977). The Deichman et al. (1971) was a mixed exposure to aldrin and DDT from which no conclusions can be drawn. Unfortunately, none of the multigeneration studies mentioned above was conducted according to current scientific standards; flaws exist in the areas of adequate sample sizes, statistical testing (an lack thereof), and reporting of sufficient experimental detail. Thus, there is a critical data need for a well designed multigeneration animal study to reduce the scientific uncertainties about the effects of DDT on fertility.

Well-designed experiments to identify sensitive time periods of exposure and to clarify dose-response relationships for these effects would be useful when deriving an MRL or assessing the potential hazard resulting from environmental exposures. Because exposure to DDT from hazardous waste sites is of concern, additional studies are needed to assess the reproductive toxicity following exposure to doses similar to those estimated at hazardous waste sites. However, DDT-induced effects on fertility may be difficult to detect since the baseline human infertility rate is so high. Levels in environmental media are not expected to be high enough to result in high inhalation or dermal exposures, and therefore, additional inhalation or dermal exposure reproductive studies do not seem to be warranted at this time.

\textbf{Developmental Toxicity.} There is no conclusive evidence that DDT and analogues cause adverse developmental effects in humans. Developmental effects have been observed in the offspring of animals after acute exposure to DDT, DDE, or DDD during gestation (Craig and Ogilvie 1974; Fabro et al. 1984; Gellert and Heinricks 1975; Hart et al. 1971, 1972; Kelce et al. 1995; Loeffler and Peterson 1999; You et al. 1998) or neonatally (Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996). These effects appear to be dependent on the dose administered, the timing of exposure during or after gestation, and the specific isomer administered. The \textit{o,p'}-isomers of DDT, DDE, and DDD have been associated
with estrogen-like effects in the reproductive system and \( p,p' \)-DDE has been associated with anti-androgenic effects. Further information concerning these factors and their impact on the developmental toxicity of DDT, DDE, and DDD would be helpful. For example, cross-fostering studies could help in determining the relative impact of gestational vs. lactational exposure to \( p,p' \)-DDE in relation to delays in the onset of puberty. Standardization of both \textit{in vivo} (pre and postnatal exposures) and \textit{in vitro} tests for estrogenicity and anti-androgenicity of DDT and related compounds would be helpful to compare results between research groups. There are limited data suggesting that if mice exposed to DDT \textit{in utero} and during lactation are further exposed to DDT postnatally, responses in both immunological plaque forming assays and lymphoproliferative assays are reduced (Rehana and Rao 1992). The results of this study are difficult to interpret because of experimental design issues, including the lack of a comparison unexposed group and ambiguity about whether statistical testing was done. It would be useful to try to replicate these results using a better study design. The results from the series of studies by Eriksson et al. (1990a, 1990b, 1992, 1993) and Johansson et al. (1995, 1996) on mice exposed perinatally were used as the basis for deriving an acute oral MRL. Duplication of these results by other laboratories would greatly increase the confidence in these findings. Developmental effects have also been observed in animals following intermediate- and chronic-duration oral exposures to DDT. These effects included slowed development and premature puberty (Clement and Okey 1974; Craig and Ogilvie 1974; Naishtein and Leibovich 1971; Ottoboni et al. 1977; Tomatis et al. 1972; Turusov et al. 1973). Additional studies to assess the mechanism of the developmental toxicity, the critical stages in perinatal development affected by DDT, and the dose-response relationships would be helpful. More data on prenatal and postnatal exposures and postnatal developmental effects might also be useful. No developmental studies by the inhalation and dermal routes of exposure were located. However, since levels in environmental media are not expected to be high enough to result in high inhalation or dermal exposures, additional inhalation or dermal exposure studies assessing developmental effects do not seem to be warranted at this time.

\textbf{Immunotoxicity.} Evidence of immunotoxicity in humans is inconclusive and is limited to a study with only 3 volunteers (Shiplov et al. 1972), and a study of 12 fish-consumers in Sweden (Svensson et al. 1994). Acute-, intermediate-, and chronic-duration oral studies in animals provide evidence that DDT may cause immunological effects. Effects reported included decreases in antibody titers and plaque-forming cells (Banerjee 1987a; Banerjee et al. 1986), increases in gamma globulin and serum immunoglobulin and a decreased tuberculin skin reaction (Street and Sharma 1975), alterations in the spleen (Deichmann et al. 1967), and increased growth of the leprosy bacterium (Banerjee et al. 1997a). The immunotoxicity of DDT compounds is enhanced by a low-protein diet (Banerjee et al. 1995) and physical/emotional stress (Banerjee et al. 1997b), while concurrent treatment with ascorbic acid appears
to attenuate DDT-induced immunotoxicity (Koner et al. 1998). No clear pattern of relative humoral or cell-mediated immunotoxicity was seen from either DDT, DDE, or DDD (Banerjee et al. 1996). In view of the complexity of the immune system, a multiple assay battery would be helpful in order to evaluate the effects of DDT on major components of the immune system. No immunological studies by the inhalation and dermal routes of exposure were located. However, since levels in environmental media are not expected to be high enough to result in high inhalation or dermal exposures, additional inhalation or dermal exposure studies assessing immunological effects do not seem to be warranted at this time.

**Neurotoxicity.** While there are several studies that indicate overt clinical signs of neurotoxicity to humans exposed at relatively high oral doses (Hayes 1982; Hsieh 1954; Velbinger 1947a, 1947b), there are no data to evaluate more subtle neurological effects and the significance of these effects in humans. For example, studies in animals indicate that DDT may affect the level of neurotransmitters and the amount of lipids in the brain (Eriksson and Nordberg 1986; Herr et al. 1986; Hong et al. 1986; Hudson et al. 1985; Sanyal et al. 1986). Clinical observations of overt neurotoxicity such as tremors or convulsions have been reported (Herr and Tilson 1987; Hong et al. 1986; Matin et al. 1981). Neurotoxicity can be caused in adult animals and can be manifested as tremors or convulsions. Developmental neurotoxicity has also been reported in a number of studies (Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b). This neurotoxicity that occurred during neonatal brain developmental stages resulted in behavioral deficits in the adult mouse and correlated with changes in muscarinic acetylcholine receptors in the cerebrum. Behavioral deficits in treated adult animals have also been reported (Sobotka 1971); however, doses were 50-fold higher than those given to neonates. Information clarifying the mechanism of action in the neonate and in the adult mouse as well as data to describe the dose-response relationship for these effects would be extremely useful in further identifying sensitive subpopulations. A battery of neurotoxicity tests would provide additional information on the neurotoxicity in animals, which might then be related to possible neurotoxic effects in humans. No data were located on neurological effects after inhalation exposure in humans or animals or after dermal exposure in humans. A single study reported neurological effects in animals after dermal exposure to DDT (Cameron and Burgess 1945). However, since levels in environmental media are not expected to be high enough to result in high inhalation or dermal exposures, additional inhalation or dermal exposure studies assessing neurological effects do not seem to be warranted at this time.
Epidemiological and Human Dosimetry Studies. Known acute health effects in humans at high exposure levels of DDT, DDE, or DDD are irritation of the eyes, nose, and throat, sweating, nausea, headache, tremors, and convulsions. This information comes from clinical studies and from studies in which volunteers ingested measured amounts of DDT and DDE (Hayes 1982; Hsieh 1954; Velbinger 1947a, 1947b). Effects in animals include liver alterations, developmental and reproductive effects, and neurological effects. More information on the effects of DDT, DDE, or DDD could be obtained from epidemiological studies of people who, because of proximity to areas where high concentrations of DDT, DDE, or DDD have been found, may have higher exposure to DDT, DDE, or DDD. Also, more insight could be gained through future monitoring at National Priorities List (NPL) sites. Because of the virtually ubiquitous distribution of DDT in the environment, some DDT would be expected to be detected in tissues of the majority of the general population. Studies have monitored human tissue and blood for DDT and its metabolites, but no correlation has been made between the levels found in these tissues and specific disease states. Since DDT and its metabolites accumulate in body fat and levels remain fairly constant, it is unknown whether or not levels in blood and serum are the most appropriate measurement of absorbed dose for determining exposure and body burdens, even though they are easier to measure than levels in adipose samples. Sasaki et al. (1992) compared levels of DDT in blood lipid, adipose tissue, and skin lipid of monkeys dosed subcutaneously with DDT and found a good correlation coefficient; since skin lipids were removed from the skin by swabbing with 70% ethanol, this may be a good noninvasive method to evaluate DDT body burdens in humans (Sasaki et al. 1991b). Pharmacokinetic studies to characterize the appropriate measurement of absorbed dose would be useful in future epidemiological studies.

Biomarkers of Exposure and Effect.

Exposure. DDT, DDE, and DDD can be measured in numerous body tissues and fluids including blood, serum, urine, feces, adipose tissue, breast milk, and semen. The presence of these compounds in blood or urine can be used to determine the relative amount of exposure of an individual, but total exposure cannot be quantitated. Methylsulfonyl metabolites of DDT have also been identified in samples of human adipose and breast milk. Other potential biomarkers of exposure have been identified, but again, exposure cannot be quantified. More information could be provided by studies designed to correlate biomarkers of exposure with the temporal aspect of exposure.

Effect. No biomarkers of effect specific for DDT, DDE, or DDD have been identified in the literature. Nonspecific biomarkers of effect include tremors, convulsions, and an increase in hepatic microsomal
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enzymes. Studies designed to identify specific biomarkers of effect for DDT, DDE, and DDD would be useful. Studies that assessed the association between DDT, DDE, and DDD levels in maternal blood and premature birth and spontaneous abortions have been conducted (Saxena et al. 1980, 1981, 1983; Wasserman et al. 1982); however, the question remains whether the blood levels measured in these studies are the most representative biomarker for exposure.

Absorption, Distribution, Metabolism, and Excretion. Qualitative information from occupational and ingestion studies indicates that humans absorb DDT via inhalation, dermal, and oral routes of administration (Laws et al. 1967; Morgan and Roan 1971, 1974; Morgan et al. 1980). No quantitative information exists concerning the rate or extent of absorption following inhalation or dermal exposure, although some information exists that quantifies the extent of absorption following oral administration. The bioavailability of DDT from environmental media, such as soil or food, is not well characterized. Quantitative data (e.g., absorption rates) from animals exposed by oral and dermal routes in different environmental media would be useful in providing information on absorption of DDT, DDE, and DDD to be used in estimating absorption in humans following exposure by these routes in these environmental media.

Information exists on the distribution of DDT, DDE, and DDD and on the storage and release from storage of these compounds (Hayes et al. 1971; Morgan and Roan 1971, 1974). However, there is limited information on the long-term release rates from adipose tissue. This information would be helpful in determining the retention time of DDT in humans.

The ultimate metabolites of DDT, which can be isolated from animals, have been well described. However, two models have been proposed for the intermediate products between parent and ultimate metabolites. These models differ in the quantity of potential electrophilic intermediates (an epoxide and an acylating agent) produced. These electrophilic metabolites have not been isolated, but their presence may be confirmed if DNA adducts are found. Some species-specific metabolic differences, especially in the area of efficiency of the conversion of DDT to DDE in hamsters relative to other species, have been identified (Gold and Brunk 1982, 1983). However, the role of these metabolic differences in species-specific sensitivity to toxicity, especially carcinogenicity, is not well characterized. Further information concerning the species-specific metabolic differences would be useful to provide more specific information when comparing the toxicokinetics of these substances in humans and animals.
Comparative Toxicokinetics. Metabolism studies indicate that the metabolism of DDT is qualitatively similar among several species, but that the efficiency of formation of certain metabolites and the proportion of metabolites excreted may be quantitatively different (Gingell 1976; Gold and Brunk 1982, 1983, 1984; Peterson and Robison 1964). Comparisons of elimination rates of DDT from fat showed that the process is the slowest in humans, followed by monkeys, dogs, and rats (Morgan and Roan 1974). Rats eliminate DDT 10 to 100 times faster than humans. Morgan and Roan (1974) suggested that the differences in elimination in rats could be due to differences in liver metabolism, gut bacterial metabolism, enterohepatic recirculation, or factors related to the accessibility of plasma-transported pesticide to the excretory cells of the liver. Differences in the metabolism of DDT among species may account for differences in toxic responses, especially cancer. The potential for DDT to produce toxic effects has been investigated in rats, dogs, mice, guinea pigs, and nonhuman primates, but the animal species that serves as the best model for extrapolating results to humans has not been determined. Ethical considerations limit the amount of information that can be obtained in humans, but analysis of urine of persons with known exposure to DDT to determine levels of parent compound and metabolites could provide more information on the metabolic pathways in humans. This information could help to identify the most appropriate animal model for extrapolation to humans.

Methods of Reducing Toxic Effects. The available data indicate some ways in which peak absorption of DDT, DDE, and DDD might be reduced following oral or dermal exposure (Dreisbach 1983; HSDB 1999a, 1999b, 1999c, 1999d). Studies that examine the efficacy of gastric lavage with mannitol vs. other cathartics or of combinations of cathartics would be useful. Also, studies that evaluate the effectiveness of intestinal absorbants such as sodium muconate or cholestyramine would provide valuable information. No data were located regarding methods for reducing absorption following inhalation exposure.

In humans, DDT and its fat soluble metabolites are stored in adipose tissue, where they are retained for long periods of time. During that time, short term toxicity may be expected to be minimal since exposure to target organs would be via the circulation and the equilibrium between blood and adipose tissue is such that blood levels are about 1:280 of fat levels; however, there is still the potential for chronic toxicity and interactions with other environmental chemicals. If very large amounts of DDT or its metabolites are stored in adipose tissue, then rapid release of DDT or its metabolites into the circulation during mobilization of fat stores, such as during rapid weight loss, may result in certain types of toxic effects. Release of DDT into the blood of a pregnant woman during gestation-related fat mobilization might result in toxicity to the developing fetus. Also, mobilization of adipose fat for lactation might provide an
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increased amount of DDT to a breast-feeding infant. Development of methods to enhance excretion of adipose-sequestered DDT, while minimizing toxicity would be beneficial in reducing the body burden.

DDT induces neurotoxicity (tremors and convulsions) by various mechanisms (see Section 2.5). No method is currently available for directly reducing the neurotoxic effects of DDT, DDE, or DDD by interfering with the mechanisms of action, although there are a variety of pharmacological methods for alleviating non-specific symptoms.

**Children’s Susceptibility.** The information on health effects of DDT and analogues in humans is derived mainly from accidental exposure and from controlled studies in volunteers, and the main adverse effect is neurotoxicity. No reports on exposed children were found, but it is reasonable to assume that children will exhibit signs and symptoms similar to those in adults under similar exposure conditions. There is no information on whether the developmental process is altered in humans exposed to DDT. Studies in animals have shown that DDT and analogues can alter the development and maturation of the male and female reproductive system (Bitman and Cecil 1970; Clement and Okey 1972; Duby et al. 1971; Gellert et al. 1972; Kelce et al. 1995, 1997; Loeffler and Peterson 1999; Singhal et al. 1970; You et al. 1998). Hormone-like effects have been reproduced in many types of *in vitro* test systems, but there is a need for standardized operating procedures. *In vivo* tests are preferred over *in vitro* assays because they take into account pharmacokinetic and pharmacodynamic interactions.

There are no adequate data to evaluate whether pharmacokinetics of DDT in children are different from adults. DDT and analogues can cross the placenta and are transferred to offspring via breast milk. It is unknown whether the efficiency of gastrointestinal absorption of DDT and analogues in nursing neonates differs from adults and what influence the fat content of human milk might make. Further information on the dynamics of DDT and analogues during pregnancy and lactation, such as further refinement of PBPK models to include humans would be useful. The only existing PBPK model for DDT is that of You et al. (1999), which focuses on pregnant and lactating Sprague-Dawley rats. There is no information to evaluate whether metabolism of DDT is different in children than in adults since the specific phase I and II enzymes involved in DDT metabolism have not been identified; it is unknown which phase I P-450 isozymes metabolize DDT.

There is little evidence about whether children or young animals differ in their susceptibility to the health effects from DDT from adults. In fact, some animal studies found that young rats are less susceptible than older ones to the acute neurotoxic effects produced by a single dose of DDT (Lu et al. 1965).
However, the relevance of this information to human health is unknown. There is evidence that acute perinatal exposure to DDT in mice results in altered behavioral responses in the mice tested as adults (Eriksson et al. 1992, 1993; Johansson et al. 1995, 1996). Research efforts should focus on the possible underlying mechanism(s) that are responsible for such long-lasting postexposure alterations.

Continued research into the development of sensitive and specific biomarkers of exposure and effect for DDT and analogues would be valuable for both adults and children. There are no data on the interactions of DDT with other chemicals in children or adults. There are no pediatric-specific methods to reduce peak absorption for DDT following exposure, to reduce body burdens, or to interfere with the mechanism of action. Based on the information available, it is reasonable to assume that methods recommended for treating adults will also be applicable to children; however, these methods need to be validated in children.

Issues relevant to children are explicitly discussed in Section 2.8, Children’s Susceptibility and Section 5.6, Exposures of Children.

### 2.13.3 Ongoing Studies

A number of studies concerning health effects associated with DDT, DDE, and DDD have been identified in the Federal Research in Progress (FEDRIP 1999) database and are listed in Table 2-7.
### Table 2-7. Ongoing Studies on the Health Effects of DDT and DDT Analogues

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<th>Investigator</th>
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<td>Organochlorine residue levels and risk of breast cancer</td>
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### Table 2-7. Ongoing Studies on the Health Effects of DDT and DDT Analogues (continued)

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Table 2-7. Ongoing Studies on the Health Effects of DDT and DDT Analogues (continued)

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*Post office state abbreviations used

DNA = deoxyribonucleic acid; NCI = National Cancer Institute; NICHD = National Institute of Child Health and Human Development; NIEHS = National Institute of Environmental Health Sciences; NIGMS = National Institute of General Medical Sciences; NIH = National Institutes of Health; PCB = polychlorinated biphenyl; USDA = United States Department of Agriculture
3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

When we refer to DDT, we are generally referring to \( p,p' \)-DDT, which was produced and used for its insecticidal properties. However, technical grade DDT, the grade that was generally used as an insecticide, was composed of up to fourteen chemical compounds, of which only 65–80% was the active ingredient, \( p,p' \)-DDT. The other components included 15–21% of the nearly inactive \( o,p' \)-DDT, up to 4% of \( p,p' \)-DDD, and up to 1.5% of 1-(\( p \)-chlorophenyl)-2,2,2-trichloroethanol (Metcalf 1995).

The chemical formulas, structures, and identification numbers for \( p,p' \)-DDT, \( p,p' \)-DDE, \( p,p' \)-DDD, \( o,p' \)-DDT, \( o,p' \)-DDE, and \( o,p' \)-DDD are listed in Table 3-1. The latter five compounds are either impurities or metabolites of technical DDT.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Technical DDT is a white amorphous powder that melts over the range of 80–94 \( ^\circ \)C (Metcalf 1995). Physical and chemical properties of \( p,p' \)-DDT, \( p,p' \)-DDE, \( p,p' \)-DDD, \( o,p' \)-DDT, \( o,p' \)-DDE, and \( o,p' \)-DDD are listed in Table 3-2.
### Table 3-1. Chemical Identity of \( p,p' \)- and \( \alpha,\alpha' \)-DDT, DDE, and DDD

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>( p,p' )-DDT</th>
<th>( p,p' )-DDE</th>
<th>( p,p' )-DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synonym(s)</td>
<td>4,4'-DDT; 1,1,1-trichloro-2,2-bis ( p )-chlorophenyl)ethane; dichlorodiphenyl trichloroethane; DDT; 1,1'- (2,2,2-trichloroethylidene) bis(4-chlorobenzene); ( \alpha,\alpha' )-bis( p )-chlorophenyl)- ( \beta,\beta,\beta )-trichloroethane</td>
<td>4,4'-DDE; dichlorodiphenyl-dichloroethane; 1,1-dichloro-2,2-bis( p )-chlorophenyl ethylene; 1,1'- (2,2-dichloroethylidene) bis(4-chlorobenzene); DDE</td>
<td>4,4'-DDD; DDD; 1,1-dichloro-2,2-bis( p )-chlorophenyl)ethane; 1,1-bis (4-chlorophenyl)-2,2-dichloroethane; TDE; tetrachlorodiphenylethane</td>
</tr>
<tr>
<td>Registered trade name(s)</td>
<td>Genitox, Anofex, Detoxan, Neocid, Gesarol, Pentachlorin, Dicophane, Chlorophenothane</td>
<td>No data</td>
<td>DDD; Rothane; Dile, TDE</td>
</tr>
<tr>
<td>Chemical formula</td>
<td>( C_{14}H_9Cl_5 )</td>
<td>( C_{14}H_8Cl_4 )</td>
<td>( C_{14}H_{10}Cl_4 )</td>
</tr>
<tr>
<td>Chemical structure</td>
<td><img src="image1" alt="Chemical structure of ( p,p' )-DDT" /></td>
<td><img src="image2" alt="Chemical structure of ( p,p' )-DDE" /></td>
<td><img src="image3" alt="Chemical structure of ( p,p' )-DDD" /></td>
</tr>
<tr>
<td>Identification numbers:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAS registry</td>
<td>50-29-3</td>
<td>72-55-9</td>
<td>72-54-8</td>
</tr>
<tr>
<td>NIOSH RTECS</td>
<td>KV33250000</td>
<td>KV9450000</td>
<td>KI07000000</td>
</tr>
<tr>
<td>EPA hazardous waste</td>
<td>U061</td>
<td>No data</td>
<td>U060</td>
</tr>
<tr>
<td>OHM/TADS</td>
<td>7216510</td>
<td>No data</td>
<td>7215098</td>
</tr>
<tr>
<td>DOT/UN/NA/IMCO shipping</td>
<td>IMCO 6.1; UN2761</td>
<td>No data</td>
<td>NA2761; TDE</td>
</tr>
<tr>
<td>HSDB</td>
<td>200</td>
<td>1625</td>
<td>285</td>
</tr>
<tr>
<td>NCI</td>
<td>C00465</td>
<td>C00555</td>
<td>C00475</td>
</tr>
</tbody>
</table>
Table 3-1. Chemical Identity of \( \rho,\rho' \)- and \( o,\rho' \)-DDT, DDE, and DDD\(^{a} \) (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>( o,\rho' )-DDT</th>
<th>( o,\rho' )-DDE</th>
<th>( o,\rho' )-DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synonym(s)</td>
<td>4,4'-DDT; 1,1,1-trichloro-2-((o\text{-chlorophenyl}))-2-((p\text{-chlorophenyl}))-ethane; ( o,\rho' )-dichlorodiphenyltrichloroethane</td>
<td>2,4'-DDE; 1,1-dichloro-2-((o\text{-chlorophenyl}))-2-((p\text{-chlorophenyl}))-ethylene; 1-chloro-2-((2,2-dichloro-1-(4-chlorophenyl))ethenylbenzene</td>
<td>2,4'-DDD; Mitotane; ( o,\rho' )-DDD; 1,1-dichloro-2-((o\text{-chlorophenyl}))-2-((p\text{-chlorophenyl}))-ethane; ( o,\rho' )-TDE; Chodilane; 2-((o-chlorophenyl))-2-((p-chlorophenyl))-1,1-dichloroethane</td>
</tr>
<tr>
<td>Registered trade name(s)</td>
<td>No data</td>
<td>No data</td>
<td>Lysodren</td>
</tr>
<tr>
<td>Chemical formula</td>
<td>( \text{C}<em>{14}\text{H}</em>{9}\text{Cl}_{5} )</td>
<td>( \text{C}<em>{14}\text{H}</em>{8}\text{Cl}_{4} )</td>
<td>( \text{C}<em>{14}\text{H}</em>{10}\text{Cl}_{4} )</td>
</tr>
<tr>
<td>Chemical structure</td>
<td><img src="image1" alt="Chemical structure diagram for ( o,\rho' )-DDT" /></td>
<td><img src="image2" alt="Chemical structure diagram for ( o,\rho' )-DDE" /></td>
<td><img src="image3" alt="Chemical structure diagram for ( o,\rho' )-DDD" /></td>
</tr>
<tr>
<td>Identification numbers:</td>
<td>CAS registry: 789-02-6</td>
<td>CAS registry: 3424-82-6</td>
<td>CAS registry: 53-19-0</td>
</tr>
<tr>
<td></td>
<td>NIOSH RTECS: No data</td>
<td>NIOSH RTECS: No data</td>
<td>NIOSH RTECS: KH7880000</td>
</tr>
<tr>
<td></td>
<td>EPA hazardous waste: No data</td>
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<td>EPA hazardous waste: No data</td>
</tr>
<tr>
<td></td>
<td>OHM/TADS: No data</td>
<td>OHM/TADS: No data</td>
<td>OHM/TADS: No data</td>
</tr>
<tr>
<td></td>
<td>DOT/UN/NA/IMCO shipping: No data</td>
<td>DOT/UN/NA/IMCO shipping: No data</td>
<td>DOT/UN/NA/IMCO shipping: No data</td>
</tr>
<tr>
<td></td>
<td>HSDB: No data</td>
<td>HSDB: No data</td>
<td>HSDB: No data</td>
</tr>
<tr>
<td></td>
<td>NCI: No data</td>
<td>NCI: No data</td>
<td>NCI: No data</td>
</tr>
</tbody>
</table>

\(^{a}\)All information obtained from HSDB 1999a, 1999b, 1999c, 1999d, or Howard and Neal 1992 except where noted.

\(^{b}\)Klassen et al. 1991

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances
### Table 3-2. Physical and Chemical Properties of \( p,p' \)- and \( o,p' \)-DDT, DDE, and DDD

<table>
<thead>
<tr>
<th>Property</th>
<th>( p,p' )-DDT</th>
<th>( p,p' )-DDE</th>
<th>( p,p' )-DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>354.49(^b)</td>
<td>318.03(^b)</td>
<td>320.06(^b)</td>
</tr>
<tr>
<td>Color</td>
<td>Colorless crystals, white powder(^c)</td>
<td>White</td>
<td>Colorless crystals, white powder</td>
</tr>
<tr>
<td>Physical state</td>
<td>Solid(^d)</td>
<td>Crystalline solid</td>
<td>Solid</td>
</tr>
<tr>
<td>Melting point</td>
<td>109 EC(^b)</td>
<td>89 EC(^b)</td>
<td>109–110 EC(^b)</td>
</tr>
<tr>
<td>Boiling point</td>
<td>Decomposes</td>
<td>336 EC(^b)</td>
<td>350 EC(^b)</td>
</tr>
<tr>
<td>Density</td>
<td>0.98–0.99 g/cm(^3)</td>
<td>No data</td>
<td>1.385 g/cm(^3)</td>
</tr>
<tr>
<td>Odor</td>
<td>Odorless or weak aromatic odor(^e)</td>
<td>No data</td>
<td>Odorless</td>
</tr>
<tr>
<td>Odor threshold:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>0.35 mg/kg(^c)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Air</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Solubility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>0.025 mg/L at 25 EC(^b)</td>
<td>0.12 mg/L at 25 EC(^b)</td>
<td>0.090 mg/L at 25 EC(^b)</td>
</tr>
<tr>
<td>Organic solvents</td>
<td>Slightly soluble in ethanol, very soluble in ethyl ether and acetone(^e)</td>
<td>Lipids and most organic solvents</td>
<td>No data(^c)</td>
</tr>
<tr>
<td>Partition coefficients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log ( K_{ow} )</td>
<td>6.91(^b)</td>
<td>6.51(^b)</td>
<td>6.02(^b)</td>
</tr>
<tr>
<td>Log ( K_{oc} )</td>
<td>5.18(^h)</td>
<td>4.70(^i)</td>
<td>5.18(^i)</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>1.60x10(^{-7}) at 20 EC, torr(^d)</td>
<td>6.0x10(^{-6}) at 25 EC, torr(^d)</td>
<td>1.35x10(^{-6}) at 25 EC, torr(^d)</td>
</tr>
<tr>
<td>Henry's law constant</td>
<td>8.3x10(^{-6}) atm-m(^3)/mol(^b)</td>
<td>2.1x10(^{-5}) atm-m(^3)/mol(^b)</td>
<td>4.0x10(^{-6}) atm-m(^3)/mol(^b)</td>
</tr>
<tr>
<td>Autoignition temperature</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Flashpoint</td>
<td>72.2–77.2 EC</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>flammability limits</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Conversion factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ppm(v/v) to mg/m(^3) in air at 20 EC</td>
<td>Not applicable(^h)</td>
<td>Not applicable(^h)</td>
<td>Not applicable(^h)</td>
</tr>
<tr>
<td>mg/m(^3) to ppm(v/v) in air at 20 EC</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Explosive limits</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

\(^a\) Data compiled from references and scientific literature.
### Table 3-2. Physical and Chemical Properties of p,p'- and o,p'-DDT, DDE, and DDD*

<table>
<thead>
<tr>
<th>Property</th>
<th>o,p'-DDT</th>
<th>o,p'-DDE</th>
<th>o,p'-DDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>354.49(^b)</td>
<td>318.03(^b)</td>
<td>320.05(^c)</td>
</tr>
<tr>
<td>Color</td>
<td>White crystalline powder(^c)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Physical state</td>
<td>Solid(^d)</td>
<td>No data</td>
<td>Solid</td>
</tr>
<tr>
<td>Melting point</td>
<td>74.2 EC(^e)</td>
<td>No data</td>
<td>76–78 EC</td>
</tr>
<tr>
<td>Boiling point</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Density</td>
<td>0.98–0.99 g/cm(^3)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Odor</td>
<td>Odorless or weak aromatic odor(^e)</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Odor threshold:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Air</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Solubility:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water</td>
<td>0.085 mg/L at 25 EC(^b)</td>
<td>0.14 mg/L at 25 EC(^b)</td>
<td>0.1 mg/L at 25 EC(^b)</td>
</tr>
<tr>
<td>Organic solvents</td>
<td>No data(^g)</td>
<td>No data(^g)</td>
<td>Soluble in ethanol, isooctane, carbon tetrachloride(^i)</td>
</tr>
<tr>
<td>Partition coefficients:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log (K_{oc})</td>
<td>6.79(^b)</td>
<td>6.00(^b)</td>
<td>5.87(^b)</td>
</tr>
<tr>
<td>Log (K_{oc})</td>
<td>5.35(^j)</td>
<td>5.19(^j)</td>
<td>5.19(^j)</td>
</tr>
<tr>
<td>Vapor pressure</td>
<td>1.1x10(^{-7}) at 20 EC, torr(^b)</td>
<td>6.2x10(^{-6}) at 25 EC, torr(^b)</td>
<td>1.94x10(^{-6}) at 30 EC, torr(^b)</td>
</tr>
<tr>
<td>Henry's law constant</td>
<td>5.9x10(^{-7}) atm-m(^3)/mol(^b)</td>
<td>1.8x10(^{-5}) atm-m(^3)/mol(^b)</td>
<td>8.17x10(^{-6}) atm-m(^3)/mol(^b)</td>
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<tr>
<td>Autoignition temperature</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Flashpoint</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Flammability limits</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
<tr>
<td>Conversion factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ppm(v/v) to mg/m(^3) in air at 20 EC</td>
<td>Not applicable(^h)</td>
<td>Not applicable(^h)</td>
<td>Not applicable(^h)</td>
</tr>
<tr>
<td>mg/m(^3) to ppm(v/v) in air at 20 EC</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Explosive limits</td>
<td>No data</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

\(^a\)All information obtained from HSDB 1999a, 1999b, 1999c, 1999d unless otherwise noted
\(^b\)Howard and Meylan 1997
\(^c\)Verschueren 1988
\(^d\)NIOSH 1985
\(^e\)Sax 1979
\(^f\)Lide 1998
\(^g\)Chemical is expected to be soluble in most organic compounds.
\(^h\)Swann et al. 1981
\(^i\)Sablejic 1984
\(^j\)Meylan et al. 1992 (values estimated from a fragment constant method)
\(^k\)Exists partially in particulate form in air. Conversion factors are only applicable for compounds that are entirely in the vapor phase.

