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**TOXICOLOGICAL PROFILE FOR  
DDT, DDE, and DDD**

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

September 2002

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## **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

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

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


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

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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

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

  
Julie Louise Gerberding, M.D., M.P.H.  
Administrator  
Agency for Toxic Substances and  
Disease Registry

### \*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepared toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

## 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.

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### *Primary Chapters/Sections of Interest*

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

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

**Chapter 3: Health Effects:** Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

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

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

<b>Section 1.6</b>	<b>How Can (Chemical X) Affect Children?</b>
<b>Section 1.7</b>	<b>How Can Families Reduce the Risk of Exposure to (Chemical X)?</b>
<b>Section 3.8</b>	<b>Children's Susceptibility</b>
<b>Section 6.6</b>	<b>Exposures of Children</b>

### **Other Sections of Interest:**

<b>Section 3.9</b>	<b>Biomarkers of Exposure and Effect</b>
<b>Section 3.12</b>	<b>Methods for Reducing Toxic Effects</b>

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### **ATSDR Information Center**

**Phone:** 1-888-42-ATSDR or (404) 498-0110    **Fax:** (404) 498-0057

**E-mail:** [atsdric@cdc.gov](mailto: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.

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## ***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.

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## ***Referrals***

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

*The American College of Occupational and Environmental Medicine (ACOEM)* is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.

## CONTRIBUTORS

### CHEMICAL MANAGER(S)/AUTHORS(S):

Obaid Faroon, Ph.D.  
M. Olivia Harris, M.A.  
ATSDR, Division of Toxicology, Atlanta, GA

Fernando Lladós, Ph.D.  
Steven Swarts, Ph.D.  
Gloria Sage, Ph.D.  
Mario Citra, Ph.D.  
Daniel Gefell, M.S.  
Syracuse Research Corporation, North Syracuse, NY

### 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.



## PEER REVIEW

A peer review panel was assembled for DDT, DDE, and DDD. The panel consisted of the following members:

1. Dr. D. Andrew Crain, Assistant Professor, Maryville College, Maryville, TN;
2. Dr. Donald Michael Fry, Director, Center for Avian Biology, University of California at Davis;
3. Dr. Christopher Metcalfe, Professor and Chair, Environmental and Resource Studies, Trent University, Peterborough, Ontario, Canada; and
4. Dr. Mary S. Wolff, Professor of Community Medicine, Mt. Sinai School of Medicine, New York, NY.

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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## 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 442 of the 1,613 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'*-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 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.

## 1. PUBLIC HEALTH STATEMENT

**1.1 WHAT ARE DDT, DDE, AND DDD?**

DDT (1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)ethane) is a pesticide that was once widely used to control insects on agricultural crops and insects that carry diseases like malaria and typhus, but is now used in only a few countries to control malaria. 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, most notably for controlling malaria. 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 4 and 5 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.

## 1. PUBLIC HEALTH STATEMENT

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 mosquitos. Although the use of DDT is no longer permitted in the United States, DDT may 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. 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) has been calculated to be approximately 1.5–3 days. However, in reality, this half-life estimate is too short to account for the ability of DDT, DDE, and DDD to be carried long distances in the atmosphere.

DDT, DDE, and DDD last in the soil for a very long time, potentially for hundreds of years. Most DDT breaks down slowly into DDE and DDD, generally by the action of microorganisms. 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,  $\Sigma$ DDT may disappear in much less than a year. In temperate areas, half of the  $\Sigma$ DDT initially present

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usually disappears in about 5 years. However, in some cases, half of the  $\Sigma$ DDT 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 their adipose tissue. 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 6.

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

People in the United States are exposed to DDT, DDE, and DDD mainly by eating foods containing small amounts of these compounds. Although not common today, exposure to DDT could also occur through inhalation or absorption through the skin during the handling or application of DDT. 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, poultry, dairy products, and fish, including the consumption of sport fish. 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

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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/m<sup>3</sup>), 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, inhaling DDT vapor, or breathing in DDT in dust.

You can find more information on exposure to DDT, DDE, and DDD in Chapter 6 of this profile.

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

Today in the United States, 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, especially DDE. Some of these stored amounts leave the body very slowly. Levels in fatty tissues may either remain relatively the same over time or even increase with continued

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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 and pass directly to nursing infants. See Chapter 3 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 (grams) 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. The same type of effects would be expected by breathing DDT particles in the air or by contact of the skin with high amounts of DDT. Tests in laboratory animals confirm the effect of DDT on the nervous system.

No effects have been reported in adults given small daily doses of DDT by capsule for 18 months (up to 35 milligrams [mg] every day). People exposed for a long time to small amounts of DDT (less than 20 mg per day), such as people who worked in factories where DDT was made, had some minor changes in the levels of liver enzymes in the blood. A study in humans showed that increasing concentrations of *p,p'*-DDE in human breast milk were associated with reductions in the duration of lactation. An additional study in humans found that as the DDE levels in the blood of pregnant women increased, the chances of having a pre-term baby also increased. It should be mentioned, however, that the levels of DDE in the blood at which this was noticed were higher than those currently found in women from the general population in the United States, but not higher than those that may be found in women in countries where DDT is still being used.

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.

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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 moderate amounts of DDT (20–50 mg per kilogram [kg] of body weight every day) 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 (substances produced by organs and released to the bloodstream to regulate the function of other organs).

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. Based on all of the evidence available, the Department of Health and Human Services has determined that DDT is reasonably anticipated to be a human carcinogen. Similarly, the International Agency for Research on Cancer (IARC) has determined that DDT is possibly carcinogenic to humans. EPA has determined that DDT, DDE, and DDD are probable human carcinogens. See Chapter 3 for more information on the health effects associated with exposure to DDT, DDE, and DDD.

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**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.

Children can be exposed to DDT, DDE, or DDD by eating food or drinking breast milk 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, intake of an equivalent amount of DDT by children and adults would result in a higher dose (amount of DDT ingested per kilogram of body weight) in children than in 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 much smaller than the amounts that have been tested in studies in animals.

DDT from the mother can enter her unborn baby through the placenta. DDT has been found in amniotic fluid, human placentas, fetuses, and umbilical cord blood. DDT has been measured in human milk; therefore, nursing infants are also exposed to DDT. In most cases, however, the benefits of breast-feeding outweigh any risks from exposure to DDT in mother's milk. Nevertheless, women with unusually high amounts of DDT or metabolites in their bodies (compared to background amounts measured in the general population) should be informed of the potential exposure of the fetus if they become pregnant and the potential risks of breast-feeding.

We do not know whether children differ from adults in their susceptibility to health effects from DDT. There are few studies of young children exposed to DDT. A child who drank DDT in kerosene only once 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

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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 4 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 in people. One study in U.S. children 12 to 14 years of age found that boys whose mothers had higher DDE levels in their bodies when they were pregnant were taller than those whose mothers had lower DDE levels. A study of German children found that girls with higher DDE in the blood at 8 years of age were shorter than those with lower DDE levels. The reason for the discrepancy between the two studies is unknown. Studies in animals have shown that DDT given during pregnancy can slow the growth of the fetus. Exposure to DDT or its metabolites during development may change how the reproductive and nervous systems work. This seems to be caused by the property of DDT or its metabolites to mimic the action of natural hormones. 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 3.8.

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**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 insure that pesticide residues are below FDA 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. DDT in the air can be deposited on to the surfaces of plants. Washing fruits and vegetables before eating them is a healthful practice.

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

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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 6.5, 6.6, and 6.7.

**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 Chapters 3 and 7 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

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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 ( $1 \text{ mg/m}^3$ ) 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. FDA has set action levels for DDT/DDE/DDD; these are limits at or above which FDA will take legal action to remove products from the market. Action levels for a variety of products are listed in Table 8-1. See Chapter 8 for more information on regulations.

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**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  
Web site: <http://www.atsdr.cdc.gov>

\* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)  
Fax: 1-404-498-0057

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: 1-800-553-6847 or 1-703-605-6000



## **2. RELEVANCE TO PUBLIC HEALTH**

### **2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO DDT/DDE/DDD IN THE UNITED STATES**

DDT is an organochlorine insecticide that has found a broad range of agricultural and nonagricultural applications in the United States and worldwide beginning in 1939. In 1972, DDT use was banned in the United States and in many parts of the world, except for use in controlling emergency public health problems. DDT is still used in certain parts of the world to control vector-borne diseases, such as malaria. The release of DDT into the environment occurs primarily through spraying applications onto agricultural crops, forest lands, other nonagricultural land, and homes (for the control of disease-bearing vectors). Exposures in the home occurred through the use of DDT as a mothproofing agent, to control lice and, in some parts of the world, to control mosquitoes and other disease-bearing vectors. Both DDD and DDE are degradation products of DDT. DDD was also manufactured and used as an insecticide, but to a much lesser extent than DDT. DDE has no commercial use, but is commonly detected along with DDT at concentrations in the environment that often exceed those measured for DDT.

Upon introduction into the environment, DDT will enter soil, water, or air. DDT and its metabolites are essentially immobile in soil, becoming strongly absorbed onto the surface layer of soils. Likewise, as a consequence of their extremely low water solubilities, DDT and its metabolites become absorbed onto particulates in water and settle into sediments. Because of its chemical characteristics, DDT can undergo long-range transport through the atmosphere in a process known as “global distillation” where DDT migrates from warmer regions to colder regions through repeated cycles of volatilization from soil and water surfaces followed by deposition of DDT onto surfaces through dry and wet deposition processes. This long-range transport of DDT results in the wide dispersion of DDT and its metabolites throughout the world, even into remote areas, such as the Arctic or Antarctic regions. The rate and extent of disappearance of DDT may result from transport processes as well as from degradation and transformation. Both the slow degradation of DDT and its metabolites and the ban on DDT use in the early 1970s in the United States and most of the world have contributed to a decrease in the levels of these compounds in the environment over the past 30 years. DDT can be degraded through atmospheric photooxidation in air or photolysis on the surface of water or soil. DDT can undergo slow biodegradation through reductive dechlorination to form DDE and DDD, and then be further degraded to form other metabolites. The persistence of DDT and its metabolites, in combination with their high lipophilicity, have contributed to the bioaccumulation (increasing concentration of a chemical in an organism which

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exceeds that in its environment) and biomagnification (increasing concentration of a chemical in an organism as a function of trophic level) of DDT and its degradation products in the environment. DDT, DDE, and DDD accumulate in fatty tissues, with tissue concentrations typically increasing with the trophic level of the organism. In addition to DDT, DDE, and DDD, methylsulfonyl derivatives of DDE can be formed in higher organisms, such as seals, polar bears, beluga whales, and humans, and are found predominantly in the liver and fatty tissues.

Exposure of the general public to DDT, DDE, and DDD has been declining since the ban on the use of DDT, at rates that depend on geographic location and environmental conditions. The predominant route of exposure of the general public to DDT and its metabolites is through the diet. Although DDT and its metabolites are ubiquitous in the atmosphere, they are present in such low concentrations that exposures through inhalation or dermal contact are considered to be negligible. From the standpoint of dietary exposures, the main exposure route is through the consumption of foods either obtained from areas of the world where DDT is still used or that have the potential to contain bioaccumulated residues of DDT and its metabolites (e.g., meat, fish, poultry, dairy products). Exposure to DDT in drinking water is considered negligible because of the extremely low water solubility of DDT and the efficiency of standard drinking water methods. With the ban on the use of DDT, occupational exposures that result from formulation, packaging, and application activities should be negligible, except in areas where DDT use remains. Activities that result in the mobilization of DDT (e.g., site remediation) may increase exposure of workers to DDT and its metabolites. With the discontinued use of DDT, exposure of populations living near areas of heavy DDT use or deposition may not be much greater than for the general public, except in areas of the world where DDT is still used to control disease-bearing vectors or under conditions where DDT and metabolites become mobilized (e.g., site remediation, sediment resuspension, erosion, etc.). Residents living near National Priorities List (NPL) sites that contain DDT may be exposed to higher ambient levels of DDT and its metabolites than the general population through dermal (deposition onto plants, objects), ingestion (contaminated food, water), and/or inhalation of DDT vapor, although inhalation exposures are thought to be insignificant compared to dietary sources of DDT. These exposures can lead to greater body burdens of DDT and its metabolites; for example, residents living near a pesticide dump site in Aberdeen, North Carolina, which is known to contain DDT, have higher age-adjusted mean levels of DDE in their blood than residents of neighboring communities (4.05 vs. 2.85 ppb).

Exposures of wildlife to DDT and its metabolites have been declining since the early 1970s, as evidenced by marked decreases in the levels of these compounds in fish, shellfish, aquatic mammals, birds,

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invertebrates and many other species. Yet, DDT and its metabolites were detected in 94% of whole fish samples in the 1990s even though total DDT concentration in fish continues to decline. This is due to the presence of DDT in stream beds and the continued input of DDT to streams through long-range aerial transport and deposition of DDT and erosion of soil. The DDT metabolite, *p,p'*-DDE, was detected with the highest frequency in fish, followed by *p,p'*-DDD and *p,p'*-DDT; accumulation of *p,p'*-DDE in fish is due to absorption of DDE from the diet rather than to recent exposures to DDT. Differences in exposures of benthic and pelagic feeders to DDT and its metabolites have been observed. In the marine environment, there is evidence to suggest that benthic organisms feeding at the bottom of the oceans accumulate higher levels of *p,p'*-DDT and its metabolites, *p,p'*-DDE and *o,p'*-DDE, than do surface feeders. This is attributed to the absorption of *p,p'*-DDT, *p,p'*-DDE, and *o,p'*-DDE onto organic particulates and detritus that then settle to the ocean floor. However, in a fresh water lake system, it was found that bioaccumulation of GDDT was greater in the pelagic food web than in the benthic food web due to the increased mobility of pelagic organisms and their ultimate reliance on benthos. The GDDT that has accumulated in these aquatic food webs can then be further accumulated in organisms in higher trophic levels of the food chain. Exposure of wildlife to DDT and its metabolites can also occur through DDT-contaminated soils and sediments.

Since the ban on DDT was instituted in the United States and most of the world in 1972, the environmental concentrations of DDT and its metabolites have been decreasing. Average adult intakes of DDT were estimated to be 62 µg/person/day in 1965 and 240 µg/person/day in 1970, before the DDT ban was instituted. The FDA Total Diet Studies show that the daily intakes have fallen since the ban, with daily intakes (for a 16-year-old, 70 kg male) averaging 6.51, 2.38, 1.49, and 0.97 µg/person/day for 1978–1979, 1979–1980, 1984–1986, and 1986–1991, respectively. As would be expected from the decline in the concentrations of DDT in the environment, the levels of DDT, DDE, and DDD measured in foodstuffs have also fallen over the last 30 years. Yet, there are still measurable quantities of DDT, DDE, and DDD in many commodities. The mean concentrations of *p,p'*-DDE within specific food groups ranged from 0.1 to 25.7 ppb in dairy products, 0.7–6.5 ppb in meat, 0.2–9.2 ppb in fish, and 0.3–0.7 ppb in poultry, as determined from the data collected in the FDA Total Diet Studies conducted between 1991 and 1999. DDT was detected in 312 out of 2,464 plain milk samples at a maximum concentration of 0.92 ppm and in 8 out of 180 vitamin D fortified milk samples at a maximum concentration of 0.10 ppm in 1985–1991. In a recent FDA Total Diet Study, the mean concentrations of *p,p'*-DDT, *o,p'*-DDT, and *p,p'*-DDE ranged from 0.0001 to 0.0257 ppm. People who eat fish caught in the Great Lakes were found to consume larger amounts of DDT in their diets. However, this route of exposure to DDT is expected to decline as the levels of DDT in the environment continue to diminish. Even so, it is anticipated that low

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levels of DDT and its metabolites will be present in the human diet for several more decades, especially in food items, such as fish, that are expected to contain bioaccumulated DDT residues.

Exposures of the general public to DDT and its metabolites result in the accumulation of these compounds in adipose tissue. Due to the persistence of DDT and its metabolites, the concentrations of these compounds in adipose tissue are determined by both past and current exposures. Estimated national means for DDT concentrations in adipose tissue on a lipid basis were 189, 123, and 177 ppb in 1982, 1984, and 1986, respectively. For DDE, the mean concentrations were found to be 1,840, 1,150, and 2,340 ppb, respectively. In a study of people from northern Texas, the concentrations of DDT and DDE in adipose tissues decreased from 7,950 ppb in 1970 to 5,150 ppb in 1974, and then to 1,670 ppb in 1983. More current measurements of the mean concentrations (lipid basis) of DDT, DDE, and DDD in breast adipose tissue collected during 1995–1996 in the United States were 267.3, 709.1, and 24.0 ppb, respectively, (DDT+DDE+DDD=1,000.4 ppb), which are consistent with the expectation of continuing declines in GDDT body burdens. The adrenocorticolytic agent, 3-methylsulfonyl-DDE, has been detected in the human liver (1.1 ppb), lung (0.3 ppb), and adipose tissue (6.8 ppb) (based on wet weight), and also in breast milk (0.1 ppb). In a study of Swedish women, concentrations of 3-methylsulfonyl-DDE in breast milk ranged from 0.4 to 5 ppb.

At risk populations include indigenous peoples of the arctic who have diets that are high in fatty tissues from the consumption of traditional foods like seal, caribou, narwhales, etc. Intake of GDDT averaged 24.2–27.8 µg/day for eastern Arctic communities and 0.51–1.0 µg/day for western Arctic communities. It is likely that fish-eating populations in the higher latitudes of the Southern Hemisphere may also be at risk; however, these exposures have not been well documented. Children are also at risk to exposure to DDT, mainly through dietary sources. The mean intakes of DDT and its metabolites during 1986–1991 have been estimated to be 0.0448 and 0.0438 µg/kg body weight/day for a 6–11-month-old infant and a 2-year-old child, respectively, which is roughly 4 times the intake per body weight for an adult. Increased infant exposure to DDT has been attributed to breast feeding. The average levels of DDT in human breast milk fat were about 2,000–5,000 ppb in the early 1970s, but have steadily declined at a rate of 11–21% per year since 1975. For example, Norén reported concentrations of *p,p'*-DDT in breast milk fat of 0.71, 0.36, 0.18, and 0.061 ppm for the years 1972, 1976, 1980, and 1984–1985, respectively. These investigators also reported concentrations of *p,p'*-DDE of 2.42, 1.53, 0.99, and 0.50 ppm for these same years, respectively. The mean concentrations of *p,p'*-DDE are roughly 10 times greater than those obtained for *p,p'*-DDT concentrations. Some more recent measurements taken in 1992 show a mean DDE concentration of 222.3 ppb in breast milk of Canadian women. Measurements of DDE and DDT in

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Swedish women in 1997 show levels of 129 and 14 ppb, respectively. Consumption of cow's milk is another route of potential exposure of DDT to children; however, the concentrations of DDT and its metabolites are typically lower in cow's milk than in human breast milk. The mean level of *p,p'*-DDE in cow's milk was measured at 96 ppb in 1970 and 16 ppb in 1985–1986, showing a sharp decline over the years.

**2.2 SUMMARY OF HEALTH EFFECTS**

Numerous studies have been conducted on the effects of DDT and related compounds in a variety of animal species, but the human data are somewhat limited. Most of the information on health effects in humans comes from studies of workers in DDT-manufacturing plants or spray applicators who had occupational exposure to DDT over an extended period and also from some controlled exposure studies with volunteers. Epidemiological studies of the general population are also available. Because of limitations inherent to all epidemiological studies, disease causality cannot be determined from them; however, epidemiological studies have been conducted that allow the evaluation of the potential role of DDT and related compounds in specific health outcomes.

DDT is an organochlorine pesticide whose best known effect is impairment of nerve impulse conduction. Effects of DDT on the nervous system have been observed in both humans and animals and can vary from mild altered sensations to tremors and convulsions. Humans have been reported to tolerate doses as high as 285 mg/kg without fatal result, although because vomiting occurred, the absorbed dose is not known. There are no documented unequivocal reports of a fatal human poisoning occurring exclusively from ingestion of pure DDT, but deaths have been reported following ingestion of commercial preparations containing also other substances. Death in animals following high exposure to DDT is usually caused by respiratory arrest. In addition to being a neurotoxicant, DDT is capable of inducing marked alterations on reproduction and development in animals. This is attributed to hormone-altering actions of DDT isomers and/or metabolites. Of all the DDT-related compounds, the *o,p'*-DDT isomer has the strongest estrogen-like properties, although it is still several orders of magnitude less potent than the natural hormone, 17 $\beta$ -estradiol. *p,p'*-DDE, a metabolite of DDT and a persistent environmental pollutant, has antiandrogenic properties and has been shown to alter the development of reproductive organs when administered perinatally to rats. There have been studies in humans suggesting that high DDT/DDE burdens may be associated with alterations in end points that are controlled by hormonal function such as duration of lactation, maintenance of pregnancy, and fertility. High blood levels of DDE during

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pregnancy have also been associated with increased odds of having pre-term infants and small-for-gestational-age infants and height abnormalities in children.

Studies in animals have shown that DDT, DDE, and DDD can cause cancer, primarily in the liver. The possible association between exposure to DDT and various types of cancers in humans has been studied extensively, particularly breast cancer. Thus far, there is no conclusive evidence linking DDT and related compounds to cancer in humans. Possible genotoxic effects in humans have been reported in a few studies, but simultaneous exposure to other chemicals and lack of control for relevant confounders make the results inconclusive. For the most part, DDT and related compounds are not mutagenic in prokaryotic organisms. Studies in animals have shown that DDT can cause adverse liver effects, but studies of humans exposed occupationally or of volunteers given DDT have reported only mild liver alterations of no clinical significance. Very limited information exists on immunological effects of DDT in humans. A recent study of subjects residing near a waste site found that individuals with higher blood DDE levels had minor changes in some immune markers, which the authors considered of uncertain clinical importance. Studies in animals suggest that exposure to DDT may impair immunocompetence. There is sufficient information indicating that the adrenal gland is a target for *o,p'*-DDD toxicity in humans and animals and of the sulfonyl metabolite 3-MeSO<sub>2</sub>-DDE in animals. *o,p'*-DDD has been used in humans to treat adrenocortical carcinoma and benign Cushing's disease.

Discussion of some end points affected by exposure to DDT/DDE/DDD has been expanded below. These include end points that have generated considerable interest due to public health implications such as various types of cancer and reproductive/developmental effects that may be caused by alterations of the endocrine system. Also included are neurological effects, since the main effect of DDT is on the nervous system, and hepatic effects, since the liver is significantly affected in several animal species.

**Reproductive/Developmental Effects.** In recent years, concern has been raised that many pesticides and industrial chemicals are endocrine-active compounds capable of having widespread effects on humans and wildlife. Hormones influence the growth, differentiation, and functioning of many target tissues, including male and female reproductive organs and ducts such as mammary gland, uterus, vagina, ovary, testes, epididymis, and prostate. Therefore, mimicking the effects of hormones or antagonizing hormonal effects can potentially affect a number of organs and systems, especially if this occurs at vulnerable times such as during development. Developing organisms respond to endocrine-disrupting chemicals very differently than adults. Fetuses lack feedback regulatory mechanisms and active metabolism of steroid hormones that regulate maintenance of secondary sex tissues, estrous cycling, and

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pregnancy. Consequently, low levels of exogenous hormones or xenobiotics may induce severe effects in the development of the reproductive organs. Thus far, there is no conclusive evidence that exposure to DDT/DDE/DDD at the levels found in the environment has affected reproduction and development in humans, but there is sufficient information from animal studies that these chemicals have the potential for doing so.

Several studies in humans have examined possible associations between body burdens of DDT and analogues and the incidence of alterations in reproduction and development and in other end points in which hormones may play a pivotal role such as lactation, infertility, miscarriages, and pre-term labor. For example, duration of lactation was inversely related to the concentration of *p,p'*-DDE in a group of women from Mexico who had lactated previously and similar findings were reported in a study in the United States. A plausible explanation for this decrease in the longevity of lactation is the antiandrogenic/weak estrogenic effect of DDE, as estrogens inhibit milk secretion. In a study of 240 women, there was no association between blood DDE levels (<6 ppb) and miscarriages, but there was suggestive evidence of an association in a study of 89 German women, 13 of whom had DDE blood levels >2.5 ppb; the highest DDE level was 8.6 ppb. A weak association between infertility and DDT blood levels was observed in an additional study of 489 German women. Studies in India and Israel have reported higher levels of DDT, DDE, and DDD 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, but the possible role of other potentially endocrine-disrupting chemicals, such as PCBs and other chlorinated pesticides, could not be ruled out. A smaller study in the United States of only 20 women did not find the same association between serum DDE levels and pre-term delivery. Yet another study found no differences in DDT levels in maternal blood at delivery between full-term babies and cases of pre-term delivery; however, they found that umbilical cord blood from pre-term newborns had higher levels of DDT than full-term newborns. A recent study of 361 pre-term infants and 221 small-for-gestational-age cases found that the odds for both outcomes increased steadily with increasing maternal blood concentrations of DDE in samples taken in the third trimester of pregnancy. The association was evident at DDE concentrations  $\geq 10$  ppb, but there was essentially no relation at lower DDE concentrations. It is important to point out that while levels of DDE in the general population in the United States continue to decline and current serum levels average <10 ppb, it is not unusual to find higher levels in populations from countries where DDT is still used for controlling vector-transmitted diseases. High blood levels of DDE during pregnancy have also been associated with height abnormalities in children.

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Technical DDT is a mixture of various isomers of which *p,p'*-DDT is the most prevalent (65–80%), followed by *o,p'*-DDT (15–21%). Although *p,p'*-DDT is more acutely toxic than *o,p'*-DDT, it has been known for several decades that the latter had marked effects on reproduction in animals. In most experiments, *o,p'*-DDT mimicked the action of the natural ligand, 17 $\beta$ -estradiol. In general, results from *in vivo* studies indicate that DDT and analogues have much lower estrogenic potency (1,000–1,000,000-fold lower) than the endogenous hormone, 17 $\beta$ -estradiol. Experiments in rats have shown that *o,p'*-DDT can induce delayed vaginal opening and increased uterine and ovarian weights. In another study in rats, using the uterine glycogen response assay, it was observed that *o,p'*-DDT was the most potent among several isomers. *p,p'*-DDT and *o,p'*-DDE were approximately 16 times less potent than *o,p'*-DDT, and *o,p'*-DDD was inactive in this assay. In yet another study, the lowest dose of *o,p'*-DDT needed to produce estrogenic effects in the immature rat uterus was about  $1 \times 10^5$  times greater than that of DES. An *in vivo* assay with rats and mink showed that *o,p'*-DDT had uterotrophic 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. Many other *in vivo* studies have shown the estrogenic potential of DDT and related analogues. Most recent studies have been conducted using a wide variety of *in vitro* assays and the results vary greatly. Still, the estrogenicity of DDT-related compounds in these tests has been determined to be  $10^4$ – $10^6$  times lower than 17 $\beta$ -estradiol, depending on the testing conditions.

Safe 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 in *in vivo* and *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 estimated a dietary estrogen equivalent level of  $2.5 \times 10^{-6}$   $\mu\text{g/day}$  from estrogenic pesticides and of 102  $\mu\text{g/day}$  from bioflavonoids. Studies from the literature also suggested that the estrogenic potencies of bioflavonoids relative to 17 $\beta$ -estradiol (potency=1) 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 estimated to be  $4 \times 10^7$  times higher than that from estrogenic pesticides. A similar exercise with the antiestrogenic compounds led Safe to the conclusion that the sum of antiestrogen

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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. One additional fact to keep in mind is that DDT and analogues bioconcentrate in the food chain and accumulate in the body.

Recent studies *in vivo* have also demonstrated that *p,p'*-DDE, the most environmentally relevant DDT derivative, has antiandrogenic properties when administered to rodents at relatively high doses. Studies *in vitro* have confirmed the findings *in vivo*. In particular, *p,p'*-DDE functions as an antagonist after it has bound to the androgen receptor. This androgen antagonism or antiandrogenic 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; delayed puberty in rats exposed either during juvenile development or at very high doses during gestation and lactation; and reduced accessory sex organ weights in exposed adult males. In addition to being antiandrogenic by an action on the androgen receptor, *p,p'*-DDE was shown to increase liver CYP enzyme systems that hydroxylate testosterone in perinatally exposed rats. This effect can be also considered an antiandrogenic effect since hydroxylated testosterone is more polar than testosterone and can be conjugated and excreted. It is not known, however, whether the increase in activity of enzymes that hydroxylate testosterone resulted in a reduction of circulating androgens since the authors did not measure serum testosterone. In general, altering steroid metabolism is another possible mechanisms by which DDT and related compounds can alter reproduction and development. *p,p'*-DDE also was shown to increase liver aromatase activity in adult male rats; aromatase plays a critical role in steroidogenesis by catalyzing the conversion of C19 androgens into estrogens. Thus, like DDT, DDE can have an overall feminizing effect on animals by antagonizing the androgen receptor at the same time that it increases estrogens concentration.

Administration of DDT *in utero* or to neonates during sensitive periods in nervous system development has caused behavioral and neurochemical changes in adult mice. 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 minimum risk level (MRL) for DDT.

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**Cancer.** The possibility that exposure to DDT and related compounds might increase the risk of certain cancers in humans has been explored in many studies. Special attention has been devoted, but not limited, to breast cancer. Moreover, the interest is not limited to DDT/DDE only, but to persistent organochlorine compounds in general (e.g., PCBs, dieldrin, hexachlorobenzene). In addition to factors inherent to epidemiological studies that play a role in trying to establish associations between exposure and health outcome, for breast cancer, one must consider additional factors that are thought to play important roles such as menopause, estrogen receptor status, and concurrent exposure to other estrogenic and antiestrogenic compounds. Several methods for assessing combined current and past exposures to DDT have been used. Most DDT (and the most prominent environmental residue, DDE) is stored in the fat, so an accurate method of assessing body burden is measuring levels in adipose tissue samples. However, procedures for obtaining adipose tissue samples are usually invasive and not easy to obtain (unless done during cancer surgery). 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. 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. Adjusting for lipid content provides a standardized body burden estimation and makes comparisons between studies easier. Studies have shown that on a fat-weight basis, DDT residue levels in serum correlate well with adipose tissue samples, making serum an adequate biological medium for estimating DDT body burden.

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 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, but it could also represent residues originating from past high exposures to the pesticide. In developed countries where DDT use is banned and average exposures in food have declined considerably with time, current DDT burdens most likely represent past exposure. 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-

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stored DDT/DDE/DDD to the blood, and hence, the concentration of DDT/DDE/DDD in blood, fat, and other tissues. Several studies have had access to blood samples collected several years before the diagnosis of cancer was made; however, there is no information available regarding possible exposures *in utero* or during adolescence that may have contributed to the development of cancer later in life. Third, recent reports have shown that obese and lean women metabolize organochlorines at a different rate. Therefore, there may be misclassification of exposure depending on time of measurement.

Thus far, the majority of the epidemiological studies conducted in the United States and abroad, particularly the most recent ones and those that included larger sample sizes, have found no association between DDT/DDE and breast cancer. However, some studies did find positive associations between DDT/DDE body burdens and breast cancer. The study of Canadian women by Demers et al. provided a new and important finding that deserves special attention. Demers et al. found that while mean plasma concentrations of DDT and DDE in women with breast cancer were not significantly different from those of controls, there seemed to be an association between DDE and cancer aggressiveness, as judged by increased tumor size and axillary lymph node involvement. A similar finding was reported by Woolcott et al., who found that the concentrations of DDE and DDT were higher in adipose tissue from cases with more poorly differentiated tumors than cases with moderately or well differentiated tumors. It seems that replication of these results is necessary before further speculating on the clinical significance of these findings. Details of these studies can be found in Section 3.2.2.7.

Possible associations with other cancers that have been investigated include pancreatic cancer, lymphoma, multiple myeloma, prostate and testicular cancer, endometrial cancer, and liver cancer. Overall, in spite of some positive correlations, there is no clear evidence that exposure to DDT/DDE causes cancer in humans. The case of pancreatic cancer deserves special mention because, as discussed by Hoppin et al., this cancer is characterized by cachexia, and the impact of this on serum organochlorine levels is difficult to predict. As the lipid pool decreases, the concentration of a fixed amount of lipid soluble chemical increases. While in the Hoppin et al. study, cases and controls had almost the same DDE serum levels before adjusting for lipid contents, adjusted values were much higher in cases than in controls. This points to the need to better understand changes in pharmacokinetics that occur as a result of a disease state and how these changes can influence the interpretation of the results. While there is no clear evidence of carcinogenicity of DDT/DDE/DDD in humans, there is sufficient evidence of carcinogenicity of these compounds in rodents, that developed tumors primarily in the liver following long-term oral treatment with these compounds. Two earlier studies in monkeys treated chronically with DDT reported no evidence of carcinogenicity, but a more recent study that involved Rhesus and Cynomolgus monkeys

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administered *p,p'*-DDT in the diet for up to 130 months reported that 2 out of 13 *Cynomolgus* monkeys developed malignant tumors, one hepatocellular carcinoma and one adenocarcinoma of the prostate. This corresponds to an incidence of 15%, which is significant compared to no neoplasms found in a group of nine contemporary untreated control monkeys.

The EPA has assigned DDT, DDE, and DDD to Group B2, probable human carcinogens. The International Agency for Research on Cancer (IARC) has determined that DDT, DDE, and DDD are possibly carcinogenic to humans (Group 2B). The Department of Health and Human Services (DHHS) has determined that DDT, DDE, and DDD may reasonably be anticipated to be human carcinogens.

**Neurological Effects.** The main neurophysiological effect of DDT is to prolong the sodium current in axons drastically, which accounts for the increase in depolarizing after-potential and the resultant repetitive afterdischarges in nerve fibers and synaptic junctions. As many basic functions such as respiratory and cardiovascular functions are controlled by the nervous system, exposure to high amounts of DDT is expected to produce a wide array of symptoms and central and peripheral signs of toxicity. High oral doses of DDT in humans result in paresthesia of the tongue, lips, and face, as well as apprehension, hypersusceptibility to external stimuli, irritability, dizziness, vertigo, tremor, and tonic and clonic convulsions. In general, results from studies in animals are consistent with observations in humans. Earlier studies of workers exposed to DDT (approximately 42 mg/man/day) and also studies with volunteers who ingested up to 35 mg DDT/man/day up to 18 months did not report adverse neurological effects, as assessed by tests of motor and sensory functions. However, a recent study of 27 workers in Costa Rica who used DDT for malaria control between 1955 and 1986 found that exposed subjects performed worst on tests of verbal attention and visuomotor speed and sequencing than a group of controls. However, because exposure levels were not available and current body burdens that could have been used to back estimate exposure were not determined, it is difficult to reconcile these findings with those from the earlier studies.

**Hepatic Effects.** Although there is no conclusive evidence in the available studies that the human liver is a primary target for DDT toxicity or that exposure to DDT causes liver toxicity in humans, many studies have reported hepatic effects in animals following exposure to DDT and related compounds. Effects observed include induction of microsomal enzymes, increased serum transaminase activities of hepatic origin, liver hypertrophy, hyperplasia, and necrosis, and liver cancer. Induction of microsomal enzymes is important because it can lead to altered metabolism of exogenous and endogenous substrates, including steroid hormones. In fact, as previously mentioned, alteration of hormone metabolism has been

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suggested to be at least a contributing factor in the DDT-induced reproductive and developmental effects. Based on induction profiles obtained in rats, DDT and related compounds are considered primarily, although not exclusively, phenobarbital-type inducers. Liver effects were the most sensitive effects observed in animals treated with DDT by relevant routes of exposure. Thus, an intermediate-duration study in rats that provided dose-response information for liver effects was used to derive an intermediate oral MRL for DDT.

### 2.3 MINIMAL RISK LEVELS

#### *Inhalation MRLs*

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

#### *Oral MRLs*

CAAn acute 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; Talts et al. 1998). An uncertainty factor of 1,000 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) (this same single dose level was used in all studies from the series). 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

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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  $^{14}C$ -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  $M_1$  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. In 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

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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 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). Also, treatment with DDT followed by bioallethrin significantly increased the density of muscarinic receptors in the cerebral cortex relative to DDT alone. This increase was later attributed to increased expression of muscarinic receptor m4 mRNA (Talts et al. 1998). 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 were measured 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 lowest-observed-adverse-effect level (LOAEL).

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

This MRL is based on a no-observed-adverse-effect level (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 values for the NOAEL range 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,

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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). The selected effects for the intermediate-duration oral MRL represent reliable effects that occurred at the lowest administered dose (including endocrine effects), as seen in Table 3-1 (see Chapter 3); therefore, the intermediate oral MRL is protective for endocrine effects and other non-cancer effects.

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

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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.



### 3. HEALTH EFFECTS

#### 3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of 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 3.2 Discussion of Health Effects by Route of Exposure, whereas information on the effects of these compounds in wildlife is presented in Appendix D, 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 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 4). 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. Levels of Significant Exposure (LSE) for the *o,p'*-isomers are presented in separate tables to emphasize the point that these isomers have a somewhat different spectrum of effects than the *p,p'*-isomers.

## 3. HEALTH EFFECTS

**3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE**

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

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

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

### 3. HEALTH EFFECTS

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of DDT, DDE, and DDD are indicated in Table 3-1 and Figure 3-1. Because cancer effects could occur at lower exposure levels, Figure 3-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 ( $10^{-4}$  to  $10^{-7}$ ), 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.

#### 3.2.1 Inhalation Exposure

Occupational exposure to DDT involves 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.

## 3. HEALTH EFFECTS

**3.2.1.1 Death**

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

**3.2.1.2 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.

### 3. HEALTH EFFECTS

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

#### **3.2.1.3 Immunological and Lymphoreticular Effects**

#### **3.2.1.4 Neurological Effects**

#### **3.2.1.5 Reproductive Effects**

#### **3.2.1.6 Developmental Effects**

#### **3.2.1.7 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 1–20 years (OR=1.6; 95% confidence interval [CI]=0.9–4.6), in 16 workers who had been exposed for greater than 20 years (OR=2.0; 95% CI=0.9–4.7), and in 50 workers who had ever been exposed to DDT (OR=1.7; 95% CI=1.0–2.8). 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=1.5–8.9) or in 57 with adenocarcinoma (OR=2.3; 95% CI=1.2–4.7). 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 3.2.2.8 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 2001a, 2001b, 2001c) calculated an inhalation unit risk of  $9.7 \times 10^{-5}$  per  $\mu\text{g}/\text{m}^3$  for DDT from oral data in animals (Section 3.2.2.8). The air concentrations corresponding to excess cancer risk levels of  $1 \times 10^{-4}$ ,  $1 \times 10^{-5}$ ,  $1 \times 10^{-6}$ , and  $1 \times 10^{-7}$  are  $1 \times 10^{-3}$ ,  $1 \times 10^{-4}$ ,  $1 \times 10^{-5}$ , and  $1 \times 10^{-6}$  mg/m<sup>3</sup>, respectively.