---

**DDT, DDE, and DDD**
4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

Figures relating to the production, import/export, use, and disposal of a pesticide generally refer to those of the active ingredient. In the case of DDT, the active ingredient is \( p,p' \)-DDT. Most DDT production can be assumed to have been technical grade material that included 15–21% of the nearly inactive \( o,p' \)-DDT, up to 4% of \( p,p' \)-DDD, and up to 1.5% of \( 1-(p\text{-chlorophenyl})-2,2,2\text{-trichloroethanol} \) (Metcalf 1995).

4.1 PRODUCTION

Technical DDT is made by condensing chloral hydrate with chlorobenzene in concentrated sulfuric acid. It was first synthesized in 1874, but it was not until 1939 that Müller and his coworkers discovered its insecticidal properties. Production of DDT in 1971 in the United States was estimated to be 2 million kg. This represented a sharp decline from the 82 million kg produced in 1962, and from the 56 million kg produced in 1960. At the peak of its popularity in 1962, DDT was registered for use on 334 agricultural commodities and about 85,000 tons were produced (Metcalf 1995). Production then declined and by 1971, shortly before it was banned in the United States, production had dipped to about 2,000 tons. The cumulative world production of DDT has been estimated as 2 million tons. As of January 1, 1973, all uses of DDT in the United States were canceled except emergency public health uses and a few other uses permitted on a case-by-case basis (Meister and Sine 1999). Currently, no companies in the United States manufacture DDT (Meister and Sine 1999). DDT is presently produced by companies in Mexico and China (Meister and Sine 1999). \( p,p' \)-DDD has been used as an insecticide, but is no longer produced commercially. It was prepared by condensing dichloroacetaldehyde with chlorobenzene (Budavari et al. 1996). No past production figures are available for this chemical, and there are no indications that production was ever very high. \( o,p' \)-DDD (Mitotane) is produced by Bristol, Meyer, Squibb under the brand name Lysodren® for use as a chemotherapy drug for adrenal gland cancer (PDR 1999). DDD and DDE are degradation products formed by dehydrohalogenation of DDT.

Analytical studies have shown that DDT compounds, including \( p,p' \)-DDT and \( p,p' \)-DDE, may be contaminants in technical grades of the insecticide, dicofol (Risebrough et al. 1986). In addition, another DDT-related impurity in dicofol, \( 1,1,1,2\text{-tetrachloro-2,2-bis(p-chlorophenyl}) \text{ethane}, has been shown to degrade to \( p,p' \)-DDE.
4.2 IMPORT/EXPORT

DDT was last imported into the United States in 1972, when imports amounted to 200 tons. Although the use of DDT was banned in the United States after 1972, it was still manufactured for export. In 1985, there were two producers of DDT in the United States, and in that year, 303,000 kg of DDT were exported (HSDB 1988). Presently, there are no producers of DDT in the United States, and therefore, there are no exports of DDT.

4.3 USE

DDT is a broad spectrum insecticide that was very popular due its effectiveness, long residual persistence, low acute mammalian toxicity, and low cost (Metcalf 1989). DDT was first used as an insecticide starting in 1939 and widely used until about 1970 (Van Metre et al. 1997). Its usage peaked in the United States in the early 1960s. During World War II, it was extensively employed for the control of malaria, typhus, and other insect-transmitted diseases. DDT has been widely used in agriculture to control insects, such as the pink boll worm on cotton, codling moth on deciduous fruit, Colorado potato beetle, and the European corn borer. In 1972, 67–90% of the total United States consumption of DDT was on cotton; the remainder was primarily used on peanuts and soybeans. DDT has been used extensively to eradicate forest pests, such as the gypsy moth and spruce budworm. It was used in the home as a mothproofing agent and to control lice. The amount of DDT used in U.S. agriculture was 27 million pounds in 1966 and 14 million pounds in 1971 (Gianessi and Puffer 1992). Since 1973, use of DDT has been limited to the control of emergency public health problems. \( p,p' \)-DDD was also used as an insecticide. \( o,p' \)-DDD (Mitotane) is used medically in the treatment of cancer of the adrenal gland (PDR 1999). DDE has no commercial use.

4.4 DISPOSAL

Under current federal guidelines, DDT and DDD are potential candidates for incineration in a rotary kiln at 820–1,600 °C. Disposal of DDT formulated in 5% oil solution or other solutions is mainly by using liquid injection incineration at 878–1,260 °C, with a residence time of 0.16–1.30 seconds and 26–70% excess air. Destruction efficiency with this method is reported to be >99.99%. Multiple-chamber incineration is also used for 10% DDT dust and 90% inert ingredients at a temperature range of 930–1,210 °C, a residence time of 1.2–2.5 seconds, and 58–164% excess air. DDT powder may be disposed of by molten salt combustion at 900 °C (no residence time or excess air conditions specified). A
low temperature destruction method involving milling DDT with Mg, Ca, or CaO is under development on a laboratory scale (Rowlands et al. 1994). Landfill disposal methods are rarely used at the present time.
5. POTENTIAL FOR HUMAN EXPOSURE

While this document is specifically focused on the primary forms or isomers of DDT, DDE, and DDD (namely $p,p'$-DDT, $p,p'$-DDE, and $p,p'$-DDD), other isomers of these compounds will be discussed when appropriate. It should be noted that DDT, DDE, and DDD are also synonyms for $p,p'$-DDT, $p,p'$-DDE, and $p,p'$-DDD, respectively, and it is usually understood that when DDT, for example, is mentioned $p,p'$-DDT is being referred to and not both $o,p'$- and $p,p'$-DDT. Technical grade DDT, the grade that was generally used as an insecticide was composed of up to 14 chemical compounds, of which only 65–80% was the active ingredient, $p,p'$-DDT. The other components included 15–21% of the nearly inactive $o,p'$-DDT, up to 4% of $p,p'$-DDD, and up to 1.5% of 1-($p$-chlorophenyl)-2,2,2-trichloroethanol (Metcalf 1995). In some cases, the term DDT will be used to refer to the collection of all forms of DDT, DDE, and DDD. Should this not be clear from the context, the term $\Sigma$DDT ($\Sigma$ is used to mean sum of) will be used.

5.1 OVERVIEW

DDT and its primary metabolites, DDE and DDD, are manufactured chemicals and are not known to occur naturally in the environment (WHO 1979). Historically, DDT was released to the environment during its production, formulation, and extensive use as a pesticide in agriculture and vector control applications. DDD was also used as a pesticide, but to a far lesser extent than was DDT. Although it was banned for use in the United States after 1972, DDT is still being used in some areas of the world. DDT and its metabolites are very persistent and bioaccumulate in the environment.

DDT gets into the atmosphere as a result of spraying operations in areas of the world where it is still used and from the volatilization of residues in soil and surface water, much of it a result of past use. These chemicals will be deposited on land and in surface water as a result of dry and wet deposition. The process of volatilization and deposition may be repeated many times, and results in what has been referred to as a ‘global distillation’ from warm source areas to cold polar regions. As a result, DDT and its metabolites are transported to the Arctic and Antarctic regions where they are found in the air, sediment, and snow and accumulate in biota.

In the atmosphere, about 50% of DDT will be found adsorbed to particulate matter and 50% will exist in the vapor phase (Bidleman 1988). A smaller proportion of DDE and DDD are adsorbed to particulate matter than DDT. Vapor-phase DDT, DDE and DDD react with photochemically-produced hydroxyl radicals in the atmosphere; their estimated half-lives are 37, 17, and 30 hours, respectively.
The dominant fate processes in the aquatic environment are volatilization and adsorption to biota, suspended particulate matter, and sediments. Transformation includes biotransformation and photolysis in surface waters. The fate of DDT in the aquatic environment is illustrated by a microcosm study in which DDT was applied to a pond, and a material balance was performed after 30–40 days. At this time, DDT concentrations in the water column had declined to below the detectable limit (EPA 1979c). It was found that 90% of the initial DDT was not present in the water, sediment, algae, invertebrates, or fish, and was presumed to have volatilized. ΣDDT was present in water mainly as DDT during the first 30 days, as DDT and DDD during the next 30 days, and as DDD in the last 30 days. ΣDDT levels rapidly rose in invertebrates, reaching equilibrium in 5 days and then declining as the ΣDDT content of the water declined. ΣDDT levels in fish rose rapidly and reached a high equilibrium level.

When deposited on soil, DDT, DDE, and DDD are strongly adsorbed. However, they may also revolatilize into the air, which is more likely to occur from moist soils than dry soils. They may photodegrade on the soil surface and biodegrade. DDT biodegrades primarily to DDE under unflooded conditions and to DDD under flooded conditions. As a result of their strong binding to soil, DDT, DDE, and DDD mostly remain on the surface layers of soil; there is little leaching into the lower soil layers and groundwater. DDT may be taken up by plants that are eaten by animals and accumulate to high levels, primarily in adipose tissue and milk of the animals.

In discussing DDT and other pesticides in soil, agricultural chemists generally speak of persistence and degradation, but it is not always clear what mechanisms are responsible for the loss or dissipation of the chemical. This issue is further complicated in the case of DDT because what is often reported is the disappearance of ΣDDT residues rather than just p,p'-DDT. Many studies use first-order kinetics to model the dissipation of DDT in soils because a half-life for the chemical can be defined. The half-life represents the calculated time for loss of the first 50% of the substance, but the time required for the loss of half of that which remains may be substantially longer, and the rate of disappearance may decline further as time progresses. The rate and extent of disappearance may result from transport processes as well as degradation or transformation processes. Initially, much of the disappearance of DDT is a result of volatilization losses, after which biodegradation becomes more important. When more than one process is responsible for loss, the decrease in the amount of substance remaining will be nonlinear. Recent assessments of long-term monitoring studies have indicated that even DDT biodegradation does not follow first-order kinetics (Alexander 1995, 1997). The reason is that over long periods of time, DDT may become sequestered in soil particles and become less available to microorganisms. The term half-life in this document is used to indicate the estimated time for the initial disappearance of 50% of the
compound, and does not necessarily imply that first-order kinetics were observed throughout the experiment unless otherwise noted. The persistence of DDT in soil is highly variable. Dissipation is much greater in tropical than in temperate regions. In tropical and subtropical regions, most of the DDT is lost within a year; the half-life of $\Sigma$DDT in 13 countries ranged from 22 to 327 days. The half-life of DDE, the primary metabolite of DDT, ranged from 151 to 271 days. In a fourteenth country where the soil was extremely acidic, the half-life was >672 days. Comparable half-lives in temperate regions have been reported to range from 837 to 6,087 days. One investigator concluded that the mean lifetime of DDT in temperate U.S. soils was about 5.3 years. In a study of sprayed forest soils in Maine, the half-time for the disappearance of DDT residues was noted to be 20–30 years. Highest residues are found in muck soils and in deeply plowed, unflooded fields (Aigner et al. 1998; Spencer et al. 1996). Significant concentrations of DDT have been found in the atmosphere over agricultural plots. Irrigating the soil dramatically increased the volatilization flux of DDT, which is probably related to the amount of DDT in the soil solution. Volatilization, air transport, and redeposition were found to be the main avenues of contaminating forage eaten by cows.

When deposited in water, DDT will adsorb strongly to particulate matter in the water column and primarily partition into the sediment. Some of the DDT may revolatilize. DDT bioconcentrates in aquatic organisms and bioaccumulates in the food chain. Marine mammals in the Arctic often contain very high levels of DDT and DDE.

Concentrations of DDT in all media have been declining since DDT was banned in the United States and most of the world. However, because of the extensive past use of DDT worldwide and the persistence of DDT and its metabolites, these chemicals are virtually ubiquitous and are continually being transformed and redistributed in the environment.

Human exposure to DDT is primarily through the diet. Exposure via inhalation at the ambient levels in air (Whitmore et al. 1994) is thought to be insignificant compared with dietary intake. The main source of DDT in food is meat, fish, poultry, and dairy products. DDT residues in food have declined since it was banned. Residues are more likely to occur in food imported from countries where DDT is still used. People eating fish from the Great Lakes were found to consume greater amounts of DDT in their diets, but as DDT levels in Great Lakes fish continue to decline, exposure from consuming fish should also decline (Hovinga et al. 1993). The populations having the greatest exposure to DDT are indigenous people in the Arctic who eat traditional foods (e.g., seals, cariboo, narwhal whales) (Kuhnlein et al. 1995).
DDT, DDE, or DDD have been identified in at least 397 of the 1,560 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 1999). However, the number of sites evaluated for DDT, DDE, and DDD is not known. The frequency of these sites can be seen in Figure 5-1. Of these sites, 395 are located in the United States, 1 is located in the Commonwealth of Puerto Rico (not shown), and 1 is located in the U.S. Virgin Islands (not shown). \( p,p' \)-DDT, \( p,p' \)-DDD, and \( p,p' \)-DDE, the only DDT-related compounds targeted for analysis at NPL sites (EPA 1994), were respectively found at 326, 276, and 219 sites. While not targeted, \( o,p' \)-DDT, \( o,p' \)-DDD, and \( o,p' \)-DDE were nevertheless listed as detected at 4, 3, and 4 sites, respectively. Releases of DDT, DDE, or DDD are not required to be reported in the Toxics Release Inventory (TRI) database (EPA 1999).

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

During the period when DDT was extensively used, a large source of DDT release to air occurred during agricultural or vector control applications. Emissions could also have resulted during production, transport, and disposal. Because use of DDT was banned in the United States after 1972, release of DDT in recent years should be negligible in this country.

Nevertheless, DDT residues in bogs or peat lands across the midlatitudes of North America indicate that DDT was still released, even after it was banned for use in the United States (Rapaport et al. 1985). These areas are unique in that they receive all of their pollutant input from the atmosphere, and therefore, peat cores are important indicators of the atmospheric deposition of a substance and also of its atmospheric levels in the present and the past. An analysis of peat cores, as well as rain and snow samples, indicated that DDT was still present in the atmosphere, although levels were lower compared to those in the 1960s. The implication is that DDT is still being released to the atmosphere either from its current production and use in other countries and transport to the United States or from the volatilization of residues resulting from previous use. The estimated release of DDT into the atmosphere from the Great Lakes in 1994, excluding Lake Huron, was 14.3 kg (Hoff et al. 1996). DDT, DDE, or DDD have been identified in air samples collected from 11 of the 397 NPL hazardous waste sites where it was detected in some environmental media (HazDat 1999).

***DRAFT FOR PUBLIC COMMENT***
Figure 5-1. Frequency of NPL Sites with DDT, DDE, and DDD Contamination
5.2.2 Water

Historically, DDT was released to surface water when it was used for vector control in the vicinity of open waters. This source of release may still be occurring in countries that rely on DDT in insect pest control near open waters. DDT also enters surface water as a result of dry and wet deposition from the atmosphere and direct gas transfer. Atmospheric DDT deposited into tributaries will contribute to the loading in rivers, lakes, and oceans. In 1994, the estimated loading of ΣDDT into the Great Lakes as a result of dry and wet deposition was estimated as 148 kg, down from 278 kg in 1988 (Hoff et al. 1996). Fluvial sources and erosion also contribute to the DDT burden, and they were the predominant source of DDT in many areas in the past. This was clearly shown in a United States Geological Survey (USGS) study of sediment in reservoirs and lakes in Georgia and Texas compared with DDT levels in nearby peat bogs (Van Metre et al. 1997).

Contaminated sediment near an outfall can act as a source of contamination in distant parts of a body of water. This was clearly illustrated in a Norwegian lake that received insecticidal wastes. Nineteen years after closing the outfall, DDT concentrations in pike and perch were 5–10 times those in uncontaminated lakes (Brevik et al. 1996). DDT was disposed to the Joint Water Pollution Control Plant, Los Angeles County by Montrose Chemical Company from about 1950 to 1970, and eventually to the Palos Verdes Shelf via sewer pipes. The distribution of DDT with respect to the outfall diffusers and the fact that the DDT concentration in the overlying water column exponentially decreased with increasing distance from the sea floor indicated that the main source of DDT in the water column was contaminated sediments (Zeng et al. 1999). Studies have shown that a variety of organisms live in sediments at the Palos Verde site to depths of at least 35 cm and disturb the reservoir of contaminants there (Stull et al. 1996). Sediment-bound DDT is being biodiffused up from the subsurface to upper sediments, where they undergo resuspension and redistribution.

DDT, DDE or DDD have been identified in surface water collected at 52 sites and groundwater collected at 107 of the 397 NPL hazardous waste sites where it was detected in some environmental media (HazDat 1999).

5.2.3 Soil

In the United States, large amounts of DDT were released to the soil during spraying operations or from direct or indirect releases during manufacturing, formulation, storage, or disposal. Since almost all of the
DDT produced was used to control insects damaging crops and trees or responsible for insect-transmitted diseases, we can assume that a large fraction of the DDT produced was released to soil during spraying operations. The largest amounts of DDT released to soil were those used in agriculture which amounted to 27 million pounds in 1966 and 14 million pounds in 1971, shortly before it was banned (Gianessi 1992). With the banning of DDT use in the United States, some stores of these products were placed in hazardous waste sites where they are potential sources of release to soil.

DDT, DDE, or DDD have been identified in soil samples collected from 248 sites and sediment samples at 122 of the 397 NPL hazardous waste sites where it was detected in some environmental media (HazDat 1999).

5.3 ENVIRONMENTAL FATE

A large proportion of the environmental fate studies on pesticides such as $p,p'$-DDT are performed in laboratory or field studies by agricultural chemists interested in the persistence of the active ingredient of the pesticide in the tilled layer of soil. Therefore, studies may not reveal whether the loss of active ingredient is a result of volatilization, leaching, or microbial degradation. Field studies may also report the occurrence of obvious metabolites remaining in surface soil months or years after a pesticide was applied. Clearly, it is not possible to separate these studies into ‘Transport and Partitioning’ (Section 5.3.1) and ‘Transformation and Degradation’ (Section 5.3.2). These studies are discussed in Section 5.3.2 with the understanding that ‘degradation’ may only account for part of the reported loss.

5.3.1 Transport and Partitioning

DDT and its metabolites may be transported from one medium to another by the processes of solubilization, adsorption, remobilization, bioaccumulation, and volatilization. In addition, DDT can be transported within a medium by currents, wind, and diffusion. These processes will be discussed in the following paragraphs.

Organic carbon partition coefficients ($K_{oc}$) of $1.5 \times 10^5$ (Swann et al. 1981), $5.0 \times 10^4$ (Sablejic 1984), and $1.5 \times 10^5$ (Meylan et al. 1992) reported for $p,p'$-DDT, $p,p'$-DDE, and $p,p'$-DDD, respectively, suggest that these compounds adsorb strongly to soil. These chemicals are only slightly soluble in water, with solubilities of 0.025, 0.12, and 0.090 mg/L for $p,p'$-DDT, $p,p'$-DDE, and $p,p'$-DDD, respectively (Howard and Meylan 1997). Therefore, loss of these compounds in runoff is primarily due to transport of...
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Particulate matter to which these compounds are bound. The amount of DDT transported into streams as runoff is dependent on the methods of irrigation used (USGS 1999). In the Western United States, DDT concentrations in streambed sediment increased as the percentage of furrow irrigation, as opposed to sprinkler or drip irrigation, increased. In the San Joaquin River Basin, more DDT was transported during winter runoff than during the irrigation season. Since the compounds are bound strongly to soil, DDT would remain in the surface layers of soil and not leach into groundwater. However, DDT can adsorb to free-moving dissolved organic carbon, a soluble humic material that may occur in the soil solution. This material behaves as a carrier and facilitates transport of DDT into subsurface soil (Ding and Wu 1997). DDT released into water adsorbs to particulate matter in the water column and sediment. Sediment is the sink for DDT released into water. There it is available for ingestion by organisms, such as bottom feeders. Reich et al. (1986) reported that DDT, DDE, and DDD were still bioavailable to aquatic biota in a northern Alabama river 14 years after 432,000–8,000,000 kg of DDT was discharged into the river. DDT in the water column above the outfall of Los Angeles County’s Joint Water Pollution Control Plant’s outfall was present both in the dissolved phase and the particulate phase (defined as particles size >0.7 µm) (Zeng et al. 1999). It is interesting to note that more of the DDT was present in the dissolved phase than in the particulate phase despite its high hydrophobicity.

There is evidence that DDT, as well as other molecules, undergoes an aging process in soil whereby the DDT is sequestered in the soil so as to decrease its bioavailability to microorganisms, extractability with solvents, and toxicity to some organisms (Alexander 1995, 1997; Peterson et al. 1971; Robertson and Alexander 1998). At the same time, analytical methods using vigorous extractions do not show significant decreases in the DDT concentration in soil. In one such study, DDT was added to sterile soil at various concentrations and allowed to age (Robertson and Alexander 1998). At intervals, the toxicity of the soil was tested using the house fly, fruit fly, and German cockroach. After 180 days, 84.7% of the insecticide remained in the soil, although more than half of the toxicity had disappeared when the fruit fly was the test species, and 90% had disappeared when the house fly was the test species. The effect with the German cockroach was not as marked. Recently, a study was conducted to determine the bioavailability of DDT, DDE, and DDD to earthworms (Morrison et al. 1999). It was shown that the concentrations of DDT, DDE, DDD, and ΣDDT were consistently lower in earthworms exposed to these compounds that had persisted in soil for 49 years than in earthworms exposed to soil containing freshly added insecticides at the same concentration. The uptake percentages of DDT and its metabolites by earthworms were in the range of 1.30–1.75% for the 49-year-aged soil, but were 4.00–15.2% for the fresh soil (Morrison et al. 1999). Long term monitoring data have also indicated that aged and sequestered DDT are not subject to significant volatilization, leaching, or degradation (Boul et al. 1994).
concentrations of DDT, DDE, and DDD monitored at two sites in a silt loam in New Zealand declined from 1960 to 1980, but very little loss was evident from 1980 to 1989 (Boul et al. 1994). The lack of appreciable biodegradation as DDT ages in soil suggests that the compound is not bioavailable to microorganisms. Aging is thought to be associated with the continuous diffusion of a chemical into micropores within soil particles where it is sequestered or trapped, and is therefore unavailable to microorganisms, plants, and animals (Alexander 1995). In the case of biodegradation, the aging process results in the gradual unavailability of substrate that makes the reaction kinetics appear to be nonlinear.

There is abundant evidence that DDT gets into the atmosphere as a result of emissions or volatilization. The process of volatilization from soil and water may be repeated many times and, consequently, DDT may be transported long distances in the atmosphere by what has been referred to as a ‘global distillation’ from warm source areas to cold polar regions. As a result, DDT and its metabolites are found in arctic air, sediment, and snow with substantial accumulations in animals, marine mammals, and humans residing in these regions (Harner 1997). An analysis of sediment cores from eight remote lakes in Canada indicated that $\Sigma$DDT concentrations in surface sediments (0–1.3 cm depth) declined significantly with latitude (Muir et al. 1995). The maximum $\Sigma$DDT concentrations in core slices in midcontinent lakes date from the late 1970s to 1980s, which is about 5–10 years later than the maximum for Lake Ontario.

Volatilization of DDT, DDE, and DDD is known to account for considerable losses of these compounds from soil surfaces and water. Their tendency to volatilize from water can be predicted by their respective Henry's law constants, which for the respective $p,p'$- and $o,p'$- isomers are $8.3 \times 10^{-6}$, $2.1 \times 10^{-5}$, $4.0 \times 10^{-6}$, $5.9 \times 10^{-7}$, $1.8 \times 10^{-5}$, and $8.2 \times 10^{-6}$ atm-m$^3$/mol (Howard and Meylan 1997). The predicted volatilization half-lives from a model river 1 m deep, flowing at 1 m/sec, with a wind of 3 m/sec are 8.2, 3.3, 10.5, 6.3, 3.7, and 8.2 days, respectively. Laboratory studies of the air/water partition coefficient of DDE indicate that it will volatilize from seawater 10–20 times faster than from freshwater (Atlas et al. 1982). The authors suggest that this process may be related to interaction at the bubble-water surface.

Volatilization from moist soil surfaces can be estimated from the Henry’s law constant divided by the adsorptivity to soil (Dow Method) (Thomas 1990). The predicted half-life for DDT volatilizing from soil with a $K_{oc}$ of 240,000 is 23 days, compared to an experimental half-life of 42 days. Sleicher and Hopcraft (1984) estimated a volatilization half-life of 110 days for DDT from soil in Kenya based on mass transfer through the boundary layers, and claimed that volatilization of DDT was sufficient to account for its rapid disappearance from soil. However, laboratory experiments in which $^{14}$C-$p,p'$-DDT was incubated in an acidic (pH 4.5–4.8), sandy loam soil maintained at 45 EC for 6 hours/day for 6 weeks resulted in neither
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Volatilization of DDT or its metabolites nor mineralization (Andrea et al. 1994). Other studies using a latosol soil (pH 5.7) found that 5.9% of the radioactivity was lost through volatilization during a 6 week incubation at 45°C (Sjoeib et al. 1994). The volatilization rate of DDT from soil is significantly enhanced by temperature, sunlight, and flooding of the soil (Samuel and Pillai 1990).

Transport of DDT in the atmosphere of central and eastern North America is facilitated by a circulation pattern that brings moisture from the Gulf of Mexico into the Midwest and the airflow patterns across the eastern seaboard (Rapaport et al. 1985). DDT is removed from the atmosphere by wet and dry deposition and diffusion into bodies of water. The largest amount of DDT is believed to be removed from the atmosphere in precipitation (Woodwell et al. 1971).

DDT, DDE, and DDD are highly lipid soluble, as reflected by their log octanol-water partition coefficients (log $K_{ow}$) of 6.91, 6.51, and 6.02, respectively for the $p,p'$-isomers and 6.79, 6.00, and 5.87, respectively for the $o,p'$-isomers (Howard and Meylan 1997). This lipophilic property, combined with an extremely long half-life is responsible for its high bioconcentration in aquatic organisms (i.e., levels in organisms exceed those levels occurring in the surrounding water). Organisms also feed on other animals at lower trophic levels. The result is a progressive biomagnification of DDT in organisms at the top of the food chain. (Biomagnification is the cumulative increase in the concentration of a persistent contaminant in successively higher trophic levels of the food chain (i.e., from algae to zooplankton to fish to birds). Ford and Hill (1991) reported increased biomagnification of DDT, DDE, and DDD from soil sediment to mosquito fish, a secondary consumer. No distinct pattern of biomagnification was evident in other secondary consumers such as carp and small mouth buffalo fish. The biomagnification of DDT is exemplified by the increase in DDT concentration in organisms representing four trophic levels sampled from a Long Island estuary. The concentrations in plankton, invertebrates, fish, and fish-eating birds were 0.04, 0.3, 4.1, and 24 mg/kg, whole body basis (Leblanc 1995). Evans et al. (1991) reported that DDE biomagnified 28.7 times in average concentrations from plankton to fish and 21 times from sediment to amphipods in Lake Michigan. In some cases, humans may be the ultimate consumer of these contaminated organisms.

The bioconcentration factor (BCF) is defined as the ratio of the equilibrium concentration of contaminant in tissue compared to the concentration in ambient water, soil, or sediment to which the organism is exposed. There are numerous measurements and estimates of BCF values for DDT in fish. Oliver and Niimi (1985) estimated the steady-state BCF in rainbow trout as 12,000. Other BCF values that have been reported include 51,000–100,000 in fish, 4,550–690,000 in mussels, and 36,000 in snails (Davies...
DDT bioconcentration studies in aquatic environments with representatives of various trophic levels demonstrate that bioconcentration increases with increasing trophic level (LeBlanc 1995). Trophic level differences in bioconcentration are largely due to increased lipid content and decreased elimination efficiency among higher level organisms. However, biomagnification also contributes to the increased concentration of DDT in higher trophic organisms (LeBlanc 1995).