### **3.2.2 Oral Exposure**

Tables 3-1 and 3-2 and Figures 3-1 and 3-2 present the health effects observed in humans and animals associated with levels of significant oral exposure for each designated exposure duration. The levels of

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except as Noted)							
Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat (NS)	Once (NS)				300 (LD50)	Ben-Dyke et al. 1970 DDT, NS
2	Rat (NS)	Once (NS)				400 (LD50)	Ben-Dyke et al. 1970 DDD, NS
3	Rat (NS)	Once (G)				800 (LD50)	Cameron and Burgess 1945 DDT, NS
4	Rat (Sherman)	Once				113 (LD50)	Gaines 1969 DDT, p,p'
5	Rat (Sherman)	Once (G)				4000 (LD50)	Gaines 1969 DDD, Tech
6	Rat (Sherman)	Once (G)				880 (LD50)	Gaines 1969 DDE, Tech
7	Rat (NS)	4 d (G)				279.2 (4-day LD50, preweanling; cumulative dose)	Lu et al. 1965 DDT, Tech
8	Rat (NS)	4 d (G)				285.6 (4-day adult LD50; cumulative dose)	Lu et al. 1965 DDT, Tech
9	Rat (NS)	Once (G)				355.2 (LD50, weanling rats)	Lu et al. 1965 DDT, Tech
10	Rat (NS)	Once (G)				194.5 (LD50, adult rats)	Lu et al. 1965 DDT, Tech

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
11	Rat (NS)	Once (IG)				4000 (LD50, newborn rats)	Lu et al. 1965 DDT, Tech
12	Rat (NS)	Once (G)				437.8 (LD50, preweanling rats)	Lu et al. 1965 DDT, Tech
13	Mouse (Inbred Swiss)	Once (G)				300 M (LD50)	Kashyap et al. 1977 DDT, Tech
14	Mouse (C3H)	6 d (F)				85.7 F (50% of mice killed after a 6-day feeding period)	Okey and Page 1974 DDT, p,p'
15	Mouse (CF1)	Once (G)				1466 (LD50)	Tomatis et al. 1972 DDD, p,p'
16	Mouse (CF1)	Once (G)				237 (LD50)	Tomatis et al. 1972 DDT, Tech
17	Gn Pig (NS)	Once (G)				400 (LD50)	Cameron and Burgess 1945 DDT, NS
18	Rabbit (NS)	Once (G)				300 (LD50)	Cameron and Burgess 1945 DDT, NS
<b>Systemic</b>							
19	Monkey (Rhesus)	Once (G)	Hepatic		150 (increased serum LDH, AP, and transaminases)		Agarwal et al. 1978 DDT, NS

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/duration/frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
20	Rat (Wistar)	12 d (G)	Hepatic		40 (18% increase in relative liver weight; increased liver GSH and AHH enzyme activities)		DeWaziers and Azais 1987 DDT, NS
21	Rat (Sprague Dawley)	Once (GO)	Endocr	25	50 (reduced capacity to concentrate iodine in thyroid)		Goldman 1981 DDT, Tech
22	Rat (Wistar)	14 d 1 x/d (GO)	Hepatic		12 M (increased relative liver weight; necrotic changes)		Kostka et al. 2000 DDT, Tech
23	Mouse (CF1)	1 wk (F)	Hepatic		42.9 (29% increase absolute liver weight; increase cytochrome-c reductase and P-450)		Pasha 1981 DDE, NS
24	Dog (Mongrels and Beagles)	Once (C)	Endocr		200 (reversible degenerative adrenal changes)		Powers et al. 1974 DDD, Tech
25	Dog (Mongrels and Beagles)	6 d or 15d (C)	Endocr			100 (necrosis, adrenal)	Powers et al. 1974 DDT, Tech
<b>Immunological/Lymphoreticular</b>							
26	Rabbit (New Zealand)	10 d (G)		4.3			Shiplov et al. 1972 DDT, NS
<b>Neurological</b>							
27	Human	Once (F)		10.3		16 (convulsions)	Hsieh 1954 DDT, NS

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
28	Monkey (Rhesus)	Once (G)			150 (decrease CNS total lipids, phospholipids and cholesterol)		Sanyal et al. 1986 DDT, Tech
29	Rat (Wistar)	Once (GO)				160 (tremors)	Hietanen and Vainio 1976 DDT, NS
30	Rat (Fischer)	Once (G)		25		50 (tremors)	Hong et al. 1986 DDT, p,p'
31	Rat (Albino Sprague Dawley)	Once (G)				100 (myoclonus)	Hwang and Van Woert 1978 DDT, p,p'
32	Mouse (albino)	once (GO)				160 M (tremors)	Hietanen and Vainio 1976 DDT, p,p'
33	Mouse (Albino)	Once (G)				200 (convulsions)	Matin et al. 1981 DDT, p,p'
34	Gn Pig (NS)	Once (G)				160 (paralysis of hind legs)	Hietanen and Vainio 1976 DDT, NS
35	Hamster (NS)	Once (G)		160			Hietanen and Vainio 1976 DDT, NS
<b>Reproductive</b>							
36	Rat (Long-Evans)	1 x/d 4 d (GO)			200 M (reduced seminal vesicle and ventral prostate weight)		Kelce et al. 1995 DDE, p,p'

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/duration/frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
37	Rat (Sprague-Dawley)	1 x/d 5 d (GO)			200 M (reduced seminal vesicle and ventral prostate weight)		Kelce et al. 1997 DDE, p,p'
38	Rabbit (New Zealand)	Gd7-9 (GO)				50 (increased resorptions, 1.8% in controls, 25% in treated)	Hart et al. 1971 DDT, p,p'
39	Rabbit (New Zealand)	Gd7-9 (GO)				10 (increased resorptions, 1.3% in controls, 9.5% in treated)	Hart et al. 1972 DDT, p,p'
<b>Developmental</b>							
40	Rat (Sprague-Dawley)	Gd15-19 (G)		28			Gellert and Heinrichs 1975 DDT, p,p'
41	Rat (Long-Evans)	5 d Gd 14-18 (GO)				100 M (significant decrease in ventral prostate weight)	Gray et al. 1999 DDE, p,p'
42	Rat (Sprague-Dawley)	5 d Gd 14-18 (GO)				100 M (decreased weight of glans penis; epididymis and ventral prostate; reduced anogenital distance)	Gray et al. 1999 DDE, p,p'
43	Rat (Long-Evans)	1 x/d Gd 14-18 (GO)				100 M (reduced anogenital distance at birth: ppd 13 retained thoracic nipples)	Kelce et al. 1995 DDE, p,p'
44	Rat (Holtzman)	1 x/d Gd 14-18 (GO)		10 M		50 M (reduced anogenital distance on ppd1 and relative ventral prostate weight on ppd21)	Loeffler and Peterson 1999 DDE, p,p'

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
45	Rat (Long-Evans)	1 x/d Gd 14-18 (GO)		10		100 M (reduced anogenital distance on ppd2; retained thoracic nipples on ppd13)	You et al. 1998 DDE, p,p'
46	Rat (Sprague-Dawley)	1 x/d Gd 14-18 (GO)			10 M (ppd13 males retained thoracic nipples)		You et al. 1998 DDE, p,p'
47	Mouse (NMRI)	Once ppd 10 (GO)			0.5 <sup>b</sup> M (increased motor activity at 4 months)		Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b DDT, Tech
48	Mouse (NMRI)	Once ppd 10 (GO)			0.5 M (decrease in cerebral cortex muscarinic acetylcholine receptors at 4 months)		Eriksson et al. 1992 DDT, Tech
49	Mouse (NMRI)	once ppd 10 (GO)			0.5 M (decreased muscarinic receptors in cerebral cortex; increased spontaneous activity at 5 months)		Johansson et al. 1995 DDT, Tech
50	Mouse (NMRI)	once ppd 10 (GO)			0.5 M (decreased muscarinic receptors in cerebral cortex; increased spontaneous activity at 5 and 7 months)		Johansson et al. 1996 DDT, Tech
51	Rabbit (New Zealand)	Gd4-7 (G)			1 (decreased fetal weight)		Fabro et al. 1984 DDT, NS

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
52	Rabbit (New Zealand)	Gd7-9 (GO)				50 (22% decreased offspring weight )	Hart et al. 1971 DDT, p,p'
53	Rabbit (New Zealand)	Gd7-9 (GO)			10 (11% decreased fetal weight on day 28)	50 (19% decreased fetal weight on day 28)	Hart et al. 1972 DDT, p,p'

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Death							
54	Monkey (Squirrel)	2,4 or 6 mo  (G)				50 (death of 6/6 in 14 weeks)	Cranmer et al. 1972a DDT, p,p'
55	Mouse (B6C3F1)	6wk (F)				35 F (4 out 5 died)	NCI 1978 DDT, Tech
56	Mouse (B6C3F1)	6wk (F)				66 M (4 out of 5 died)	NCI 1978 DDE, p,p'
Systemic							
57	Rat (albino)	120 d (GO)	Endocr  Bd Wt			0.2 M (degeneration of adrenal cortex and medulla)  0.2 M (30% reduced body weight gain)	Chowdhury et al. 1990 DDT, Tech
58	Rat (Wistar)	3 wk (GO)	Hepatic		15 (significant increase in liver weight and in cytochrome P-450 enzymes)		Gupta et al. 1989 DDT, p,p'
59	Rat (Sprague Dawley)	36 wk 7d/wk (F)	Hepatic		6.6 (focal necrosis/regeneration)		Jonsson et al. 1981 DDT, NS
60	Rat (Osborne- Mendel)	15-27 wk (F)	Hepatic	0.05 <sup>c</sup>	0.25 (cellular hypertrophy, cytoplasmic eosinophilia)		Laug et al. 1950 DDT, Tech

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/duration/frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
61	Rat (Osborne-Mendel)	6 wk (F)	Bd Wt	28 M	50 M (16% reduced body weight gain)	97 F (45% reduced body weight gain)	NCI 1978 DDT, Tech
62	Rat (Osborne-Mendel)	6wk (F)	Bd Wt		88 M (11% decrease in body weight gain)	157 M (22% decrease in body weight gain)	NCI 1978 DDE, p,p'
63	Rat (Sherman)	2-18 mo (F)	Hepatic		5 M (minor liver vacuolation, hypertrophy and cell margination) 20 F		Ortega 1956 DDT, Tech
64	Mouse (B6C3F1)	6wk (F)	Bd Wt	310 F			NCI 1978 DDD, Tech
65	Mouse (B6C3F1)	6wk (F)	Bd Wt	101 F			NCI 1978 DDE, p,p'
66	Mouse (B6C3F1)	6wk (F)	Bd Wt	35			NCI 1978 DDT, Tech
67	Mouse (NMRI)	28 d (G)	Hepatic		6.25 (increased liver weight and P-450 induction)		Orberg and Lundberg 1974 DDT, p,p'
<b>Immunological/Lymphoreticular</b>							
68	Rat (Wistar)	4 wk (F)		2.3 M	5.7 M (decreased IgG and IgM, increased albumin/globulin ratio)		Banerjee et al. 1995 DDT, p,p'
69	Rat (albino)	31 d 24hr/d (F)			1.9 (decreased mast cells)		Gablík et al. 1975 DDT, NS

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
70	Mouse (Hissar)	3-12 wk (F)		10.5	21 M (decreased IgM antibody titer)		Banerjee 1987a DDT, NS
<b>Neurological</b>							
71	Monkey (Squirrel)	2, 4, or 6 mo (G)		5		50 (staggering, weakness, loss equilibrium)	Cranmer et al. 1972a DDT, p,p'
72	Monkey (Rhesus)	100 d (G)			10 (15-20% decrease in brain lipids, CNS phospholipids, and cholesterol)		Sanyal et al. 1986 DDT, Tech
73	Rat (Osborne- Mendel)	26 wk (F)				16 F (body tremors)	NCI 1978 DDT, Tech
74	Rat (Wistar)	9 wk (F)				34.1 F (tremors in 80% of females after 9 weeks of treatment).	Rossi et al. 1977 DDT, Tech
<b>Reproductive</b>							
75	Rat (Sprague Dawley)	36 wk (F)		6		12 (sterility)	Jonsson et al. 1976 DDT, Tech
76	Rat (Long-Evans)	1 x/d ppd 21-57 (GO)				100 M (delayed onset of puberty by 5 days)	Kelce et al. 1995 DDE, p,p'
77	Rat (Sprague Dawley)	9 wk (G)		10			Kornburst et al. 1986 DDE, p,p'

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
78	Rat (Wistar)	3 wk 3 x/wk (GO)			100 (marginal, but significant decrease in testosterone in the testis)		Krause 1977 DDT, NS
79	Rat (NS)	ppd 4-23 (G)			200 (decreased absolute testis weight)		Krause et al. 1975 DDT, NS
80	Mouse (C-57)	60-90 d (F)				51.4 (78% decreased fertility)	Bernard and Gaertner 1964 DDT, Tech
81	Mouse (B6C3F1)	86 d (F)		3.4			Ledoux et al. 1977 DDT, Tech
82	Mouse (NMRI)	7d/wk 12 wk (F)				1.67 (decreased implanted ova, increased-persistent- estrus)	Lundberg 1974 DDT, p,p'
83	Mouse (NMRI)	28 d (G)				1.67 (decreased corpora lutea and implants)	Lundberg 1974 DDT, p,p'
84	Mouse (NMRI)	28 d (G)		6.25			Orberg and Lundberg 1974 DDT, p,p'
85	Mouse (BALB/c)	120 d (F)		1.3			Ware and Good 1967 DDT, Tech
86	Rabbit (New Zealand)	3 x/wk 12 wk (GO)			3 F (reduced ovulation rate and slight decrease circulating progesterone post-insemination)		Lindenau et al. 1994 DDT, Tech

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
Developmental							
87	Rat (Wistar)	42 d Gd 1-21 Ld 1-21  (F)		1.7	16.8 (decreased growth of nursing pups)	42.1 (pup death by 10 days)	Clement and Okey 1974 DDT, p,p'
88	Mouse (CF1)	Gd 1-21 Ld 1-21  (F)			34.3 (decreased maze performance learning at 1 and 2 months in survivors)		Craig and Ogilvie 1974 DDT, Tech
Cancer							
89	Mouse (CF1)	15-30 wk  (F)				42.8 (liver hepatomas)	Tomatis et al. 1974b DDT, p,p'

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Death							
90	Monkey (Cynomolgus)	130 mo (F)				6.9 F (lowest dose associated with early death)	Takayama et al. 1999 DDT, p,p'
91	Rat (Osborne-Mendel)	78wk (F)				19 F (16% death rate compared to 0% in controls)	NCI 1978 DDE, p,p'
92	Mouse (B6C3F1)	78wk (F)				15.0 F (10% mortality compared to 0% in controls)	NCI 1978 DDT, Tech
93	Mouse (B6C3F1)	78wk (F)				49 F (40% death rate compared to 5% in controls)	NCI 1978 DDE, p,p'
Systemic							
94	Human	12-18 mo (F)	Cardio	0.5			Hayes et al. 1956 DDT, Tech
			Hemato	0.5			
			Hepatic	0.5			
			Bd Wt	0.5			
95	Monkey (Rhesus)	3.5-7 yr (F)	Hepatic	3.9			Durham et al. 1963 DDT, NS
96	Monkey (Cynomolgus)	130 mo (F)	Hepatic		6.4 F (lowest dose associated with fatty changes in the liver)		Takayama et al. 1999 DDT, p,p'

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/duration/frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
97	Rat (Osborne Mendel)	27 mo (F)	Resp	20			Deichmann et al. 1967 DDT, NS
			Hemato		20 (hemolysis in spleen)		
			Hepatic		20 (focal hepato-cellular necrosis)		
			Renal			20 (some tubular epithelial necrosis and polycystic degeneration; small hemorrhages)	
98	Rat (Osborne-Mendel)	2 yr (F)	Hepatic		7 (focal hepatocellular necrosis)		Fitzhugh and Nelson 1947 DDT, Tech
99	Rat (Osborne-Mendel)	78 wk (F)	Resp	45 M			NCI 1978 DDT, Tech
			Cardio	45 M			
			Gastro	45 M			
			Musc/skel	45 M			
			Hepatic		23 M (fatty metamorphosis)		
			Renal	45 M			
			Endocr	45 M			
			Dermal	45 M			
			Bd Wt		32 F (20% decrease in body weight gain)		

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
100 Rat (Osborne-Mendel)	78wk (F)	Resp		231 M			NCI 1978 DDD, Tech
			Cardio	231 M			
			Gastro	231 M			
			Musc/skel	231 M			
			Hepatic	231 M			
			Renal		66 F (chronic inflammation of the kidney)		
			Endocr	231 M			
			Dermal	231 M			
			Bd Wt			66 F (26% decrease in body weight gain)	
101 Rat (Osborne-Mendel)	78wk (F)	Resp		59 M			NCI 1978 DDE, p,p'
			Cardio	59 M			
			Gastro	59 M			
			Musc/skel	59 M			
			Hepatic		31 M (fatty metamorphosis)		
			Renal	59 M			
			Endocr	59 M			
			Dermal	59 M			
			Bd Wt			19 F (21% decrease in body weight gain)	

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
102	Mouse (B6C3F1)	78wk (F)	Resp	30.2 F			NCI 1978 DDT, Tech
			Cardio	30.2 F			
			Gastro	30.2 F			
			Musc/skel	30.2 F			
			Hepatic		3.7 M (amyloidosis)		
			Renal	30.2 F			
			Endocr	30.2 F			
			Dermal	30.2 F			
			Bd Wt	30.2 F			NCI 1978 DDD, Tech
			Resp	142 F			
			Cardio	142 F			
			Gastro	142 F			
			Musc/skel	142 F			
			Hepatic	142 F			
			Renal	142 F			
			Endocr	142 F			
			Dermal	142 F			
			Bd Wt		71 F (17% decrease in body weight gain)	142 F (28% decrease in body weight gain)	

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/duration/frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
104	Mouse (B6C3F1)	78wk (F)	Resp	49 F			NCI 1978 DDE, p,p'
			Cardio	49 F			
			Gastro	49 F			
			Musc/skel	49 F			
			Hepatic	49 F			
			Renal		27 M (chronic inflammation of the kidney)		
			Endocr	49 F			
			Dermal	49 F			
			Bd Wt			28 F (29% decrease in body weight gain)	
105	Hamster (Syrian)	life (F)	Hepatic	20	40 (focal necrosis)		Cabral et al. 1982a DDT, Tech
			Bd Wt	40			
106	Hamster (NS)	life (F)	Hepatic		67 (50% increase in relative liver weight)		Graillot et al. 1975 DDT, Tech
107	Hamster (Syrian)	128 wk (F)	Hepatic		47.5 (liver necrosis)		Rossi et al. 1983 DDE, p,p'
			Bd Wt		47.5 (unquantified reduction in body weight gain)		
108	Dog (NS)	39-40 mo (F)	Hepatic	16	80 (focal or diffuse liver alterations)	160 (severe liver damage)	Lehman 1965 DDT, Tech

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (mg/kg/day)							
Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological							
109	Human	12-18 mo (F)		0.61			Hayes et al. 1956 DDT, Tech
110	Monkey (Cynomolgus)	130 mo (F)				6.9 F (lowest dose associated with severe tremors)	Takayama et al. 1999 DDT, p,p'
111	Mouse (Swiss)	80 wk (F)				16.5 (tremors)	Kashyap et al. 1977 DDT, Tech
112	Mouse (CF1)	130-140 wk (F)		1.7		8.3 (tremors)	Turusov et al. 1973 DDT, Tech
Reproductive							
113	Rat (Sprague- Dawley)	2 gen (F)		1.2			Duby et al. 1971 DDT, p,p'
114	Rat (Sprague- Dawley)	2 gen (F)		0.75			Duby et al. 1971 DDT, Tech
115	Rat (Sprague- Dawley)	2 gen (F)		10			Ottoboni 1969 DDT, Tech
116	Rat (Sprague Dawley)	7d/wk life (F)		1.6			Ottoboni 1972 DDT, Tech
117	Rat (Sprague- Dawley)	3 gen (F)		1.25			Treon et al. 1954 DDT, Tech

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
118	Mouse (Swiss-Webster)	3 gen (F)				20 (decreased fertility)	Keplinger et al. 1970 DDT, NS
119	Mouse (NS)	15 mo (F)		2.4			Wolfe et al. 1979 DDT, Tech
120	Dog (Beagle)	7d/wk- F2 gen (F)		10			Ottoboni et al. 1977 DDT, Tech
<b>Developmental</b>							
121	Rat (Sprague Dawley)	2 gen (F)		1.9	18.6 (tail abnormalities, constriction rings)		Ottoboni 1969 DDT, Tech
122	Mouse (ICR)	70 wk (F)				16.5 (decreased neonatal survival)	Del Pup et al. 1978 DDT, Tech
123	Mouse (B6C3F1)	7d/wk- 2gen (F)		10		50 (increased preweanling death)	Tomatis et al. 1972 DDT, p,p'
124	Mouse (CF1)	life (F)		8.3		41.3 (increased in preweanling death)	Turusov et al. 1973 DDT, Tech
<b>Cancer</b>							
125	Rat (MRC Porton)	life (F)				19.7 F (liver tumors, NS)	Cabral et al. 1982b DDT, Tech
126	Rat (Osborne-Mendel)	78wk (F)				116 M (CEL: thyroid follicular cell adenoma and carcinoma)	NCI 1978 DDD, Tech

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
127	Rat (Wistar)	120 wk (F)				34.1 M (liver cell tumors; 33.3% incidence, 0% in controls)	Rossi et al. 1977 DDT, Tech
128	Mouse (C57BL/6N)	81 wk (F)				28 (liver tumors, NS)	Innes et al. 1969 DDT, Tech
129	Mouse (Swiss)	80 wk (F)				16.5 (lymphomas; lung and liver tumors NS)	Kashyap et al. 1977 DDT, Tech
130	Mouse (B6C3F1)	78wk (F)				27 M (CEL: hepatocellular carcinomas; 0/19, 7/41, 17/47)	NCI 1978 DDE, p,p'
131	Mouse (A strain)	5 gen (G)				1.3 (lung tumors, NS, lung adenomas)	Shabad et al. 1973 DDT, Tech
132	Mouse (BALB/c)	life 6 gen (F)				0.4 (lung adeno-carcinomas in F2, leukemia in F3)	Tarjan and Kemeny 1969 DDT, p,p'
133	Mouse (BALB/c)	life 2-gen (F)				50 F (liver tumors in F0 and F1)	Terracini et al. 1973 DDT, Tech
134	Mouse (CF1)	2 yr (F)				15.8 (liver tumors, NS)	Thorpe and Walker 1973 DDT, p,p'
135	Mouse (CF1)	life multi-gen (F)				0.38 M (liver tumors in F0 and F1)	Tomatis et al. 1972 DDT, Tech
						45.5 F (liver tumors in F0 and F1)	

Table 3-1. Levels of Significant Exposure to DDT, DDE, DDD (Except o,p'-Isomers) - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
136	Mouse (CF1)	130 wk (F)				42.6 M (significant increase in liver tumors)	Tomatis et al. 1974a DDE, p,p'
137	Mouse (CF1)	130 wk (F)				42.6 M (significant increase in lung and liver tumors)	Tomatis et al. 1974a DDD, p,p'
138	Mouse (CF1)	6 gen (F)				0.33 (liver tumors, NS)	Turusov et al. 1973 DDT, Tech
139	Hamster (Syrian)	128 wk (F)				95 (CEL: adrenal neoplasms; 14% in controls, 34% in treated)	Rossi et al. 1983 DDT, Tech
140	Hamster (Syrian)	128 wk (F)				47.5 (CEL: hepatocellular tumors; 0/73, 11/69, 14/78)	Rossi et al. 1983 DDE, p,p'

<sup>a</sup>The number corresponds to entries in Figure 3-1.