The BCF values of $p,p'$-DDT in brine shrimp (Artemia nauplii) exposed to a mixture containing 0.5 or 1.0 ng/mL of four DDT analogs for 24 hours were significantly higher than for the three other chemicals. The BCF values were 41, 54, 128 and 248, for $p,p'$-DDE, $p,p'$-DDD, $o,o'$-DDT, and $p,p'$-DDT, respectively (Wang and Simpson 1996). The differences in BCF values are due to the different lipid solubility and selectivity of the compounds partitioned in the zooplanktonic organisms. $p,p'$-DDT, which has the greatest polarity of the 4 tested analogs, may have been adsorbed to a greater extent to the surface of the shrimp. In addition to absorbing DDT directly from the water, fish obtain DDT from their diet (Miller 1994; Wang and Simpson 1996). Wang and Simpson (1996) fed brook trout contaminated A. nauplii for 24 days followed by depuration for another 24 days during which the trout were fed uncontaminated A. nauplii. Although the concentration of $p,p'$-DDE was the lowest of the 4 analogs in the contaminated brine shrimp, the concentration of this compound in the trout at day 24 was 42.5 ng/g which was roughly 5 times more than the other analogs. The levels of the $p,p'$-isomers initially ranged from 1.0 to 2.7 ng/g, while $o,o'$-DDT was absent. The abnormal accumulation of $p,p'$-DDE in the fish suggests that mixed-function oxidases may have induced the dechlorination of $p,p'$-DDT to $p,p'$-DDE. This may account for the fact that about 70% of ΣDDT in fish is $p,p'$-DDE (Schmitt et al. 1990). After the fish were fed uncontaminated food, $p,p'$-DDE had the lowest percentage depuration. After feeding the trout for 24 days with the more highly contaminated brine shrimp, 14, 62, 17, and 32% depuration were observed for $p,p'$-DDE, $p,p'$-DDD, $o,o'$-DDT, and $p,p'$-DDT, respectively.

Fish move from the Great Lakes or other bodies of water with elevated DDT levels to rivers that feed into these lakes. In doing so, they transport DDT, which may represent a risk to wildlife along the tributaries (Giesy et al. 1994).

Despite being strongly bound to soil, at least a portion of DDT, DDE, and DDD is bioavailable to plants and soil invertebrates. Nash and Beall (1970) studied the DDT residues in soybean plants resulting from the application of $[14C]$DDT to the surface or subsurface soil. They found that the major source of DDT contamination was due to sorption of volatilized residues from surface-treated soil. This was 6.8 times...
greater than that obtained through root uptake and translocation after subsurface treatment. In other experiments with oats and peas, root uptake of DDT was low and there was little or no evidence of translocation of the insecticide (Fuhremann and Lichtenstein 1980; Lichtenstein and Schultz 1980). Verma and Pillai (1991a) reported that grain, maize, and rice plants accumulate DDT adsorbed to soil. Most of the residues were found in the roots of the plant, and the lowest concentration of DDT residues was found in the shoots, indicating low translocation of DDT. Earthworms are capable of aiding the mobilization of soil-bound DDT residues to readily bioavailable forms (Verma and Pillai 1991b). DDT may collect on the leafy part of plants from the deposition of DDT-containing dust.

5.3.2 Transformation and Degradation

5.3.2.1 Air

In the atmosphere, about 50% of DDT is adsorbed to particulate matter and 50% exists in the vapor phase (Bidleman 1988). In the vapor phase, DDT reacts with photochemically produced hydroxyl radicals with an estimated rate constant of 3.44x10^-12 cm^3/molecule-sec determined from a fragment constant estimation method (Meylan and Howard 1993). Assuming an average hydroxyl radical concentration of 1.5x10^6 per cm^3, its half-life will be 37 hours. Both DDE and DDD have higher vapor pressures than DDT, and a smaller fraction of these compounds will be adsorbed to particulate matter. The estimated half-lives of vapor-phase DDE and DDD are 17 and 30 hours, respectively. Direct photolysis may also occur in the atmosphere. DDT, DDE, and DDD adsorbed on particulate matter are not expected to undergo photooxidation rapidly, and therefore, may be subject to long-range transport. When atmospheric sampling of pesticides was performed at nine localities in the United States during a time of high DDT usage, DDT was mostly present in the particulate phase (Stanley et al. 1971).

5.3.2.2 Water

DDT, DDE, and DDD present in water may be transformed by both photodegradation and biodegradation. Since the shorter wave radiation does not penetrate far into a body of water, photolysis primarily occurs in surface water and is dependent on the clarity of the water. Direct photolysis of DDT and DDD are very slow in aquatic systems, with estimated half-lives of more than 150 years (EPA 1979c). Direct photolysis of DDE results in a half-life of about 1 day in summer and 6 days in winter. DDE also undergoes photoisomerization when exposed to sunlight. Photolysis of DDE photoisomers is slower by at least one order of magnitude compared to DDE. Indirect photolysis of DDT appears to be
rapid in some natural waters. In one study, 50% of DDT was lost in San Francisco Bay water after 7 days of exposure to sunlight. No DDE or DDD photoproducts were found, although DDE would be expected to be produced based on photolysis studies with the DDT analog, methoxychlor, in several freshwaters. This may reflect different mechanisms in natural waters containing different photosensitizers. Studies with DDT at shorter wavelengths suggest that the initial reaction results in the dissociation of the Cl₂C–Cl bond. No information on the indirect photolysis of DDE or DDD was located (Coulston 1985; EPA 1979c; Zepp et al. 1977).

Photoinduced 1,2 addition of DDT to a model lipid, methyl oleate, indicates that light-induced additions of DDT to unsaturated fatty acids of plant waxes and cutins may occur on a large scale (Schwack 1988).

DDT undergoes hydrolysis by a base-catalyzed reaction resulting in a half-life of 81 days at pH 9. The product formed in the hydrolysis is DDE. Hydrolysis of DDE and DDD is not a significant fate process (EPA 1979c).

Biodegradation of DDT in water is reported to be a minor mechanism of transformation (Johnsen 1976). Biodegradation of DDE and DDD in the aquatic environment is slower than that of DDT (EPA 1979c).

### 5.3.2.3 Sediment and Soil

Four mechanisms have been suggested to account for most losses of DDT residues from soils: volatilization, removal by harvest (e.g., plants that have absorbed the residue), water runoff, and chemical transformation (Fishbein 1973). Three of these are transport processes, and the fourth, chemical transformation, may occur by abiotic and biotic processes. Photooxidation of DDT and DDE is known to occur on soil surfaces or when adsorbed to sediment (Baker and Applegate 1970; Lichtenstein and Schultz 1959; Miller and Zepp 1979). The conversion of DDT to DDE in soil was enhanced by exposure to sunlight in a 90-day experiment with 91% of the initial concentration of DDT remaining in the soil for an unexposed dark control and 65% remaining for the sample exposed to light (Racke et al. 1997).

However, UV-irradiation of \(^{14}\text{C-}p,p'\)-DDT on soil for 10 hours mineralized less than 0.1% of the initial amount (Vollner and Klotz 1994). (Mineralization is the complete degradation of a chemical, generally to carbon dioxide and water for an organic chemical containing carbon, hydrogen, and oxygen.) The amount of DDT that may have been converted to DDE was not reported. Biodegradation may occur under both aerobic and anaerobic conditions due to soil microorganisms including bacteria, fungi, and algae (Arisoy 1998; EPA 1979c; Lichtenstein and Schulz 1959; Menzie 1980; Stewart and Chisholm...
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1971; Verma and Pillai 1991b). Since biodegradation studies generally focus on the loss of the parent compound rather than complete degradation or mineralization, and since DDT initially biodegrades to DDD or DDE, there still may be dangerous compounds after almost all of the DDT that was originally present has biodegraded.

During biodegradation of DDT both DDE and DDD are formed in soils. Both metabolites may undergo further transformation but the extent and rate are dependent on soil conditions and, possibly, microbial populations present in soil. The degradation pathways of DDT under aerobic and anaerobic conditions have been reviewed by Zook and Feng (1999) and Aislabie et al. (1997). Ligninolytic or lignin-degrading fungi have been shown to possess the biodegradative capabilities for metabolizing a large variety of persistent compounds, including DDT. Mineralization of DDT was even observed in laboratory experiments using a member of this group of fungi, Phanerochaete chrysosporum (a white rot fungus) (Aislabie et al. 1997). Biodegradation of DDT and its metabolites involves cometabolism, a process in which the microbes derive nutrients for growth and energy from sources other than the compound of concern. DDE, the dominant DDT metabolite found, is often resistant to biodegradation under aerobic and anaerobic conditions (Strompl and Thiele 1997). Recent laboratory experiments in marine sediment showed that DDE is dechlorinated to DDMU (1-chloro-2,2-bis(p-chlorophenyl)ethylene) under methanogenic or sulfidogenic conditions (Quensen et al. 1998). DDD is also converted to DDMU, but at a much slower rate. DDMU degrades further under anaerobic conditions. No evidence was found that methylsulfonyl metabolites of DDT are formed as a result of microbial metabolism. The rate at which DDT is converted to DDD in flooded soils is dependent on the organic content of the soil (Racke et al. 1997). In a laboratory study, Hitch and Day (1992) found that soils with a low metal content degrade DDT to DDE much more slowly than do soils with high metal content.

As mentioned earlier, the half-life represents the estimated time for the initial disappearance of 50% of the compound in question and does not necessarily imply that first-order kinetics were observed throughout the experiment unless otherwise noted. In the case of DDT, the disappearance rate slows considerably so that after the initial concentration is reduced by half, the time required for the loss of half of that which remains is substantially longer. This is largely because much of the initial loss of compound is due to volatilization, rather than biodegradation. However, the biodegradation rate also slows in time as discussed in Section 5.3.1. This is because DDT migrates into micropores in soil particles where it becomes sequestered and unavailable to soil microorganisms (Alexander 1995, 1997). In addition, the disappearance of DDT is often reported as the disappearance of ΣDDT residues, and therefore, the reported rate of loss is a summation of the component DDT-related chemicals. DDT breaks
down into DDE and DDD in soil, and the parent-to-metabolite ratio (DDT to DDE or DDD) decreases in time. However, this ratio may vary considerably with soil type. In a 1995–1996 study of agricultural soils in the corn belt of the central United States, the ratio of \(p,p'\)-DDT/\(p,p'\)-DDE varied from 0.5 to 6.6 with three-quarters of the soils having ratios above 1 (Aigner et al. 1998). In a study of forest soils in Maine, the half-life for the disappearance of DDT residues was noted to be 20–30 years. DDT was much more persistent in muck soils than in dry forest soils. A study of DDT in agricultural soils in British Colombia, Canada reported that over a 19-year period, there was a 70% reduction of DDT in muck soils and a virtual disappearance of DDT from loamy sand soils (Aigner et al. 1998).

Land management practices also affect the persistence of DDT. In 1971, an experiment was conducted in a field containing high amounts of DDT to evaluate the effect of various management tools in the disappearance of the insecticide (Spencer et al. 1996). The site was revisited in 1994 to determine the residual concentrations of DDT and its metabolites and to measure volatilization fluxes. Concentrations of DDT were reduced in all plots and the major residue was \(p,p'\)-DDE. The highest concentrations of residues were found in deep plowed and unflooded plots. Deep plowing places the DDT deeper into the soil profile, possibly reducing volatilization. As was noted in Section 5.3.1, the volatilization rate of DDT is enhanced by flooding the soil (Samuel and Pillai 1990). Under flooded, reducing conditions, DDD was a more common degradation product of DDT than DDE. Significant concentrations of both \(o,p'\)- and \(p,p'\)-DDE and \(p,p'\)-DDT were detected in the atmosphere over the plots. Irrigating the soil dramatically increased the volatilization flux of all DDT analogs, especially \(p,p'\)-DDE. This is probably related to the amount of DDT in the soil solution. Volatilization, air transport, and redeposition were found to be the main avenues of contaminating forage eaten by cows. In microcosm experiments, Boul (1996) found that increasing soil water content enhanced DDT loss from generally aerobic soil. His results suggested that increased biodegradation contributed to these effects. Boule et al. (1994) analyzed DDT residues in pasture soil as they were affected by long-term irrigation and superphosphate fertilizer application. They found that \(\Sigma\)DDT residues in irrigated soil were about 40% that of unirrigated soil. The predominant residue was \(p,p'\)-DDE, and these residues were much higher in unirrigated than in irrigated soil. \(p,p'\)-DDE is lost at a lower rate than \(p,p'\)-DDT. \(p,p'\)-DDD residues were very low in both irrigated and unirrigated soil indicating that loss of \(p,p'\)-DDD must occur at a rate at least as great as it is generated from \(p,p'\)-DDT. Superphosphate treatment, which is known to increase microbial biomass, also resulted in lower levels of \(p,p'\)-DDT and \(\Sigma\)DDT than in unfertilized controls. The distribution of \(\Sigma\)DDT with depth suggests that irrigation did not cause increased leaching of the insecticide.
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A set of experiments was conducted during 1982–1987 and 1989–1993 in 14 countries under the auspices of the International Atomic Energy Agency (IAEA) on the dissipation of $^{14}$C-DDT from soil under field conditions in tropical and subtropical areas (Racke et al. 1997). After 12 months, the quantity of DDT and metabolites remaining in soil at tropical sites ranged from 5% of applied in Tanzania to 15% in Indonesia. The half-life of $\Sigma$DDT ranged from 22 days in Sudan to 365 days in China. One exception was in an extremely acidic soil (pH 4.5) in Brazil in which the half-life was $>672$ days. The conclusion of the study was that DDT dissipated much more rapidly under tropical conditions than under temperate conditions. The major mechanisms of dissipation under tropical conditions were volatilization, biological and chemical degradation, and to a lesser extent, adsorption. Comparable half-lives in temperate regions that have been reported range from 837 to 6,087 days (Lichtenstein and Schulz 1959; Racke et al. 1997; Stewart and Chisholm 1971). One investigator concluded that the mean lifetime of DDT in temperate U.S. soils was about 5.3 years (Racke et al. 1997). The primary metabolite detected in tropical soil was DDE. With the exception of highly acidic soil from Brazil, the half-lives for DDE ranged from 151 to 271 days, much less than the $>20$ years reported for DDE in temperate areas. The increased dissipation of DDT in the tropics compared with that in temperate zones is believed to be largely due to increased volatility under tropical conditions (Racke et al. 1997).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

DDT is transported long distances from source areas to the Arctic and Antarctic. Mean $\Sigma$DDT levels in air over a period of 17 weeks at Signy Island, Antarctica in 1992 and over the ocean separating New Zealand and Ross Island, Antarctica between January and March, 1990 were 0.07–0.40 and 0.81 pg/m$^3$, respectively (Bidleman et al. 1993; Kallenborn et al. 1998). The concentration declined with increasing latitudes.

Ten samples taken over the Gulf of Mexico in 1977 contained an average of 34 pg/m$^3$ of DDT, with a range of 10–78 pg/m$^3$ (Bidleman et al. 1981). Iwata et al. (1993) collected and analyzed 71 samples of air over several oceans (18 sampling locations) from April 1989 to August 1990. The range of mean and maximum concentrations of DDTs were (substance, range of means, maximum concentration): $p,p'$-DDE, 0.3–180 pg/m$^3$, 180 pg/m$^3$; $o,p'$-DDT, 0.3–180 pg/m$^3$, 420 pg/m$^3$; $p,p'$-DDT, 1.2–220 pg/m$^3$, 590 pg/m$^3$; and $\Sigma$DDT, 2.4–580 pg/m$^3$, 1,000 pg/m$^3$. The highest concentrations of DDT were found at locations near areas where DDT is still used, such as the Arabian Sea off the west coast of India. Other locations
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with high air concentrations of DDT were the Strait of Malacca, South China Sea, and the Gulf of Mexico. \( p,p'\)-DDT concentrations obtained from monthly air samples collected from Saginaw Bay, Sault Ste. Marie, and Traverse City, Michigan between November 1990 and October 1991 were below the detection limit during most of the winter months at Saginaw and Traverse City, and were above the detection limit at Sault Ste. Marie only in March, May, July, and August (Monosmith and Hermanson 1996). The highest monthly \( p,p'\)-DDT concentrations were 35 pg/m\(^3\) in Saginaw (August), 31 pg/m\(^3\) in Sault Ste. Marie (May), and 21 pg/m\(^3\) in Traverse City (July). The corresponding highs for \( p,p'\)-DDE were 63 pg/m\(^3\) (August), 119 pg/m\(^3\) (May), and 92 pg/m\(^3\) (July). An analysis of the results suggests that higher DDT and DDE levels correlated with air mass movement from the south, perhaps from areas where DDT is still used (i.e., Central America or Mexico). The fact that the ratio of DDT to DDE was <1 in each instance suggests that there is no new DDT use in Michigan. DDT and DDE levels over Green Bay, Wisconsin in 1989 were 8.7 and 15 pg/m\(^3\), and those over the four lower Great Lakes obtained during a cruise were 38 and 59 pg/m\(^3\) (McConnell et al. 1998). An analysis of air masses indicated that the atmospheric sources were not long-range transport, but rather local or regional volatilization.

Stanley et al. (1971) measured atmospheric levels of pesticides in the United States during a time of high DDT usage. Nine localities were sampled representing both urban and agricultural areas. Of 12 pesticides evaluated, only DDT was detected at all localities. Maximum levels of \( p,p'\)-DDT ranged from 2.7 ng/m\(^3\) in Iowa City, Iowa to 1,560 ng/m\(^3\) in Orlando Florida. Maximum levels of \( o,p'\)-DDT and \( p,p'\)-DDE ranged from 2.4 to 131 ng/m\(^3\). The highest levels were found in the agricultural areas of the South. The pesticides were predominantly detected in the particulate phase. Some agricultural areas in which DDT was extensively used have been monitored periodically since usage was halted. Atmospheric conditions in the Mississippi Delta were monitored intermittently from 1972 to 1975 (Arthur et al. 1977). Air samples taken in 1975 from an area with extensive cotton acreage had a mean \( \Sigma \)DDT concentration of 7.5 ng/m\(^3\), compared to 11.9 ng/m\(^3\) in 1974. This represents a 36% decline in \( \Sigma \)DDT levels in 1 year. Between 1972 and 1974, the first 2 years after the use of DDT was banned, the atmospheric \( \Sigma \)DDT levels had declined by 88%. In 3 years, the decrease in \( \Sigma \)DDT air levels was 92%, representing a much more rapid decline than had been expected.

\( p,p'\)-DDT, \( p,p'\)-DDE, and \( p,p'\)-DDD have all been detected in the dissolved and particulate phases of fogwater and air and in rainwater (Millet et al. 1997). Fogwater samples were 1.5 to 30 times higher than rainwater samples, and the distribution between dissolved and particulate phase appeared to be governed by the solubility of the chemical. The site of the measurements was a rural area in France between 1991 and 1993. DDT had not been used in the area since the 1970s. Ligocki et al. (1985) conducted
concurrent rain and air sampling for rain events in Portland, Oregon, in 1984. In rain samples, no p,p'-DDT, p,p'-DDE, or p,p'-DDD were detected. However, in the gas phase associated with this rainfall, p,p'-DDE was detected in five of seven samples. Levels detected in the samples ranged from nondetected to 420 pg/m³. More recently, Poissant et al. (1997) reported the mean concentration of p,p'-DDT in precipitation over a rural site near the St. Lawrence river was 500 pg/L with a 75% frequency of detection. Rapaport et al. (1985) measured DDT residues in rain and snow samples in Minnesota. Samples of snow taken in 1981–1982, 1982–1983, and 1983–1984 contained an average of 0.32, 0.60, and 0.18 ng/L of p,p'-DDT, respectively. Two rain samples taken in 1983 contained 0.2 and 0.3 ng/L of p,p'-DDT.

5.4.2 Water

Although there are numerous reports in the literature of DDT levels in specific bodies of water throughout the United States, there is little information providing evidence of trends in the DDT levels over time. EPA operates STORET (STOrage and RETrieval), a computerized water quality database. Staples et al. (1985) reported limited data on priority pollutants from STORET. Information from data collected from 1980 to 1983 indicated that 3,500–5,700 ambient water samples were analyzed for DDT, DDE, and DDD with approximately 45% of the samples containing one of these compounds. The median level reported for both DDT and DDE was 0.001 µg/L, while the median level reported for DDD was 0 µg/L. Approximately 50 samples of industrial effluents were sampled and showed median levels of 0.010 µg/L for all three compounds. DDT was monitored in surface water and sediment as part of the National Surface Water Monitoring Program in 1976–1980. The percent occurrence and maximum concentrations of the reported DDT-related compounds in surface water were: p,p'-DDT, 0.5%, 0.70 µg/L (ppb); o,p'-DDT, 0.1%, 0.42 µg/L; p,p'-DDE, 0.7%, 0.55 µg/L; and o,p'-DDE, 0.3%, 0.54 µg/L (Carey and Kutz 1985). The USGS and EPA cooperatively monitored levels of pesticides in water and sediment at Pesticide Monitoring Network stations between 1975 and 1980 (Gilliom 1984). Of the 177 stations (approximately 2,700 samples) monitored, 2.8%, 0.6%, and 4.0% contained detectible levels of DDT, DDE, and DDD in water, respectively. Fewer than 0.4% of the samples contained detectable DDT-related residues. The levels detected in water were not reported, but the limit of detection was 0.05 µg/L for DDT and DDD, and 0.3 µg/L for DDE. The percentage of sites having detectable levels of DDT-related residues in sediment was much higher (see Section 5.4.3).

Johnson et al. (1988b) reported DDT and metabolite levels in the Yakima River basin in Washington State. Use of DDT was halted in this area when the 1972 ban was initiated; however, considerable
residues are present in the river and sediments. Whole unfiltered water samples, collected mainly from
the tributaries between May and October 1985, were reported to contain between nondetectable to
0.06 µg/L of DDT-related compounds. Concentrations of \( p,p' \)-DDT in water equaled or exceeded those
of \( p,p' \)-DDE: an unexpected finding in light of what is believed concerning biological half-lives of DDT
and its normal environmental degradation. The authors indicated that these findings suggest an unusually
long half-life for DDT in Yakima basin soils that were getting into the river in runoff.

A summary of pesticide levels in surface waters of the United States during 1967 and 1968 was reported
by Lichtenberg et al. (1970). During these 2 years (which were prior to the ban of DDT use), a total of
224 samples (unfiltered) were analyzed from various sites in all regions of the country. DDT was found
in 27 samples at levels ranging from 0.005 to 0.316 µg/L; DDE was found in 3 samples at levels of
0.02–0.05 µg/L; and DDD was found in 6 samples at levels of 0.015–0.840 µg/L.

According to the U.S. Geological Survey’s National Water Quality Assessment Plan initiated in 1991,
that focuses on the water quality in more than 50 major river basins and aquifer systems, the frequency of
detection of DDT and its metabolites in streams and groundwater was very low (USGS 1999). The top 15
pesticides found in water were those with high current use.

Only a few studies report levels of DDT in drinking water. Drinking water in Oahu, Hawaii, was found
to contain \( p,p' \)-DDT at an average level of 0.001 µg/L in 1971 (Bevenue et al. 1972). Keith et al. (1979)
reported that DDE was found in 2-month equivalent (the amount of water a person would theoretically
consume over a 2 month period) samples collected over 2 days from two of three drinking water plants in
New Orleans in 1974; the DDE concentration was 0.05 µg/L in both samples.

Iwata et al. (1993) collected and analyzed 68 samples of surface water from several oceans (18 sampling
locations) mainly affected by atmospheric deposition from April 1989 to August 1990. The range of
mean and maximum concentrations of DDTs were (substance, range of means, maximum concentration):
\( p,p' \)-DDE, 0.2–3.0 pg/L, 7.9 pg/L; \( o,p' \)-DDT, <0.1–5.8 pg/L, 14 pg/L; \( p,p' \)-DDT, 0.1–7.5 pg/L, 19 pg/L;
and \( \Sigma \)DDT, 0.3–16 pg/L, 41 pg/L. The highest concentrations of DDT-related compounds were in the
East China Sea. Other seas with high concentrations of DDT were the Bay of Bengal, Arabian Sea, and
South China Sea.

Canter and Sabatini (1994) reviewed Records of Decision at 450 Superfund Sites and found 49 cases in
which contaminated groundwater threatened local public water supply wells. However, chlorinated
organic pesticides were not found to be a major class of contaminants in these cases. In only one of the six sites in which the findings were presented in any detail was a DDT analog found at detectable levels. *p,p’*-DDD was found in monitoring wells from the upper aquifer at Pristine, Inc., an industrial site in Reading, Ohio at 0–0.14 µg/L but not in the lower aquifer or in water supply samples that were taken from the lower aquifer. No *p,p’*-DDT, or *p,p’*-DDE was detected in groundwater samples. Surface water samples contained levels of *p,p’*-DDE, *p,p’*-DDD, and *p,p’*-DDE at ranges of 0–0.86, 0–0.78, and 0–1.82 µg/L, respectively.

### 5.4.3 Sediment and Soil

Gilliom (1984) presented results of pesticide monitoring in sediment at USGS/EPA Pesticide Monitoring Network stations between 1975 and 1980. Of the 171 stations (approximately 900 samples) monitored, 26, 42, and 31 contained detectible levels of DDT, DDE, and DDD, respectively. Fewer than 17% of the samples contained detectable DDT-related residues (limit of detection was 0.5 µg/kg for DDT and DDD, and 3 µg/kg for DDE). The percentage of sites with detectable levels of DDT-related residues in sediment was much higher than in water, reflecting the preferential partitioning of DDT to sediment (see Section 5.4.2). From 1980 to 1983, approximately 1,100 samples of sediments in EPA’s STORET database were analyzed for DDT, DDE, and DDD (Staples et al. 1985). The median levels for DDT, DDE, and DDD were 0.1, 0.1, and 0.2 µg/kg dry weight, respectively. In order to investigate circumstances contributing to the high level of DDT in fish and wildlife, soil and sediment samples (n=28) were collected in 1987 from the Upper Steele Bayou Watershed in west-central Mississippi at two depths (2.54–7.62 cm and 25.40–30.48) (Ford and Hill 1991). The results are given below:

<table>
<thead>
<tr>
<th>Compound</th>
<th>Depth (cm)</th>
<th>Occurrence</th>
<th>Concentration (µg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean</td>
</tr>
<tr>
<td><em>p,p’</em>-DDD</td>
<td>2.54–7.62</td>
<td>86%</td>
<td>40</td>
</tr>
<tr>
<td><em>p,p’</em>-DDD</td>
<td>25.40–30.48</td>
<td>64%</td>
<td>20</td>
</tr>
<tr>
<td><em>p,p’</em>-DDE</td>
<td>2.54–7.62</td>
<td>93%</td>
<td>100</td>
</tr>
<tr>
<td><em>p,p’</em>-DDE</td>
<td>25.40–30.48</td>
<td>79%</td>
<td>40</td>
</tr>
<tr>
<td><em>p,p’</em>-DDT</td>
<td>2.54–7.62</td>
<td>79%</td>
<td>30</td>
</tr>
<tr>
<td><em>p,p’</em>-DDT</td>
<td>25.40–30.48</td>
<td>64%</td>
<td>20</td>
</tr>
</tbody>
</table>

ND = not detected
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River bed sediment samples collected in 1985 from the Yakima River basin in Washington contained 0.1–234 µg/kg (dry weight) of ΣDDT and its metabolites (Johnson et al. 1988b). Use of DDT was halted in this area in 1972 when the ban was initiated.

The concentrations of DDE, DDD, DDT, and ΣDDT in bed sediment from the San Joaquin River and its tributaries in California (7 sites) in 1992 were 1.4–115, 0.7–14, 0.4–39, and 2.2–170 ng/L, respectively (Pereira et al. 1996). One of the seven sites, Orestimba Creek, had DDT levels far higher than the other sites. Land use along this creek was dominated by orchards and a variety of row crops.

Total DDT in surface sediment collected in eight remote lakes in Canada along a midcontinental transect from 49°N to 82°N declined significantly with latitude from 9.7 µg/kg (dry weight) to 0.10 µg/kg (Muir et al. 1995). The pattern of DDT deposition in lake sediment in the continental United States is exemplified by that in White Rock Lake in Dallas. Total DDT concentrations in the lake sediment increased from the mid-1940s to a maximum of 27 µg/kg in about 1965 when DDT usage peaked in the United States and have decreased by 93% to 2 µg/kg in the most recent samples collected in 1994 (Van Metre and Callender 1997; Van Metre et al. 1997). On the average, DDE accounted for 58% of the total DDT in the lake. DDD levels were about half those of DDE. The mean concentration of ΣDDT in sediment in the Newark Bay Estuary, New Jersey collected between February 1990 and March 1993 ranged from about 100 to 300 µg/kg except for the Arthur Kill, where the mean concentrations exceeded 700 µg/kg (Gillis et al. 1995). These levels may pose a potential threat to aquatic organisms. The maximum concentrations of p,p'-DDT, p,p'-DDE, and p,p'-DDT in sediment from 168 sites sampled along the southeastern coast of the United States as part of the Environmental Monitoring and Trends Program (EMAP) in 1994–1995 were 150.9, 34.2, and 35.0 µg/kg, respectively (Hyland et al. 1998). The median concentrations of these compounds were below the detection limit. DDT was monitored in surface water and sediment as part of the National Surface Water Monitoring Program in 1976–1980. The percent occurrence and maximum concentrations of the reported DDT analogs in sediments were: p,p'-DDT, 13.2%, 110.6 µg/kg; o,p'-DDT, 2.9%, 7.2 µg/kg; p,p'-DDE, 22.7%, 163.0 µg/kg; and o,p'-DDE, 0.5%, 1.3 µg/kg (Carey and Kutz 1985). Results were not presented for DDD. In 1983–1984, quarterly samples of bottom sediment were taken from six sites on tributaries of the Tennessee River near Huntsville, Alabama, and were analyzed for ΣDDT (Webber et al. 1989). From 1947 to 1970, DDT was manufactured along the tributary, and DDT-contaminated waste water was discharged into the river. The concentration of ΣDDT in sediment above the discharge point averaged less than 1 mg/kg dry weight. Remaining stations showed a decreasing gradient of ΣDDT with annual means ranging from 2,730 µg/kg
at the closed site to the point of discharge to 12 mg/kg where the tributary empties into the Tennessee River 18 km away.

According to the U.S. Geological Survey’s National Water Quality Assessment Plan initiated in 1991, which focuses on the water quality in more than 50 major river basins and aquifer systems, the frequency of detection of DDT and its metabolites in bed sediment in the 1990s remains high (USGS 1999). The metabolite with the highest frequency of detection was \( p,p' \)-DDE which was approximately 60% in urban areas, 48% in agricultural areas, and 46% in mixed land use areas followed by \( p,p' \)-DDD, \( p,p' \)-DDT, \( o,o' \)-DDD, \( o,o' \)-DDT, and \( o,p' \)-DDE. The frequency of detection of \( o,p' \)-DDT and \( o,p' \)-DDE was below 5%.

The U.S. National Soils Monitoring Program has provided valuable information on the overall pattern of DDT residues in soil during the years following the DDT ban. Each year since the ban of DDT, approximately 1,500 samples were taken. The results for 1970 are tabulated below (Crockett et al. 1974):

<table>
<thead>
<tr>
<th>Substance</th>
<th>Occurrence</th>
<th>Concentration (( \text{mg/kg} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( p,p' )-DDT</td>
<td>20%</td>
<td>Mean: 180, Range: 10–69,300</td>
</tr>
<tr>
<td>( o,o' )-DDT</td>
<td>14%</td>
<td>Mean: 40, Range: 10–11,700</td>
</tr>
<tr>
<td>( p,p' )-DDE</td>
<td>31%</td>
<td>Mean: 50, Range: 10–6,820</td>
</tr>
<tr>
<td>( o,p' )-DDE</td>
<td>3%</td>
<td>Mean: &lt;10, Range: ND–510</td>
</tr>
<tr>
<td>( \Sigma )DDT</td>
<td>23%</td>
<td>Mean: 300, Range: 10–113,090</td>
</tr>
</tbody>
</table>

ND = not detectable

The mean \( \Sigma \)DDT level in five U.S. cities ranged from 120 to 560 \( \mu \text{g/kg} \) in 1971 (Carey et al. 1979a). Urban areas generally had higher pesticide levels than did nearby agricultural areas except in some southern cities near which the agricultural use of pesticides was traditionally heavy.

DDT was heavily used in the corn belt in the mid-central United States. In a 1995–1996 sampling of 38 soils in this region, \( \Sigma \)DDT varied from below quantitation to 11,846 \( \mu \text{g/kg} \), with a geometric mean value of 9.63 \( \mu \text{g/kg} \) (Aigner et al. 1998). The geometric mean concentrations for \( p,p' \)-DDE, \( p,p' \)-DDT, \( p,p' \)-DDD, and \( o,p' \)-DDT were 3.75, 4.67, 1.20, and 1.79 \( \mu \text{g/kg} \), respectively. At least one DDT analog was found in 33 of the soils. Nine of the samples contained \( \Sigma \)DDT above 200 \( \mu \text{g/kg} \), while the concentrations in the rest of the samples were below 40 \( \mu \text{g/kg} \). Two garden soils had \( \Sigma \)DDT levels of 30
and 1.07 µg/kg. The soil with the high ΣDDT level was a muck soil with a concentration that was 10 times higher than the sample next highest in concentration and 1,000 times higher than most sample concentrations. o,p'-DDD was not found in any of the samples. The DDT/DDE ratio was determined in 21 of the samples and ranged from 0.5 to 6.6. It is interesting to note that the geometric mean o,p'-DDT concentration is 38% of the p,p'-DDT concentration. Since o,p'-DDT comprises between 15 and 21% of technical grade DDT and 5.5% is comprised of other compounds, it would appear that o,p'-DDT degrades more slowly than p,p'-DDT. It was shown that the residue level of p,p'-DDT decreased about 70% in a silt loam in New Zealand over a 30-year period (1960–1989), while the o,p'-DDT level only decreased by about 50% in the same time frame (Boul et al. 1994). Most of the degradation occurred during the time frame of 1960–1980, with very little loss occurring from 1980–1989. Forest soils in Maine that had been subject to aerial spraying with DDT had ΣDDT levels ranging from 270 to 1,898 µg/kg compared with a maximum concentration of 11 µg/kg in unsprayed locations. A study of DDT in agricultural soils in British Colombia, Canada report that ΣDDT levels ranged from 194 to 763 µg/kg in silt loam soils and from 2,984 to 7,162 µg/kg in muck soils (Aigner et al. 1998). The difference in residue levels reflects DDT’s longer persistence in muck soil.

Hitch and Day (1992) reported that three soil samples taken near Dell City, Texas in 1980 contained an average of 4.94 and 0.46 mg/kg (dry weight) of DDT and DDE, respectively. It was suspected that the higher DDT concentrations indicated the possible illegal use of DDT. However, further analysis indicated that the "suspect" soil degraded DDT much slower than most soils and the high levels originally detected in soil were attributed to DDT persistence for many years. DDD was not measured in this study. DDT was extensively used in Arizona for 18 years, after which agricultural residues were closely monitored following a statewide moratorium on DDT use in January 1969. Levels of DDT plus metabolites in green alfalfa fell steadily from an average level of 0.22 mg/kg at the time of the ban to a level of 0.057 mg/kg 18 months later, and a level of 0.027 mg/kg after almost 7 years (Ware et al. 1978). After 3 years, residues in agricultural soils had decreased 23%. Furthermore, the ratio of DDE to DDT was increasing, indicating a transformation of DDT to DDE. Buck et al. (1983) reported similar results from monitoring these same sites over 12 years following the ban on DDT use. After 12 years, residues in green alfalfa averaged 0.020 mg/kg. At the end of the same period, combined DDT and DDE residues in agricultural soils had fallen from 1.2 to 0.39 mg/kg, while those in surrounding desert soil had fallen from 0.40 to 0.09 mg/kg.

In 1985, DDT, DDE, and DDD levels were measured at the Baird and McGuire Superfund Site in Holbrook, Massachusetts. Contamination was due to 60 years of mixing and batching of insecticides. In
the highly contaminated areas, the average concentrations of DDT, DDE, and DDD were 61, 10, and 70 mg/kg, respectively. DDT, DDE, and DDD levels in leaf litter and leaf litter invertebrates ranged from 0.2 to 8.4, nondetected to 60, and 0.4 to 25 mg/kg, respectively (Menzie et al. 1992). The high levels of DDT relative to DDE probably indicate that the Superfund Site is largely anaerobic, and that DDT is largely degrading to DDD. In the Palos Verdes Shelf off of Los Angeles where waste from a large DDT manufacturer was discharged via a sewer outfall, sediments contain high levels of DDT isomers and metabolites. The levels of these compounds in surface sediment (0–2 cm) at five sites in the area were (chemical, concentration range): o,p’-DDE, 6–45 mg/kg; p,p’-DDE, 10–327 mg/kg; p,p’-DDD, 1–13 mg/kg; p,p’-DDD, 9–25 mg/kg; o,p’-DDT, not detectible–2 mg/kg; and p,p’-DDT, not detectible–6 mg/kg (Venkatesan et al. 1996).

In summary, DDT, DDE, and DDD have been detected in many soil and sediment surfaces throughout the world. Concentrations are highest in areas with a history of extensive DDT use and are often detected at concentrations close to 1 mg/kg (ppm) or more. Even though concentrations of DDT, DDE, and DDD in soils are declining due to the discontinued production and use of DDT in most countries, detectable levels will probably exist for decades to come because of the long persistence time of these compounds.

### 5.4.4 Other Environmental Media

From 1980 to 1983, 19, 59, and 14 samples of aquatic biota in EPA’s water quality STORET database were analyzed for DDT, DDE, and DDD, respectively (Staples et al. 1985). The median levels for DDT, DDE, and DDD were 14, 26, and 15 µg/kg (wet weight), respectively. All samples tested had detectable levels of these chemicals.

According to the U.S. Geological Survey’s National Water Quality Assessment Plan initiated in 1991, which focuses on the water quality in more than 50 major river basins and aquifer systems, DDT and its metabolites were detected in 94% of whole fish samples analyzed in the 1990s even though the total DDT concentration in fish continues to decline (USGS 1999). This is attributed to the presence of DDT in stream beds and continued inputs of DDT to streams as contaminated soils erode. The metabolite with the highest frequency of detection was p,p’-DDE followed by p,p’-DDD, p,p’-DDT, o,p’-DDD, o,p’-DDE, and o,p’-DDT. The frequency of detection of the o,p’-isomers was below 15%.

ΣDDT concentrations in fish (8 species, 23 samples) collected in August and September 1990 from 3 rivers in Michigan ranged from 4.71 to 976.92 µmol/kg, wet weight with a median of 82.1 µmol/kg.
The range of concentrations of DDT and metabolites were (chemical, range in µg/kg wet weight): \( p,p'\)-DDE, 3.54–627.13; \( o,p'\)-DDE, 0.15–37.95; \( p,p'\)-DDD, 0.43–58.82; \( o,p'\)-DDD, 0.13–81.70; and \( p,p'\)-DDT, <0.42–89.58. The mean ΣDDT concentrations in samples taken below dams that separated the rivers from the Great Lakes, 0.5–1.6 µmol/kg, were higher than those taken above, 0.05–0.35 µmol/kg. The relative contribution of DDE to ΣDDT was fairly constant in all three rivers both above and below the dams. The ratio of DDE:DDT ranged from 5 to 758, which suggests that the accumulation of DDE resulted from direct exposure to DDE in the diet rather than from recent exposure to parent DDT. The fact that DDT is still observed in the fish was ascribed to long-range transport and deposition.

From 1986 to 1988, elements of the arctic marine food web near the Canadian Ice Island in the Arctic Ocean were sampled for DDT, DDE, and DDD (Hargrave et al. 1992). The average concentration of ΣDDT in plankton was 11.8 ng/g dry weight (43.5 µg/kg lipid), and the level increased with decreasing size of the plankton. Amphipods collected under pack ice in the open sea, over the Canadian continental shelf (190–315 m depth), and near the bottom of the Alpha Ridge (2,075 m depth), had mean ΣDDT concentrations of <57, 299, and 3,769 µg/kg dry weight (<347, 1,594, and 12,511 µg/kg lipid), respectively. Pelagic fish contained a mean ΣDDT of 200 µg/kg lipid, while abyssal fish (2,075 m) contained 819 µg/kg dry weight (1,465 µg/kg lipid). The DDT levels in Arctic plankton are generally lower than those reported elsewhere. It is not clear why the DDT levels are higher in organisms living at greater depths since DDT appears to be evenly distributed in the water column. Since DDT adsorbs to particulate matter that sinks into the sediment, as with detritus from aquatic organisms, fish and other organisms living at the bottom of the sea may accumulate higher levels of DDT than organisms living at the surface because their food chain is associated with benthic feeders. Regional differences in DDT levels in biota may be associated with the productivity of the ocean and greater sedimentation of detritus from aquatic organisms. Arctic mammals feeding on DDT-contaminated fish bioaccumulate the chemical in their fat. The ringed neck seal (n=19) and polar bear (n=10) had mean ΣDDT concentrations of 1,482 and 266 µg/kg (lipid basis) (Muir et al. 1988). Beluga whales, ringed neck seals, and walruses near Baffin Island in the eastern Arctic had mean ΣDDT levels (wet weight) of 3.16, 0.33, and 1.42 µg/g, respectively (Kuhnlein et al. 1995).

Exposure to DDT could occur to populations that consume fish from DDT-contaminated marine environments. DDT in white croaker and Dover sole of the Southern California Bight, especially the Palos Verdes shelf area, are the highest in the United States. This is due to the fact that this area receives a large amount of sewage outfall from the southern California region. Historically, DDT levels in these
5. POTENTIAL FOR HUMAN EXPOSURE

Fish exceeded the Food and Drug Administration (FDA) action level of 5 mg/kg wet weight of fish tissue, and fish intended for human consumption were confiscated to prevent human exposure to DDT (NOAA 1988).

Levels of ΣDDT have declined markedly since the early 1970s in fish, shellfish, and aquatic mammals (Lauenstein 1995; Lieberg-Clark et al. 1995; Odsjo et al. 1997; Schmitt et al. 1990). Levels of DDT in fish were determined at 112 locations across the United States by the National Contaminant Biomonitoring Program in 1976 and 1984 (Schmitt et al. 1990). The mean concentrations of \( p,p' \)-DDT, \( p,p' \)-DDE, \( p,p' \)-DDD, and ΣDDT decreased from 50, 260, 80, and 370 µg/kg, respectively, in 1976 to 30, 190, 60, and 260 µg/kg, respectively, in 1984. A follow-up study of DDT in California sea lions reported a decrease in ΣDDT and DDE of over two orders of magnitude between 1970 and 1992 (Lieberg-Clark et al. 1995). ΣDDT for mussels and oysters analyzed as part of the National Oceanic and Atmospheric Administration’s National Status and Trends Mussel Watch Project in 1992 reported a geometric mean ΣDDT concentration for mussels and oysters at 51 sites of 20 µg/kg dry weight, down from a high of 53 µg/kg in 1977 (Lauenstein 1995). Over 90% of the ΣDDT present was as metabolites rather then the parent compounds (\( p,p' \)- and \( o,p' \)-DDT). The methylsulfonyl metabolites of DDE which are known to be persistent, have been determined in several species of mammals (Bergman et al. 1994). In pooled adipose tissue of polar bears from 12 arctic regions, the concentration of 3-MeSO₂-DDE ranged from 0.60 to 11 µg/kg lipids, and the ratio of sulfone to DDE ranged from 0.009 to 0.056 with a mean of 0.033 (Letcher et al. 1995). These may be the result of both biotransformation in the animal and bioaccumulation (Letcher et al. 1998).

From 1979 to 1983, a study was conducted on the presence of DDT and metabolites in wildlife, predominantly birds, in orchards in central Washington State (Blus et al. 1987). Technical DDT was applied at very high rates to orchards in Washington between 1946 and 1970 with some areas probably receiving more than 1,000 kg/ha over this period. High levels of DDE, DDT, and DDD were found in the wildlife. Ninety-six percent of the wildlife samples (n=552) contained >0.01 µg/g of DDE, and 70% contained levels > 0.1 µg/g. In addition, many samples contained unusually low (\#10:1) DDE:DDT ratios. The study attempted to identify whether the residues resulted from past legal use of DDT, ongoing illegal use, use of dicofol and related compounds, or foreign sources. While this matter wasn’t completely resolved, it was suspected that residues were from several sources. However, residues in certain samples, particularly resident wildlife, apparently originated from past legal use of the insecticide. DDT was also applied at very high rates in the Delta region of Mississippi. The geometric mean concentration of \( p,p' \)-DDE residues in resident wood ducks decreased from 0.75 mg/kg in 1984 to
5. POTENTIAL FOR HUMAN EXPOSURE

0.21 mg/kg in 1988 (Ford and Hill 1990). This decrease also corresponded with the reduction of residue levels in wood duck eggshells. Recent studies reporting concentrations of DDT and its metabolites in various biota is shown in Table 5-1.

Market Basket Surveys indicated that there were decreases in the overall residue levels on a lipid basis of DDT and DDE in all classes of food tested from 1965 to 1975 (EPA 1980a). Between 1970 and 1973, DDE residues decreased only 27% compared to decreases of 86 and 89% for DDT and DDD, respectively (EPA 1980a). A study by Duggan et al. (1983) reported the following average residues of \( p,p' \)-DDT and \( o,p' \)-DDT in grocery items from 1969 to 1976: domestic cheese, 3 ppb; ready-to-eat meat, fish, and poultry, 5 ppb; eggs, 4 ppb; domestic fruits, 13 ppb; domestic leaf and stem vegetables, 24 ppb; domestic grains, 7 ppb; corn and corn products, 0.7 ppb; and peanuts and peanut products, 11 ppb.

Mean DDT residues by food group have been reported by Gartrell et al. (1985, 1986a, 1986b) as part of the FDA Total Diet Studies for October 1979–September 1980 and October 1980–March 1982. The average DDE and DDT residues for 12 food groups and the daily intake for each of these groups obtained from the Total Diet Studies are shown in Table 5-2. The highest intake of DDE is shown to come from meat, fish, and poultry. More recent Total Diet Studies have only reported the number of occurrences of a pesticide and not the concentration levels. In the survey for 1984–1986, there were 433 findings of DDE out of 1,872 samples analyzed (Gunderson 1995b). In the Total Diet Study for 1993–1994, \( p,p' \)-DDE was found in 115 out of 783 items analyzed (FDA 1995). Analyses of samples from 10 states taken during fiscal years (FY) 1988 (n=13,980) and 1989 (n=13,085) resulted in a frequency of detection of 0.028 and 0.12%, respectively, for \( p,p' \)-DDT. DDE (any isomer) was detected in 1.5 and 0.99% of samples and \( p,p' \)-DDE in 0.18 and 0.25% of samples in 1988 and 1989, respectively (Minyard and Roberts 1991). Overall, these surveys indicate that DDT and DDE levels are very low in food commodities. However, with continued use of DDT in other countries, imported foods may continue to contribute small amounts of DDT and DDE to the daily diet of consumers. From 1981 to 1986, the FDA analyzed 13,283 imported agricultural commodities for pesticide residues. No commodities exceeded the EPA tolerance levels for DDT or DDE; however, 3.1% of the samples had detectable levels of DDT or DDE (Hundley et al. 1988). A pesticide residue survey of produce from 1989 to 1991 found that 41 out of 6,970 samples analyzed contained \( p,p' \)-DDE (Schattenberg and Hsu 1992).

Baking, frying, broiling, smoking, and microwaving all effectively reduce the total DDT concentration in fish and meat tissue (Bayarri et al. 1994; Khanna et al. 1997; Wilson et al. 1998). The average reduction in fish ranged from 16 to 82% and in lamb from 37 to 56% depending on cooking method. It is not clear
### Table 5-1. Concentrations of DDT and Metabolites in Biota

<table>
<thead>
<tr>
<th>Species</th>
<th>Location</th>
<th>Year</th>
<th>Concentration</th>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Marine Mammals</strong></td>
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<tr>
<td>Pilot whale (n=7)</td>
<td>North Atlantic</td>
<td>Since 1987</td>
<td>3,847 (942–7,118) ng/g (f.w.) [DDE]</td>
<td>mean (range)</td>
<td>Becker et al. 1997a</td>
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<td></td>
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<td>7,748 (1,708–13,035) ng/g (f.w.) [ΣDDT]</td>
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<tr>
<td>Harbor Porpoise (n=5)</td>
<td>North Atlantic</td>
<td>Since 1987</td>
<td>3,260 (1,880–4,900) ng/g (f.w.) [DDE]</td>
<td>mean (range)</td>
<td>Becker et al. 1997a</td>
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<td>7,280 (4,690–11,200) ng/g (f.w.) [ΣDDT]</td>
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<tr>
<td>Beluga whale (n=12)</td>
<td>Arctic</td>
<td>Since 1987</td>
<td>1,415 (142–2,230) ng/g (f.w.) [DDE]</td>
<td>mean (range)</td>
<td>Becker et al. 1997a</td>
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<td>2,492 (332–3,820) ng/g (f.w.) [ΣDDT]</td>
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<tr>
<td>Beluga whale (n=12)</td>
<td>Cook Inlet</td>
<td>Since 1987</td>
<td>624 (65.9–1,630) ng/g (f.w.) [DDE]</td>
<td>mean (range)</td>
<td>Becker et al. 1997a</td>
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<td></td>
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<td>1,050 (133–2,350) ng/g (f.w.) [ΣDDT]</td>
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<tr>
<td>Northern fur seal</td>
<td>North Pacific</td>
<td>Since 1987</td>
<td>1,190 (1,050–1,330) ng/g (f.w.) [DDE]</td>
<td>mean (range)</td>
<td>Becker et al. 1997a</td>
</tr>
<tr>
<td>(n=2)</td>
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<td>1,280 (1,090–1,480) ng/g (f.w.) [ΣDDT]</td>
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<tr>
<td>Ringed seal (n=4)</td>
<td>Arctic</td>
<td>Since 1987</td>
<td>198 (27–350) ng/g (f.w.) [DDE]</td>
<td>mean (range)</td>
<td>Becker et al. 1997a</td>
</tr>
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<td>543 (35–1,430) ng/g (f.w.) [ΣDDT]</td>
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<tr>
<td>Harbour seals (n=18)</td>
<td>Northern Sea</td>
<td>1987</td>
<td>3,161 (355–6,598) µg/kg (f.w.) [ΣDDT]</td>
<td>mean (range)</td>
<td>Vetter et al. 1996</td>
</tr>
<tr>
<td>Harbour seals (n=32)</td>
<td>Northern Sea</td>
<td>1988</td>
<td>3,903 (1,501–11,475) µg/kg (f.w.) [ΣDDT]</td>
<td>mean (range)</td>
<td>Vetter et al. 1996</td>
</tr>
<tr>
<td>Beluga whale</td>
<td>Canadian Arctic</td>
<td>1988</td>
<td>3.16 µg/g (w.w.) [ΣDDT]</td>
<td>mean</td>
<td>Kuhnlein et al. 1995</td>
</tr>
<tr>
<td>Narwhal whale</td>
<td>Canadian Arctic</td>
<td>1988</td>
<td>2.73 µg/g (w.w.) [ΣDDT]</td>
<td>mean</td>
<td>Kuhnlein et al. 1995</td>
</tr>
<tr>
<td>Walrus (n=unspecified)</td>
<td>Canadian Arctic</td>
<td>1988</td>
<td>1.42 µg/g (w.w.) [ΣDDT]</td>
<td>mean</td>
<td>Kuhnlein et al. 1995</td>
</tr>
<tr>
<td>Ringed seal (n=unspecified)</td>
<td>Canadian Arctic</td>
<td>1988</td>
<td>0.33 µg/g (w.w.) [ΣDDT]</td>
<td>mean</td>
<td>Kuhnlein et al. 1995</td>
</tr>
</tbody>
</table>
Table 5-1. Concentrations of DDT and Metabolites in Biota (continued)

<table>
<thead>
<tr>
<th>Species</th>
<th>Location</th>
<th>Year</th>
<th>Concentration</th>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beluga whale (neonate) (n=1)</td>
<td>St. Lawrence estuary near Quebec</td>
<td>1991</td>
<td>702 ng/g (brain); 2,332 ng/g (kidney); 3,467 ng/g (liver); 2,230 ng/g (fat) [ΣDDT] 689 ng/g (brain); 2,289 ng/g (kidney); 3,357 ng/g (liver); 2,106 ng/g (fat) [DDE] ND (brain); ND (kidney); 15 ng/g (liver); 17 ng/g (fat) [DDD]</td>
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<td>Gauthier et al. 1998</td>
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<tr>
<td>Terrestrial Mammals</td>
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<tr>
<td>Polar Bear (n=320)</td>
<td>Arctic (16 regions)</td>
<td>1989–1993</td>
<td>219 µg/kg (f.w.) [DDE]</td>
<td>median range of geomeans</td>
<td>Norstrom et al. 1998</td>
</tr>
<tr>
<td>Arctic ground squirrel (n=13)</td>
<td>Elusive Lake</td>
<td>1991–1993</td>
<td>6.13 (0.34–34.08) µg/kg (w.w.) (liver) [ΣDDT] 1.51 (0.33–5.77) µg/kg (w.w.) (liver) [DDE]</td>
<td>mean (range)</td>
<td>Allen-Gil et al. 1997</td>
</tr>
<tr>
<td>Arctic ground squirrel (n=6)</td>
<td>Feniak Lake</td>
<td>1991–1992</td>
<td>1.43 (0.19–5.16) µg/kg (w.w.) (liver) [ΣDDT] 0.86 (0.19–3.10) µg/kg (w.w.) (liver) [DDE]</td>
<td>mean (range)</td>
<td>Allen-Gil et al. 1997</td>
</tr>
<tr>
<td>Arctic ground squirrel (n=17)</td>
<td>Schrader Lake</td>
<td>1992–1993</td>
<td>12.25 (0.12–39.76) µg/kg (w.w.) (liver) [ΣDDT] 4.47 (0.12–13.63) µg/kg (w.w.) (liver) [DDE]</td>
<td>mean (range)</td>
<td>Allen-Gil et al. 1997</td>
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<tr>
<td>Birds</td>
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<tr>
<td>Bald eagle chicks (n=51)</td>
<td>Great Lakes region</td>
<td>1990–1996</td>
<td>ND–0.0171 mg/kg (plasma) [DDT]</td>
<td>range</td>
<td>Donaldson et al. 1999</td>
</tr>
<tr>
<td>Bald eagle eggs (n=6)</td>
<td>Lake Erie</td>
<td>1974–1980</td>
<td>24.4 (13.8–35.8) mg/kg [DDE]</td>
<td>mean (range)</td>
<td>Donaldson et al. 1999</td>
</tr>
<tr>
<td>Bald eagle eggs (n=6)</td>
<td>Lake Erie</td>
<td>1989–1994</td>
<td>10.8 (2.7–22.2) mg/kg [DDE]</td>
<td>mean (range)</td>
<td>Donaldson et al. 1999</td>
</tr>
<tr>
<td>Bald eagle eggs (n=7)</td>
<td>Lake of the Woods, Canada</td>
<td>1993–1996</td>
<td>3.3 (0.9–12.6) mg/kg [DDE]</td>
<td>mean (range)</td>
<td>Donaldson et al. 1999</td>
</tr>
</tbody>
</table>
**Table 5-1. Concentrations of DDT and Metabolites in Biota (continued)**

<table>
<thead>
<tr>
<th>Species</th>
<th>Location</th>
<th>Year</th>
<th>Concentration Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blue heron eggs (n=10)</td>
<td>Southern Lake Michigan</td>
<td>1993</td>
<td>DDT: 0.02 (ND–0.12) (µg/g) (w.w.)</td>
<td>Custer et al. 1998</td>
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<td></td>
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<td>DDE: 1.58 (0.23–13.00) (µg/g) (w.w.)</td>
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<td></td>
<td>DDD: 0.03 (ND–0.12) (µg/g) (w.w.)</td>
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<tr>
<td>Fish and shellfish</td>
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<tr>
<td>Mussels and oysters</td>
<td>United States (51 sites)</td>
<td>1992</td>
<td>ΣDDT: 0.51–1,400 ng/g (d.w.)</td>
<td>Lauenstein 1995</td>
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<tr>
<td></td>
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<td></td>
<td>DDD: 20 ng/g (d.w.)</td>
<td></td>
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<tr>
<td>Clams</td>
<td>San Joaquin River (Orestimba Creek)</td>
<td>1992</td>
<td>ΣDDT: 4,350 ng/g (w.w.)</td>
<td>Pereira et al. 1996</td>
</tr>
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<td></td>
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<td>DDE: 3,300 ng/g (w.w.)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>DDD: 390 ng/g (w.w.)</td>
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<tr>
<td>Clams</td>
<td>San Joaquin River (Dry Creek)</td>
<td>1992</td>
<td>ΣDDT: 29 ng/g (w.w.)</td>
<td>Pereira et al. 1996</td>
</tr>
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<td></td>
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<td></td>
<td>DDE: 25 ng/g (w.w.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DDD: 0.5 ng/g (w.w.)</td>
<td></td>
</tr>
<tr>
<td>Clams</td>
<td>San Joaquin River (Mokelumne River)</td>
<td>1992</td>
<td>ΣDDT: 15 ng/g (w.w.)</td>
<td>Pereira et al. 1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DDE: 13 ng/g (w.w.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DDD: 0.5 ng/g (w.w.)</td>
<td></td>
</tr>
<tr>
<td>Clams</td>
<td>San Joaquin River (Stanislaus River)</td>
<td>1992</td>
<td>ΣDDT: 24 ng/g (w.w.)</td>
<td>Pereira et al. 1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DDE: 22 ng/g (w.w.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DDD: &lt;0.5 ng/g (w.w.)</td>
<td></td>
</tr>
<tr>
<td>Mountain whitefish (10 composites from 7 sites)</td>
<td>Yakima River Basin, WA</td>
<td>1989–1991</td>
<td>ΣDDT: 0.10–1.7 mg/kg (w.w.) (whole fish)</td>
<td>Marien and Laflamme 1995</td>
</tr>
<tr>
<td>Largerscale sucker (18 composites from 13 sites)</td>
<td>Yakima River Basin, WA</td>
<td>1989–1991</td>
<td>ΣDDT: 0.05–4.37 mg/kg (w.w.) (whole fish)</td>
<td>Marien and Laflamme 1995</td>
</tr>
</tbody>
</table>
## Table 5-1. Concentrations of DDT and Metabolites in Biota (continued)

<table>
<thead>
<tr>
<th>Species</th>
<th>Location</th>
<th>Year</th>
<th>Concentration</th>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perch (n=5)</td>
<td>Lake Ørsjøen,</td>
<td>1994</td>
<td>1.15 ng/g (w.w.), 1,643 ng/g (f.w.) [ΣDDT]</td>
<td>mean</td>
<td>Brevik et al. 1996</td>
</tr>
<tr>
<td></td>
<td>Norway Mid-lake</td>
<td></td>
<td>0.53 ng/g (w.w.), 757 ng/g (f.w.) [DDE]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.26 ng/g (w.w.), 371 ng/g (f.w.) [DDD]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.28 ng/g (w.w.), 400 ng/g (f.w.) [DDT]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perch (n=5)</td>
<td>Lake Ørsjøen,</td>
<td>1994</td>
<td>5.59 ng/g (w.w.), 11,180 ng/g (f.w.) [ΣDDT]</td>
<td>mean</td>
<td>Brevik et al. 1996</td>
</tr>
<tr>
<td></td>
<td>Norway</td>
<td></td>
<td>2.56 ng/g (w.w.), 5,120 ng/g (f.w.) [DDE]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.48 ng/g (w.w.), 2,960 ng/g (f.w.) [DDD]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.15 ng/g (w.w.), 2,300 ng/g (f.w.) [DDT]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pike (n=5)</td>
<td>Lake Ørsjøen,</td>
<td>1994</td>
<td>7.3 ng/g (w.w.), 8,111 ng/g (f.w.) [ΣDDT]</td>
<td>mean</td>
<td>Brevik et al. 1996</td>
</tr>
<tr>
<td></td>
<td>Norway Mid-lake</td>
<td></td>
<td>3.5 ng/g (w.w.), 3,888 ng/g (f.w.) [DDE]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.5 ng/g (w.w.), 1,667 ng/g (f.w.) [DDD]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.8 ng/g (w.w.), 2,000 ng/g (f.w.) [DDT]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lake trout (n=59)</td>
<td>Lake Ontario</td>
<td>1992</td>
<td>1.159 µg/g (w.w.) [DDE]</td>
<td>mean</td>
<td>Kiriluk et al. 1995</td>
</tr>
<tr>
<td>Rainbow smelt (n=8)</td>
<td>Lake Ontario</td>
<td>1992</td>
<td>0.256 µg/g (w.w.) [DDE]</td>
<td>mean</td>
<td>Kiriluk et al. 1995</td>
</tr>
</tbody>
</table>

*aU.S. National Biomonitoring Specimen Bank

d.w. = dry weight; f.w. = fat weight basis; n = number; ND = not detected; geomean = geometric mean; w.w. = wet weight
### Table 5-2. Average Residues in Food Groups and Average Daily Intake from U.S. FDA Total Diet Studies

<table>
<thead>
<tr>
<th>Food Group</th>
<th>Residue (ppb)</th>
<th>Intake (µg/day)</th>
<th>Residue (ppb)</th>
<th>Intake (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dairy products</td>
<td>0.9</td>
<td>0.626</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Meat, fish, and poultry</td>
<td>4.8</td>
<td>1.28</td>
<td>0.8</td>
<td>0.219</td>
</tr>
<tr>
<td>Grains and cereal</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Potatoes</td>
<td>0.5</td>
<td>0.0847</td>
<td>&lt;0.1</td>
<td>0.0079</td>
</tr>
<tr>
<td>Leafy vegetables</td>
<td>1.7</td>
<td>0.0954</td>
<td>0.2</td>
<td>0.0137</td>
</tr>
<tr>
<td>Legumes</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Root vegetables</td>
<td>1.0</td>
<td>0.0309</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Garden vegetables</td>
<td>0.2</td>
<td>0.0185</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fruits</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Oils and fats</td>
<td>&lt;0.1</td>
<td>0.0028</td>
<td>0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Sugar</td>
<td>&lt;0.1</td>
<td>0.0042</td>
<td>0</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Beverages</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Adapted from Gartrell et al. 1985

*Adapted from Gartrell et al. 1986b
5. POTENTIAL FOR HUMAN EXPOSURE

whether residues are lost as a result of volatilization or decomposition. \( p,p' \)-DDT (but not \( p,p' \)-DDE or \( p,p' \)-DDD) decomposes on heating (see Table 3-2).