<sup>b</sup>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 intraspecies variability, 10 for interspecies variability, and 10 for the use of a LOAEL).

<sup>c</sup>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; LD<sub>50</sub> = 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 3-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (Except o,p' isomers)

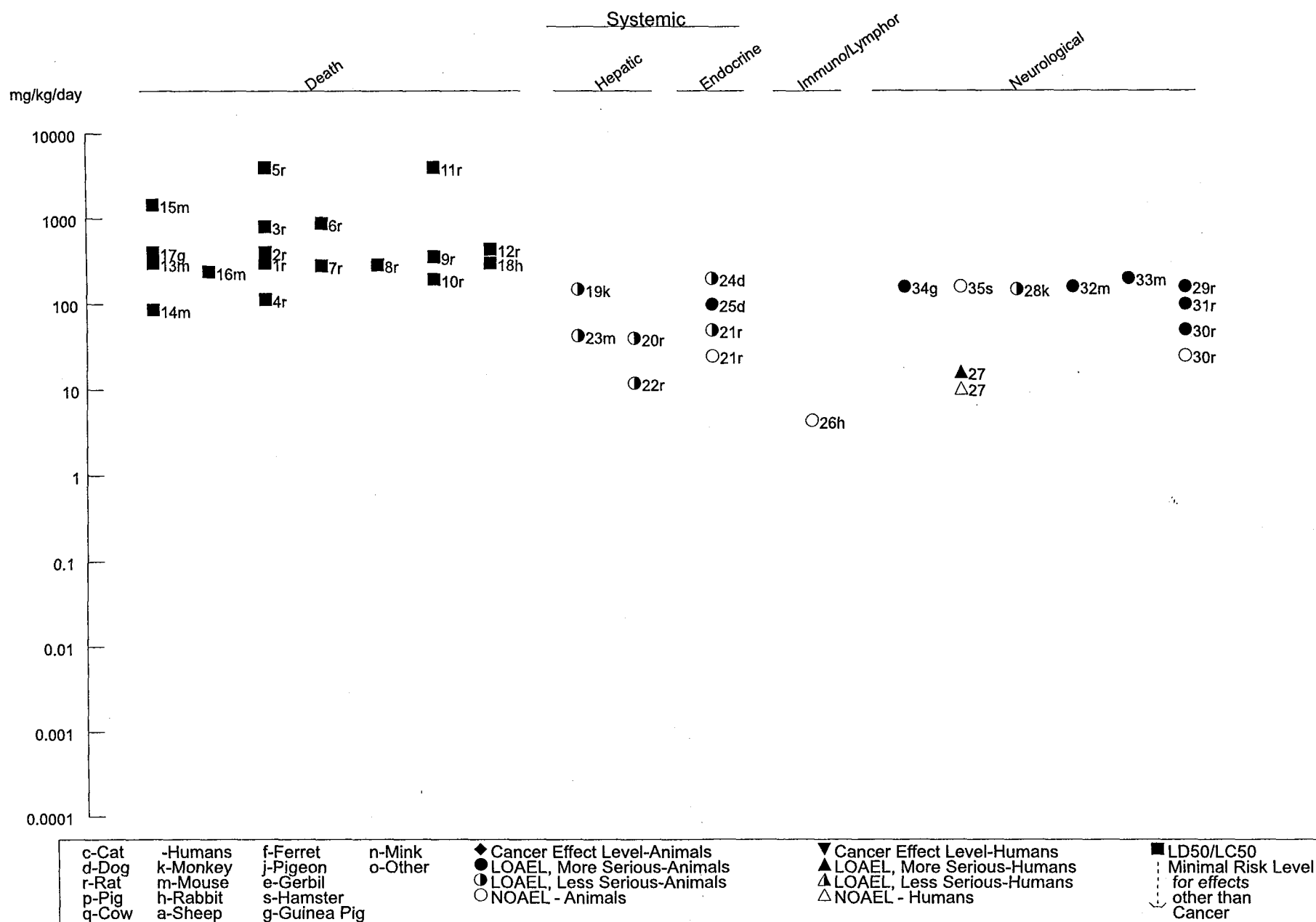
Acute ( $\leq 14$  days)

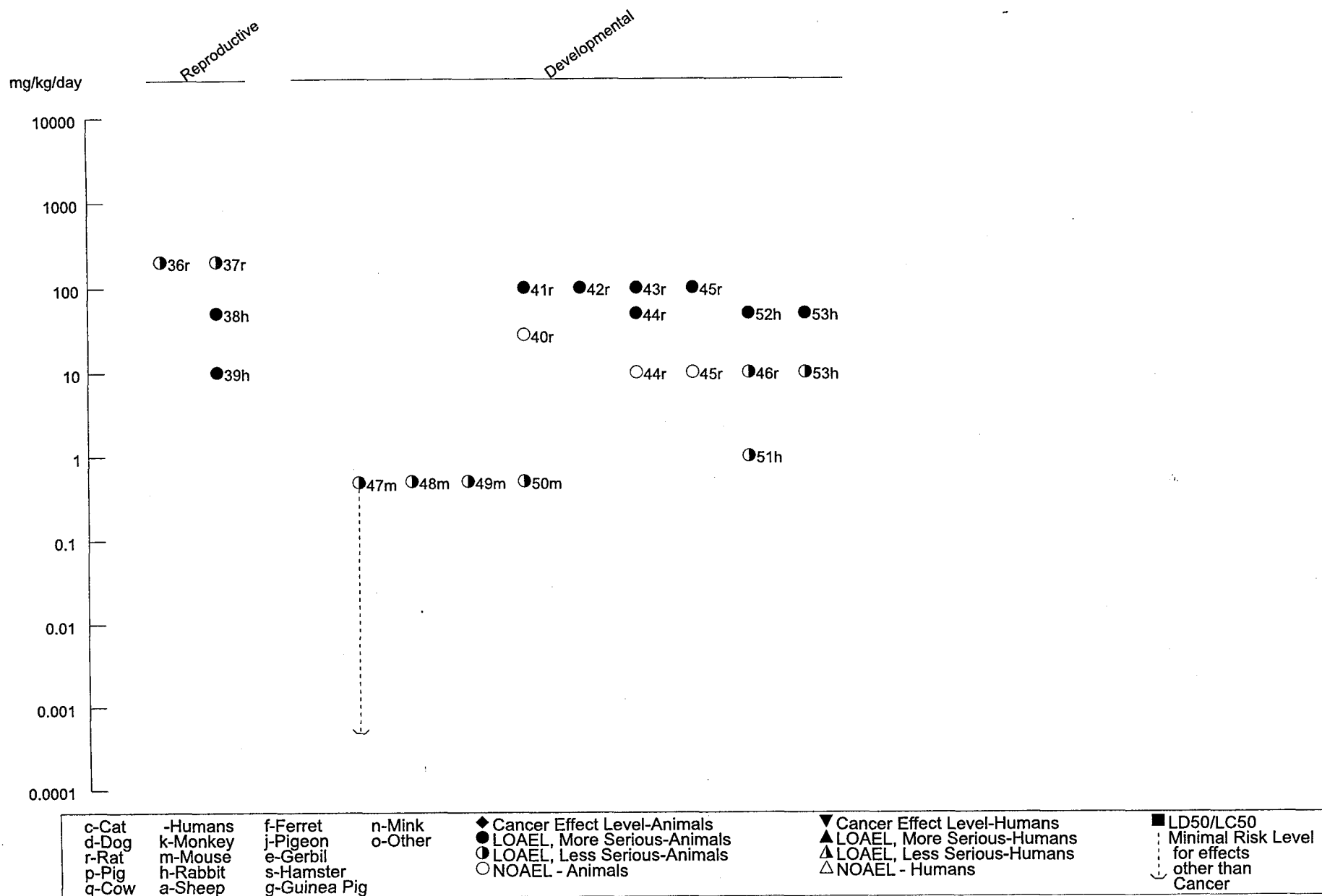
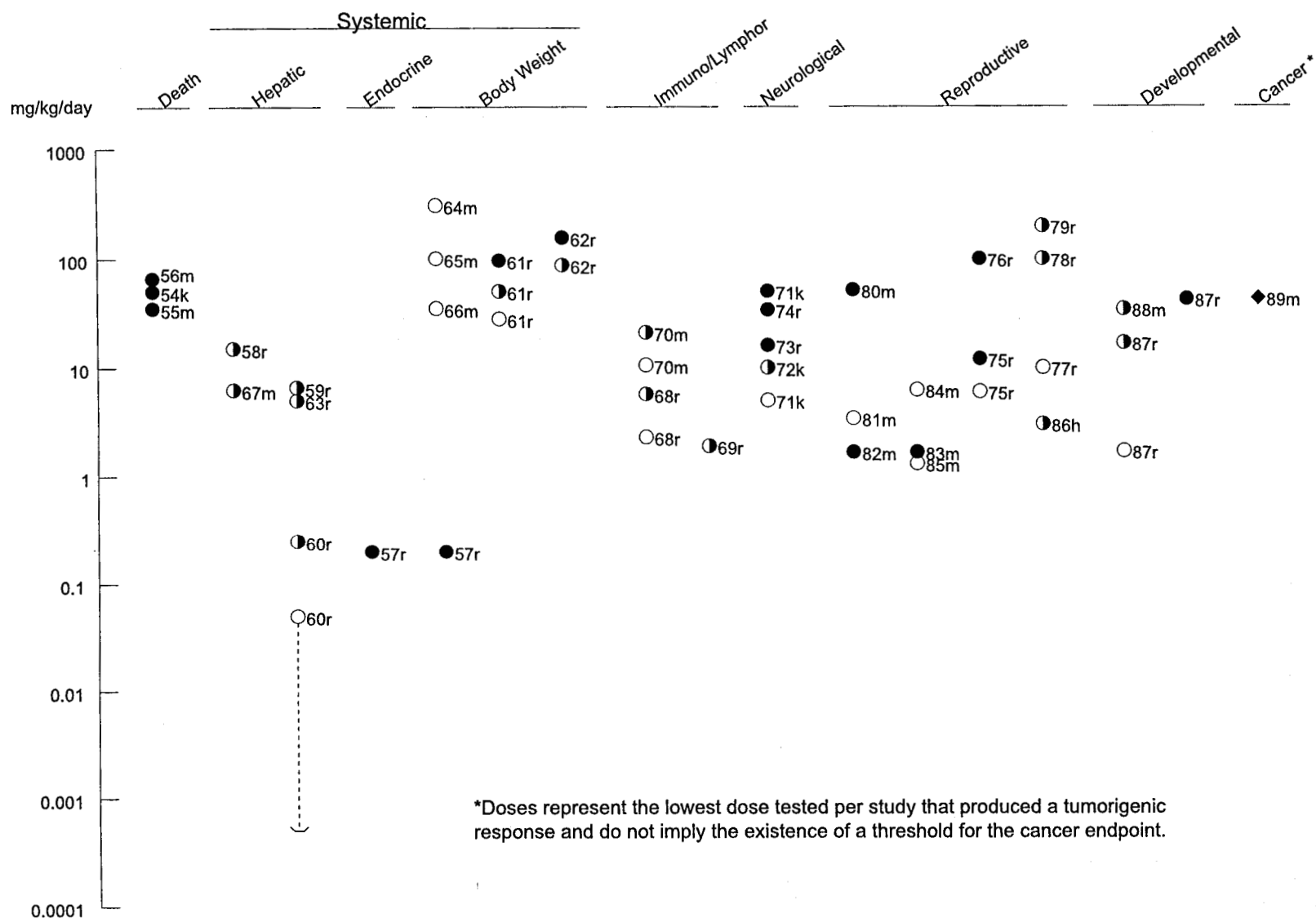
Figure 3-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (Except o.p' isomers) (*continued*)Acute ( $\leq 14$  days)

Figure 3-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (Except o,p' isomers) (continued)

Intermediate (15-364 days)



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 Level
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
q-Cow	a-Sheep	g-Guinea Pig				Cancer

Figure 3-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (Except for o,p' isomers) (continued)

Chronic ( $\geq 365$  days)

Systemic

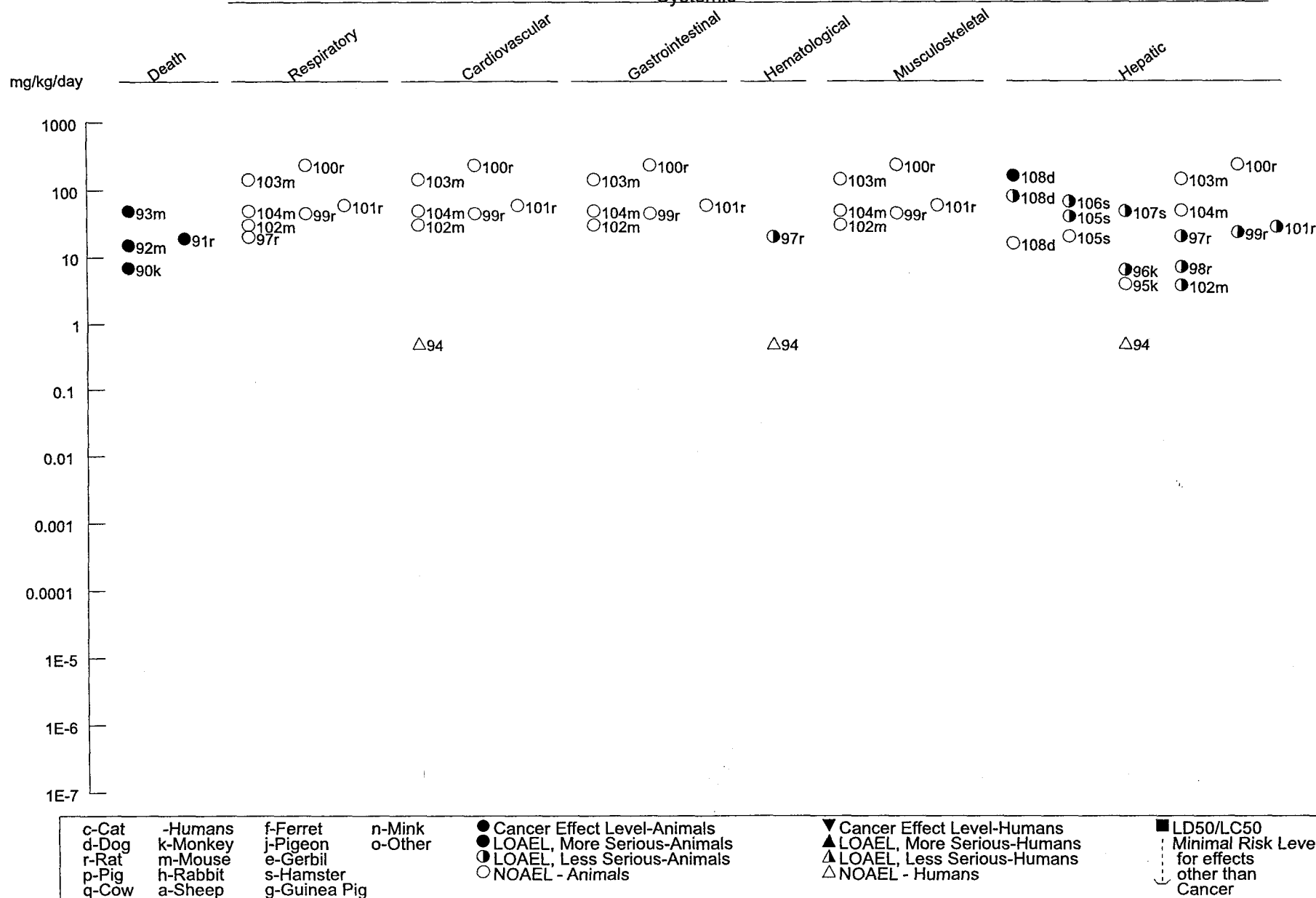


Figure 3-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (Except o,p' isomers) (continued)  
Chronic ( $\geq 365$  days)

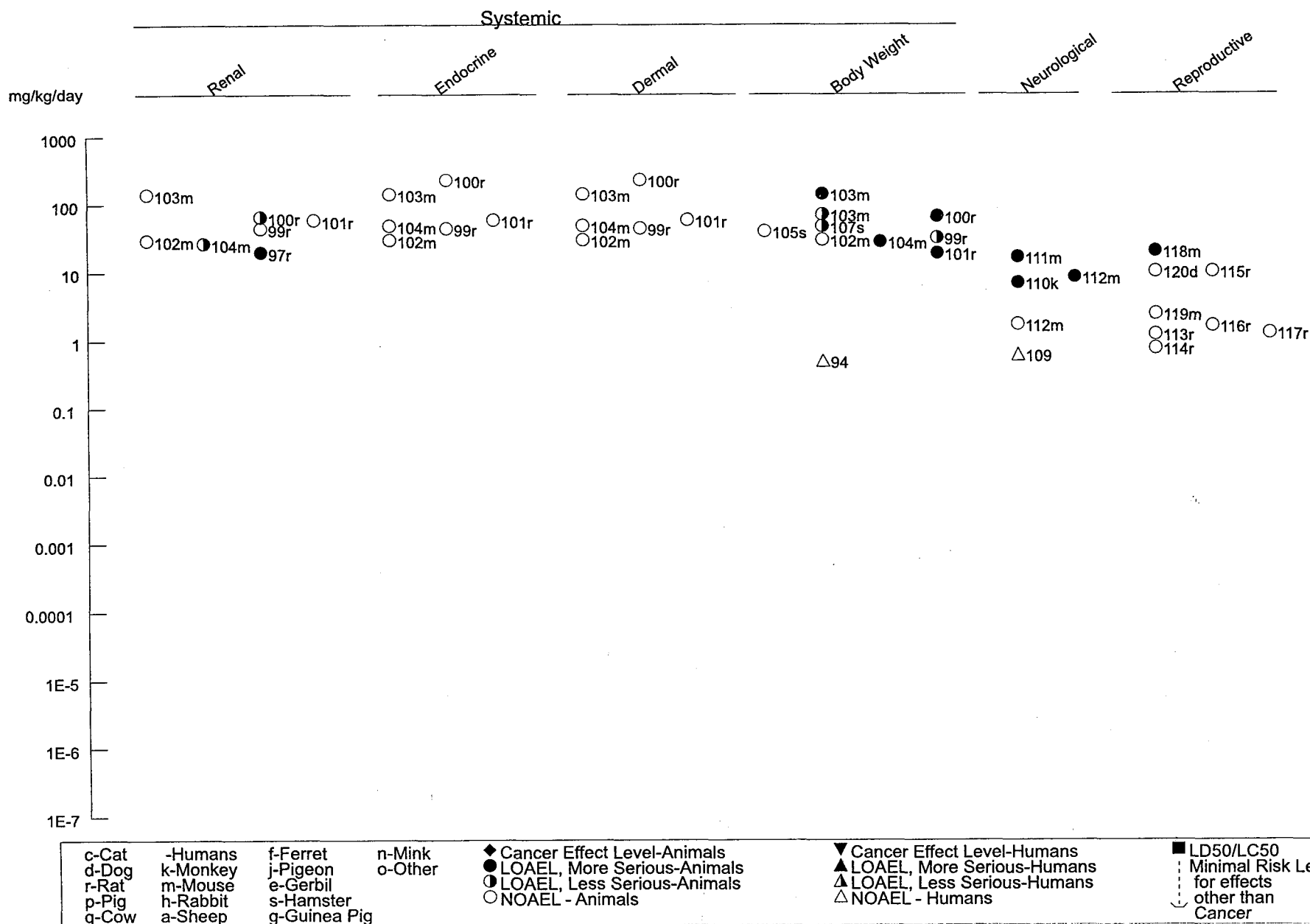


Figure 3-1. Levels of Significant Exposure to DDT, DDE, DDD - Oral (Except o,p' isomers) (continued)  
Chronic ( $\geq 365$  days)