Djordjevik et al. (1995) assessed the chlorinated pesticide residues in U.S. and foreign cigarettes manufactured from the 1960s to the 1990s. Since 1970, the concentration of DDT analogs decreased by >98%. Concentration ranges of DDT-related compounds in samples of cigarettes manufactured between 1961 and 1979 and between 1983 and 1994 were (chemical, 1961–1979 levels, 1983–1994 levels):

- \( p,p' \)-DDD, 1,540–30,100 ng/g, 12.6–99.7 ng/g;
- \( o,p' \)-DDD, 396–7,150 ng/g, ND-19.0 ng/g;
- \( p,p' \)-DDT, 720–13,390 ng/g, 19.7–145 ng/g;
- \( o,p' \)-DDT, 105–1,940 ng/g, ND-88 ng/g;
- \( p,p' \)-DDE, 58–959 ng/g, 6.6–15.8 ng/g;
- \( p,p' \)-DDMU (1-chloro-2,2-bis(\( p \)-chlorophenyl)ethylene), 92.7–2,110 ng/g, ND-27.5 ng/g. The transfer rate from tobacco into mainstream smoke amounts to 22% for DDD, 19% for DDT, and 27% for DDE.

Monitoring in older homes reveal that carpeting in these homes may have high levels of DDT, DDE, and DDD (Lewis et al. 1994). In one house built in 1930, the carpeting, that was believed to be at least 25 years old, contained up to 10.8 µg/m² or 5.7 µg/g of \( \Sigma \) DDT (\( p,p' \)-DDT, DDD, and DDE).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The general population is currently exposed to DDT and its metabolites primarily in food. As indicated in the previous section, although residue levels in food continue to slowly decline, there are measurable quantities in many commodities. A 1989 pesticide screening program of produce delivered to supermarkets in Texas, for example, found \( p,p' \)-DDE residues in 41 of the 6,970 produce samples tested (Schattenberg and Hsu 1992). An FDA study of residues in infant foods and adult food eaten by infants and children in which over 10,000 samples of domestic and imported foods were analyzed during 1985–1991 was published (Yess et al. 1993). \( \Sigma \) DDT was detected in 2 of 2,464 apples at a maximum concentration of 0.08 ppm; 312 of 2,464 plain milk samples at a maximum concentration of 0.92 ppm; 8 of 180 vitamin D fortified milk samples at a maximum concentration of 0.10 ppm; and 1 of 735 imported apple juice samples at 0.18 ppm (Yess et al. 1993). A similar 1992–1994 Canadian survey found DDE or DDT residues in 1 of 380 domestic heads of lettuce; 1 of 769 domestic potatoes; 36 of 612 imported carrots; 4 of 721 imported cucumbers; 1 of 702 imported heads of lettuce; 14 of 121 imported green onions; 7 of 17 imported parsnips; 1 of 933 imported peppers; 5 of 264 imported spinach; 1 of 155 imported tomato pastes; and 1 of 1,153 imported tomatoes (Neidert and Saschenbrecker 1996). In a U.S. Market Basket study of ready to eat foods, \( o,p' \)-DDE was detected 8 times in 4 different food items at an
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The average concentration of 0.0025 µg/g; \( p,p' \)-DDE was detected 1,700 times in 142 different food items at an average concentration of 0.0026 µg/g; \( o,p' \)-DDT was detected 5 times in 4 different food items at an average concentration of 0.0053 µg/g; \( p,p' \)-DDT was detected 98 times in 31 different food items at an average concentration of 0.0045 µg/g (KAN-DO Office and Pesticide Team 1995).

Because of the extreme persistence of DDT and DDE, it is anticipated that low levels of residues will be present in commodities for decades. In fact, depending on use and export patterns in other countries, levels in the diet may even increase (Coulston 1985). Even in domestic commodities, the potential for low levels of dietary exposure of consumers may result from residues bioaccumulated in some food items, including fish.

The estimated dietary intake of DDT and metabolites in the United States was 62 µg/person/day in 1965, 240 µg/person/day in 1970, and 8 µg/person/day in 1974 (Coulston 1985). The FDA Adult Total Diet Study for October 1979–September 1980 (FY 1980) found that the intakes of \( \Sigma \) DDT, DDE, DDT, and DDD were 0.034, 0.003, 0.031, and <0.001 µg/kg body weight/day, respectively, down from highs of 0.093, 0.004, 0.087, and 0.002, respectively, in FY 1979 (Gartrell et al. 1986a). The adult intake was assumed to be the diet of a 16- to 19-year-old male. Analogous studies for infants and toddlers for FY 1980 reported daily intakes of the respective DDTs as 0.034, 0.034, ND, and ND µg/kg body weight/day for infants and 0.049, 0.045, 0.002, and 0.002 µg/kg body weight/day for toddlers (Gartrell et al. 1986b).

Estimated dietary intakes of DDT determined from the FDA Total Diet Studies for June 1984–April 1986 and July 1986–April 1991 for eight population groups appear in Table 5-3 (Gunderson 1995a, 1995b). To facilitate comparisons of DDT intakes from Gunderson (1995a, 1995b) with those of earlier estimates (Coulston 1985), the daily intake of \( \Sigma \) DDT for a 70 kg 16-year-old male as reported by Gunderson (1995a, 1995b) would have been 6.51, 2.38, 1.49, and 0.97 µg/day for 1978–1979, 1979–1980, 1984–1986, and 1986–1991, respectively. The acceptable daily intake of DDT established by WHO/FAO is 20 µg/kg/day (WHO 1991).

Exposure to DDT, DDE, and DDD in imported foods is minimized due to FDA enforcement programs. FDA randomly collects and analyzes a wide variety of imported commodities (e.g., coffee, tropical fruits) to determine if pesticide residues are above EPA tolerances. Pesticide tolerances established by EPA apply equally to domestic and imported food (Wessel and Yess 1991).
Table 5-3. Mean Daily Intake of DDT Per Unit Body Weight (µg/kg body weight/day) for Various Age Groups in the United States

<table>
<thead>
<tr>
<th>Analyte</th>
<th>6–11 mo</th>
<th>2 yr</th>
<th>14–16 yr F</th>
<th>14–16 yr M</th>
<th>25–30 yr F</th>
<th>25–30 yr M</th>
<th>60–65 yr F</th>
<th>60–65 yr M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1984–1986</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΣDDT</td>
<td>0.0485</td>
<td>0.0499</td>
<td>0.0154</td>
<td>0.0213</td>
<td>0.0128</td>
<td>0.0155</td>
<td>0.0111</td>
<td>0.0124</td>
</tr>
<tr>
<td>o,p'-DDE</td>
<td>0.0002</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p,p'-DDE</td>
<td>0.0468</td>
<td>0.0484</td>
<td>0.0149</td>
<td>0.0207</td>
<td>0.0123</td>
<td>0.0150</td>
<td>0.0105</td>
<td>0.0119</td>
</tr>
<tr>
<td>p,p'-DDT</td>
<td>0.0004</td>
<td>0.0010</td>
<td>0.0003</td>
<td>0.0004</td>
<td>0.0003</td>
<td>0.0003</td>
<td>0.0003</td>
<td>0.0003</td>
</tr>
<tr>
<td>p,p'-DDD</td>
<td>0.0011</td>
<td>0.0004</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>1986–1991</strong></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΣDDT&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.0448</td>
<td>0.0438</td>
<td>0.0138</td>
<td>0.0139</td>
<td>0.0106</td>
<td>0.0127</td>
<td>0.0090</td>
<td>0.0104</td>
</tr>
<tr>
<td>o,p'-DDE</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p,p'-DDE</td>
<td>0.0441</td>
<td>0.0420</td>
<td>0.0130</td>
<td>0.0151</td>
<td>0.0099</td>
<td>0.0119</td>
<td>0.0082</td>
<td>0.0096</td>
</tr>
<tr>
<td>p,p'-DDT</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p,p'-DDD</td>
<td>0.0004</td>
<td>0.0011</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.0005</td>
<td>0.0006</td>
<td>0.0006</td>
</tr>
<tr>
<td>p,p'-DDD</td>
<td>0.0003</td>
<td>0.0007</td>
<td>0.0003</td>
<td>0.0003</td>
<td>0.0002</td>
<td>0.0003</td>
<td>0.0002</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

Source: Gunderson 1995a, 1995b

<sup>1</sup>The average daily ΣDDT intake of 0.8 Fg/day for an adult used in Section 1.3 was derived from the average intakes for 25–30 year old males and females assuming a body weight of 70 kg.

F=female; M=male; mo=month; yr=year
5. POTENTIAL FOR HUMAN EXPOSURE

Arctic indigenous people ingest high levels of DDT from traditional foods. A study covering three age groups in communities in the eastern and western Canadian Arctic found the average daily ΣDDT intake of 24.2 to 27.8 µg/day for the eastern Arctic community and 0.51 to 1.0 µg/day for the western Arctic communities (Kuhnlein et al. 1995). The foods with the highest ΣDDT concentrations were raw Beluga whale blubber (316 µg/g wet weight) and aged Narwhal whale blubber (273 µg/g wet weight) in the eastern Arctic, and baked Loch (species of fish) liver (1.85 µg/g wet weight) and smoked Canada goose meat (1.47 µg/g wet weight) in the western Arctic.

In 1986–1988, EPA collected data at two sites, Jacksonville, Florida and Springfield/Chicopee, Massachusetts, to assess the nonoccupational exposure to pesticides (NOPES) for residents of these cities (Whitmore et al. 1994). Indoor p,p’-DDE and p,p’-DDT levels in air were higher than outdoor levels in these communities, and the highest number of indoor air samples with detectable DDT was observed in the spring in Jacksonville (14%) and in the winter in Springfield/Chicopee (20%), with estimated mean air DDE and DDT concentrations of ≥1.0 ng/m³. Mean ΣDDT air exposures were estimated as 22 ng/day in Jacksonville and 94 ng/day in Springfield/Chicopee. For comparison, dietary exposures in these two communities for 1982–1984 were estimated to be around 1,900 ng/day. Nine of 11 carpets tested in Jacksonville contained ΣDDT with median and mean levels of 0.7 and 1.2 µg/g, respectively.

Until 1970, tobacco smoke contributed significantly to the intake of DDT by people, but since then, the amount of DDT in tobacco has dropped markedly and today, cigarette smoke is a minor source of human exposure (Djordjevic et al. 1995).

Because of the extremely low solubility of DDT and DDE in water and the efficiency of standard water treatment methods in eliminating DDT-type chemical residues, intake of these compounds via drinking water is believed to be negligible. The criterion cited in the EPA Ambient Water Quality Criteria document is 0.059 ng/L, based on ingestion of 2L of drinking water per day plus 6.5 g of fish and shellfish per person (EPA 1999a). This criterion corresponds to an estimated increased cancer risk level of 1x10⁻⁷ or 1 in 10 million.

Data indicate that, even with relatively high doses, there is minimal absorption of DDT through skin (Gaines 1969; Wester et al. 1990; Wolfe and Armstrong 1971). Therefore, exposure via dermal absorption was considered to be negligible. However, in reviewing the literature and using a dermal absorption factor of 15% measured in their laboratory, Moody and Chu (1995) calculated that in the worse-case scenario where a swimmer was in contact with 1 ppm of DDT from a water slick or sediment...
for 1 hour, a swimmer would absorb 200 µg of DDT, equivalent to a dose from a meal of contaminated fish.

DDT and its metabolites are ubiquitous in the atmosphere but are present in such low concentrations that exposure via inhalation is negligible. Potential inhalation of relatively high levels of DDT should be possible only in areas of production or formulation. Wolfe and Armstrong (1971) estimated a respiratory exposure potential of 14.1 mg/person/hour for formulating plant workers; however, no current data were located on exposure of workers utilizing modern technology in the production and formulation of these compounds.

DDT and DDE elimination from the body is not an efficient process; therefore, tissue levels will increase with repeated exposure if the absorbed dose is high enough. For this reason, body burdens of DDT and DDE tend to correspond with exposure levels, as indicated in long-term studies. From July 1969 to 1975, residues of DDT and its metabolites were measured in human adipose tissue collected through an annual, national survey — the National Human Monitoring Program for Pesticides (Kutz et al. 1977). During that time, levels of DDT and DDE in tissue samples declined. However, the frequency of occurrence in lipid samples did not decline, indicating both a long biological half-life and the ubiquitous occurrence of these compounds in the population. For FY 1970–1974, all samples were positive for DDT and metabolites (a total of 1,412 samples). Using all age groups sampled, the geometric mean lipid DDT and metabolite (combined) levels reported for each year from 1970–1974 were 7.88, 7.95, 6.88, 5.89, and 5.02 ppm, respectively. Notable trends reported in Kutz et al. (1977) included increasing body burden with increasing age as well as a significant increase in residues in blacks when compared to whites. Results published for 1975 showed little change compared to 1974 (Kutz et al. 1979). Exposure to DDT in nonoccupationally exposed individuals, as manifested by their plasma DDE concentrations, was most reliably predicted by age and serum cholesterol concentration (Laden et al. 1999). Kutz et al. (1991) contains a listing of studies on DDT, DDE, and DDD levels in human adipose tissue in the general population of various countries from the 1950s to the mid 1980s.

The Second National Health and Nutrition Examination Survey (NHANES II) has served as a continuation of the National Human Monitoring Program; however, published results have been few. Murphy and Harvey (1985) published selected results from the NHANES II survey for 1976–1980 based on data from the Northeast, Midwest, and South. These results are based, not on adipose samples, but on serum samples. For the years covered, 3,300 serum specimens were analyzed for DDT and DDE. In 31% of those samples \( p,p'-\text{DDT} \) was detected, with a median quantifiable level of 3.3 ppb (0.0033 ppm).
However, p,p'-DDE was detected in 99% of samples tested, with a median quantifiable level of 11.8 ppb (0.0118 ppm). The limits of detectability was 2 ppb for p,p'-DDT and 1 ppb for p,p'-DDE. These results offered further proof of the extensive biological half-life of DDE as compared to DDT. Again, for both compounds, serum levels increased with increasing age. These data were not reported for each year, but a decreasing trend could be expected based on the data of Murphy and Harvey (1985). A more recent report on NHANES II for the period of 1976–1980 confirmed the above results on serum samples from 5,994 persons. p,p'-DDE was detected in the serum of 99.5% of persons with a median level of 12.6 ppb (range: 0–379 ppb) whereas p,p'-DDT was quantifiable (>2 ppb) in only 10% of serum samples (Stehr-Green 1989). Levels of p,p'-DDE increased with age and were higher in farm residents and in the South and West.

Results of EPA’s 1986 National Human Adipose Tissue Survey (NHATS) in which 671 adipose tissue specimens were pooled into composite samples according to age, census region, sex, and race showed significant differences in p,p'-DDT and p,p'-DDE levels depending on age and census region (Lordo et al. 1996). The concentration of both compounds increased with age group, and while levels of p,p'-DDT were highest in the Northeast and lowest in the South, those of p,p'-DDE were highest in the West and lowest in the North Central region. Levels of both compounds had significantly increased from the 1984 NHATS. The estimated national mean with relative standard error (%) p,p'-DDT concentrations for the 1982, 1984, and 1986 NHATS were 189 (31%), 123 (11%), and 177 (20%) ng/g, respectively. Those for p,p'-DDE were 1,840 (350%), 1,150 (90%), and 2,340 (270%) ng/g, respectively. A 1985 survey of 108 Canadian autopsy samples resulted in mean and maximum levels of p,p'-DDE at 811 and 6,070 ng/g and p,p'-DDT as 48 and 250 ng/g (Mes et al. 1990). Adeshina and Todd (1990) analyzed DDT isomer and metabolite levels in 35 human adipose tissue samples of North Texas residents who were not occupationally exposed to DDT. The samples were obtained during autopsy in 1987 and 1988. The geometric mean concentrations were (substance, ng/g lipid): o,p'-DDE, 8 ng/g; p,p'-DDE, 679 ng/g; o,p'-DDT, 14 ng/g; p,p'-DDT, 294 ng/g; and ΣDDT, 1,031 ng/g. The ΣDDT levels can be compared with those from the human adipose tissue survey which were 7,950 ng/g lipid in 1970, 5,150 ng/g lipid in 1974, and 1,670 ng/g lipid in 1983 (Adeshina and Todd 1990).

DDT in milk is discussed in Section 5.6. Levels of DDE and DDT in human milk, blood, and tissue appear in Table 5-4. Methyl sulfonyl metabolites of p,p'-DDE, primarily the 3-methylsulfone isomer, have been found in seven surveys of human milk in Sweden between 1972 and 1992 (Noren et al. 1996). In that time, levels declined from 5.05 to 0.46 ng/g lipids and the ratio of the 3-methyl sulfone metabolite to p,p'-DDE remained constant at 0.002.
Table 5-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies

<table>
<thead>
<tr>
<th>DDT compound</th>
<th>Population</th>
<th>Tissue</th>
<th>Mean* concentration</th>
<th>Units as reported</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Milk</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>p,p</em>-DDT</td>
<td>Maternity patients in Mexico City</td>
<td>Milk fat</td>
<td>0.162</td>
<td>mg/kg</td>
<td>Torres-Arreola et al. 1999</td>
</tr>
<tr>
<td><em>p,p</em>-DDT</td>
<td>Women in Germany</td>
<td>Milk fat</td>
<td>0.7 (estimated from graph)</td>
<td>mg/kg</td>
<td>Scheele et al. 1995</td>
</tr>
<tr>
<td><em>o,p</em>-DDT</td>
<td>Maternity patients in Mexico City</td>
<td>Milk fat</td>
<td>0.138</td>
<td>mg/kg</td>
<td>Torres-Arreola et al. 1999</td>
</tr>
<tr>
<td><em>p,p</em>-DDE</td>
<td>Quebec women between 1989 and 1990 (n=536)</td>
<td>Milk fat</td>
<td>0.34</td>
<td>mg/kg</td>
<td>Dewailly et al. 1996</td>
</tr>
<tr>
<td><em>p,p</em>-DDE</td>
<td>Maternity patients in Mexico City</td>
<td>Milk fat</td>
<td>0.594</td>
<td>mg/kg</td>
<td>Torres-Arreola et al. 1999</td>
</tr>
<tr>
<td><em>p,p</em>-DDE</td>
<td>Maternity patients in Veracruz, Mexico</td>
<td>Milk fat</td>
<td>5.302</td>
<td>mg/kg</td>
<td>Pardio et al. 1998</td>
</tr>
<tr>
<td><em>p,p</em>-DDE</td>
<td>Mothers of hospitalized children in Zagreb, Croatia</td>
<td>Milk fat</td>
<td>0.318</td>
<td>mg/kg</td>
<td>Krauthaker et al. 1998</td>
</tr>
<tr>
<td><strong>ΣDDT</strong></td>
<td>Canadian women - 1986 (n=412)</td>
<td>Milk fat</td>
<td>0.385</td>
<td>mg/kg</td>
<td>Smith 1999</td>
</tr>
<tr>
<td><strong>ΣDDT</strong></td>
<td>Arkansas women - 1986 (n=536)</td>
<td>Milk fat</td>
<td>0.99</td>
<td>mg/kg</td>
<td>Smith 1999</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>p,p</em>-DDT</td>
<td>Workers in Sao Paulo, Brazil</td>
<td>Serum</td>
<td>13.5 (DDT appliers) 1.5 (unexposed)</td>
<td>µg/L</td>
<td>Minelli and Ribeiro 1996</td>
</tr>
<tr>
<td><em>o,p</em>-DDT</td>
<td>Workers in Sao Paulo, Brazil</td>
<td>Serum</td>
<td>&lt;0.7–4.7 (range; DDT appliers)</td>
<td>µg/L</td>
<td>Minelli and Ribeiro 1996</td>
</tr>
<tr>
<td>DDT compound</td>
<td>Population</td>
<td>Tissue</td>
<td>Mean concentration</td>
<td>Units as reported</td>
<td>Reference</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>$p,p'$-DDE</td>
<td>Workers in Sao Paulo, Brazil</td>
<td>Serum</td>
<td>64.3 (DDT appliers) 14.3 (unexposed)</td>
<td>µg/L</td>
<td>Minelli and Ribeiro 1996</td>
</tr>
<tr>
<td>$p,p'$-DDT</td>
<td>Men in southeast Sweden</td>
<td>Blood plasma</td>
<td>0.11(lipid adjusted)</td>
<td>ng/g</td>
<td>Asplund et al. 1994</td>
</tr>
<tr>
<td>$p,p'$-DDE</td>
<td>Woman hospital patients in New Haven, CT</td>
<td>Serum (lipid-adjusted)</td>
<td>967 (median), &lt;1.0–2261.5 (range) (n=36)</td>
<td>ng/g</td>
<td>Archibeque-Engle et al. 1997</td>
</tr>
<tr>
<td>$p,p'$-DDE</td>
<td>Iowa and North Carolina farmers and spouses</td>
<td>Serum</td>
<td>0.39–6.51 (range)</td>
<td>µg/L</td>
<td>Brock et al. 1998</td>
</tr>
<tr>
<td>$o,p'$-DDE</td>
<td>Iowa and North Carolina farmers and spouses</td>
<td>Serum</td>
<td>0.71–2.31 (range)</td>
<td>µg/L</td>
<td>Brock et al. 1998</td>
</tr>
<tr>
<td>$p,p'$-DDE</td>
<td>Women without breast cancer in Long Island</td>
<td>Serum</td>
<td>4.7</td>
<td>µg/L</td>
<td>Stellman et al. 1998</td>
</tr>
<tr>
<td>$p,p'$-DDE</td>
<td>New York University Women’s Health Study (1985 to 1991)</td>
<td>Serum</td>
<td>11.0±9.1 in cancer patients (n=58) 7.7±6.8 controls (n=171)</td>
<td>µg/L</td>
<td>Wolff et al. 1993</td>
</tr>
<tr>
<td>$p,p'$-DDE</td>
<td>Female hospital patients in New York City</td>
<td>Plasma</td>
<td>6.93–7.29 (range of mean values)</td>
<td>µg/L</td>
<td>Gammon et al. 1997</td>
</tr>
<tr>
<td>$p,p'$-DDE</td>
<td>Female hospital patients in New York City</td>
<td>Plasma (lipid-adjusted)</td>
<td>0.963–0.997 (range of mean values)</td>
<td>µg/mL</td>
<td>Gammon et al. 1997</td>
</tr>
<tr>
<td>$p,p'$-DDE</td>
<td>Men in southeast Sweden</td>
<td>Plasma</td>
<td>2.4–14 (range of mean values among groups of men with different levels of fish consumption)</td>
<td>ng/g</td>
<td>Asplund et al. 1994</td>
</tr>
<tr>
<td>$p,p'$-DDE</td>
<td>Men in southeast Sweden</td>
<td>Plasma (lipid-adjusted)</td>
<td>750–4500 (range of mean values among groups of men with different levels of fish consumption)</td>
<td>ng/g</td>
<td>Asplund et al. 1994</td>
</tr>
</tbody>
</table>
**Table 5-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies (continued)**

<table>
<thead>
<tr>
<th>DDT compound</th>
<th>Population</th>
<th>Tissue</th>
<th>Mean* concentration</th>
<th>Units as reported</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDE</td>
<td>Controls in a case-control study nested within the Nurses Health Study (n=240)</td>
<td>Plasma</td>
<td>7.09</td>
<td>ppb</td>
<td>Laden et al. 1999</td>
</tr>
<tr>
<td>(p,p')-DDE</td>
<td>Four groups of refugees from Asia, ‘USSR’, Africa, ‘Yugoslavia’ (n=103); Controls from Germany (n=34)</td>
<td>Plasma</td>
<td>2.30–16.90 (range of median values) 12.20–93.00 (range of maximum values) (refugees) 1.14 (median), 4.97 (maximum) (controls)</td>
<td>µg/L</td>
<td>Schmid et al. 1997</td>
</tr>
<tr>
<td>(p,p')-DDT</td>
<td>Great Lakes fishermen (n=30); Controls (n=180)</td>
<td>Serum</td>
<td>0.3 (median), 0.05–0.8 (range) ND (controls)</td>
<td>ppb</td>
<td>Anderson et al. 1998</td>
</tr>
<tr>
<td>(o,p')-DDT</td>
<td>Great Lakes fishermen (n=30); Controls (n=180)</td>
<td>Serum</td>
<td>0.06 (median), 0.03–0.3 (range) ND (controls)</td>
<td>ppb</td>
<td>Anderson et al. 1998</td>
</tr>
<tr>
<td>(p,p')-DDE</td>
<td>Great Lakes fishermen (n=30); Controls (n=180)</td>
<td>Serum</td>
<td>5.2 (median), 0.6–23.9 (range) 2.8 (median), ND–38.5 (range) (controls)</td>
<td>ppb</td>
<td>Anderson et al. 1998</td>
</tr>
<tr>
<td>DDE</td>
<td>Frequent GLSCF (Lake Michigan) males (n=98); females (n=83); male controls (n=23); female controls (n=22)</td>
<td>Serum</td>
<td></td>
<td>ppb</td>
<td>Hanrahan et al. 1999</td>
</tr>
<tr>
<td>DDE</td>
<td>Frequent GLSCF (Lake Huron) males (n=65); females (n=37); male controls (n=3); female controls (n=3)</td>
<td>Serum</td>
<td></td>
<td>ppb</td>
<td>Hanrahan et al. 1999</td>
</tr>
</tbody>
</table>
Table 5-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies (continued)