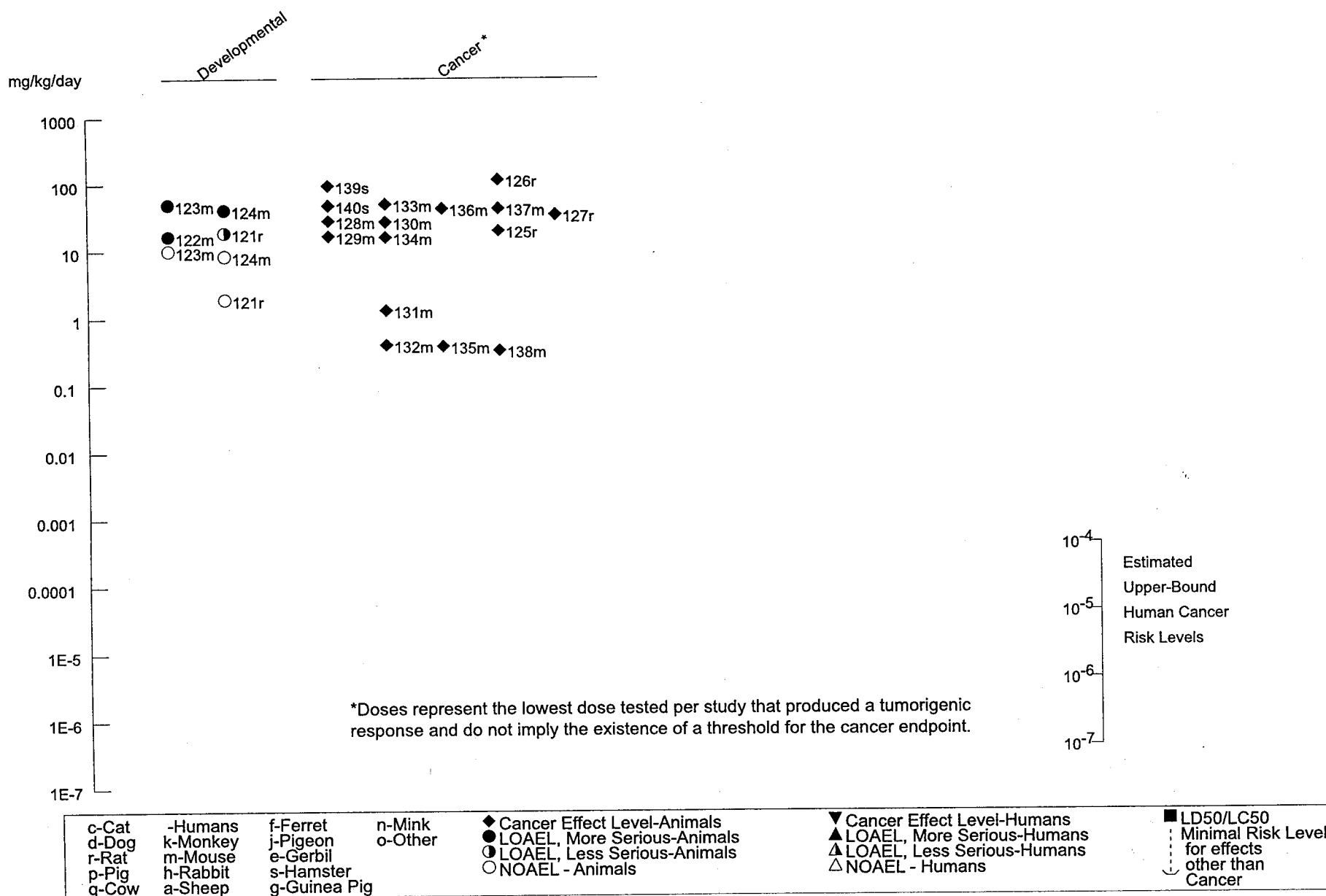


Table 3-2. Levels of Significant Exposure to o,p'-DDT, -DDE, -DDD - Oral

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Mouse (CF1)	Once (G)				810 (LD50)	Tomatis et al. 1972 DDE, o,p'
Systemic							
2	Dog (NS)	14 d	Cardio			50 (decrease in contractile force)	Cueto 1970 DDD, o,p'
			Endocr		50 (decreased plasma glucocorticoids)		
3	Dog (NS)	10 d (C)	Endocr			138.5 (adrenal hemorrhage)	Kirk et al. 1974 DDD, o,p'
Reproductive							
4	Rat (Wistar)	7 d (F)			100 (increased uterus weight; premature vaginal opening)		Clement and Okey 1972 DDT, o,p'
5	Rat (DA/Han)	3 d 1 x/d (G)		10 F	100 F (significant increase in wet uterine weight)		Diel et al. 2000 DDT, o,p'
Developmental							
6	Rat (Sprague Dawley)	Gd15-19 (G)		28			Gellert and Heinrichs 1975 DDE, o,p'

Table 3-2. Levels of Significant Exposure to o,p'-DDT, -DDE, -DDD - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
7	Rat (Sprague Dawley)	Gd15-19 (G)		28			Gellert and Heinrichs 1975 DDT, o,p'
8	Rat (Sprague- Dawley)	Gd15-19 (G)			28 (delayed vaginal opening)		Gellert and Heinrichs 1975 DDD, o,p'
9	Mouse (CD-1)	7 d Gd 11-71 (GO)			0.018 M (decreased testes weight)		Palanza et al. 1999 DDT, o,p'
10	Mouse (CF1)	1 x/d Gd 11-17 (GO)		0.018 M	1.82 M (altered behavior; increase urine marking in a novel territory)		vom Saal et al. 1995 DDT, o,p'

Table 3-2. Levels of Significant Exposure to o,p'-DDT, -DDE, -DDD - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Systemic							
11	Dog (NS)	36-150 d (C)	Endocr			50 (adrenocortical necrosis)	Kirk and Jenson 1975 DDD, o,p'
Immunological/Lymphoreticular							
12	Rat (Sprague- Dawley)	16 d (F)				121 (atrophy thymus)	Hamid et al. 1974 DDD, o,p'
Reproductive							
13	Rat (Wistar)	20 wk (F)		4.0			Wrenn et al. 1971 DDT, o,p'
Developmental							
14	Rat (Wistar)	pre-conception Gd 1-21 Ld 1-21 (F)		16.8	84 (17% less weight than controls at age 21 days)		Clement and Okey 1974 DDT, o,p'

Table 3-2. Levels of Significant Exposure to o,p'-DDT, -DDE, -DDD - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Reproductive							
15	Rat (Sprague- Dawley)	2 gen (F)		0.3			Duby et al. 1971 DDT, o,p'

<sup>a</sup>The number corresponds to entries in Figure 3-2.

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; LD<sub>50</sub> = 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 3-2. Levels of Significant Exposure to o,p'-DDT, -DDE, -DDD - Oral  
Acute ( $\leq 14$  days)

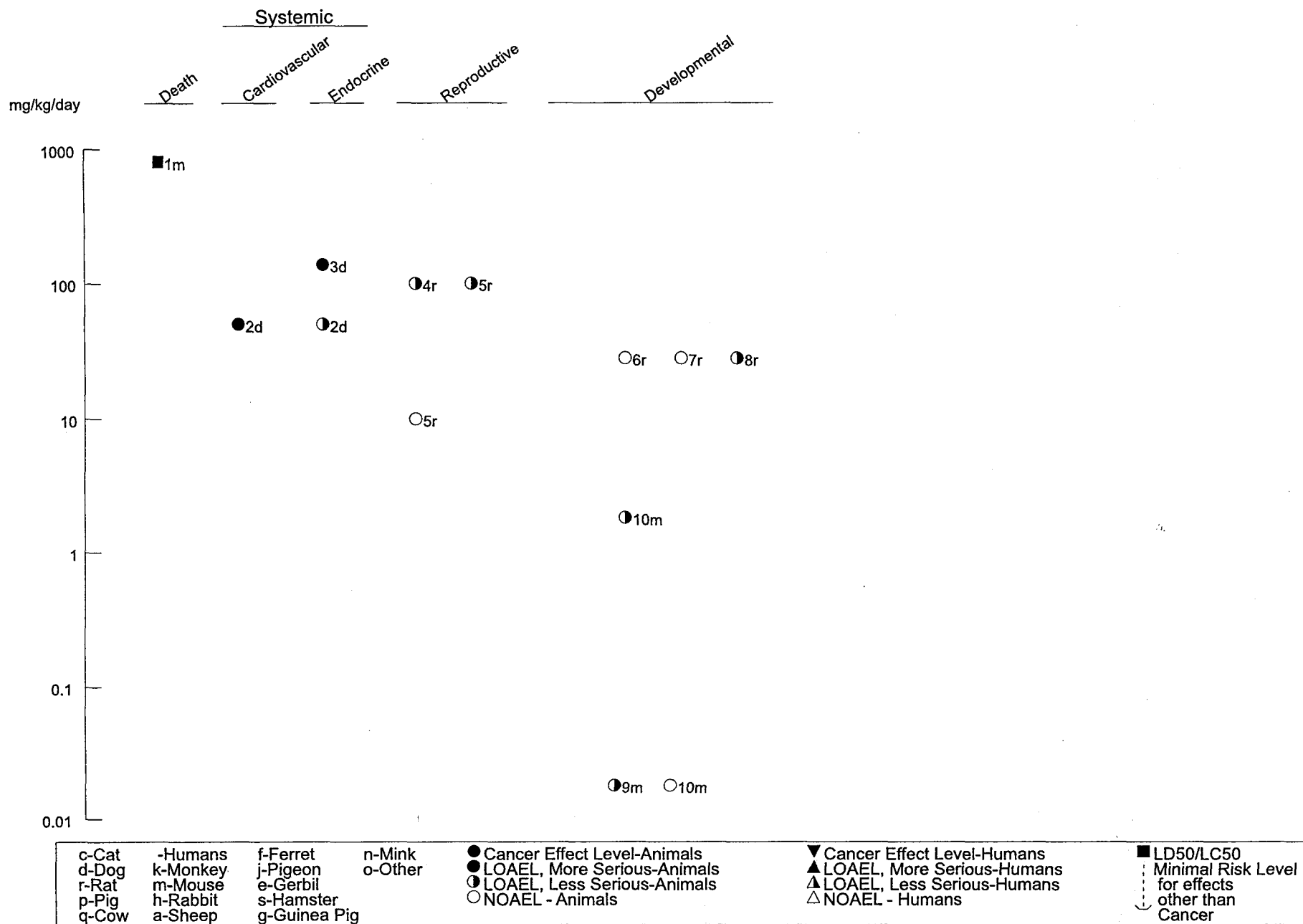


Figure 3-2. Levels of Significant Exposure to o,p'-DDT, -DDE, -DDD - Oral (*Continued*)

Intermediate (15-364 days)

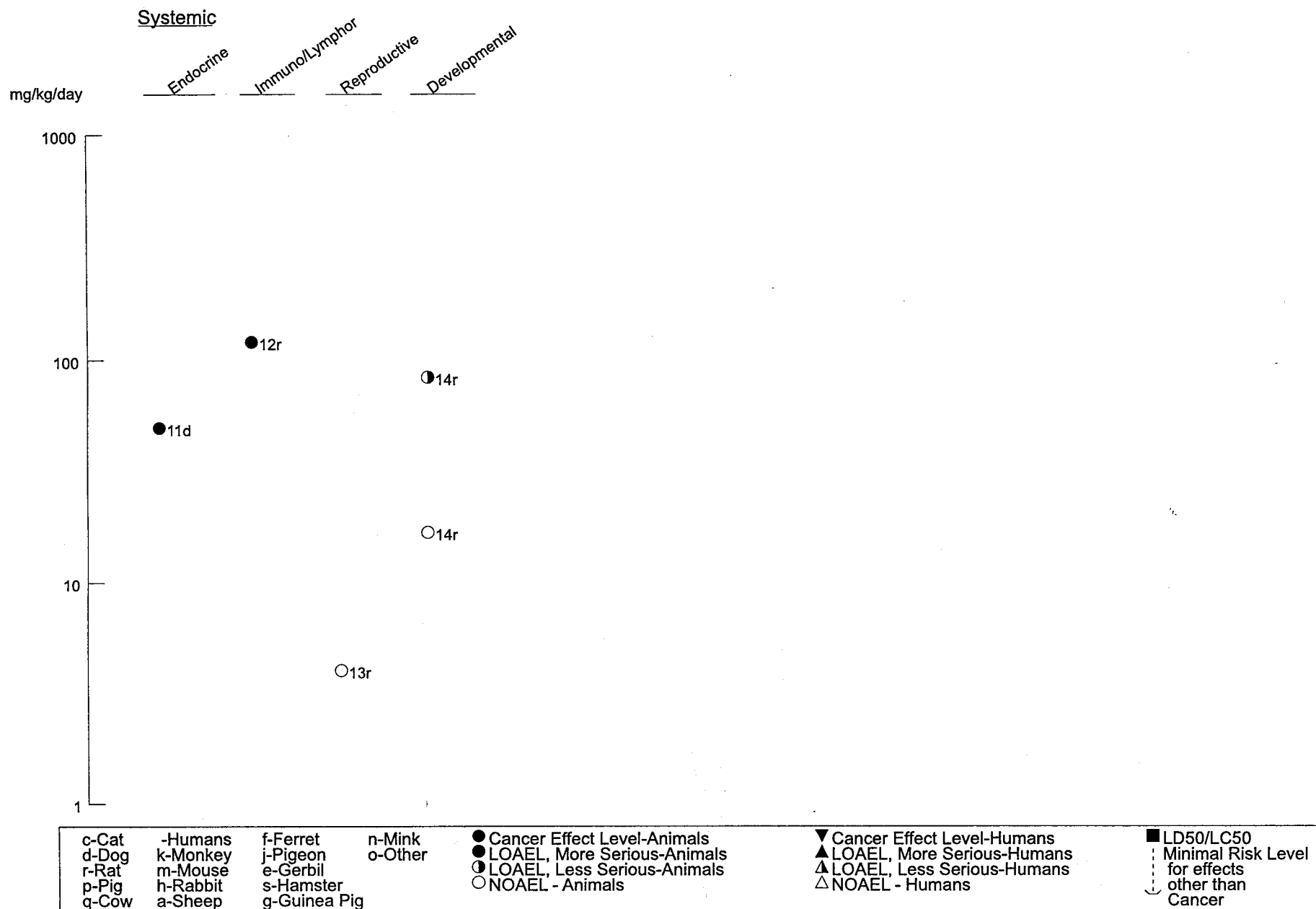
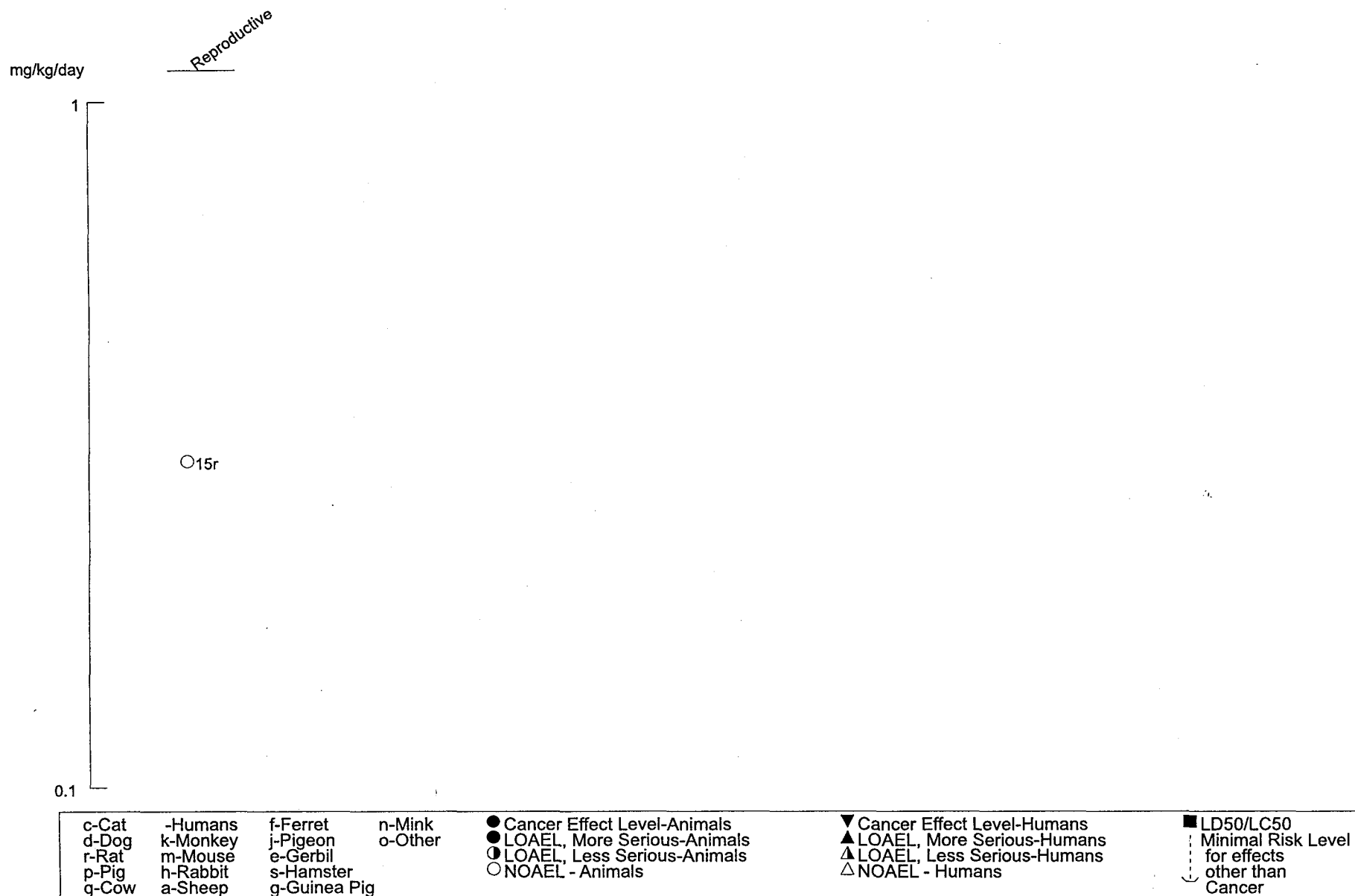


Figure 3-2. Levels of Significant Exposure to o,p'-DDT, -DDE, -DDD - Oral (Continued)

Chronic ( $\geq 365$  days)



### 3. HEALTH EFFECTS

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.

#### 3.2.2.1 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 3.2.2.2), Morgan et al. (1980) analyzed morbidity and mortality in an extensive cohort of male and female workers exposed (formulators, applicators, farmers) to organochlorine pesticides. The follow-up included 73% of an original cohort of 2,600 workers. The median duration of work in a pesticide-related occupation was 13 years. Disease incidence rates were studied in relation to job exposure categories 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 standardized 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 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

## 3. HEALTH EFFECTS

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<sub>50</sub> 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<sub>50</sub> values in rats. The LD<sub>50</sub> 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<sub>50</sub> daily for 4 days, there was no significant difference in the 4-day LD<sub>50</sub> 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 preweaning 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<sub>50</sub> 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 4 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). In a 130-month study that administered approximately 6.4–15.5 mg of *p,p'*-DDT/kg/day to 11 Rhesus and 14 Cynomolgus monkeys, there were 6 early deaths; the lowest dose associated with death was approximately 6.9 mg/kg/day (Takayama et al. 1999). 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).

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DDE mortality studies also have been conducted. An LD<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> for DDD in rats of >4,000 mg/kg was reported by Gaines (1969). Tomatis et al. (1974a) reported an LD<sub>50</sub> in mice after a single oral dose ranging from 1,466 to 1,507 mg DDD/kg.

The LD<sub>50</sub> values for the various isomers and technical-grades of DDT, DDE, and DDD are recorded in Tables 3-1 and 3-2 and plotted in Figures 3-1 and 3-2.

#### 3.2.2.2 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 Tables 3-1 and 3-2 and plotted in Figures 3-1 and 3-2.

**Respiratory Effects.** No studies were located regarding respiratory effects in humans after oral exposure to DDT, DDE, or DDD. Rats fed a diet containing 20 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 0.05–0.063 or 0.36–0.5 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 effects.

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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, but the statistical power in some of these studies is practically nil because of the small number of subjects. 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 (not adjusted for lipid content). None of the many hematological parameters measured had a correlation coefficient with DDT and/or DDE blood levels >0.17 (meaning that at best, 2.89% of the variance could be attributed to the pesticide levels) although a number of coefficients showed statistical significance. Morgan and Lin (1978) acknowledged that because the analysis was based on such large numbers of measurements, some statistically significant differences were likely to be found.

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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".

Fifty-one male volunteers were exposed to 3.5 or 35 mg DDT/day, resulting in administered doses of 0.05–0.063 or 0.36–0.5 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 (variation in erythrocyte cell width change; often a sign of anemia) was significantly greater in the

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high DDE group than in the low DDE group; no differences were seen in other hematological parameters.

In a chronic study, exposure of rats to DDT at 20 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.

Overall, the existing information does not suggest that hematological parameters are sensitive targets for DDT toxicity. The extent to which this is due to limitations in the available studies is uncertain.

**Musculoskeletal Effects.** The relationship between serum levels of DDE and bone mineral density was examined in a group of 103 (50 black, 53 white) women who had participated in the Mount Sinai Medical Center Longitudinal Normative Bone Density Study (1984–1987) (Bohannon et al. 2000). Because bone metabolism is both estrogen- and androgen-dependent, and DDT and related compounds have shown hormone-like properties, the authors hypothesized that high levels of DDE (the main stored metabolite of DDT) would be associated with lower bone density in peri- and postmenopausal women than in premenopausal women. Bone mineral density was measured at the lumbar spine and radius at 6 months intervals during a 2-year period. The results showed that black women had serum DDE levels significantly higher than white women (mean 13.9 vs. 8.4 ppb), but there was no correlation between either DDE and bone density or between DDE and the rate of bone loss. In a study of 68 sedentary Australian women (45–64 years of age), the authors state that an association was found between bone mineral density (lumbar spine) and serum DDE levels >2 ppb (Beard et al. 2000). However, the correlation coefficient was 0.269, meaning that only about 7.24% of the variance could be attributed to DDE; a stronger correlation was found for the relationship between bone mineral density and age.

An additional study examined associations between bone mineral density and serum levels of organochlorines (five DDT-related compounds among them) in 115 men (40–75 years of age) from the general Swedish population (Glynn et al. 2000). The most concentrated DDT-related compound was *p,p'*-DDE, with a mean value of 784 ppb (lipid basis). After adjusting for confounding factors in linear regression analyses, there was no significant association between serum concentrations of single organochlorines and bone mineral density.

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Limited information exists from studies in animals. 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).

The existing information suggests that neither skeletal muscle nor bone are targets for DDT/DDE toxicity.

**Hepatic Effects.** Based on the data available, there is no conclusive evidence that DDT, DDD, and DDE cause adverse liver effects in humans, but in animals, the liver appears to be a sensitive target for 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; data on alcohol consumption were not available. Weak correlations were reported between increasing serum DDT and DDE and elevated serum levels of alkaline phosphatase and lactic dehydrogenase. No significant correlation was found for serum glutamic oxaloacetic transaminase (SGOT; aspartate aminotransferase [AST]) and serum glutamic pyruvic transaminase (SGPT; alanine aminotransferase [ALT]). Morgan and Lin (1978) pointed out that the effects on serum enzyme activities were of such small magnitude that they were only detectable by exhaustive statistical analysis of data from thousands of subjects. 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 (as measured by the Bromsulphthalein test, also known as sulfobromophthalein sodium) was found. Only one subject had an elevated Bromsulphthalein retention and slightly elevated serum levels of alkaline phosphatase and AST. Hayes et al. (1956) exposed 51 male volunteers to 3.5 or 35 mg DDT/day, resulting in administered doses of 0.05–0.063 or 0.36–0.5 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 (as measured by liver function tests) 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

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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, 6 $\beta$ -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 6 $\beta$ -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).

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 transpeptidase (GGTP) were increased 2-fold in rats treated with a single dose of 200 mg DDT/kg (Garcia and Mourelle 1984).

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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

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(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 1,000 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, centrilobular 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 67–133 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 71 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). However, in a 130-month dietary study in Rhesus and Cynomolgus monkeys, a dose of approximately 6.4 mg of *p,p'*-DDT/kg/day, the lowest dose tested, produced significant liver alterations including hepatocyte vacuolation, proliferation of bile duct cells, clear hepatocyte foci, and liver cell necrosis (Takayama et al. 1999).

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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). A dose of 100 mg of *p,p'*-DDE/kg/day for 7 days caused elevated hepatic aromatase (enzyme involved in steroid metabolism) activity in adult rats, a potential mechanism by which DDE can affect reproduction (You et al. 2001). 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 *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 20 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

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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 *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.** Exposure to DDT and DDT-related compounds, particularly during development, can adversely affect the development and function of the reproductive system of both female and male animals. This is due primarily to the ability of some of these compounds to disrupt the action of natural steroids and bind to receptors for estrogens and androgens. Hormonal effects of DDT and residues that lead to altered reproduction and/or development are discussed in Sections 3.2.2.5 Reproductive Effects, 3.2.2.6 Developmental Effects, and 3.6.2 Mechanisms of Toxicity. Reported endocrine effects unrelated to reproduction or development are briefly mentioned below.

No studies were located regarding endocrine effects in humans after oral exposure to DDT or DDE. However, *o,p'*-DDD has been used to treat adrenocortical carcinoma for almost four decades (Bergental et al. 1960; Wooten and King 1993). The therapeutic action is based on the activation of the compound by local cytochrome P-450 (CYP11 $\beta$ ) to a reactive metabolite that binds to macromolecules in the adrenal cortex (see Section 3.6.2, Mechanisms of Toxicity, 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). Studies in animals have also shown that the adrenal gland is affected

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by sulfonyl metabolites of DDT. The metabolic pathways leading to these metabolites are discussed in Section 3.5.3, Metabolism, whereas information on their mechanism of toxic action can be found in Section 3.6.2, Mechanisms of Toxicity.

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 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).

**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.

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**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 0.5 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 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 71 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).

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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.

#### 3.2.2.3 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.

A different type of study assessed parameters of immunocompetence in a group of 23 men chronically exposed to DDT through consumption of fish 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.

Further information on the potential immunological effects of DDT is available in a study of 302 individuals residing near a waste site in North Carolina (Vine et al. 2001). Of 20 organochlorines tested, only DDE was detected in the blood of the participants; the median concentration in plasma was 2 ppb and the highest concentration was 32 ppb. End points evaluated included white blood cell counts, lymphocyte phenotypes, immunoglobulins, and mitogen-induced lymphoproliferative activity; a skin test

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was also conducted to evaluate delayed-type hypersensitivity. When DDE levels were divided into five categories from #1 ppb or \$7.6 ppb, subjects with higher blood DDE levels had lowered mitogen-induced lymphoproliferative activity (concanavalin A) and slightly increased total lymphocytes and immunoglobulin A levels. Results from the skin test showed no differences in response by blood DDE levels. Vine et al. (2001) concluded that relatively low DDE levels were associated with changes in immune markers, although the magnitude of the effects are of uncertain clinical importance.

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 diphtheria toxoid were fed DDT in the diet for 31 days at an intake of 1.9 or 19 mg/kg/day. When challenged with diphtheria 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 0.006 mg/kg/day had no effect on the humoral immune response but doses of 0.06 or 0.63 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 3.2.2.6 (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

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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 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 22.2 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,

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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 EC) 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, 49 mg *p,p'*-DDE/kg/day, or 142 mg technical DDD/kg/day (NCI 1978). Immunocompetence was not evaluated in this study.

The overall evidence suggests that DDT and related compounds can affect immunocompetence in animals, but there is no conclusive evidence regarding effects in humans.

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Tables 3-1 and 3-2 and plotted in Figures 3-1 and 3-2.

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**3.2.2.4 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 from these acute effects 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).

Few studies have 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 (0.05–0.05 or 0.36–0.5 mg/kg/day) for 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. Somewhat different findings were described in a recent study of retired malaria-control workers in Costa Rica (van Wendel de Joode et al. 2001). Neurological tests assessing cognitive, motor, and sensory functions were conducted on 27 former workers and 27 matched controls.

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The men had been involved in DDT use between 1955 and 1986; the mean number of years of DDT application was 4.6 years. The exposed group had overall poorer performance; verbal attention and visuomotor speed and sequencing differed most between the groups. When years of DDT application was entered in the analysis as the explanatory variable, significant exposure-effect relations were seen for five tests in cognitive, motor, and sensory domains. Although the population sample was small, the study seems to have been well controlled. However, neither exposure levels nor past or current levels of DDT (or DDE) in blood or in adipose tissue were available.

As in humans, 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 3.6.2). 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).

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The effects of acute DDT exposures on adult learning and motor activity are discussed in Section 3.2.2.6 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 that 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 of *p,p'*-DDE/kg/day and in male mice after 22 weeks of treatment with approximately 27 mg of *p,p'*-DDE/kg/day in 78-week duration studies (NCI 1978).

Some Rhesus and Cynomolgus monkeys exposed to approximately 6.9 mg of *p,p'*-DDT/kg/day or more in a 130-month dietary study experienced severe tremors (Takayama et al. 1999). 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 3-1 and plotted in Figure 3-1.

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**3.2.2.5 Reproductive Effects**

Effects discussed in this section are those that result from alterations affecting reproduction from the time of gametogenesis through implantation of the conceptus in the endometrium. In addition, this section includes descriptions of effects on male and female reproductive organs; these effects may be direct effects or triggered by hormonal changes. Developmental effects are distinguished from reproductive effects by evaluation of the conceptus after it is implanted and can be categorized as structural abnormalities, altered growth, functional deficiencies, and death of the developing organisms. Developmental effects are discussed in Section 3.2.2.6.

The potential association between DDT (and DDT metabolites) and reproductive end points has been examined in numerous studies. For example, a study of 240 women showed no difference in maternal DDT blood levels between 120 individuals who had a miscarriage and 120 controls; in both groups, the mean blood DDT levels were similar and below 6 ppb (Leoni et al. 1989). A more recent study of 89 women with a history of at least two miscarriages found that 15% of them had DDE blood levels above a reference value of 2.5 ppb; the mean was 1.2 ppb and the range was between 0.01 ppb (detection limit) and 8.6 ppb (Gerhard et al. 1998). Hexachlorobenzene, pentachlorophenol, and PCBs were also above reference values in 15–22% of the women. A study by Ron et al. (1988) reported no significant differences in DDT blood levels between 20 cases of premature rupture of fetal membranes and 15 controls; the mean concentrations of DDT in blood were comparable, approximately 24 ppb.

A difference in maternal DDE blood levels for women delivering full-term and premature infants was reported in a brief communication by O'Leary et al. (1970a). Twenty-three women who delivered early had infants with mean DDE blood levels of 19–22.1 ppb, while 44 women who delivered at full-term had infants with mean DDE blood levels of 4.9–6.1 ppb; DDE was the only organochlorine monitored.

Studies of women from India reported that total DDT residues (DDT plus DDE and DDD) in maternal blood from 25 full-term cases ranged from 7 to 73 ppb (mean 26 ppb) compared to 48–481 ppb (mean 66 ppb) in 15 pre-term and 90–1,280 ppb (mean 394 ppb) in 10 cases of spontaneous abortion (Saxena et al. 1980, 1981). Mean DDT residues in the respective placentas were 24, 66, and 162 ppb. Other organochlorine pesticides were also elevated in the pre-term and abortion cases relative to full-term cases. A study of 54 women from Brazil found no differences in maternal blood (at delivery) DDT residue levels between 30 cases of full-term delivery (31 ppb) and 24 cases of pre-term delivery (30 ppb) (Procianoy and Schwartsman 1981). However, analyses of umbilical cord blood showed significantly

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elevated levels of DDT in pre-term newborns compared to full-term. No other chemical was monitored in this study. A similar study of Israeli women reported that maternal blood of 10 full-term cases had a concentration of 27 ppb of total DDT residues vs. 120 ppb in blood from 17 pre-term cases (Wassermann et al. 1982); other organochlorines such as PCBs, lindane, heptachlor epoxide, and dieldrin were also elevated in pre-term delivery cases. A more recent study of New York City women found no association between blood DDE levels and pre-term birth after comparing 20 cases with 20 matched controls (Berkowitz et al. 1996). The median DDE blood levels were 1.4 ppb in cases and 1.3 ppb in controls. Recently, Longnecker et al. (2001) presented the results of an analysis of 2,380 children, of whom 361 were born pre-term and 221 were small-for-gestational-age. The children were born between 1959 and 1966 and were part of the U.S. Collaborative Perinatal Project. Serum samples were taken from the mothers in the third trimester of pregnancy and were stored at -20 EC without recorded thaws. Analyses of DDE in serum were conducted between 1997 and 1999. DDE concentrations were evaluated in relation to odds of pre-term birth and small-for-gestational-age birth with logistic regression models. The median concentration of DDE in serum was 25 ppb and the range was 3–178 ppb. The authors found that the adjusted odds ratios for pre-term birth increased steadily with increasing DDE concentrations (trend  $p < 0.0001$ ). Quadratic spline models showed that the odds of pre-term birth began to increase at a DDE concentration of 10 ppb. Adjusted odds for small-for-gestational-age also increased, but less consistently (trend  $p = 0.04$ ).

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 ecological 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. A possible association between chlorinated hydrocarbons in blood and infertility was investigated in a group of 489 infertile women from Germany (Gerhard et al. 1999). Only eight of the women had total DDT blood levels higher than a reference value of 2.5 ppb; the

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mean concentration was 1.0 ppb and the range span was 0–9.6 ppb. The authors reported that elevated *o,p'*-DDT and *p,p'*-DDT were found less often in women who conceived during the study than in women who did not. In addition, the conception rate was reduced with increasing total DDT levels from 18% for DDT levels below 0.5 ppb to 10% for DDT levels above 1.0 ppb.

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 (Gladden 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 ( $>4$  ppm) in maternal milk fat were associated with hyporeflexia in infants (Rogan et al. 1986). The effects of DDE on lactation duration are likely due to the ability of DDE to disrupt the normal endocrine regulation of lactation, as estrogen is a potent inhibitor of milk secretion (Guyton and Hall 2000).

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; Fry and Toone 1981; Fry et al. 1987; 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 (uterotrophic: 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 with estrogen; *p,p'*-DDT did not have such 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. Recently, Diel et al. (2000) showed that oral administration of *o,p'*-DDT to juvenile ovariectomized rats produced the typical increase in uterine weight, although it induced a

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pattern of gene expression different from ethinylestradiol. Much of the research in this area has been conducted in experimental animals administered the test substance parenterally or, more recently, in *in vitro* systems. Representative studies are discussed in Section 3.6.2, 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 (LH) and follicle stimulating hormone (FSH) 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/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 F<sub>1</sub> 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 12 mg/kg/day, and this was accompanied by a decrease in serum progesterone; 6 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,

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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 2.0 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 (Ledoux 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 size (Ware and Good 1967). Treatment of pregnant rabbits with 10 mg *p,p'*-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'*-DDE, is an androgen receptor antagonist; this evidence is discussed in Section 3.6.2, Mechanisms of Toxicity. A number of experiments have investigated *in vivo* antiandrogenic effects. Kelce et al. (1995) conducted a series of experiments in male rats administered *p,p'*-DDE at different ages. Effects from prenatal plus juvenile exposure are discussed in Section 3.2.2.6, Developmental Effects. Treatment of adult male rats (120 days old) with 200 mg *p,p'*-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 3.6.2) on receptor (androgen and estrogen) binding, suggested that the antagonistic effects of DDT on the male reproductive system are mediated by *p,p'*-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

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rats given 200 mg *p,p'*-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 5 mg/kg/day; 20 mg/kg/day caused decreased fertility evidenced by decreased viability and lactation indices, and the 50 mg technical-grade DDT/kg/day dose caused frank toxic effects and was discontinued after three generations. No adverse effects on litter size 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 (end points assessed limited mostly to fecundity and fertility) 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 1.7 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 (0.5 mg/kg/day), *p,p'*-DDT (1.5 mg/kg/day) or *o,p'*-DDT (0.3 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 significant effect noted was a 2–3-month reduction in the age at first estrus in females of the  $F_2$  generation, but the relationship of this effect to DDT administration is questionable. 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.

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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 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). Reproductive function was not evaluated in this study.

In summary, studies in humans suggest that high DDT/DDE burdens may be associated with alterations in end points that are controlled by hormonal function such as duration of lactation, maintenance of pregnancy, and fertility. High blood levels of DDE during pregnancy have also been associated with increased odds of having pre-term infants and small-for-gestational-age infants. Perinatal exposure of animals to DDT/DDE has caused alterations in the reproductive organs and infertility.

The highest NOAEL values and all LOAEL values from reliable studies for reproductive effects in each species and duration category are recorded in Tables 3-1 and 3-2 and plotted in Figures 3-1 and 3-2.

#### 3.2.2.6 Developmental Effects

The proper development of many systems and functions depends on the timely action of hormones, particularly sex steroids; therefore, interfering with such actions can lead to a wide array of effects that may include altered metabolic, sexual, immune, and neurobehavioral functions. Effects of this type, that occur following exposure during fetal life via the placenta or early in life caused by either direct exposure to chemicals or exposure via maternal milk, are discussed in this section.

A prospective longitudinal study of children from North Carolina examined whether prenatal or lactational exposure to background levels of DDE (or PCB) were associated with altered pubertal growth and development (Gladen et al. 2000). Exposure was estimated by measuring *p,p'*-DDE in maternal breast milk, maternal blood, cord blood, and placenta. The original cohort consisted of 856 children, and follow-up analysis at puberty was conducted on 594 of these individuals (316 girls and 278 boys). Most of the children were between 12 and 14 years old when they were first contacted and the duration of participation ranged from 1 to 5 years. The transplacental DDE index ranged from 0.3 to 23.8 ppm (median 2.4 ppm) and the lactational DDE index from 0.2 to 96.3 mg (median 6.2 mg). Height and weight adjusted for height of boys at puberty increased with transplacental exposure to DDE; those with the highest exposures were 6.3 cm taller and 6.9 kg larger than those with the lowest exposures; no such

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effect was seen among girls. There was no effect on the age at which pubertal stages were attained. Lactational exposures to DDE had no apparent effects. Children from this cohort had normal birth weight and normal growth in the first year of life.

A study of German children examined the potential association between height and serum levels of DDE (Karmaus et al. 2002). The children were from three different regions from Germany; two regions were industrial and agricultural regions, but no information was given regarding the third region, or the distribution of children by region. Data on weight and height from birth to the age of 4 years (seven measurements) were obtained from medical records; measurements at the ages of 8, 9, and 10 years old were conducted by the investigators. Blood was collected only once, when the children were 8 years old, and was analyzed for DDE and PCBs. The number of children from whom weight and height were measured at each time point varied between 202 (at 43–48 months) and 323 (at birth). At all time points, boys outnumbered girls. Whole blood DDE concentrations were stratified in quartiles: 0.08–0.2, 0.21–0.29, 0.3–0.43, and 0.44–40.4 ppb. Analysis of the results controlling for relevant confounders showed that DDE was a significant predictor of height in girls starting at 1.3 months and remained significant through 8 years of age. On the average, girls in the highest DDE quartile were 1.8 cm shorter than girls in the lowest quartile. At 10 years old, no association was evident between height and DDE. The fact that only one DDE measurement was made, at 8 years of age, casts some uncertainty on the significance of the results.

Evaluation of Inuit infants exposed to *p,p'*-DDE (and other organochlorines) *in utero* revealed no association between immunological parameters (white blood cell counts, lymphocyte subsets, immunoglobulins) and prenatal exposure to organochlorines (Dewailly et al. 2000). Organochlorine concentration in breast milk fat was used as an index of exposure and evaluations were conducted at 3, 7, and 12 months of age. The authors also examined whether organochlorine exposure was associated with the incidence of infectious diseases and found that during the second evaluation period, that the risk of otitis media increased with prenatal exposure to *p,p'*-DDE, hexachlorobenzene, and dieldrin. They also found that the relative risk for 4- to 7-month-old infants in the highest tertile of *p,p'*-DDE exposure was 1.87 (95% CI, 1.07–3.26) compared to infants in the lowest tertile. In addition, the relative risk of otitis media over the entire first year of life also increased with prenatal exposure to hexachlorobenzene and *p,p'*-DDE. Dewailly et al. (2000) pointed out that “because all organochlorines originate from the same few food items and share a number of properties (persistence, liposolubility), their concentrations in breast milk are correlated with each other. Therefore, associations of health outcomes with *p,p'*-DDE or hexachlorobenzene may be due to other organochlorines found in the organochlorine mixture.”

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In animals, DDT can produce embryotoxicity, fetotoxicity, and abnormal development of the sex organs. 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 to rats in the first few days of life can seriously affect the development and maturation of the reproductive system. 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 mg *p,p'*-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 *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 3.2.2.5 Reproductive Effects, the DDT metabolite, *p,p'*-DDE, has been found to have antiandrogenic activity (Kelce et al. 1995, 1997). *In vivo* antiandrogenic 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

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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. Further studies by the same group showed that prenatal exposure to 100 mg/kg *p,p'*-DDE reduced prostate ventral weight in 85-day-old males, but did not alter the weight of the testes, epididymis, and seminal vesicles (You et al. 1999a); serum levels of testosterone and LH were not significantly altered by DDE, but treatment with DDE was associated with expression of TRPM-2, an androgen-repressed gene.

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). On postnatal day 4, anogenital distance was reduced only at 200 mg/kg/day. Nipple retention on postnatal day 13 was significantly increased at 100 and 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 3 $\alpha$ -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. Gray et al. (1999) conducted similar studies and reported that gestational exposure (gestation day [Gd] 14–18) to *p,p'*-DDE (100 mg/kg/day) resulted in a significant decrease in ventral prostate weight at 15 months of age in Sprague-Dawley rats and also in decreases in weights of glans penis, ventral prostate, and epididymis in 10-month-old Long-Evans rats. Newborn Long-Evans rats also showed reduced anogenital distance and increased mean number of retained nipples. Exposure of pregnant mice to 0.18 mg/kg of the estrogenic *o,p'*-DDT during gestation days 11–17 had no significant

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effect on preputial gland weight or testes weight at 6 months of age, but a lower dose of 0.018 mg/kg/day reduced absolute testes weight by 13% (Palanza et al. 1999b). This was associated with a decreased intensity of aggressive behavior in the mice.

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; Palanza et al. 1999b; 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 (Eriksson 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;

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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  $M_1$  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 (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

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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. However, treatment with DDT followed by bioallethrin significantly increased the density of muscarinic receptors in the cerebral cortex relative to DDT alone. This increase was later attributed to increased expression of muscarinic receptor m4 mRNA (Talbot et al. 1998).