<table>
<thead>
<tr>
<th>DDT compound</th>
<th>Population</th>
<th>Tissue</th>
<th>Mean concentration</th>
<th>Units as reported</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDE</td>
<td>Frequent GLSCF (Lake Erie) males (n=89); females (n=67); males controls (n=31); female controls (n=17)</td>
<td>Serum</td>
<td>3.8 (males), 2.0 (females), 2.0 (controls, males), 1.7 (controls, females) (geometric means)</td>
<td>ppb</td>
<td>Hanrahan et al. 1999</td>
</tr>
<tr>
<td>ΣDDT</td>
<td>1982 Great Lakes fish eaters (n=572); Controls (n=419)</td>
<td>Serum</td>
<td>28.8 10.6 (controls)</td>
<td>ppb</td>
<td>Hovinga et al. 1992</td>
</tr>
<tr>
<td>ΣDDT</td>
<td>1982 Southern Great Lakes fish eaters (n=115); Controls (n=95)</td>
<td>Serum</td>
<td>25.8 9.6 (controls)</td>
<td>ppb</td>
<td>Hovinga et al. 1992</td>
</tr>
<tr>
<td>ΣDDT</td>
<td>1989 Southern Great Lakes fish eaters (n=115); Controls (n=95)</td>
<td>Serum</td>
<td>15.6 6.8 (controls)</td>
<td>ppb</td>
<td>Hovinga et al. 1992</td>
</tr>
</tbody>
</table>

Adipose and other tissue

- **p,p'-DDT**
  - Children in Germany
    - Adipose: 0.6 (estimated from graph) mg/kg | Scheele et al. 1995
  - Bone marrow (lipid-adjusted): 1.75 (estimated from graph) mg/kg | Scheele et al. 1995

- **p,p'-DDE**
  - Woman hospital patients in New Haven, CT
    - Adipose, breast (lipid-adjusted): 132.2 (median), 54.0–418.2 (range) ng/g | Archibeque-Engle et al. 1997
    - 970 (median), 240.0–2,644.1 (range) ng/g | Archibeque-Engle et al. 1997

- **p,p'-DDT**
  - Adults in Germany
    - Bone marrow (dry lipid-adjusted): 0.364 ppm | Scheele 1998
### Table 5-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies (continued)

<table>
<thead>
<tr>
<th>DDT compound</th>
<th>Population</th>
<th>Tissue</th>
<th>Mean concentration</th>
<th>Units as reported</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>p,p’-DDE</strong></td>
<td>Adults in Germany</td>
<td>Bone marrow (dry lipid-adjusted)</td>
<td>1.689 ppm</td>
<td>ppm</td>
<td>Scheele 1998</td>
</tr>
<tr>
<td><strong>p,p’-DDE</strong></td>
<td>Women without breast cancer in Long Island</td>
<td>Adipose</td>
<td>546.7 ng/g</td>
<td>ng/g</td>
<td>Stellman et al. 1998</td>
</tr>
<tr>
<td><strong>p,p’-DDE</strong></td>
<td>Adults in Sweden who suffered sudden death</td>
<td>Liver (lipid-adjusted)</td>
<td>836 ng/g</td>
<td>ng/g</td>
<td>Weistrand and Norén 1998</td>
</tr>
<tr>
<td><strong>p,p’-DDE</strong></td>
<td>Adults in Sweden who suffered sudden death</td>
<td>Adipose, abdominal</td>
<td>788 ng/g</td>
<td>ng/g</td>
<td>Weistrand and Norén 1998</td>
</tr>
<tr>
<td><strong>p,p’-DDE</strong></td>
<td>FY1986 National Adipose Tissue Survey Composite samples (n=50, from 671 specimens)</td>
<td>Adipose</td>
<td>2,340 (SE 12) (nation) 1,710 (SE 22%) (0–14 years) 2,150 (SE 17%) (15–44 years) 3,080 (SE 13%) (45+ years)</td>
<td>ng/g</td>
<td>Lordo et al. 1996</td>
</tr>
<tr>
<td><strong>p,p’-DDT</strong></td>
<td>FY1986 National Adipose Tissue Survey Composite samples (n=50, from 671 specimens)</td>
<td>Adipose</td>
<td>177 (SE 11%) (nation) 73.0 (SE 36%) (0–14 years) 177 (SE 16%) (15–44 years) 252 (SE 13%) (45+ years)</td>
<td>ng/g</td>
<td>Lordo et al. 1996</td>
</tr>
<tr>
<td><strong>p,p’-DDE</strong></td>
<td>Women patients at Hartford Hospital, Hartford, CT</td>
<td>Adipose, breast (lipid basis)</td>
<td>2,200±1,470 cancer patients (n=20) 1,487±842 controls (n=20)</td>
<td>ng/g</td>
<td>Falck et al. 1992</td>
</tr>
<tr>
<td><strong>p,p’-DDT</strong></td>
<td>Women patients at Hartford Hospital, Hartford, CT</td>
<td>Adipose, breast (lipid-adjusted)</td>
<td>216±174 cancer patients (n=20) 148±75 controls (n=20)</td>
<td>ng/g</td>
<td>Falck et al. 1992</td>
</tr>
</tbody>
</table>

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*a* Arithmetic mean concentrations are reported unless otherwise specified.

*b* Same Southern Great Lakes fish eaters that participated in the 1982 study.

FY = fiscal year; ND = not detected; SE = standard error
Fish from areas like the Great Lakes and Baltic Sea appear to be an important source of exposure to DDT and DDE, and human blood levels of these compounds have been found to correlate with the consumption of fish containing high levels of DDT and DDE (Anderson et al. 1998; Asplund et al. 1994; Hovinga et al. 1992). A Swedish study found that the mean plasma lipid concentrations of \( p,p' \)-DDE were 750, 1,200, and 4,500 ng/g in groups of men eating no fish, moderate quantities of fish, and large quantities of fish, respectively, from the Baltic Sea (Asplund et al. 1994). The respective lipid plasma concentrations of \( p,p' \)-DDT in these groups of men were 20, 45, and 130 ng/g. The mean serum DDT level in individuals eating more than 20 pounds of sport-caught Great Lakes fish dropped from 25.8 to 15.6 ppb (65% decrease) during the period from 1982 to 1989. Mean serum DDT levels in the controls dropped from 9.6 to 6.8 ppb (41% decrease). It was concluded that the decrease in serum DDT concentrations was due to lower levels of DDT in the fish and in the environment, rather than to a decrease in fish consumption (Hovinga et al. 1992).

A study of residents in Triana, Alabama, living downstream from a former DDT manufacturing facility revealed mean serum levels of total DDT of 76.2 ppb (Kreiss et al. 1981). This was several times higher than other reported levels. Kreiss et al. (1981) also found that serum DDT levels increased with increasing age.

Mean levels of total equivalent of DDT, DDE, and DDD in maternal blood in pregnant women in India (20 samples) were found to be 25.3 ppb compared to levels in placental tissue of 22.2 ppb (Saxena et al. 1987). Similar levels (30.8 ppb) were seen in maternal blood in Brazilian women (Procianoy and Schwartsman 1981). Saxena et al. (1981, 1983) presented data on a limited number of samples of blood and placental tissues of women that aborted or delivered prematurely, which suggested that \( p,p' \)-DDE concentrations were elevated compared to control groups.

Adipose tissue from a subgroup of 40 workers engaged in spraying DDT for malaria control in Mexico contained the following median and maximum levels of DDT metabolites (µg/g): \( \Sigma \)DDT, 114.60, 665.56; \( p,p' \)-DDT, 46.96, 344.98; \( o,p' \)-DDT, 2.96, 29.74; \( p,p' \)-DDE, 64.96, 298.42; and \( p,p' \)-DDD, 0.62, 3.51 (Rivero-Rodriguez et al. 1997). Based on these measurements and a survey of the work habits of other workers, a geometric mean \( p,p' \)-DDE concentration of 67.41 µg/g was predicted for the population of 331 workers, 80% of whom were employed in the sanitation campaign for 20 years. Mean \( \Sigma \)DDT serum level in a group of 26 malaria control sprayers in Brazil was 76.9 µg/L and ranged from 7.5 to 473.5 µg/L, whereas 16 unexposed workers had mean serum levels of 16.1 µg/L (range: 5.1–32.9 µg/L) (Minelli and
Ribeiro 1996). \( p,p' \)-DDT and \( p,p' \)-DDE serum levels in the exposed workers ranged from 1.6 to 62.9 and 5.9 to 405.9 \( \mu g/L \), respectively.

## 5.6 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 2.7 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, and breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child’s diet often differs from that of adults. The developing human’s source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child’s behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not have the judgment of adults to avoid hazards (NRC 1993).

Children are exposed to DDT through their diet. Since the greatest dietary intake of DDT is from meat, fish, poultry, and dairy products, infants and young children for whom a substantial part of their food is milk may be exposed to DDT. According to the FDA study of 1986–1991, the mean daily intake of DDT and its metabolites is 0.0448, and 0.0438 \( \mu g/kg \) body weight/day for a 6–11-month-old infant and 2-year-old child, respectively (Gunderson 1995b). This is roughly four times the intake per unit body weight for an adult (see Table 5-3).

DDT and DDE selectively partition into fatty tissue and into human breast milk, which has a higher fat content than cow's milk. The concentration of DDT, or other hydrophobic pollutants, in milk is often expressed on a lipid basis (i.e., \( \mu g/g \) lipid rather than \( \mu g/mL \) milk) as it is a more accurate measure of DDT content due to the fluctuating fat content of the milk. Generally, these compounds are found in human breast milk in concentrations higher than in cow's milk or other infant foods. As a result, breast-fed infants may receive higher dietary exposure than those who are not breast-fed. If a woman has been exposed to high levels of DDT in the past, her milk may contain high levels of DDT, which would be transferred to her child. Women exposed to high levels of DDT would include Eskimos and Indian women in Arctic regions who eat traditional foods as well as women who eat large quantities of fish from lakes and rivers known to have high concentrations of DDT in fish, such as the Great Lakes and the
Yakima River, Washington (Kuhnlein et al. 1995; Marien and Laflamme 1995). Methods have been proposed for estimating breast milk lipid concentrations of DDT from a mother’s daily intake (Marien and Laflamme 1995). Mean levels of \( p,p' \)-DDT in human breast milk in pooled milk from the Mothers’ Milk Center in Stockholm steadily declined from 0.71 µg/g lipid in 1972 to 0.36, 0.18, and 0.061 µg/g lipid in 1976, 1980, and 1984–1985, respectively (Noren 1988). Mean levels of \( p,p' \)-DDE for these years were 2.42, 1.53, 0.99, and 0.50 µg/g lipid, respectively. Between 1967 and 1985, the levels of \( p,p' \)-DDE and \( p,p' \)-DDT in human milk in Sweden declined by 75 and 95% (Noren 1993). The use of DDT was banned in Sweden in 1970. Mean (maximum) \( p,p' \)-DDT concentrations in 54 samples of mothers’ milk from Hawaii (1979–1980) were 0.16 (0.52) µg/g lipid compared with 0.19 (1.7) µg/g lipid in 102 samples from the mainland U.S. (Takei et al. 1983). Mean (maximum) \( p,p' \)-DDE levels in Hawaiian and mainland samples were 2.0 (5.7) and 1.9 (11.0) µg/g lipid. A 1982 Canadian survey that included 210 samples of breast milk from across the country resulted in mean levels of \( p,p' \)-DDE, \( p,p' \)-DDT, \( p,p' \)-DDD, and \( o,p' \)-DDT in ng/g milk (ng/g milkfat) of 34 (911), 3 (80), 1 (27), and trace (12), respectively, down from 103, 33, 4, and 5 ng/g milk, respectively, obtained in a 1967 survey (Mes et al. 1986). The maximum \( p,p' \)-DDE, \( p,p' \)-DDT, \( p,p' \)-DDD, and \( o,p' \)-DDT levels in the 1982 survey were 5,500, 450, 113, and 58 ng/g milkfat. Levels of DDT in breast milk have shown a downward trend starting in about 1970. In 28 studies from the United States and Canada, average DDT levels in breast milk were about 4,000–5,000 ng/g lipid in the early 1970s, and then steadily declined by 1975. For 13 studies from 1975 on, there was an 11–21% reduction in mean \( \Sigma \)DDT levels per year. Another way of viewing this is that the mean breast milk level in the population is being reduced by one-half in 4.2–5.6 years. Similar reductions have been observed in Western European countries. While exposure of humans by eating fish from the Great Lakes has been a source of concern, in one study, Mes and Malcolm (1992) found that levels of DDE and DDT in breast milk were lower in women in the Great Lake’s Basin than in women in the rest of Canada. Levels of DDE in cow’s milk have similarly declined. The mean level of DDE in milk supplies in Southern Ontario, Canada declined from 96 ng/g lipid in 1970–1971 to 16 ng/g lipid in 1985–1986, indicating that the levels are being reduced by one-half in 5.8 years (Frank and Braun 1989). Since levels of DDT in food have been declining, exposure of children to DDT through their diet would be much less than in the past.

Children may be exposed to DDT by ingesting contaminated soil or dust, from dermal contact with the soil, or by inhaling in the dust and then swallowing it after mucociliary transport up out of the lungs. DDT is extremely persistent in soil and there are soils that still contain high levels of the insecticide. No reports have been found, however, concerning childhood exposures to DDT by ingesting dirt. DDT is strongly adsorbed to soil, especially when the organic content of the soil is high. No studies were found
as to how bioavailable DDT-adsorbed soil is when ingested. In addition, no information was found on the absorption of ingested DDT in any form in children. Children may also be exposed to DDT improperly stored at waste sites. A recent study indicated that old carpeting may contain high levels of DDT (Lewis et al. 1994). The DDT may have contaminated the carpet material or may have been tracked in from outside. Children may be exposed to this DDT while crawling around or playing on contaminated carpeting.

Since DDT partitions into lipids and is not readily metabolized, levels of DDT in adipose tissue increase with age. Levels of DDT and DDE in children aged 0–14 as reported in EPA’s FY 1986 National Adipose Tissue Survey appear in Table 5-4 (Lordo et al. 1996).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Because of the ban on DDT use after 1972, fewer persons in the United States should be exposed to high levels of these compounds today than in the past. Only fish and marine mammal consumption in the Arctic appear to be significant dietary contributors to human exposure to DDT in the general population (Laden et al. 1999). A 1982 study by the Michigan Department of Public Health found that people eating large quantities of Great Lakes fish had significantly higher serum DDT levels compared to non-fish-eating controls. Furthermore, fish consumption was a major predictor of exposure. A follow-up study in 1989 found that serum DDT levels were primarily a reflection of historic exposures and previously established body burden rather than recent exposure (Hovinga et al. 1993). Other studies confirm these findings (Anderson et al. 1998; Hanrahan et al. 1999). The best predictors of serum DDE levels in frequent Great Lakes sport fish consumers were found to be age, years of eating sport caught fish, male gender, and body mass index (BMI) which respectively accounted for 20%, 10%, 9%, and 9% of the variance (Hanrahan et al. 1998). In general, DDT-contaminated fish are caught by sport or subsistence fisherman and not purchased at the market (Laden et al. 1999). As the levels of DDT in Great Lakes fish decline, fish consumption is less likely to be a source of potentially high exposure. Because of the partitioning of DDT and DDE into fatty tissue and fluids, breast-fed infants are likely to receive doses in excess of those occurring from ingestion of cow's milk or other infant foods. Monitoring exposure of infants via breast milk has been extensive and provides evidence of the persistence of DDT and DDE in fatty tissues. The finding that old carpeting may contain high levels of DDT indicates that this may be an important, but unevaluated source of exposure, especially in small children crawling on the carpeting (Lewis et al. 1994). More details about children’s exposures can be found in Section 5.6 Exposures of Children.
5. POTENTIAL FOR HUMAN EXPOSURE

Workers involved with formulation, packaging, and application of DDT in the past would be expected to have been exposed to levels higher than those encountered in the environment. Persons who live near NPL sites containing DDT, DDE, or DDD might be exposed to higher levels than the general population since DDT has been detected in 397 of the 1,560 hazardous waste sites that have been proposed for inclusion on the EPA NPL (HazDat 1999).

5.8 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 DDT, DDE, and DDD is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of DDT, DDE, and DDD.

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.

5.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of \( p,p' \)-DDT, DDE, and DDD are well described in the literature although there are some gaps in data for the \( o,p' \)-isomers (see Table 3-2). The \( p,p' \)-isomers are those of primary environmental concerns and the data available are sufficient to allow estimation of the environmental fate of DDT, DDE, and DDD.

Production, Import/Export, Use, Release, and Disposal. Since the banning of DDT in the early 1970s in the United States, there has been little information published on the production of DDT. DDT is no longer produced in the United States or in most countries in the world. The most recent information indicates that it is produced in at least two countries, and is used in some underdeveloped countries for vector control. However, data would be useful on the production and use of DDT worldwide. This type of information is important for estimating the potential for environmental releases from
various uses, as well as estimating the potential environmental burden. In turn, this would provide a basis for estimating potential exposure and public health risk.

Disposal information is equally important for determining environmental burden and areas where environmental exposure may be high. Although disposal methods for DDT and its metabolites are reported to a limited extent, no current information on disposal sites and quantity disposed was located. Information on how the current users (e.g., hazardous waste clean-up crews) wash DDT equipment and dispose of the remaining waste would be helpful for estimating potential environmental and human exposure.

**Environmental Fate.** DDT, DDE, and DDD released to the environment may be transported from one medium to another by the processes of solubilization, adsorption, bioaccumulation, or volatilization. The transport of DDT, DDE, and DDD between environmental compartments has been predicted mostly from their physical and chemical properties. Volatilization and adsorption account for loss of DDT and its metabolites from surface water and soil. Monitoring studies indicate that DDT and its isomers and metabolites are extremely persistent in soil (EPA 1986a) and substantiate their predicted environmental fate. DDT, DDE, and DDD are highly lipid soluble. This, combined with their extremely long persistence, contributes to bioaccumulation of DDT and its metabolites in freshwater and marine life. Limited data were located on the soil degradation rates of DDT and its metabolites. Data are available for disappearance rates including losses due to transport processes. While adequate data are available on the time for the disappearance of 50% of the DDT initially applied to a variety of soils, there is abundant evidence that subsequent declines in DDT in soil occur at a much slower rate largely due to an aging process. More data on the biodegradation rates of DDT and its metabolites as well as how soil properties and aging affect these rates would be useful. Experimental information characterizing the environmental fate of DDT, DDE, and DDD, particularly on those properties that govern transport to air, would be helpful to further confirm their predicted environmental behavior and potential human exposure.

**Bioavailability from Environmental Media.** Limited information was located regarding the bioavailability of DDT, DDE, and DDD from environmental media. It has been shown that the bioavailability of DDT in soil declines with time (Alexander 1995, 1997; Robertson and Alexander 1998) and soil properties that influence the bioavailability of DDT and its toxicity to certain organisms have been studied (Peterson et al. 1971). More information regarding the aging process of DDT in soil and its affect on bioavailability would be helpful in identifying potential routes of human exposure. It is known that fish and some plants bioaccumulate these compounds and that those who consume these fish and
plants will incur some exposure to these compounds. However, because of universal body burdens of these compounds, the relative contribution of any particular medium, especially soil and sediment, is not clearly understood. Even if DDT, DDE, and DDD concentrations in various media are known, the difference between the exposure level and the absorbed dose is still unknown.

**Food Chain Bioaccumulation.** Information was located regarding food chain biomagnification of total DDT in the arctic marine food web (Hargrave et al. 1992). However, little information was located regarding food chain biomagnification of DDT, DDE, and DDD in food webs to which most humans are likely to be exposed. Fairly extensive monitoring of fish populations has been performed and a bioconcentration factor in fish is available. The steady-state BCF in rainbow trout was reported as 12,000, suggesting that bioconcentration in aquatic organisms is very high (Oliver and Niimi 1985). Although DDT has been detected in plants and vegetables, root uptake of DDT is considered low (Fuhrmann and Lichtenstein 1980; Lichtenstein and Schultz 1980). A clearer understanding of the potential for bioaccumulation would aid in determining how levels in the environment affect the food chain and potentially impact human exposure levels. This type of information could be obtained by studying accumulation of these compounds in organisms from several trophic levels.

**Exposure Levels in Environmental Media.** Information on environmental levels of DDT, DDE, and DDD are abundant for the 1970s and 1980s (Blus et al. 1987; Carey et al. 1979b; Crockett et al. 1974; Ford and Hill 1990; Hargrave et al. 1992; Lichtenberg et al. 1970; Stanley et al. 1971). More recent information has been more limited in scope (Aigner et al. 1998; McConnell et al. 1998; Monosmith and Hermanson 1996). Continuation of data collection on environmental levels would contribute to the understanding of current worldwide concentrations and trends.

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

Estimates of human intake have been limited to dietary intakes based on current market basket surveys (EPA 1980a; Gartrell et al. 1985, 1986a, 1986b; Gunderson 1995a). Additional information is needed relating to the levels in environmental media to which the general population is exposed, particularly at or near hazardous waste sites, and the subsequent development of health effects.
5. POTENTIAL FOR HUMAN EXPOSURE

**Exposure Levels in Humans.** Data are available on levels of DDT and its metabolites in adipose tissue, blood, and milk (Hovinga et al. 1992; Lordo et al. 1996; Smith 1999). Recent monitoring data appear in Table 5-4.

**Exposures of Children.** More data are needed on the concentrations of DDT in breast milk of exposed women and on the DDT intake of breast-fed infants. In addition, the oral availability of DDT from soil and dust is lacking. Such data would allow for the estimation of the exposure of children to DDT from eating soil and dust.

Child health data needs relating to susceptibility are discussed in Section 2.12.2, Identification of Data Needs: Children’s Susceptibility.

**Exposure Registries.** No exposure registries for DDD, DDE, or DDD were located. The ATSDR Division of Health Studies will consider these chemicals when primary chemical selection is made for future subregistries for the National Exposure Registry. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to these substances.

**5.8.2 Ongoing Studies**

The bioavailability of DDT, DDE, and DDD in soils to earthworms and the estimation of bioavailability by chemical extraction methods is being investigated by Professor Martin Alexander and coworkers at Cornell University. These studies will aid in the understanding of how the aging process of chemicals affects bioavailability.
6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and monitoring DDT, DDE, and DDD, their metabolites, and other biomarkers of exposure and effect to DDT, DDE, and DDD. 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.

6.1 BIOLOGICAL SAMPLES

Table 6-1 lists the analytical methods used for determining DDT in biological fluids and tissues. DDT, DDE, and DDD residues have been measured in biological samples such as adipose tissue, skin lipids, blood serum, urine, milk, and other samples primarily by gas chromatographic (GC) methods coupled with electron capture detectors (ECD). GC methodology can distinguish between the \( p,p' \)- and \( o,p' \)-isomers of the compounds. The GC methodology proposed by Cranmer et al. (1972b) has detected DDT, DDE, and DDD in human urine at levels as low as 50 pg/sample. Various authors cited in Table 6-1 used GC methods to monitor the residues of these compounds in blood, serum, semen, liver, human milk, and adipose tissue, which were detectable at the ppm and ppb level. Since DDT partitions in fat, analyses are often performed on adipose tissue, milk fat, or a lipid extract of serum or other material. In the latter case, the results may be reported on a lipid or fat basis (i.e., ng DDT/g lipids). By reporting monitoring studies of DDT on a lipid basis, variability in results due to variability in fat content is reduced (McKinney et al. 1984).

A methyl sulfonyl metabolite of DDE that has been found in many tissue samples, 3-methyl sulfonyl 2,2-bis(4-chlorophenyl)-1,1-dichloroethene, can be analyzed by GC/mass spectrometry (MS) or GC/ECD, which are the principle methods of analysis for DDT and its analogs (Janak et al. 1998; Noren et al. 1996). However, the use of atomic emission detection significantly improves its determination (Janak et al. 1998).
## Table 6-1. Analytical Methods for Determining DDT, DDE, and DDD in Biological Samples

<table>
<thead>
<tr>
<th>Sample matrix</th>
<th>Sample preparation</th>
<th>Analytical method</th>
<th>Sample detection limit</th>
<th>Percent recovery</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood/plasma/serum</td>
<td>Extract with hexane</td>
<td>GC/ECD</td>
<td>2 ppb (DDT); 1 ppb (DDE); 2 ppb (DDD)</td>
<td>&gt;90% (DDT); 100–110% (DDE); No data (DDD)</td>
<td>EPA 1980b; Nachman et al. 1972</td>
</tr>
<tr>
<td>Blood/plasma/serum</td>
<td>Extract with methanol and hexane-ethyl ethers; cleanup with Florisil</td>
<td>GC/ECD</td>
<td>0.8 ppb (DDE); No data (DDT, DDD)</td>
<td>90–100% (DDE); No data (DDT, DDD)</td>
<td>McKinney et al. 1984</td>
</tr>
<tr>
<td>Blood</td>
<td>Extract with hexane; concentrate to 5 mL</td>
<td>GC/ECD HERL_004</td>
<td>No data</td>
<td>No data</td>
<td>EMMI 1997</td>
</tr>
<tr>
<td>Semen</td>
<td>Extract with acetone; cleanup with Florisil</td>
<td>GC/ECD</td>
<td>No data</td>
<td>96–97% (DDT); 91.4% (DDE); 91.4% (DDD)</td>
<td>Waliszewski and Syzmczneki 1983</td>
</tr>
<tr>
<td>Urine</td>
<td>Extract with acetic acid in hexane followed by methylation</td>
<td>HPLC/NAA</td>
<td>0.01 mg/mL (DDT); No data (DDE, DDD)</td>
<td>No data</td>
<td>Opelanio et al. 1983</td>
</tr>
<tr>
<td>Urine</td>
<td>Extract with hexane</td>
<td>GC/ECD</td>
<td>2 pg (DDE); No data (DDT, DDD)</td>
<td>93.2–106.2% (DDE); No data (DDT, DDD)</td>
<td>Muhlebach et al. 1985</td>
</tr>
<tr>
<td>Liver, Kidney, Human milk</td>
<td>Macerate sample with acetonitrile; cleanup with Florisil</td>
<td>GC/ECD</td>
<td>No data</td>
<td>81% (DDD); No data (DDT, DDD)</td>
<td>Ando 1979; EPA 1980b</td>
</tr>
<tr>
<td>Muscle</td>
<td>Homogenized and extracted with hexane</td>
<td>GC/ECD</td>
<td>2 pg (DDE); No data (DDT, DDD)</td>
<td>93.2–106.2% (DDE); No data (DDT, DDD)</td>
<td>Muhlebach et al. 1985</td>
</tr>
<tr>
<td>Sample matrix</td>
<td>Sample preparation</td>
<td>Analytical method</td>
<td>Sample detection limit</td>
<td>Percent recovery</td>
<td>Reference</td>
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<td>------------------------</td>
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</tr>
<tr>
<td>Human milk</td>
<td>Triple solvent extraction with ethanol, hexane, and hexane-ethyl ether; Florisil cleanup</td>
<td>GC/ECD</td>
<td>2 ppb (DDE); No data (DDT, DDD)</td>
<td>81–108% (DDE); No data (DDT, DDD)</td>
<td>McKinney et al. 1984</td>
</tr>
<tr>
<td>Human milk</td>
<td>Extract with hexane; cleanup with Florisil</td>
<td>GC/MS</td>
<td>2 ppb (DDT); 1.5 ppb (DDD); No data (DDE)</td>
<td>80–100% (DDD); No data (DDT, DDE)</td>
<td>Krauthacker et al. 1980</td>
</tr>
<tr>
<td>Milk/Adipose tissue</td>
<td>Extract with hexane and petroleum ether; cleanup with GPC</td>
<td>GC/ECD HERL_026</td>
<td>No data</td>
<td>No data</td>
<td>EMMI 1997</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Digest with perchloric-acetic acid; extract with n-hexane</td>
<td>GC/ECD</td>
<td>2 pg (DDE); No data (DDT, DDD)</td>
<td>93.2–106.2% (DDE); No data (DDT, DDD)</td>
<td>Muhlebach et al. 1985</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>Extract with petroleum ether, cleanup with Florisil</td>
<td>GC/ECD</td>
<td>No data</td>
<td>85–100% (DDT); No data (DDD, DDE)</td>
<td>EPA 1980b</td>
</tr>
<tr>
<td>Feces</td>
<td>Hexane extraction; evaporate and reconstitute with isooctane</td>
<td>GC/ECD</td>
<td>20 ppb (DDT, DDE); No data (DDD)</td>
<td>92–111% (DDT); 96–109% (DDE); No data (DDD)</td>
<td>Saady et al. 1992</td>
</tr>
<tr>
<td>Lymph</td>
<td>Co-extract with ether; final extraction with cyclopentanone</td>
<td>HPLC</td>
<td>No data</td>
<td>96.4% (DDT); No data (DDE, DDD)</td>
<td>Noguchi et al. 1985</td>
</tr>
<tr>
<td>Skin lipids</td>
<td>Purify with GPC, wash with sulfuric acid</td>
<td>GC/ECD</td>
<td>No data</td>
<td>96–109% (DDE); No data (DDT, DDD)</td>
<td>Sasaki et al. 1991b</td>
</tr>
</tbody>
</table>
Table 6-1. Analytical Methods for Determining DDT, DDE, and DDD in Biological Samples *(continued)*

<table>
<thead>
<tr>
<th>Sample matrix</th>
<th>Sample preparation</th>
<th>Analytical method</th>
<th>Sample detection limit</th>
<th>Percent recovery</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milk (MeSO₂-DDE*)</td>
<td>Liquid-gel partitioning followed by adsorption and GPC cleanup</td>
<td>capillary GC/MS</td>
<td>No data</td>
<td>80%, mean (MeSO₂-DDE)</td>
<td>Noren et al. 1996</td>
</tr>
<tr>
<td>Lung, blubber, liver</td>
<td>Extraction with GPC cleanup</td>
<td>GC/ECD</td>
<td>No data</td>
<td>No data</td>
<td>Janak et al. 1998</td>
</tr>
<tr>
<td>(MeSO₂-DDE)</td>
<td></td>
<td>GC/AED</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aDDE methyl sulfone

AED = atomic emission detection; ECD = electron capture device; GC = gas chromatography; GPC = gel permeation chromatography; HERL = Health and Environmental Research Laboratory of the Environmental Protection Agency; HPLC = high performance liquid chromatography; MS = mass spectrometry; NAA = neutron activation analysis.
6. ANALYTICAL METHODS

While methods exist for measuring DDT, DDE, and DDD in liver, breast milk, and adipose tissue, samples of blood, urine, and semen are most frequently analyzed to determine exposure because of ease of sample collection. DDT, DDE, and DDD can also be measured in skin lipids collected by wiping the face with cotton (Sasaki et al. 1991b). Although these methods can detect and quantify levels of DDT, there is no information available to quantitatively correlate levels in these fluids with environmental levels or toxic effects.