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. In a different study, the same group of investigators reported that exposure of mice to *o,p'*-DDT (0.018 or 0.18 mg/kg/day) during gestation days 11–17 had no significant effect on the behavior of the male progeny at 30 days of age towards mouse pups (Palanza et al. 1999b). However, the lowest dose tended

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to increase the proportion of males exposed *in utero* that attacked a male intruder, although the intensity of the attacks was lower than observed in controls.

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).

In summary, there is no conclusive evidence that DDT/DDE at the levels found in the environment cause developmental effects in humans, although two studies suggested that there may be an association between prenatal exposure and/or exposure early in life to DDE and alterations in height in children. In animals, DDT/DDE can produce embryotoxicity, fetotoxicity, and abnormal development of the sex organs. *o,p'*-DDT has been shown to have estrogenic properties, whereas *p,p'*-DDE has shown anti-androgenic properties. In addition, adult mice administered DDT early in life showed neurobehavioral alterations when tested later in life.

The highest NOAEL values and all LOAEL values from reliable studies for developmental effects in each species and duration category are recorded in Tables 3-1 and 3-2 and plotted in Figures 3-1 and 3-2. 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 3-1 and in Section 2.3.

#### 3.2.2.7 Cancer

Numerous studies in the United States and abroad have examined the possible association between exposure to DDT and related compounds and cancer in humans. Studies have been conducted of members of the general population as well as of occupationally exposed individuals. Exposure has been traditionally assessed by measuring DDT residues (most often DDE because of its persistence in the body and in the environment) in blood or in adipose tissue. Current data indicate that DDT in either media is a valid biomarker of exposure to DDT residues and each media correlate well with one another providing that the concentration of residues is adjusted for lipid content. The drawback of trying to associate current residue levels determined at or near the time of diagnosis with the occurrence of cancer is that levels at diagnosis may be very different than those at the time when cancer began to develop, and this is particularly relevant for cancers that exhibit a long latency. These and other issues inherent to epidemiological studies make it difficult to draw definite conclusions about exposure to DDT/DDE/DDD and cancer. However, taking all factors into consideration, the existing information does not support the

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hypothesis that exposure to DDT/DDE/DDD increase the risk of cancer in humans. The human studies below are presented 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.** Many epidemiological studies have investigated the association between breast cancer and levels of DDT and DDT-derived compounds in blood or adipose tissue from humans. Some studies have suggested a positive association (Aronson et al. 2000; Dewailly et al. 1994; Falck et al. 1992; Güttes et al. 1998; Romieu et al. 2000; Wasserman et al. 1976; Wolff et al. 1993), while others do not support such an association (Demers et al. 2000; Dorgan et al. 1999; Helzlsouer et al. 1999; Laden et al. 2001a; Krieger et al. 1994; Liljegren et al. 1998; Lopez-Carrillo et al. 1997; Mendonca et al. 1999; Moysich et al. 1998; Schecter et al. 1997; Unger et al. 1984; van't Veer et al. 1997; Ward et al. 2000; Wolff et al. 2000a, 2000b; Zheng et al. 1999, 2000). Below, studies that found an association between DDT/DDE burdens and breast cancer are summarized first, followed by those that found no significant association. In each case, serum DDT/DDE as a biomarker of exposure is discussed before adipose tissue.

Evidence of a positive association between breast cancer and exposure to DDT and DDT-related compounds was found 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 ppb) than in control subjects (7.7 ppb) (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=1.01–13.50), 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

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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 supported a positive relation between serum DDE and breast cancer, in spite of a short follow-up period and a relatively small number of subjects. See below for follow-up data from this study (Wolff et al. 2000b).

The association between elevated serum DDE levels and risk of breast cancer was examined among a subsample of women from a larger breast cancer case-control study of women living in Mexico City (Romieu et al. 2000). The final analysis was restricted to 120 cases and 126 controls who had given birth to at least one child and had complete information on all key variables. Major predictors of DDE levels included DDT levels, age, duration of lactation, parity, and socioeconomic level. Mean lipid-adjusted serum DDE levels were higher among cases (3.84 ppm) than in controls (2.51 ppm) ( $p=0.02$ ). This difference was more apparent for postmenopausal women; among premenopausal women, the difference was only marginally significant. Age-adjusted serum DDE levels were significantly related to breast cancer risk, but serum DDT levels were not. When DDE levels were examined as quartiles, after adjusting for age at menarche, duration of breast feeding, quetelet index, and menopausal status, there was a positive trend in the risk of breast cancer with increasing levels of serum DDE that was marginally significant ( $OR_{Q1-Q4}=2.16$ ; CI 95%, 0.85–5.50;  $p$  for the trend=0.06). The association was found to be stronger among those women who had experienced menopause; no association was found among premenopausal women.

Several studies have reported positive associations between DDT/DDE/DDD body burden, measured in adipose tissue, and 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,p'*-DDD in malignant breast tissue of hospitalized Brazilian women ( $n=9$ ) 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,p'*-DDT, and *o,p'*-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

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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 (Gütttes et al. 1998). A hospital-base case-control study of Canadian women found a weak association between *p,p'*-DDE in breast adipose tissue and breast cancer (Aronson et al. 2000). Biopsy tissues from 217 cases and 213 benign controls were analyzed for *p,p'*-DDT, *p,p'*-DDE, and other organochlorines. The geometric mean concentrations of *p,p'*-DDE in cases and controls were 693 and 596 ppb, respectively; those of *p,p'*-DDT were 22.0 and 19.3 ppb, respectively. The only increased risk for *p,p'*-DDE was among a subgroup excluding current hormone replacement therapy users. Further evaluation of this cohort showed that the odds ratio of DDE was higher with risk of estrogen receptor-negative breast cancer than estrogen receptor-positive breast cancer (Woolcott et al. 2001). A possible explanation suggested by the investigators was that tumors that are receptor-negative when diagnosed may have a faster rate of progression than tumors that are receptor-positive when diagnosed.

Several 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 (Dorgan et al. 1999; Helzlsouer et al. 1999; Hunter et al. 1997; Krieger et al. 1994; Ward et al. 2000). 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. A follow-up report to the Hunter et al. (1997) study included the results of adding to the analysis 143 postmenopausal cases and controls and of adjusting plasma organochlorines for triglycerides in addition to cholesterol (Laden et al. 2001a). Median (lipid-adjusted) concentrations of DDE in cases and controls were 0.768 and 0.817 ppm, respectively. The study found no evidence of an association between DDE and breast cancer within strata of age, age at menarche, age at birth of first child, number of children, history of benign breast disease, or family history of breast cancer. For DDE, the multivariate relative risk of breast cancer for women in the highest quintile (1.5–6.0 ppm) of exposure as compared with women in the lowest quintile (0.007–0.43 ppm) was 0.82 (95% CI=0.49–1.37).

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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 significant difference in DDE serum level was observed in the combined analysis of 150 pairs of cases and controls (43.1 vs. 43.3 ppb). 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. However, when ethnic groups were compared separately, high serum DDE concentrations were correlated with breast cancer incidence in Caucasian and African American women, but not Asian American women. 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.

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. Mean and median lipid-adjusted DDE concentrations were nonsignificantly higher in controls than in women who subsequently developed breast cancer. Separate risk analyses conducted for quintiles of DDE concentration in samples from 1974 and for tertile samples from 1989 of lipid-adjusted serum DDE showed no association between DDE and breast cancer. Women who donated in both 1974 and 1989 and who were diagnosed with breast cancer after 1989 were included in both program-specific analyses.

A hospital-based case-control study investigated risk for breast cancer associated with organochlorine exposure among 175 cancer patients, 181 control patients with benign breast disease, and 175 women in a

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second hospital control group (Wolff et al. 2000a). Fifty-seven percent of the subjects were Caucasian, 21% Hispanic, and 22% African-American. Chemicals evaluated in blood serum included *p,p'*-DDT, *p,p'*-DDE, *trans*-nonachlor, and higher and lower chlorinated biphenyls. Also, four tumor markers (estrogen, progesterone, p53, and erbB-2) were examined among cases. Most blood samples were collected prior to surgery, and none were taken more than 2 months after surgery. African-American women had significantly higher lipid-adjusted DDE levels (1.0 ppm, cases geometric mean) than Hispanic (0.71 ppm) and Caucasian (0.48 ppm) women, whereas DDT was highest among Hispanic women. However, organochlorine levels were not associated with risk of breast cancer, nor did organochlorines differ with respect to tumor stage or tumor markers. Higher DDE levels were associated with increasing body mass index (BMI), but with decreasing level of education, frequency of nulliparity, and frequency of family history of breast cancer. Wolff et al. (2000a) attributed their findings to historical patterns of exposure and to metabolic differences in organochlorines related to body mass index.

An additional study by Wolff et al. (2000b) provides prospective information on the cohort studied earlier (Wolff et al. 1993) by these investigators. Because the authors were interested in assessing the half-lives of DDE and PCBs, the study was restricted to only cases with at least three yearly blood donations, after the first year of serum analysis. Lipid measurements were available on 110 cases and 213 controls. Half-lives for DDE and PCBs were calculated for 84 cases and 196 controls who had contributed more than one blood donation. Odds ratios were calculated using conditional logistic regression analysis with DDE and PCB levels as both quartiles and continuous variables; some analyses, however, were conducted tertiles rather than quartiles. Adjustments were made for the following potential confounders: age at menarche, number of full-term pregnancies, age at first full-time pregnancy, first degree family history of breast cancer, months of lactation, height, BMI, and an interaction term for BMI and menopausal status. Breast cancer was significantly associated with nulliparity and family history of breast cancer. DDE levels were similar in cases and controls, whether lipid adjusted or not (geometric mean 977 ppb adjusted in cases vs. 1,097 ppb in controls). The lack of significance of these differences was maintained when estrogen receptor status of tumors was considered. Half-lives of DDE and PCBs were similar in cases and controls, and there was a strong correlation between the two chemicals. Half-life of DDE, but not serum level, was correlated with BMI (shorter among leaner women). The reason for the discrepancy between the earlier results (Wolff et al. 1993) and those from the present study was not apparent, and the authors could not rule out their earlier finding was a chance observation.

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Demers et al. (2000) conducted a case-control study among women from the Quebec City area to assess not only cancer risk, but also disease aggressiveness in relation to plasma levels of several organochlorines, including *p,p'*-DDT and *p,p'*-DDE. The cohort consisted of 315 women newly diagnosed with breast cancer, 219 hospital-based controls, and 307 population controls. Mean concentrations of *p,p'*-DDT and *p,p'*-DDE in women with breast cancer were not significantly different from those of hospital or population controls. Moreover, high concentrations of *p,p'*-DDT and *p,p'*-DDE (concentrations divided in quintiles) were not related to breast cancer risk. Additional analyses restricted to cases showed that after adjusting for confounders, the relative risk of axillary lymph node involvement increased significantly with *p,p'*-DDE tertiles (and with other organochlorines as well). When tumor size and lymph node involvement were considered in the same model, odd ratios of having involved nodes after adjustment for tumor size and confounding factors increased with tertiles of *p,p'*-DDE. However, odd ratios of having a large tumor after adjustment for lymph node involvement and confounding factors did not increase with *p,p'*-DDE plasma concentrations. There was no interaction between exposure to DDE/DDT and the hormonal status of the tumor (estrogen positive or negative) with regard to either tumor size or axillary lymph node involvement.

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 serum sampling did not alter the results. Median serum levels of *p,p'*-DDE in samples taken 5 years after the first examination were not significantly changed (1,197 vs. 1,169 ppb), but *p,p'*-DDT levels were about 3 times lower in the more recent analysis (144 vs. 46 ppb) (Høyer et al. 2000). When the values for *p,p'*-DDT from the two sampling periods were averaged and the means were stratified in quartiles, a positive association between the average serum concentration of *p,p'*-DDT and breast cancer risk was observed (*p* for the trend was 0.02).

A study of 150 breast cancer cases and 150 controls from Norway found no association between *p,p'*-DDT or *p,p'*-DDE in serum levels and breast cancer (Ward et al. 2000). In this study, the interval between blood collection and diagnosis ranged from 2 to 18.2 years with a mean of 8.8 years. The mean

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lipid-adjusted DDE concentrations in cases and controls were 1,230 and 1,260 ppb, respectively; the corresponding values for DDT were 120 and 138 ppb. Analyses of the data stratified by age at diagnosis, interval between blood collection and diagnosis, and estrogen and progesterone receptor status showed that DDE was higher in women cases age 50 years or older at diagnosis and in cancer cases with  $\geq 10$  years between blood sample and diagnosis. Neither one of these differences were statistically significant.

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.

A case-control study of only 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 breast cancer, parity, quetelet index (body mass index expressed as kg/m<sup>2</sup>), age at first birth, duration of lactation, years since last pregnancy, fruit and vegetable intake, and serum lipids. A recent study by Zheng et al. (2000) examined the relationship between serum DDE (lipid-adjusted) and breast cancer risk by menopausal status, parity, and lactation, and by cases' estrogen receptor status among 475 cases and 502 control women in Connecticut. Age-adjusted mean serum DDE levels were comparable in cases and controls, 460 and 456 ppb, respectively. Stratification by disease stage showed that DDE levels in 20 patients with later stage disease were insignificantly lower (402 vs. 456 ppb) than in 389 patients with early stage disease. The authors also found no significant differences for mean serum levels of DDE between controls and the various types of treatment groups, estrogen receptor status, parity and lactation status, and menopausal status.

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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.

Two studies of women from Brazil also found no association between blood DDT/DDE levels and breast cancer incidence. The first study investigated 177 cases of invasive breast cancer and 350 controls; cases and controls were residents of a large metropolitan region (Mendonca et al. 1999). The mean and median DDE concentrations in serum from patients were 5.1 and 3.1 ppb, respectively; the corresponding values in controls were 4.8 and 3.1 ppb. The age-adjusted odds ratio of breast cancer for women in the upper quintile compared with those in the lowest quintile was 0.90 (95% CI 0.47–1.73). The second study of 46 women with breast cancer and 152 controls found that mean total DDT serum levels was 13.6 ppb in cases and 15.9 in controls (Matuo et al. 2000). However, cases who never breast fed had significantly higher serum DDT than controls who never breast fed.

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Studies that found a lack of association between DDT/DDE in adipose tissue and breast cancer include one by Liljegren et al. (1998) who 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. Zheng et al. (1999) also found no significant association between breast adipose tissue levels of DDT and DDE and breast cancer. The study included 304 cases of breast cancer and 186 benign breast disease controls in Connecticut. The age-adjusted geometric mean concentrations of DDE in breast adipose in cases and controls were 737 and 784 ppb, respectively; the corresponding values for DDT were 52 and 56 ppb. There was no increased risk of breast cancer associated with increasing breast adipose tissue levels of either DDT or DDE. An additional study compared breast adipose tissue levels of DDT/DDE/DDD between 73 breast cancer cases and 73 women undergoing breast reduction surgery in California (Bagga et al. 2000). Analysis of unadjusted mean concentrations revealed no significant differences for DDT and DDD between cases and controls, but DDE was significantly elevated in cases relative to controls. However, when adjusted for age (cases were significantly older than controls), there was no statistically significant relationship between either DDT, DDE, or DDD, or the sum of the three chemicals and breast cancer. Another case-control study evaluated postmenopausal women from several European countries, showing no significant difference in current *p,p'*-DDE concentration in buttocks adipose tissue between women with breast cancer (n=265, 1.35 ppm) and cancer-free women matched for age and study center (n=341, 1.51 ppm) (van't Veer et al. 1997). The dates of tissue sampling were not reported.

A combined analysis of the data from five studies (Helzlsouer et al. 1999; Laden et al. 2001a; Moysich et al. 1998; Wolff et al. 2000a; Zheng et al. 2000) including 1,400 case patients and 1,642 control subjects was recently published (Laden et al. 2001a). The authors calculated pooled odds ratios and 95% confidence intervals by use of the random-effects model. When women in the fifth quintile of lipid adjusted values for DDE were compared with those in the first quintile, the multivariate pooled odds ratio for breast cancer was 0.99 (95% CI, 0.77–1.27), suggesting that there was no association between breast cancer risk and circulating DDE concentrations.

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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.

The association between pancreatic cancer and self-reported exposure to organochlorine pesticides (DDT among them) was examined in group of 66 pancreas cancer cases and 131 controls in southeastern Michigan (Fryzek et al. 1997). Analysis of the results showed a nonsignificant increased odds ratio of

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1.6 for pancreatic cancer (95% CI=0.8–3.1; cases=17, controls=23) for patients who were ever exposed to DDT, as compared to patients who had not been exposed.

A more recent study examined serum levels of *p,p'*-DDE and other organochlorine compounds in 108 pancreatic cancer cases and 82 controls (Hoppin et al. 2000). The study was part of an ongoing population-based case-control study of pancreatic cancer in the San Francisco Bay area. Controls were matched to cases by sex and age. After lipid adjustment, cases had higher concentrations of organochlorine than controls; the median *p,p'*-DDE concentration in cases was 1.3 ppm vs. 1.0 ppm in controls ( $p=0.05$ ). When the *p,p'*-DDE concentration was measured by tertiles, the odds ratio for the highest tertile (2.1, 95% CI=0.9–4.7) was elevated compared to the lowest tertile, although it did not achieve statistical significance. The odds ratio of 2.1 decreased to 1.1 after controlling for PCB level. As part of the same ongoing study, Slebos et al. (2000) investigated the association between two molecular markers, *K-ras* oncogene and *p53* tumor suppressor gene, and risk factors for pancreatic cancer in a group of 61 newly diagnosed patients. Activating point mutations of *K-ras* are common oncogene alterations in pancreatic carcinoma. Conversely, inactivation of the *p53* tumor suppressor gene is common in almost all human cancers. The study found that patients with *K-ras* positive tumors tended to have lower serum levels of DDE than those with *K-ras* negative tumors and also that serum levels of DDE were not significantly different between the *p53* positive and negative groups. In contrast to the findings of Slebos et al. (2000), Porta et al. (2000) found in a study of 51 subjects with pancreatic cancer that serum levels of *p,p'*-DDT and *p,p'*-DDE were significantly higher than among 26 controls. Among the 51 cases, 34 had mutated *K-ras* tumors and 17 had wild-type *K-ras*. A comparison of nonlipid adjusted values revealed that serum *p,p'*-DDE levels from wild-type cases did not differ from controls, but levels from mutated *K-ras* cases were about double those in controls; a similar comparison, but adjusted for lipid content, was not conducted.

**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. A crude ratio of 2.2 for subjectively reported DDT exposure was calculated for Hodgkin's disease, but no association was found when confounding factors were included into the logistic regression analysis (Persson et al. 1993). For non-Hodgkin's lymphoma, the logistic odds ratio was 2.0 (90% CI=0.3–13). 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 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. Exposure to phenoxy herbicides and fresh wood among

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sawmill workers, lumberjacks, and paper pulp workers were found to be significant risk factors for Hodgkin's disease, whereas welding, working as a lumberjack, nursing, and past-smoking were significant increased risks for non-Hodgkin's lymphoma.

No significant difference in mean concentration of *p,p'*-DDE in abdominal adipose tissue was found between a group of 28 newly diagnosed patients with non-Hodgkin's lymphoma and 17 surgical controls in Sweden (Hardell et al. 1996). The mean *p,p'*-DDE concentrations in patients and controls were 1.4 ppm (lipid basis) and 1.1 ppm, respectively. However, almost all of 34 PCB congeners were significantly higher in 27 of the cases relative to the 17 controls.

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). A 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 (3.2 ppm) was not significantly higher than in patients who did not develop the disease (2.8 ppm) (Wilcoxon signed rank test; p=0.2). Odds ratios for non-Hodgkin's lymphoma in serum DDT

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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 (n=622) and population-based controls (n=1,245) (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/m<sup>3</sup> in

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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 ( $\text{PMR} \times 100 = 341$ ) [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 ( $\text{PMR} \times 100 = 94$ ; 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.

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**Endometrial Cancer.** No association was found between newly-diagnosed endometrial cancer and lipid-corrected blood serum concentrations of *p,p'*-DDE in a multicenter case-control study of 180 women in the United States (Sturgeon et al. 1998). The median blood lipid-adjusted concentrations of *p,p'*-DDE were very similar between cases and controls (about 1.4 ppm). The adjusted relative risk of endometrial cancer in the highest quartile of exposure compared with women in the lowest quartile was 0.7 (95% CI=0.2–2.0). The blood concentration of *o,p'*-DDT was slightly higher among controls relative to cancer cases, but there was no significant association between increased cancer risk and this isomer. In contrast, cancer cases had higher blood levels of *p,p'*-DDT and a slightly higher risk of endometrial cancer. Similar overall results were obtained when the analysis was restricted to women over 50 years of age, as the authors sought to evaluate the influence of menopausal status.

The mean concentration of ' 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 ' 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.