6.2 ENVIRONMENTAL SAMPLES

DDT residues are found in the environment because of its slow transformation. DDT was used as an insecticide from the late 1940s until the early 1970s. Well-established analytical test procedures to analyze environmental samples use GC and MS (see Table 6-2). EPA methods 608 and 8081B are recommended to detect DDT, DDE, and DDD in surface water and municipal and industrial discharges (EPA 1982, 1998j). These are required procedures under the Clean Water Act. Behzadi and Lalancette (1991) described a modified isotope dilution (MID) GC/MS method to analyze DDT, DDE, and DDD in water and soil samples. Sample preparation for MID GC/MS does not require extensive extraction and cleanup compared to GC/MS. The detection limits are in the 0.001 µg/L (ppt) range, and recoveries range from 73 to 110% for soil and from 90 to 116% for water. EPA methods 8081B and 8270D are GC/MS methods used to determine DDT and its metabolites in soils with detection limits of 0.3–0.4 µg/kg (EPA 1998j, 1998k). GC/ECD and nitrogen-phosphorus detection (NPD) is used for the analysis of DDT in foods with a detection limit of 0.5 µg/kg (ppb) (Rodriguez et al. 1991). GC/ECD is also used for the analysis of DDT and its metabolites in fish, oysters, and waterfowl. Detection limits were reported in the ppb range and recoveries ranged from 66 to 97% (Blus et al. 1987; Ford and Hill 1991; Long et al. 1991b; Lott and Barker 1993). Silica acid column chromatography has been used for the analysis of DDT and its metabolites in air samples (Bidleman et al. 1978). The detection limit for DDT in air was reported to be 0.16 ng/m³ (Bidleman et al. 1978). Spectrometry with an automatic quench correction facility was used for the analysis of DDT in rice, maize, and grain plants. Recoveries ranged from 92 to 99%, and detection limits were not reported (Verma and Pillai 1991a). Even though analytical methods exist for detection of DDT in almost all samples, many references did not state detection limits or accuracy of the method.
<table>
<thead>
<tr>
<th>Sample matrix</th>
<th>Sample preparation</th>
<th>Analytical method</th>
<th>Sample detection limit</th>
<th>Percent recovery</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air</td>
<td>Separate with silicic acid column</td>
<td>GC/ECD</td>
<td>0.20 ng/m³ (DDE); 0.16 ng/m³ (DDT)</td>
<td>104–106% (DDT); 100% (DDE); No data (DDD)</td>
<td>Bidleman et al. 1978</td>
</tr>
<tr>
<td>Air</td>
<td>Filter collection and iso-octane extraction</td>
<td>GC</td>
<td>0.49–2.60 mg/m³ (DDT); No data (DDD, DDE)</td>
<td>No data</td>
<td>NIOSH 1977</td>
</tr>
<tr>
<td>Air</td>
<td>Sample collection on glass fiber filter; Soxhlet extraction; cleanup with alumina</td>
<td>GC/ECD AREAL Method TO-4</td>
<td>No data</td>
<td>No data</td>
<td>EMMI 1997</td>
</tr>
<tr>
<td>Water</td>
<td>Extract using hexane followed by acetonitrile</td>
<td>GC</td>
<td>No data</td>
<td>85% (DDT); No data (DDD, DDE)</td>
<td>Kurtz 1977</td>
</tr>
<tr>
<td>Water</td>
<td>Extract using methylene chloride cleanup with Florisil</td>
<td>GC/ECD EPA Method 608</td>
<td>0.012 µg/L (DDT); 0.004 µg/L (DDE); 0.011 µg/L (DDD)</td>
<td>92% (DDT, DDD); 89% (DDE)</td>
<td>EPA 1982</td>
</tr>
<tr>
<td>Water</td>
<td>Extract at neutral pH with methylene chloride</td>
<td>GC/ECD or GC/ELC EPA Method 8081B</td>
<td>0.081 µg/L (DDT); 0.058 µg/L (DDE); 0.050 µg/L (DDD).</td>
<td>121.1% (4,4'-DDT); 98.0% (4,4'-DDE); 86.8% (4,4'-DDD)</td>
<td>EMMI 1997; EPA 1998</td>
</tr>
<tr>
<td>Water</td>
<td>Digest with chromic acid; extract with hexane</td>
<td>GC</td>
<td>No data</td>
<td>100% (DDT, DDE); No data (DDD)</td>
<td>Driscoll et al. 1991</td>
</tr>
<tr>
<td>Water</td>
<td>Extract with methylene chloride</td>
<td>MID GC/MS</td>
<td>0.012 µg/L (DDT); 0.007 µg/L (DDE); 0.008 µg/L (DDD)</td>
<td>93–110% (DDT); 73–110% (DDE); 76–110% (DDD)</td>
<td>Behzadi and Lalancette 1991</td>
</tr>
<tr>
<td>Finished drinking water and groundwater</td>
<td>Extract with methylene chloride; solvent exchange to methyl tert-butyl ether</td>
<td>GC/ECD EPA Method 508</td>
<td>0.060 µg/L (DDT); 0.010 µg/L (DDE); 0.003 µg/L (DDD)</td>
<td>No data</td>
<td>EMMI 1997</td>
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Table 6-2. Analytical Methods for Determining DDT, DDE, and DDD in Environmental Samples (continued)

<table>
<thead>
<tr>
<th>Sample matrix</th>
<th>Sample preparation</th>
<th>Analytical method</th>
<th>Sample detection limit</th>
<th>Percent recovery</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soil</td>
<td>Extract with hexane/acetone; cleanup with Florisil</td>
<td>GC/ECD AOAC 970.52</td>
<td>No data</td>
<td>No data</td>
<td>Helrich 1990</td>
</tr>
<tr>
<td>Soil</td>
<td>Extract with hexane/acetone; cleanup with Florisil</td>
<td>GC/ECD</td>
<td>No data</td>
<td>No data</td>
<td>Williams 1984</td>
</tr>
<tr>
<td>Soil</td>
<td>Extract with hexane-acetone or methylene chloride-acetone, cleanup by appropriate method.</td>
<td>GC/ECD or GC/ELCD EPA Method 8081B</td>
<td>0.0036 µg/kg (DDT); 0.0025 µg/kg (DDD); 0.0042 µg/kg (DDE)</td>
<td>121.1% (DTT); 98.0% (DDE); 86.8% (DDD)</td>
<td>EMMI 1997; EPA 1998j</td>
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<tr>
<td>Soil</td>
<td>Extraction with methylene chloride</td>
<td>GC/MS EPA Method 8270D</td>
<td>No Data</td>
<td>111-134% (DDT)</td>
<td>EPA 1998k</td>
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<tr>
<td>Soil</td>
<td>Extraction with methylene chloride</td>
<td>MID GC/MS</td>
<td>0.4 µg/kg (DDT); 0.3 µg/kg (DDD); 0.3 µg/kg (DDE)</td>
<td>91–109% (DDT); 90–116% (DDD); 93–104% (DDE)</td>
<td>Behzadi and Lalancette 1991</td>
</tr>
<tr>
<td>Food</td>
<td>Extract with acetonitrile into petroleum ether; cleanup with Florisil</td>
<td>GC/ECD</td>
<td>No data</td>
<td>&gt;80%</td>
<td>McMahon and Burke 1978; Williams 1984</td>
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<tr>
<td>Food</td>
<td>Soxhlet extraction using redistilled hexane</td>
<td>on-line SEC-GC</td>
<td>10–50 µg/kg (DDE); No data (DDT, DDD)</td>
<td>No data</td>
<td>Grob and Kalin 1991</td>
</tr>
<tr>
<td>Food</td>
<td>Extract with n-hexane; cleanup with Florisil</td>
<td>GC-ECD/NPDMS</td>
<td>0.50–10 µg/kg (DDT, DDE); No data (DDD)</td>
<td>68—95% (DDT, DDE); No data (DDD)</td>
<td>Rodriguez et al. 1991</td>
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<tr>
<td>Food</td>
<td>Mixed ether extraction; cleanup with Florisil</td>
<td>DC-GC/ECD</td>
<td>0.05–1.5 ng (DDT, DDE); No data (DDD)</td>
<td>No data</td>
<td>Hopper 1991</td>
</tr>
<tr>
<td>Food</td>
<td>Mix sample with dried potassium bromide powder</td>
<td>IR/UV-SP</td>
<td>No data</td>
<td>No data</td>
<td>Gore et al. 1971</td>
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</tbody>
</table>
Table 6-2. Analytical Methods for Determining DDT, DDE, and DDD in Environmental Samples (continued)

<table>
<thead>
<tr>
<th>Sample matrix</th>
<th>Sample preparation</th>
<th>Analytical method</th>
<th>Sample detection limit</th>
<th>Percent recovery</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal fat</td>
<td>Extract with methylene chloride/cyclohexane; separation by GPC</td>
<td>GC/ECD AOAC 984.21</td>
<td>No data</td>
<td>No data</td>
<td>Helrich 1990</td>
</tr>
<tr>
<td>Plants</td>
<td>Extract with hexane/methanol/acetone</td>
<td>SP</td>
<td>No data</td>
<td>92–99% (DDT); No data (DDD, DDE)</td>
<td>Verma and Pillai 1991a</td>
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<tr>
<td>Plants</td>
<td>Extract with methylene chloride; organic phase concentrated</td>
<td>GC/HECD AOAC 985.22</td>
<td>No data</td>
<td>No data</td>
<td>Helrich 1990</td>
</tr>
<tr>
<td>Fish</td>
<td>Soxhlet extraction with hexane; cleanup with Florisil</td>
<td>GC/ECD</td>
<td>10 µg/kg</td>
<td>No data</td>
<td>Ford and Hill 1991</td>
</tr>
<tr>
<td>Fish</td>
<td>Extract with petroleum ether; cleanup with Florisil</td>
<td>GC/ECD AOAC 983.21</td>
<td>No data</td>
<td>No data</td>
<td>Helrich 1990</td>
</tr>
</tbody>
</table>

AOAC = Association of Official Analytical Chemists; AREAL = Atmospheric Research and Exposure Laboratory of the Environmental Protection Agency; DC = dual capacity; ECD = electron capture device; ELCD = electrolytic conductivity detector; EPA = Environmental Protection Agency, GC = gas chromatography; GPC = gel permeation chromatography, HECD = halogen-specific electron capture device, IR/UV infrared/ultraviolet, MID = modified isotope dilution, MS = mass spectrometry, NPD = nitrogenphosphorous detection, SEC = size exclusion chromatography, SP = spectro-photometry.
6.3 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 DDT, DDE, and DDD is available. Where adequate information is not available, ATSDR, in conjunction with the 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 DDT, DDE, and DDD.

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.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

*Exposure.* Methods for the analysis of DDT, DDE, and DDD in blood/plasma, semen, urine, liver, kidney, adipose tissue, skin lipids, human milk, and lymph are described in the literature. These methods are helpful in estimating the potential health risk of exposed populations. In certain cases, spike recoveries were performed in a variety of biological samples to determine the recovery efficiency and analytical sensitivity of the method. In some cases, information was unavailable on the detection limit and accuracy of a method. Obtaining detection limits and information on the accuracy of a method is important to effectively and precisely quantify the parent compound and metabolites in a biological system. Once tissue levels of DDT, DDE, and DDD are obtained, there is no acceptable methodology for extrapolating backwards from those tissue levels to the amount of exposure. Even in those studies in which volunteers were fed measured doses of DDT, such a relationship could not be determined because of bioaccumulation of DDT and its metabolites in adipose tissues and because of individual variability. Further research would help in understanding the relationship between exposure and DDT levels measured in body compartments.
6. ANALYTICAL METHODS

*Effect.* No specific biomarkers of effect have been determined. Until these biomarkers are determined, methodology needed to identify them cannot be established.

**Methods for Determining Parent Compounds and Degradation Products in Environmental Media.**

Human exposure is most likely to occur from ingesting food contaminated with small amounts of DDT, DDE, or DDD. Analytical methods are available for measuring DDT, DDE, and DDD in air, water, soil, fish, waterfowl, plants, and food. Of the techniques available, MID GC/ECD appears to be the most sensitive for measuring background levels of DDT, DDE, and DDD in all environmental media.

No information was available on background levels of DDT, DDE, or DDD at which health effects occur. Although analytical techniques are available for measuring DDT, DDE, and DDD in environmental media, further information on the accuracy and precision of these techniques is needed.

**6.3.2 Ongoing Studies**

No ongoing studies were located on the analytical methods of DDT, DDE, or DDD.
7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and advisories regarding DDT, DDE, and DDD in air, water, and other media are summarized in Table 7-1.

ATSDR has derived an acute-duration oral MRL of $5 \times 10^{-4}$ mg/kg/day for DDT based on effects on perinatal development of the nervous system in neonatal mice with behavioral neurotoxicity manifested in the adult animals (Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996). An intermediate-duration oral MRL of $5 \times 10^{-4}$ mg/kg/day was derived based on hepatic histologic changes (Laug et al. 1950). A chronic oral MRL was not derived because the most sensitive noncancer effects were observed at doses higher than doses for the most sensitive acute- and intermediate-duration effects. EPA derived an oral reference dose (RfD) of $5 \times 10^{-4}$ mg/kg/day for DDT based on liver lesions in rats (Laug et al. 1950); an uncertainty factor of 100 was used (IRIS 1999a).

EPA assigned DDT, DDE, and DDD a weight-of-evidence classification of B2, probable human carcinogens (IRIS 1999a, 1999b, 1999c). An oral slope factor of $0.34 (\text{mg/kg/day})^{-1}$ was derived for DDT based on increased incidence of liver tumors in rats and mice in several studies (Cabral et al. 1982b; Rossi et al. 1977; Terracini et al. 1973; Thorpe and Walker 1973; Tomatis and Turusov 1975; Turusov et al. 1973). Based on the oral data, EPA (IRIS 1999c) derived an inhalation unit risk of $9.7 \times 10^{-5} (\mu g/m^3)^{-1}$ for DDT. An oral slope factor of $0.24 (\text{mg/kg/day})^{-1}$ was derived for DDD based on increased incidence of liver tumors in male mice (Tomatis et al. 1974b).

IARC has assigned a weight-of-evidence classification of 2B to DDT, possibly carcinogenic to humans (IARC 1987a). The Department of Health and Human Services (DHHS) has determined that DDT may reasonably be anticipated to be a human carcinogen (NTP 1999).

The use of DDT and DDD in the United States was canceled in 1972. Exceptions include use by Public Health Service officials and other health officials for control of vector-borne disease, use by the U.S. Department of Agriculture or military for health quarantine, and use in drugs for controlling body lice (EPA 1972).
### Table 7-1. Regulations and Guidelines Applicable to DDT/DDE/DDD

<table>
<thead>
<tr>
<th>Agency</th>
<th>Description</th>
<th>Information</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTERNATIONAL</strong></td>
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<tr>
<td>IARC</td>
<td>Carcinogenic classification</td>
<td>Group 2B\textsuperscript{a}</td>
<td>IARC 1987b</td>
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<tr>
<td></td>
<td>WHO drinking water guideline</td>
<td>1µg/L</td>
<td>IARC 1991</td>
</tr>
<tr>
<td><strong>NATIONAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regulations and guidelines:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Air</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACGIH</td>
<td>Threshold limit values for occupational exposure (TLV–TWA) DDT CAS # 50-29-3</td>
<td>1 mg/m\textsuperscript{3}</td>
<td>ACGIH 1998</td>
</tr>
<tr>
<td>NIOSH</td>
<td>REL for a 100 minute TWA in a 400 L sample. DDT CAS # 50-29-3</td>
<td>0.5 mg/m\textsuperscript{3}</td>
<td>NIOSH 1999</td>
</tr>
<tr>
<td>OSHA</td>
<td>PEL (8-hour TWA) DDT CAS # 50-29-3</td>
<td>1 mg/m\textsuperscript{3}</td>
<td>OSHA 1998a</td>
</tr>
<tr>
<td></td>
<td>PEL for shipyards</td>
<td>1 mg/m\textsuperscript{3}</td>
<td>OSHA 1998b</td>
</tr>
<tr>
<td></td>
<td>PEL for construction</td>
<td>1 mg/m\textsuperscript{3}</td>
<td>OSHA 1998c</td>
</tr>
<tr>
<td>b. Water</td>
<td></td>
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<tr>
<td>EPA OW</td>
<td>Human health for consumption of:</td>
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<tr>
<td></td>
<td>DDT CAS # 50-29-3 Water and organism</td>
<td>5.9x10\textsuperscript{4} µg/L\textsuperscript{b,c}</td>
<td>EPA 1999a</td>
</tr>
<tr>
<td></td>
<td>DDT CAS # 50-29-3 Organism only</td>
<td>5.9x10\textsuperscript{4} µg/L\textsuperscript{b,c}</td>
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<tr>
<td></td>
<td>DDE CAS # 72-55-9 Water and organism</td>
<td>5.9x10\textsuperscript{4} µg/L\textsuperscript{b,c}</td>
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<td>DDE CAS # 72-55-9 Water only</td>
<td>5.9x10\textsuperscript{4} µg/L\textsuperscript{b,c}</td>
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<tr>
<td></td>
<td>DDD CAS # 72-54-8 Water and organism</td>
<td>8.3x10\textsuperscript{4} µg/L\textsuperscript{b,c}</td>
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<td>DDD CAS # 72-54-8 Organism only</td>
<td>8.4x10\textsuperscript{4} µg/L\textsuperscript{b,c}</td>
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</table>
### Table 7-1. Regulations and Guidelines Applicable to DDT/DDD/DDE (continued)

<table>
<thead>
<tr>
<th>Agency</th>
<th>Description</th>
<th>Information</th>
<th>References</th>
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<tbody>
<tr>
<td>NATIONAL (cont.)</td>
<td>Ambient water quality in navigable waters</td>
<td>1x10^{-3} g/L</td>
<td>EPA 1998b 40 CFR 129.101</td>
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<td></td>
<td>DDT, DDE, and DDD CAS #'s 50-29-3, 72-55-9, and 72-54-8, respectively</td>
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<tr>
<td>c. Food</td>
<td>FDA Pediculicide (lice) drug products</td>
<td>Yes</td>
<td>FDA 1998 21 CFR 310.545</td>
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<tr>
<td>d. Other</td>
<td>ACGIH Biological exposure index carcinogenic classification</td>
<td>No data</td>
<td>ACGIH 1998</td>
</tr>
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<td></td>
<td>CPSC Consumer product limits</td>
<td>No data</td>
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<td></td>
<td>EPA DDE</td>
<td>Cancer slope factor (q,*)</td>
<td>B2^e</td>
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<td></td>
<td>RfD (oral)</td>
<td>No data</td>
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<tr>
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<td>DDT</td>
<td>Cancer slope factor (q,*)</td>
<td>3.4x10^{-1} (mg/kg)/day</td>
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<td>Inhalation unit risk</td>
<td>9.7x10^2 (µg/m^3)^{-1}</td>
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<td></td>
<td>RfD (oral)</td>
<td>5x10^{-4} mg/kg/day</td>
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<tr>
<td></td>
<td>DDD</td>
<td>Cancer slope factor (q,*)</td>
<td>2.4x10^{-1} mg/kg/day</td>
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<td></td>
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<td>RfD (oral)</td>
<td>No data</td>
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<td></td>
<td>Reportable quantity DDT, DDE, and DDD (CAS #'s 50-29-3, 72-55-9, and 72-54-8, respectively)</td>
<td>1 pound</td>
<td>EPA 1998h 40 CFR 302.4</td>
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<td></td>
<td>Toxic pollutant—pursuant to section 307(a)(1) of the Clean Water Act DDT and metabolites</td>
<td>Yes</td>
<td>EPA 1998a 40 CFR 401.15</td>
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<tr>
<td></td>
<td>Hazardous waste listing and regulations DDT, DDE, and DDD (CAS #'s 50-29-3, 72-55-9, and 72-54-8, respectively)</td>
<td>Yes</td>
<td>EPA 1998c 40 CFR 261.33</td>
</tr>
</tbody>
</table>
### Table 7-1. Regulations and Guidelines Applicable to DDT/DDD/DDE (continued)

<table>
<thead>
<tr>
<th>Agency</th>
<th>Description</th>
<th>Information</th>
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</tr>
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<tbody>
<tr>
<td>NATIONAL (cont.)</td>
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<tr>
<td></td>
<td>Criteria for municipal solid waste landfills DDT, DDE, and DDD (CAS #’s 50-29-3, 72-55-9, and 72-54-8, respectively)</td>
<td>Yes</td>
<td>EPA 1998d</td>
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<td></td>
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<td>40 CFR 258</td>
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<td></td>
<td>Pesticide chemical effluent limitation guidelines and standards DDT, DDE, and DDD (CAS #’s 50-29-3, 72-55-9, and 72-54-8, respectively)</td>
<td>Yes</td>
<td>EPA 1998e</td>
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<td>40 CFR 455.20</td>
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<td>Pesticide residue tolerances on agricultural commodities DDT, DDE, and DDD (CAS #’s 50-29-3, 72-55-9, and 72-54-8, respectively)</td>
<td>Yes</td>
<td>EPA 1998f</td>
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<td>40 CFR 180.3</td>
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<td>Hazardous substance list in accordance with section 311(b)(2)(a) of the Act</td>
<td>Yes</td>
<td>EPA 1998g</td>
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<td>40 CFR 116.4</td>
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<td>Toxic pollutant—subject to effluent standards</td>
<td>Yes</td>
<td>EPA 1998i</td>
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<td>40 CFR 129.4</td>
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<td>a. Air:</td>
<td>Acceptable air concentrations</td>
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<td>ID</td>
<td>Unit risk factor</td>
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<td>Acceptable ambient concentration for a carcinogen</td>
<td>9.7x10⁻⁵ (µg/m³)⁻¹</td>
<td>UATW 1999d</td>
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<tr>
<td></td>
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<td>1x10⁻² µg/m³</td>
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<tr>
<td>KS</td>
<td>DDE CAS # 72-55-9</td>
<td>&lt; 0.01 tons/year</td>
<td>CDC 1999</td>
</tr>
<tr>
<td>OK</td>
<td>DDT CAS # 50-29-3</td>
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<td>Water and organism</td>
<td>5.9x10⁻³ µg/L</td>
<td>FSTRAC 1999</td>
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<td></td>
<td>Organism only</td>
<td>5.0 mg/kg</td>
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<td>b. Water:</td>
<td>Acceptable water concentrations</td>
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<td>AL</td>
<td>DDD CAS # 72-54-8</td>
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<td>Water and organism</td>
<td>1.8x10⁻⁶ mg/L</td>
<td>UATW 1999b</td>
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<td></td>
<td>Water only</td>
<td>1.8x10⁻⁶ mg/L</td>
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<td></td>
<td>DDE CAS # 72-55-9</td>
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<tr>
<td></td>
<td>Water and organism</td>
<td>1.3x10⁻⁵ mg/L</td>
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</tr>
<tr>
<td></td>
<td>Water only</td>
<td>1.3x10⁻⁵ mg/L</td>
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### Table 7-1. Regulations and Guidelines Applicable to DDT/DDD/DDE (continued)

<table>
<thead>
<tr>
<th>Agency</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>STATE</strong> (cont.)</td>
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<td></td>
</tr>
<tr>
<td><strong>DDT CAS # 50-29-3</strong></td>
<td>Water and organism</td>
<td>$1.3 \times 10^{-5}$ mg/L</td>
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<tr>
<td></td>
<td>Water only</td>
<td>$1.3 \times 10^{-5}$ mg/L</td>
</tr>
<tr>
<td><strong>AZ</strong></td>
<td>DDT CAS # 50-29-3</td>
<td>0.10 µg/L</td>
</tr>
<tr>
<td><strong>CO</strong></td>
<td>DDD CAS # 72-54-8</td>
<td>8.3 $\times 10^{-4}$ µg/L</td>
</tr>
<tr>
<td></td>
<td>Water and organism</td>
<td>UATW 1999a</td>
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<tr>
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<td>Water only</td>
<td></td>
</tr>
<tr>
<td><strong>DDD CAS # 72-55-9</strong></td>
<td>Water and organism</td>
<td>5.9 $\times 10^{-4}$ µg/L</td>
</tr>
<tr>
<td></td>
<td>Water only</td>
<td>0.1 µg/L</td>
</tr>
<tr>
<td><strong>DDT CAS # 50-29-3</strong></td>
<td>Water and organism</td>
<td>5.9 $\times 10^{-4}$ µg/L</td>
</tr>
<tr>
<td></td>
<td>Water only</td>
<td>0.1 µg/L</td>
</tr>
<tr>
<td><strong>FL</strong></td>
<td>DDT CAS # 50-29-3</td>
<td>0.1 µg/L</td>
</tr>
<tr>
<td></td>
<td>DDD CAS # 72-54-8</td>
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</tr>
<tr>
<td></td>
<td>DDE CAS # 72-55-9</td>
<td>0.01 µg/L</td>
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<tr>
<td><strong>HI</strong></td>
<td>DDT and metabolites:</td>
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</tr>
<tr>
<td></td>
<td>Freshwater</td>
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</tr>
<tr>
<td></td>
<td>acute</td>
<td>1.1 µg/L</td>
</tr>
<tr>
<td></td>
<td>chronic</td>
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<tr>
<td></td>
<td>Saltwater</td>
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<td></td>
<td>acute</td>
<td>1.3 $\times 10^{-2}$ µg/L</td>
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<td>chronic</td>
<td>$1 \times 10^{-3}$ µg/L</td>
</tr>
<tr>
<td></td>
<td>Fish consumption</td>
<td>8 $\times 10^{-6}$ µg/L</td>
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<td><strong>IL</strong></td>
<td>DDT CAS # 50-29-3</td>
<td>50 µg/L</td>
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<tr>
<td><strong>ME</strong></td>
<td>DDT CAS # 50-29-3</td>
<td>0.83 µg/L</td>
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<tr>
<td><strong>MN</strong></td>
<td>DDT CAS # 50-29-3</td>
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<tr>
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<td>DDD CAS # 72-54-8</td>
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<tr>
<td></td>
<td>DDE CAS # 72-55-9</td>
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</tr>
<tr>
<td><strong>NH</strong></td>
<td>DDT CAS # 50-29-3</td>
<td>0.1 µg/L</td>
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Table 7-1. Regulations and Guidelines Applicable to DDT/DDD/DDE (continued)

<table>
<thead>
<tr>
<th>Agency</th>
<th>Description</th>
<th>Information</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STATE</strong> (cont.)</td>
<td>Fish and Wildlife Advisory for DDT, DDE, and DDD (CAS #'s 50-29-3, 72-55-9, and 72-54-8, respectively)</td>
<td>Fish and turtles</td>
<td>EPA 1999b</td>
</tr>
<tr>
<td>AL</td>
<td>Fish</td>
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<tr>
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<tr>
<td>OK</td>
<td>Fish</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>Fish</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Fish</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

This information, current as of 1999, is based on the EPA Fish and Wildlife Advisory Database searched 8/99 on the Internet at [http://www.epa.gov/OST/fishadvice/](http://www.epa.gov/OST/fishadvice/). For more detailed information, consult your state public health or natural resources department. A fish or wildlife advisory will specify the bodies of water or hunting areas with restrictions. The advisory will indicate the species and size of fish or game of concern. The advisory may completely ban consumption or recommend limiting the number of servings of a certain fish or wildlife species to less than a particular frequency. The advisory may indicate that only certain parts of the fish or game should be consumed and recommend preparation methods to minimize exposure. The advisory may have stricter restrictions than for the general public to protect pregnant women, nursing mothers, and young children. Each state, Native American tribe, or U.S. territory chooses its own criteria for issuing fish and wildlife advisories.

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a Group 2B: Possibly carcinogenic to humans

b This criterion has been revised to reflect The Environmental Protection Agency’s q1 or RfD, as contained in the Integrated Risk Information System (IRIS) as of April 8, 1998. The fish tissue bioconcentration factor (BCF) from the 1980 Ambient Water Quality Criteria document was retained in each case.

c This criterion is based on carcinogenicity of 10⁻⁶ risk. Alternate risk levels may be obtained by moving the decimal point (e.g., for a risk level of 10⁻⁵, move the decimal point in the recommended criterion one place to the right).

d Confirmed animal carcinogen with unknown relevance to humans

e B2 = probable human carcinogen

f derived from equation 18 for consumption of water and fish which is as follows:

\[
\text{Conc. (mg/L)} = \frac{(\text{HBW} \times \text{RL})}{(\text{CPF} \times [(\text{FCR} \times \text{BCF}) + \text{WCR}] )}
\]

Where: HBW = human body weight, set at 70 kg; RL = risk level, set at 1x10⁻⁵; CPF = cancer potency factor, given in Appendix A [DDD = 0.24 (mg/kg/day)⁻¹, DDE = 0.34 (mg/kg/day)⁻¹, DDT = 0.34 (mg/kg/day)⁻¹]; FCR = fish consumption rate, set at 0.030 kg/day; BCF = bioconcentration factor, given in Appendix A [DDD = 53,600, DDE = 53,600, DDT = 53,600]; WCR = water consumption rate, set at 2 l/day

g derived from equation 19 for consumption of fish only which is as follows:

\[
\text{Conc. (mg/L)} = \frac{(\text{HBW} \times \text{RL})}{(\text{CPF} \times \text{FCR} \times \text{BCF})}
\]

Where: HBW = human body weight, set at 70 kg; RL = risk level, set at 1x10⁻⁵; CPF = cancer potency factor, given in Appendix A [DDD = 0.24 (mg/kg/day)⁻¹, DDE = 0.34 (mg/kg/day)⁻¹, DDT = 0.34 (mg/kg/day)⁻¹]; FCR = fish consumption rate, set at 0.030 kg/day; BCF = bioconcentration factor, given in Appendix A [DDD = 53,600, DDE = 53,600, DDT = 53,600]

ACGIH = American Conference of Governmental Industrial Hygienists; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; NIOSH = National Institute of Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; OW = Office of Water; PEL = permissible exposure limit; REL = recommended exposure release; TLV = threshold limit value; TWA = time-weighted average; WHO = World Health Organization

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*Cited in text
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9. 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 ($K_d$)—The amount of a chemical adsorbed by a 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.

Biota—All living organisms that exist in an area.

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 which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.
Case Series—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and in utero death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

FEFR\textsubscript{25–75}—Forced expiratory flowrate between 25 and 75%.

FEV\textsubscript{1.0}—Forced expiratory volume in 1.0 seconds.

FVC—Forced vital capacity.

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.
**9. GLOSSARY**

**Immediately Dangerous to Life or Health (IDLH)**—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

**Incidence**—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

**Intermediate Exposure**—Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

**Immunological Effects**—Functional changes in the immune response.

**Immunologic Toxicity**—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

**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 which 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 which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time_{50} (LT_{50})**—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)**—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Lymphoreticular Effects**—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

**Malformations**—Permanent structural changes that may adversely affect survival, development, or function.

**Minimal Risk Level (MRL)**—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

**Modifying Factor (MF)**—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.
**Morbidity**—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

**Mortality**—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

**Mutagen**—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell’s DNA. Mutations can lead to birth defects, miscarriages, or cancer.

**Necropsy**—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

**Neurotoxicity**—The occurrence of adverse effects on the nervous system following exposure to a chemical.

**No-Observed-Adverse-Effect Level (NOAEL)**—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

**Octanol-Water Partition Coefficient (K_{ow})**—The equilibrium ratio of the concentrations of a chemical in n-octanol and water, in dilute solution.

**Odds Ratio (OR)**—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which 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 odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

**Organophosphate or Organophosphorus Compound**—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

**Permissible Exposure Limit (PEL)**—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40 hour workweek.

**Pesticide**—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

**Pharmacokinetics**—The science of quantitatively predicting 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 whereby the physiologically-based model compartments represent real anatomic regions of the body.
9. GLOSSARY

**Physiologically Based Pharmacodynamic (PBPD) Model**—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

**Physiologically Based Pharmacokinetic (PBPK) Model**—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

**ppbv**—Parts per billion by volume.

**ppmv**—Parts per million by volume.

**Prevalence**—The number of cases of a disease or condition in a population at one point in time.

**Proportionate Mortality Ratio (PMR)**—The ratio of a cause-specific mortality proportion in an exposed group to the mortality proportion in an unexposed group; mortality proportions may be adjusted for confounding variables such as age. Cause-specific mortality proportions can be calculated when the cohort (the population at risk) cannot be defined due to inadequate records, but the number of deaths and the causes of deaths are known.

**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.

**q1**—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q1 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/m³ for air).

**Recommended Exposure Limit (REL)**—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations 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/m³ 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 nontreshold effects such as cancer.
Relative Risk (RR)—The risk expressed as a ratio of the incidence of diseased subjects exposed to a particular risk factor to the incidence of diseased subjects in a non-exposed referent group.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—The ratio of a cause-specific mortality rate in an exposed cohort during a given period to the mortality rate of an unexposed cohort; mortality rates are often adjusted for age or other confounding variables.

Standardized Proportionate Incidence Ratio (SPIR)—Similar to a Proportionate Mortality Ratio (PMR) in that it is a ratio of a proportion of a specific disease in an exposed group compared with the proportion in an unexposed group.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.
Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose_{50} (TD_{50})—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of 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 one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—Any chemical that is foreign to the biological system.
APPENDIX A

ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.
MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide 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, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.
MINIMAL RISK LEVEL WORKSHEET

Chemical Name: DDT
CAS Number: 50-29-3
Date: April 4, 2000
Profile Status: Final Draft Pre Public
Route: [X] Oral
Duration: [X] Acute  [ ] Intermediate  [ ] Chronic
Graph Key: 51m
Species: Mice

Minimal Risk Level: 0.0005  [X] mg/kg/day  [ ] ppm


Experimental design and effects noted: The acute oral MRL is based on results from a group of studies conducted by the same group of investigators in which the most significant finding was the presence of altered motor behavior in adult mice treated with DDT perinatally. Groups of 10-day-old male NMRI mice were treated by gavage with a single dose of 0 (vehicle control) or 0.5 mg DDT/kg in a fat emulsion vehicle by gavage (Eriksson et al. 1990a). At the age of 4 months, the mice were subjected to behavioral tests of spontaneous activity (locomotion, rearing, and total activity). Tests were conducted for 1 hour, and scores were summed for three 20-minute periods. During the last 40 minutes of testing, the treated mice showed significantly more activity than untreated controls. This was interpreted as disruption of a simple, non-associative learning process, (i.e., habituation), or a retardation in adjustment to a new environment. These same results were reported in a later paper (Eriksson et al. 1990b) in which the authors also reported results of neurochemical evaluations conducted 2–3 weeks after behavioral testing. They measured muscarinic acetylcholine (MACH) receptor density and choline acetyltransferase (ChAT) activity in the cerebral cortex and hippocampus (MACH also in striatum), and also measured K⁺-stimulated ACh release from cerebral cortex slices. In addition, five 10-day-old mice were administered 0.5 mg ¹⁴C-DDT and the radioactivity in the brain was assayed 24 hours, 7 days, or 1 month after dosing. The results showed that K⁺-evoked ACh release in treated mice was significantly increased relative to controls, ChAT activity was not changed in the cerebral cortex or hippocampus, and the density of MACH was not significantly changed in the hippocampus or striatum, but a decreasing trend was seen in the cerebral cortex. DDT-derived radioactivity could be detected until day 7 after dosing, but none could be detected 1 month after dosing.

Previous studies have shown a significant increase in density of MACH in the cerebral cortex of 10-day-old mice 7 days after dosing, but not at 1 day post-exposure compared to controls (Eriksson and Nordberg 1986). No increased binding was noted in the hippocampus either 1 or 7 days post-treatment. This was further investigated by evaluating the proportion of high- and low-affinity binding sites and the affinity constants of the muscarinic receptors. A significant increase in the percentage of low-affinity binding sites accompanied by a significant decrease in high-affinity binding sites was measured in the cerebral cortex 7 days post-exposure. No significant changes in affinity constants were noted. According to the authors, these low-affinity binding sites correspond to the M₁ receptor in the cerebral cortex, which are thought to be associated with neuronal excitation. No changes were observed in the sodium-dependent choline uptake system in the cerebral cortex 7 days post-exposure.

In a follow-up study, Eriksson et al. (1992) treated 3-, 10-, and 19-day-old mice, and conducted behavioral testing and neurochemical evaluations at 4 months of age. As previously published, mice
treated at 10 days exhibited hyperactivity relative to controls and also a significant decrease in the density of MACh in the cerebral cortex. No such changes were seen in mice treated at 3 or 19 days old. The authors suggested that the changes in MACh density and behavior might be the consequence of early interference with muscarinic cholinergic transmission specifically around the age of 10 days. In subsequent studies by the same group, 5- and 7-month-old mice were tested (Eriksson et al. 1993; Johansson et al. 1995). At both time points, mice treated with DDT perinatally showed increased spontaneous motor activity relative to controls, and decreased density of MACh in the cerebral cortex. No changes were seen regarding percentages of high- or low-affinity muscarinic binding sites in the cerebral cortex. Mice in these studies were also treated orally at the age of 5 months with the type I pyrethroid insecticide, bioallethrin, and tested for motor activity at this age (Eriksson et al. 1993) and at 7 months (Johansson et al. 1995). In general, mice treated with DDT at the age of 10 days and later with bioallethrin showed increased motor behavior relative to those treated with bioallethrin alone, suggesting a DDT-induced increased susceptibility to bioallethrin. Mice treated first with DDT and later on with bioallethrin also showed increased difficulties in learning a skill, such as the swim maze test, compared with untreated mice, mice treated with DDT alone, or mice treated with bioallethrin alone (Johansson et al. 1995). In yet another study from this group, paraoxon replaced bioallethrin, and the mice were tested at 5 and 7 months (Johansson et al. 1996). In addition, acetylcholinesterase activity was measured in cerebral cortex of 5-month-old mice and MACh and nicotinic cholinergic receptors in cortex of 7-month-old mice. Relevant new findings include that: (1) DDT did not significantly alter acetylcholinesterase activity; (2) DDT did not alter the effects of paraoxon on acetylcholinesterase activity (decreased); (3) DDT altered (increased or decreased) some of motor responses due to paraoxon alone at 7 months but not at 5 months; (4) none of the treatments altered performance in the swim maze test; and (5) none of the treatments altered the density of nicotinic cholinergic receptors in the cortex.

In this series of studies, two responses seem to be consistent from study to study in mice treated with DDT perinatally and tested as adults, a decrease in the density of muscarinic cholinergic receptors in the cerebral cortex and increased spontaneous motor activity. It is not clear whether there is a causality relationship. DDT also altered some motor responses induced by other pesticides, but a pattern was not always clear. The investigators interpreted the latter findings as DDT inducing changes early in the brain that translated into increased susceptibility to other pesticides later in life. The DDT-induced increase in spontaneous motor activity at the dose of 0.5 mg/kg is considered a less serious LOAEL.

Dose and end point used for MRL derivation: 0.5 mg/kg; neurodevelopmental effects.

[ ] NOAEL  [X] LOAEL

Uncertainty Factors used in MRL derivation:

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

The DDT in this experiment was administered in a fat emulsion vehicle via gavage. There was no adjustment made for effects of the fat vehicle on absorption because neonatal children are likely to be exposed to DDT via high fat breast milk.

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
No

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: NA
Was a conversion used from intermittent to continuous exposure? No

Agency Contact (Chemical Manager): Olivia Harris
MINIMAL RISK LEVEL WORKSHEET

Chemical Name: DDT  
CAS Number: 50-29-3  
Date: April 4, 2000  
Profile Status: Final Draft Pre Public  
Route: [ ] Inhalation  [X] Oral  
Duration: [ ] Acute  [X] Intermediate  [ ] Chronic  
Graph Key: 65r  
Species: Rat

Minimal Risk Level: 0.0005  [X] mg/kg/day  [ ] ppm

In this dietary study the amount of DDT added to the food was measured, but the actual food consumption and body weights of the rats were not measured. The calculated value for the NOAEL on which the MRL is based ranges from 0.05 to 0.09 mg/kg/day depending on the food consumption values used to calculate the actual dose of DDT consumed. More details are provided below in the discussion of conversion factors.

In protecting public health ATSDR recommends using the conservative lower end of this calculated NOAEL range, 0.05 mg/kg/day, to derive an intermediate duration MRL of 0.0005 mg/kg/day. This MRL value is consistent with and supported by the acute duration MRL of 0.0005 mg/kg/day, particularly if intermediate exposure were to occur during the sensitive critical window of development (postnatal day 10 in the mouse model) identified in the acute duration MRL exposure studies (Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996).


Experimental design: Groups of male and female Osborne-Mendel rats (15/sex/group) were administered technical DDT(dissolved in corn oil) added to the diet at dosage levels of 0, 1, 5, 10, or 50 ppm for 15–27 weeks. This study was essentially designed to examine whether DDT accumulates in adipose tissue and, to what extent, how age and dose level affect accumulation, and how rapidly it is eliminated. Seventy-seven rats were used for microscopic evaluation of only the liver and kidney. This was based on findings from a previous study from the same group (Fitzhugh and Nelson 1947, see below) in which higher dietary levels of DDT had been used. Based on the previous findings, only the liver was expected to show microscopic changes. Although not explicitly stated, it is assumed that morphologic evaluations were conducted at the times when DDT levels in fat were determined (after 15, 19, 23, and 27 weeks of treatment).

Effects noted in study and corresponding doses: These dose ranges were calculated as shown below in the discussion of conversion factors. There were no morphologic alterations in the kidneys. Liver alterations were noticed at the 5 ppm (0.25 - 0.5 mg/kg/day) dietary level of DDT and higher, but not at 1 ppm (0.05 - 0.09 mg/kg/day). Liver changes consisted of hepatic cell enlargement, especially in central lobules, increased cytoplasmic oxyphilia with sometimes a semihyaline appearance, and more peripheral location of the basophilic cytoplasmic granules. Necrosis was not observed. The severity of the effects was dose-related, and males tended to show more hepatic cell changes than females. Changes seen at the 5 ppm level (0.25 - 0.5 mg/kg/day) were considered by the authors as "minimal"; changes seen at the 50 ppm level (2.5 - 4.6 mg/kg/day) were slight, sometimes moderate; the authors do not comment about what they saw in the 10 ppm (0.5 - 0.9 mg/kg/day) group, presumably the results were intermediate to the doses above and below. The results from the kinetic studies revealed that accumulation of DDT in fat occurred at all dietary levels tested and that females stored more DDT than males; storage reached a maximum at
19 to 23 weeks; age did not affect the rate of DDT-accumulation; about 50 to 75% of DDT stored in fat remained after a 1-month DDT-free diet, and 25% remained after 3 months.

Dose and end point used for MRL derivation: 0.05 mg/kg/day; liver effects.

[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

In this dietary study the amount of DDT added to the food was measured, but the actual food consumption and body weights of the rats were not measured. The calculated value for the NOAEL on which the MRL is based ranges from 0.05 to 0.09 mg/kg/day depending on the food consumption values used to calculate the actual dose of DDT consumed. Using the most conservative estimates of food consumption, the NOAEL for 1 ppm DDT in food = 0.05 mg DDT/kg/day; this was the value used for calculating the MRL.

Calculation of Food Consumption Values (Three Models)

(1) Using EPA 1986d Reference Values

Using the EPA 1986d Reference Values for Risk Assessment, as was done in the 1994 edition of this Toxicological Profile, yields a NOAEL of 0.05 mg/kg/day equivalent to feeding 1 ppm DDT in the food. This reference considers the food consumption of an average rat to be 0.05 kg food/kg body weight-day (averaged over a lifetime) and the average weight of a rat to be 0.35 kg. No allometric equation is used for calculating the food factor. However, this reference recommends using a food consumption value of 0.09 mg/kg/day for a subchronic 90 day study.

NOAEL= 1 ppm in food = 1 mg/kg food
1 mg DDT/kg food x 0.05 kg food/kg body weight/day=0.05 mg/kg/day

Equivalents for other food concentrations used in this study, as calculated by using the EPA 1986d Reference Values for Risk Assessment:
5 ppm= 0.25 mg/kg/day
10 ppm= 0.5 mg/kg/day
50 ppm= 2.5 mg/kg/day

(2) EPA 1988g Method, Chronic Duration Average Body Weights

The NOAEL is 1 ppm of DDT in dietary study feeding Osborne-Mendel rats for 15-27 weeks (105-109 days). EPA 1988g has time weighted average body weights for male or female Osborne-Mendel rats for either of two study durations: subchronic (weaning to 90 days) and chronic (weaning to 730 days or 2 years). This study does not exactly fall into either of the intervals for which the time weighted average weights were calculated, but the convention is to pick the chronic category for studies longer than 90
days. The risk assessment calculations recommended in EPA 1988g were used for calculating doses for all the dietary studies discussed in this Toxicological Profile.

\[ F = 0.056(W)^{0.6611} \]  
where \( F = \text{kg food/day} \) and \( W = \text{body weight in kilograms} \)

For chronic duration, the average body weight of male and female Osborne-Mendel rats is 0.452 kg, yielding an \( F = 0.033 \text{ kg/food/day} \)

NOAEL= 1 ppm in food = 1 mg/kg food  
1 mg DDT/kg food x 0.033 kg food/day/0.452 kg bw = 0.07 mg DDT/kg/day.

Equivalents for other food concentrations used in this study, as calculated by using the EPA 1986d Reference Values for Risk Assessment:
- 5 ppm= 0.4 mg/kg/day  
- 10 ppm= 0.7 mg/kg/day  
- 50 ppm= 3.7 mg/kg/day

(3) EPA 1988g Method, Subchronic Duration Average Body Weights

For subchronic duration (actually less than the duration of this study), the average body weight of male and female Osborne-Mendel rat 0.232 kg, yielding an \( F = 0.0213 \text{ kg/food/day} \)

NOAEL= 1 ppm in food = 1 mg/kg food  
1 mg DDT/kg food x 0.0213 kg food/day/0.232 kg body weight = 0.09 mg DDT/kg/day.

Equivalents for other food concentrations used in this study, as calculated by using the EPA 1986d Reference Values for Risk Assessment:
- 5 ppm= 0.5 mg/kg/day  
- 10 ppm= 0.9 mg/kg/day  
- 50 ppm= 4.6 mg/kg/day

Was a conversion used from intermittent to continuous exposure?  
No

Other additional studies or pertinent information that lend support to this MRL: In the Fitzhugh and Nelson (1947) study, 16 female Osborne-Mendel rats were fed a diet containing 1,000 ppm technical DDT for 12 weeks. Using EPA 1988g reference values for female body weight and subchronic food consumption, the diet provided approximately 96 mg DDT/kg/day. Sacrifices were conducted at cessation of dosing and at various intervals after a DDT-free period. Liver changes were similar to those seen in the Laug et al. (1950) study, although of increased severity, and were still present in rats killed after 2 weeks in a DDT-free diet. Minimal liver changes were apparent after 4–6 weeks of recovery, and complete recovery was seen after 8 weeks. Hepatic effects ranging from increased liver weights to cellular necrosis have been reported in animals after chronic exposure in the diet.

The Laug et al. (1950) study serves also as the basis for an oral RfD derived by EPA for DDT (IRIS 1999). The Fitzhugh and Nelson (1947) study is considered supportive for the RfD.

Agency Contact (Chemical Manager): Olivia Harris
An oral MRL for chronic-duration exposure to DDT was not derived because of the inadequacy of the available data on liver effects in animals to describe the dose-response relationship at low-dose levels. In a brief communication, Fitzhugh (1948) stated that histopathological lesions occurred in the liver of rats fed 10 ppm DDT in the diet for 2 years, but no experimental details were given, so the quality of the study cannot be evaluated. Using reference values for body weight and food consumption from EPA (1988), it can estimated that the 10 ppm dietary level provided DDT doses of approximately 0.7 mg/kg/day. This dietary level was the lowest level tested in the study, but was still higher than the lowest level resulting in hepatic effects in the Laug et al. 1950 study used for derivation of the intermediate-duration MRL.

**Agency Contact (Chemical Manager):** Olivia Harris
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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) 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, minimal risk levels (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 No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(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. When sufficient data exists, 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 Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.
(2) **Exposure Period** Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) **Health Effect** The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) **Key to Figure** Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).

(5) **Species** The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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 regimen 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 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 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, 1 systemic effect (respiratory) was investigated.

(8) **NOAEL** A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) **LOAEL** A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint 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 8 of the profile.
(11) CEL. A Cancer Effect Level (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 the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

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 intermediate and chronic 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/m³ or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL. In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. 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 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level 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 (q1*).

(19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.
### TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

<table>
<thead>
<tr>
<th>Key to figure&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Species</th>
<th>Exposure frequency/duration</th>
<th>System</th>
<th>NOAEL (ppm)</th>
<th><strong>LOAEL (effect)</strong> Less serious (ppm)</th>
<th>Serious (ppm)</th>
<th>Reference</th>
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<td>INTERMEDIATE EXPOSURE</td>
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<td></td>
<td>18</td>
<td>Rat</td>
<td>13 wk 5d/wk 6hr/d</td>
<td>Resp</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10 (hyperplasia)</td>
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<td>CHRONIC EXPOSURE</td>
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<td>38</td>
<td>Rat</td>
<td>18 mo 5d/wk 7hr/d</td>
<td></td>
<td></td>
<td>9</td>
<td>20 (CEL, multiple organs)</td>
<td>Wong et al. 1982</td>
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<tr>
<td>39</td>
<td>Rat</td>
<td>89–104 wk 5d/wk 6hr/d</td>
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<td>10 (CEL, lung tumors, nasal tumors)</td>
<td>NTP 1982</td>
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<tr>
<td>40</td>
<td>Mouse</td>
<td>79–103 wk 5d/wk 6hr/d</td>
<td></td>
<td></td>
<td>10 (CEL, lung tumors, hemangiosarcomas)</td>
<td>NTP 1982</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> The number corresponds to entries in Figure 2-1.

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5 \times 10^{-3}$ 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).
Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation

**Acute**
(≤14 days)

**Systemic**

- Death
- Respiratory
- Hematological

**Intermediate**
(15-364 days)

**Systemic**

- Death
- Respiratory
- Hematological
- Hepatic
- Reproductive
- Cancer*

### Key
- r Rat
- m Mouse
- h Rabbit
- g Guinea Pig
- k Monkey

- • LOAEL for serious effects (animals)
- ○ LOAEL for less serious effects (animals)
- ◆ NOAEL (animals)
- ◇ CEL - Cancer Effect Level
- ▲ Minimal risk level for effects other than cancer

* Doses represent the lowest dose tested per study that produced a tumorigenic response and do not imply the existence of a threshold for the cancer end point.

---

**Estimated Upper Bound Human Cancer Risk Levels**

- 10^{-4}
- 10^{-5}
- 10^{-6}
- 10^{-7}
Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section 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 section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, 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 section. If data are located in the scientific literature, a table of genotoxicity information is included.

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 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (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. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.9, "Interactions with Other Substances," and 2.10, "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 the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).
To derive an MRL, ATSDR generally selects the most sensitive endpoint 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 endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest 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 LSE Tables.
## APPENDIX C

### ACRONYMS, ABBREVIATIONS, AND SYMBOLS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
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<tbody>
<tr>
<td>ACGIH</td>
<td>American Conference of Governmental Industrial Hygienists</td>
</tr>
<tr>
<td>ADI</td>
<td>Acceptable Daily Intake</td>
</tr>
<tr>
<td>ADME</td>
<td>Absorption, Distribution, Metabolism, and Excretion</td>
</tr>
<tr>
<td>AFID</td>
<td>alkali flame ionization detector</td>
</tr>
<tr>
<td>AFOSH</td>
<td>Air Force Office of Safety and Health</td>
</tr>
<tr>
<td>AML</td>
<td>acute myeloid leukemia</td>
</tr>
<tr>
<td>AOAC</td>
<td>Association of Official Analytical Chemists</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry</td>
</tr>
<tr>
<td>AWQC</td>
<td>Ambient Water Quality Criteria</td>
</tr>
<tr>
<td>BAT</td>
<td>Best Available Technology</td>
</tr>
<tr>
<td>BCF</td>
<td>bioconcentration factor</td>
</tr>
<tr>
<td>BEI</td>
<td>Biological Exposure Index</td>
</tr>
<tr>
<td>BSC</td>
<td>Board of Scientific Counselors</td>
</tr>
<tr>
<td>C</td>
<td>Centigrade</td>
</tr>
<tr>
<td>CAA</td>
<td>Clean Air Act</td>
</tr>
<tr>
<td>CAG</td>
<td>Cancer Assessment Group of the U.S. Environmental Protection Agency</td>
</tr>
<tr>
<td>CAS</td>
<td>Chemical Abstract Services</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
</tr>
<tr>
<td>CEL</td>
<td>Cancer Effect Level</td>
</tr>
<tr>
<td>CELDS</td>
<td>Computer-Environmental Legislative Data System</td>
</tr>
<tr>
<td>CERCLA</td>
<td>Comprehensive Environmental Response, Compensation, and Liability Act</td>
</tr>
<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
</tr>
<tr>
<td>Ci</td>
<td>curie</td>
</tr>
<tr>
<td>CL</td>
<td>ceiling limit value</td>
</tr>
<tr>
<td>CLP</td>
<td>Contract Laboratory Program</td>
</tr>
<tr>
<td>cm</td>
<td>centimeter</td>
</tr>
<tr>
<td>CML</td>
<td>chronic myeloid leukemia</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CPSC</td>
<td>Consumer Products Safety Commission</td>
</tr>
<tr>
<td>CWA</td>
<td>Clean Water Act</td>
</tr>
<tr>
<td>d</td>
<td>day</td>
</tr>
<tr>
<td>Derm</td>
<td>dermal</td>
</tr>
<tr>
<td>DHEW</td>
<td>Department of Health, Education, and Welfare</td>
</tr>
<tr>
<td>DHHS</td>
<td>Department of Health and Human Services</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
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<tr>
<td>DOD</td>
<td>Department of Defense</td>
</tr>
<tr>
<td>DOE</td>
<td>Department of Energy</td>
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<tr>
<td>DOL</td>
<td>Department of Labor</td>
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<tr>
<td>DOT</td>
<td>Department of Transportation</td>
</tr>
<tr>
<td>DOT/UN/</td>
<td>Department of Transportation/United Nations/</td>
</tr>
<tr>
<td>NA/IMCO</td>
<td>North America/International Maritime Dangerous Goods Code</td>
</tr>
<tr>
<td>DWEL</td>
<td>Drinking Water Exposure Level</td>
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<tr>
<td>ECD</td>
<td>electron capture detection</td>
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<tr>
<td>ECG/EKG</td>
<td>electrocardiogram</td>
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***DRAFT FOR PUBLIC COMMENT***
EEG  electroencephalogram
EEGL  Emergency Exposure Guidance Level
EPA  Environmental Protection Agency
F  Fahrenheit
F₁  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
ft  foot
FR  Federal Register
g  gram
GC  gas chromatography
Gd  gestational day
gen  generation
GLC  gas liquid chromatography
GPC  gel permeation chromatography
HPLC  high-performance liquid chromatography
hr  hour
HRGC  high resolution gas chromatography
HSDB  Hazardous Substance Data Bank
IDLH  Immediately Dangerous to Life and Health
IARC  International Agency for Research on Cancer
ILO  International Labor Organization
in  inch
IRIS  Integrated Risk Information System
Kd  adsorption ratio
kg  kilogram
kkg  metric ton
K_{oc}  organic carbon partition coefficient
K_{ow}  octanol-water partition coefficient
L  liter
LC  liquid chromatography
LCₜ₀  lethal concentration, low
LC₅₀  lethal concentration, 50% kill
LDₜ₀  lethal dose, low
LD₅₀  lethal dose, 50% kill
LTₜ₀  lethal time, 50% kill
LOAEL  lowest-observed-adverse-effect level
LSE  Levels of Significant Exposure
m  meter
MA  trans,trans-muconic acid
MAL  Maximum Allowable Level
mCi  millicurie
MCL  Maximum Contaminant Level
MCLG  Maximum Contaminant Level Goal
mg  milligram
min  minute
mL  milliliter
mm millimeter
mm Hg millimeters of mercury
mmol millimole
mo month
mppcf millions of particles per cubic foot
MRL Minimal Risk Level
MS mass spectrometry
NAAQS National Ambient Air Quality Standard
NAS National Academy of Science
NATICH National Air Toxics Information Clearinghouse
NATO North Atlantic Treaty Organization
NCE normochromatic erythrocytes
NCI National Cancer Institute
NIEHS National Institute of Environmental Health Sciences
NIOSH National Institute for Occupational Safety and Health
NIOSHTIC NIOSH's Computerized Information Retrieval System
NFPA National Fire Protection Association
ng nanogram
NLM National Library of Medicine
nm nanometer
NHANES National Health and Nutrition Examination Survey
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
OPPTS Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT Office of Pollution Prevention and Toxics, EPA
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
PID photo ionization detector
<table>
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<th>Full Form</th>
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<tr>
<td>pg</td>
<td>picogram</td>
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<td>pmol</td>
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<td>PMR</td>
<td>proportionate mortality ratio</td>
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<td>parts per billion</td>
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<td>parts per trillion</td>
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<td>Pretreatment Standards for New Sources</td>
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<td>recommended exposure level/limit</td>
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<td>RfC</td>
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<td>RTECS</td>
<td>Registry of Toxic Effects of Chemical Substances</td>
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<td>RQ</td>
<td>Reportable Quantity</td>
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<td>sister chromatid exchange</td>
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<td>sec</td>
<td>second</td>
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<tr>
<td>SIC</td>
<td>Standard Industrial Classification</td>
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<td>selected ion monitoring</td>
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<td>standard mortality ratio</td>
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<td>STORET</td>
<td>Storage and Retrieval</td>
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<tr>
<td>TD₅₀</td>
<td>toxic dose, 50% specific toxic effect</td>
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<td>TLV</td>
<td>threshold limit value</td>
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<tr>
<td>TOC</td>
<td>Total Organic Compound</td>
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<td>Toxic Substances Control Act</td>
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<td>Toxics Release Inventory</td>
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<td>time-weighted average</td>
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<td>UF</td>
<td>uncertainty factor</td>
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<td>Volatile Organic Compound</td>
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<td>µg</td>
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<tr>
<td>q₁*</td>
<td>cancer slope factor</td>
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<td>–</td>
<td>negative</td>
</tr>
<tr>
<td>+</td>
<td>positive</td>
</tr>
<tr>
<td>(+)</td>
<td>weakly positive result</td>
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<tr>
<td>(–)</td>
<td>weakly negative result</td>
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