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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 SMR, was not elevated over expected values. Standardized 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 recent study examined the association of the 1968 adipose DDE levels of population samples from 22 U.S. states with age-adjusted mortality rates between 1975 and 1994 for multiple myeloma, non-Hodgkin's lymphoma, and breast, uterus, liver, and pancreas cancer (Cocco et al. 2000). Past body burdens were estimated by using half-lives for DDT and DDE of 7 years and several decades, respectively. Separate analyses were conducted for gender and race. The authors found no association for pancreatic cancer and multiple myeloma. Breast cancer mortality was inversely correlated with adipose DDE levels among both white and African American women. Significant inverse correlations were also observed for uterine cancer among white women, while no association was observed for African Americans and for non-Hodgkin's lymphoma among white (men and women) and African American women. Liver cancer mortality significantly increased with adipose DDE levels in white males and females, but not among African Americans. A previous study of Italian workers exposed to DDT in a malaria eradication campaign in Sardinia, Italy also found a significant increase in the PMR for liver and

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biliary tract cancer; however, liver cancer was also elevated among unexposed workers and it did not show a trend with duration of exposure (Cocco et al. 1997a).

Overall, in spite of some positive associations for some cancers within certain subgroups of people, there is no clear evidence that exposure to DDT/DDE causes cancer in humans.

#### **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 10–20 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 50 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; most studies in nonhuman primates have also been negative. Chronic exposure to DDT produced liver neoplasms in mice strains ([C57BL/6 x C3H/Anf]F<sub>1</sub>, [C57BL/6 x AKR]F<sub>1</sub>, 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 significant increases in tumors in monkeys at doses of 3.9–20 mg/kg/day for up to 5 years (Adamson and

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Sieber 1979, 1983; Durham et al. 1963); or in dogs at 80 mg/kg/day for 49 months (Lehman 1965). A more recent study that involved 11 Rhesus and 13 Cynomolgus monkeys administered approximately 6.4–15.5 *p,p'*-DDT/kg/day in the diet for up to 130 months reported that 2 out of 13 Cynomolgus monkeys (15%) developed malignant tumors, one hepatocellular carcinoma and one adenocarcinoma of the prostate (Takayama et al. 1999). No neoplasms were found in a group of nine Cynomolgus and eight Rhesus untreated control monkeys.

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 71 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 F<sub>1</sub> 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 F<sub>2</sub> 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 F<sub>1</sub> 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),

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but it was not tumorigenic in B6C3F<sub>1</sub> 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  $3.4 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$ , which was derived using the linearized multistage model (IRIS 2001a). 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,  $3.4 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$ , 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  $2.9 \times 10^{-7} \text{ mg/kg/day}$ , respectively.

The oral cancer potency factor ( $q_1^*$ ) for DDD is  $2.4 \times 10^{-1} \text{ (mg/kg/day)}^{-1}$  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 B6C3F<sub>1</sub> 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  $4.2 \times 10^{-7} \text{ mg/kg/day}$ , respectively, for DDD and  $2.9 \times 10^{-4}$ ,  $2.9 \times 10^{-5}$ ,  $2.9 \times 10^{-6}$ , and  $2.9 \times 10^{-7} \text{ mg/kg/day}$ , respectively, for DDE.

Cancer Effect Levels (CELS) are recorded in Table 3-1 and plotted in Figure 3-1.

#### 3.2.3 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.

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**3.2.3.1 Death**

The dermal LD<sub>50</sub> 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<sub>50</sub> 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.

**3.2.3.2 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).

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**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.

**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.

#### 3.2.3.3 Immunological and Lymphoreticular Effects

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

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#### 3.2.3.4 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:

#### 3.2.3.5 Reproductive Effects

#### 3.2.3.6 Developmental Effects

#### 3.2.3.7 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 3.2.2.8.

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.

### 3.3 GENOTOXICITY

DDT, DDE, and DDD have been tested in several genotoxicity studies in animals and in bacterial systems, but studies in humans are limited. Tables 3-3 and 3-4 report the results of *in vivo* and *in vitro* studies, respectively. Chromosomal aberrations have been reported in human studies, but simultaneous exposure to other chemicals and/or lack of control of potential covariates (such as smoking) make the findings inconclusive. For example, 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 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

**Table 3-3. Genotoxicity of DDT, DDE, and DDD *In Vivo***

Species (test system)	End point	Results	Reference
Mammalian cells:			
Human (plasma)	Chromosomal aberrations	+	Rabello et al. 1975
Human (plasma)	Chromosomal aberrations	+	Yoder et al. 1973
Human (lymphocytes)	Chromosomal aberrations	+	Rupa et al. 1991
Human (lymphocytes)	Micronuclei	–	Vine et al. 2001
Mouse	Chromosomal aberrations	+	Clark 1974
Rat	Chromosomal aberrations	–	Legator et al. 1973; Palmer et al. 1973
Rabbit (fetus' liver)	Chromosomal aberrations	–	Hart et al. 1972
Mouse (bone marrow)	Chromosomal aberrations	+	Johnson and Jalal 1973; Larsen and Jalal 1974
Mouse	Dominant lethal	+	Clark 1974
Rat	Dominant lethal	(+)	Palmer et al. 1973
Mouse (inhibition of testicular synthesis)	DNA synthesis	– (DDE)	Seiler 1977
Rat (liver)	DNA lesions	+	Hilpert et al. 1983
Host-mediated assays:			
<i>Serratia marcescens</i> (Mouse hosted-mediated)	Gene mutation	– (DDT, DDE) + (DDD)	Buselmaier et al. 1973
<i>Neurospora crassa</i>	Gene mutation	–	Clark 1974
Invertebrate systems:			
<i>Drosophila melanogaster</i>	Dominant lethal	+	Clark 1974

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid

Table 3-4. Genotoxicity of DDT, DDE, and DDD *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<i>Salmonella typhimurium</i> (TA1535, TA1537, TA98, TA100)	Gene mutation	—	—	McCann et al. 1975
<i>Escherichia coli</i> (Pol-A)	Gene mutation	—	—	Fluck et al. 1976
<i>E. coli</i> (Back mutation)	Gene mutation	—	No data	Fahrig 1974
<i>Escherichia marcescens</i> (glucose prototrophy)	Gene mutation	—	No data	Fahrig 1974
<i>Bacillus subtilis</i> (rec-assay)	DNA damage	—	No data	Shirasu et al. 1976
<i>E. coli</i> (col E1 plasmid DNA)	DNA damage	—	No data	Griffin and Hill 1978
<i>E. coli</i> (DNA cell binding assay)	DNA damage	—	No data	Kubinski et al. 1981
Fungal and plant cells:				
<i>Neurospora crassa</i>	Recessive lethal	—	No data	Clark 1974
<i>Saccharomyces cerevisiae</i>	Mitotic gene conversion	—	No data	Fahrig 1974
Mammalian cells:				
Chinese hamster V79 cells	Chromosomal aberrations	+ (DDE) — (DDT)	No data	Kelly-Garvert and Legator 1973
Chinese hamster (B14F28 cells [chromosomal damage])	Chromosomal aberrations	+	No data	Mahr and Miltenburger 1976
Kangaroo rat (cells)	Chromosomal aberrations	+	No data	Palmer et al. 1972
Human (hepatocyte-mediated cell)	Gene mutation	—	—	Tong et al. 1981
Chinese hamster (V79 cells [6-thioguanine resistant mutation])	Gene mutation	—	No data	Tsushimoto et al. 1983
Mouse (L51784 lymphoma cells)	Gene mutation	+	No data	Amacher and Zelljadt 1984
Rat (liver epithelial cell)	Gene mutation	—	No data	Telang et al. 1981
Human SV-40 (unscheduled DNA synthesis)	DNA damage	—	—	Ahmed et al. 1977
Mouse (hepatocytes-UDS)	DNA damage	—	—	Probst et al. 1981
Rat (hepatocytes-UDS)	DNA damage	No data	—	Probst and Hill 1980
Hamster (hepatocytes-UDS)	DNA damage	No data	—	Maslansky and Williams 1981

– = negative result; + = positive result; (+) = weakly positive; DNA = deoxyribonucleic acid

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chromosomal damage was reported; no information was provided regarding control for relevant covariates. 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). 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). A recent study of 302 individuals residing near a waste site in North Carolina found that plasma DDE levels were not associated with a higher frequency of micronuclei (Vine et al. 2001).

Studies in animals have provided mixed results (Table 3-3). 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 postmeiotic 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. BALB/C mice exposed *in vivo* to DDT exhibited chromosomal aberrations of the bone marrow (Johnson and Jalal 1973; Larsen and Jalal 1974).

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).

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).

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As shown in Table 3-4, DDT and related compounds were, for the most part, nonmutagenic in prokaryotic organisms and did not induce DNA damage under the conditions tested. However, a few studies with mammalian cells *in vitro* found positive results. For example, 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 (*Potorus tridactylis*) *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.

Collectively, the data do not suggest that DDT and related compounds present a genotoxic hazard at environmentally relevant concentrations.

#### 3.4 HEALTH EFFECTS IN WILDLIFE POTENTIALLY RELEVANT TO HUMAN HEALTH

The 1972 EPA decision to ban DDT for most uses in the United States was significantly influenced by a large body of scientific information documenting adverse effects to wildlife (EPA 1975). These observed effects were severe, including the lethality of DDT to birds and fish and the DDE-induced reproductive effects in birds, particularly eggshell thinning (EPA 1975). Although it is difficult to draw firm conclusions about adverse effects to human health based on those observed in wildlife, it is impossible to ignore that the documented effects to wildlife have motivated the investigation of human health effects. It is reasonable to assume that the adverse effects observed in wildlife may also be a concern to humans and that wildlife are possible "sentinels" for human health (NRC 1991). In order to completely address potential concerns for human health, it is necessary to review and evaluate the observed effects of DDT/DDE/DDD to terrestrial wildlife. Exposures for wildlife to DDT and its metabolites in the natural environment are primarily associated with the accumulation and persistence of these contaminants in both aquatic and terrestrial food chains. Ingestion of contaminated food results in the deposition of DDT/DDE/DDD in tissues with subsequent reproductive, developmental, and neurological effects. The most important reproductive effect observed in wildlife concerns eggshell thinning in birds. These and other effects on terrestrial wildlife are discussed in greater detail in Appendix D with the purpose of providing a qualitative synopsis of effects in terrestrial wildlife to address potential concerns that these effects from DDT/DDE/DDD exposure may also occur in humans.

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**Eggshell Thinning in Birds.** Eggshell thinning in birds reached widespread public awareness in the 1960s and 1970s largely because of field observations in wild raptor populations including the bald eagle, peregrine falcon, and osprey, and the association of these effects with abrupt population declines. 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). 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).

Numerous experimental studies have shown that dietary exposures to DDT/DDE/DDD are associated with eggshell thinning and breakage in wild birds including the barn owl (*Tyto alba*) (Mendenhall et al. 1983), the American kestrel (Porter and Wiemeyer 1969), the mallard duck (*Anas platyrhynchos*) (Heath et al. 1969; Risebrough and Anderson 1975; Vangilder and Peterle 1980), the black duck (*Anas rubripes*) (Longcore et al. 1971), the Japanese quail (*Coturnix coturnix japonica*) (Kenney et al. 1972), the bobwhite quail (*Colinus virginianus*) (Wilson et al. 1973) and the Ringed turtle doves (*Streptopelia risoria*) (Haeghele and Hudson 1973; Peakall 1970; Peakall et al. 1975). These experimental results have verified that the field observations of eggshell thinning and reductions in wild raptor populations are associated with releases of DDT. 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). The leading hypothesis for DDE-induced 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). Overall, there is still some question as to the primary mechanism and reviewers have suggested that these may differ between bird species or differ with environmental conditions or physiological state for a given species. There is some question, however, as to the relevance of avian eggshell thinning to human health. There is no anatomical or physiological counterpart of the shell gland, a specialized segment of the oviduct, in humans. The shell gland lays down calcite ( $\text{CaCO}_3$ , calcium carbonate) onto the developing avian egg to form the eggshell (EPA 1975). 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.

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**Reproductive Effects.** Exposure to DDT/DDD/DDE is associated with reproductive toxicity in avian wildlife including embryoletality (Heath et al. 1969; Longcore et al. 1971; Porter and Wiemeyer 1969), decreased egg size and weight (Jefferies 1969; Peakall 1970; Wilson et al. 1973), delayed oviposition after mating (Cecil et al. 1971; Jefferies 1967, 1969; Peakall 1970; Richie and Peterle 1979; Vangilder and Peterle 1980), ovarian effects (Bitman et al. 1968; Gish and Chura 1970; Keith and Mitchell 1993) and testicular effects (Burlington and Lindeman 1950; George and Sunararaj 1995; Gish and Chura 1970; Locke et al. 1966). Several authors have speculated that these effects are associated with DDT-induced hormonal imbalances (Jefferies 1967) such as DDT induced estrogen-like inhibition of FSH and LH secretion by the pituitary inhibiting ovary development.

In most studies, egg production is not affected by DDT/DDD/DDE exposure (Azevedo et al. 1965; Chen et al. 1994; Davison et al. 1976; Davison and Sell 1972; Heath et al. 1969; Jefferies 1969; Longcore et al. 1971; Mendenhall et al. 1983; Porter and Wiemeyer 1969; Risebrough and Anderson 1975; Scott et al. 1975; Shellenberger 1978; Vangilder and Peterle 1980; Wilson et al. 1973). There are, however, a few reported cases of decreased egg production especially in birds with restricted diets (Cecil et al. 1971; Gish and Chura 1970; Haegele and Hudson 1973; Kenney et al. 1972). Egg fertility and hatchability are not consistently affected by DDT/DDD/DDE exposure. Some studies report significantly decreased fertility and hatchability (Porter and Wiemeyer 1969; Vangilder and Peterle 1980; Wilson et al. 1973), while others do not document significant effects (Azevedo et al. 1965; Haegele and Hudson 1973; Jones and Summers 1968; Scott et al. 1975; Shellenberger 1978). When considered collectively, egg production, fertility, and hatchability were largely unaffected in numerous studies in a variety of bird species. This may be inconsequential to the overall reproductive success of birds since DDT/DDD/DDE exposure is clearly associated with decreased embryonic survival or fledgling success (Keith and Mitchell 1993).

DDT exposure has been shown to be associated with reduced post-hatch survival in avian wildlife. This effect has been observed in laboratory testing with mallards, pheasant, black duck, chicks; Japanese quail and ringed turtle doves (Azevedo et al. 1965; Genelly and Rudd 1956; Haegele and Hudson 1973; Heath et al. 1969; Jones and Summers 1968; Keith and Mitchell 1993; Longcore et al. 1971; Porter and Wiemeyer 1969; Shellenberger 1978). The mechanism of DDT-induced reduced survival after oral exposures to DDT or DDE in maternal birds is hypothesized to be associated with increased body burdens of DDT/DDD/DDE in chicks as either a result of direct toxicity to the chick, or a reduction in parental care-giving among treated birds resulting in chick malnutrition and poor survival.

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The implications of these observed effects in wildlife to human health is uncertain as the mechanisms of toxicity are not thoroughly understood. The consistency of the observed reproductive effects to avian wildlife and the field observations of effects to birds and reptiles have stimulated the investigation of reproductive effects in mammalian models that are more directly relevant to humans. *In vitro* mechanism of action studies 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). There are some interesting parallels between mammalian wildlife and human health studies. Similar to the associations made between DDT and preterm deliveries in humans (Saxena et al. 1980, 1981; Wassermann et al. 1982), premature births in California sea lions (*Zalophus californianus californianus*) are associated with elevated DDT concentrations (DeLong et al. 1973). However, the effect could not be solely, causally isolated to DDT due to the presence of PCBs.

**Developmental Effects.** The developmental effects of DDT/DDD/DDE on reptiles and avian wildlife have received considerable attention. Studies of alligator populations at Lake Apopka in Florida, where a pesticide spill occurred in 1980, have reported various reproductive effects including reduced clutch viability (Woodward et al. 1993), altered steroidogenesis (Crain et al. 1997; Guillette et al. 1995), abnormal ovarian morphology and plasma 17 $\beta$ -estradiol levels (Guillette et al. 1994), and reductions of phallus size and serum testosterone (Guillette et al. 1994, 1995, 1996, 1997, 1999). The authors hypothesized that the estrogenicity of DDT and other contaminants induced hormonal imbalance in the alligators, causing the observed effects (Guillette and Crain 1996). The contribution of DDT/DDE/DDD (only one component of the mixture of pesticides present) to the observed effects is uncertain. However, other experimental findings support the hypothesis that certain DDT-related compounds induce estrogenic effects in reptiles which could potentially adversely affect reproduction in a population (*in ovo* DDE exposures in alligators by Matter et al. 1998). In general, reptiles may be particularly susceptible to the endocrine-altering effects of DDT/DDE/DDD, as sex in many species are determined by environmental factors (temperature, etc.) compared to the genetic sex determining mechanisms in birds and mammals (Crain and Guillette 1998). Organochlorine contaminants in general and *p,p'*-DDE, specifically, are thought to influence sexual dimorphism in the common snapping turtle (*Chelydra serpentina*) (de Solla et al. 1998). Snapping turtles in Ontario, Canada, lacked the normal sexual dimorphism in the distance between cloaca and plastron which was attributed to the antiandrogenic effects of *p,p'*-DDE.

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DDT exposure is also associated with developmental abnormalities in amphibians and avian wildlife. DDT exposures are associated with delayed tadpole metamorphosis in the frog (*Rana temporaria*) (Cooke 1972, 1973a) and altered facial features (Cooke 1970a). Developmental effects in avian wildlife associated with exposure to DDT/DDD/DDE include a reduced growth (Seidensticker 1968), decreased ability to thermoregulate (Vangilder and Peterle 1980), behavioral alterations (Heinz 1976), reduced testicular development (Burlington and Lindeman 1952), and development of ovarian tissue and oviducts in genetic males (Fry and Toone 1981). 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.

**Neurological and Behavioral Effects.** Neurological effects (tremors, convulsions, hyperactivity, and behavioral changes) were observed in mammalian wildlife, amphibians, and avian wildlife experimentally exposed to DDT or DDE, particularly after administration of lethal doses or after administration of lower doses when food intake was restricted. Tremors were the most commonly reported neurological effect and have been reported in the brown bat (the short-tailed shrew (*Blarina brevicauda*) (Blus 1978), the free-tailed bat (*Tadarida brasiliensis*) (Clark and Kroll 1977) the big brown bat (*Eptesicus fuscus*) (Luckens and Davis 1964) and Pipistrelle bats (Jefferies 1972). Studies generally did not offer explanations as to the possible mechanisms that caused tremors, although it is reasonable to assume a mechanism similar to that seen in laboratory animals. 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 documented significant decreases in brain neurotransmitter levels 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. Neurological effects observed in amphibians exposed to DDT/DDE/DDD in water include uncoordinated movement (Cooke 1970b) and hyperactivity (Cooke 1972, 1973a), tremors, lack of muscular coordination and weakness (Harri et al. 1979). Most available data suggest that wildlife species exhibit neurological effects similar to those observed in humans. These neurological effects, however were observed in wildlife at lethal exposure levels or in energy-stressed animals at lower exposure levels.

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In avian wildlife DDT/DDD/DDE exposures are associated with decreased brain dopamine levels with a significant negative correlation observed between neurotransmitter levels and DDE residues in the brain (Heinz et al. 1980). Tremors have also been observed in bald eagles (*Haliaeetus leucocephalus*) (Chura and Stewart 1967; Locke et al. 1966), kestrels (*Falco sparverius*) (Porter and Wiemeyer 1972), double-crested cormorants (*Phalacrocorax auritus*) (Greichus and Hannon 1973), pheasants (Azevedo et al. 1965), bobwhite quail (*Colinus virginianus*) (Hill et al. 1971), Japanese quail (Davison et al. 1976; Gish and Chura 1970), house sparrows (*Passer domesticus*) (Boykins 1967), cardinals (*Richmondia cardinalis*), and blue jays (*Cyanocitta cristata*) (Hill et al. 1971), homing pigeons (*Columba livia*) (Jefferies and French 1971) (Jefferies and French 1972), and domestic chickens (Glick 1974). Balance disturbances have also been observed (in some cases prior to death) in pheasants that (Azevedo et al. 1965), Bobwhite quail (*Colinus virginianus*) (Hill et al. 1971), cardinals (*Richmondia cardinalis*), and blue jays (*Cyanocitta cristata*) (Hill et al. 1971). Neurological effects in avian wildlife are also manifested as behavioral effects. These include the delayed onset of nocturnal restlessness indicative of normal migratory behavior (Mahoney 1975), significantly decreased courting behavior (Haegle and Hudson 1977), and decreased nest attendance by parental birds (Keith and Mitchell 1993).

Other adverse effects observed in wildlife species are described in detail in Appendix D. This section only provides a summary of reproductive, developmental and neurological effects that are the primary adverse effects to terrestrial wildlife associated with DDT/DDD/DDE exposure.

### 3.5 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

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suggested that fecal excretion may be the major route of elimination at high doses; however, this has not been confirmed by later investigations.

#### **3.5.1 Absorption**

##### **3.5.1.1 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; Ortelée 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.

##### **3.5.1.2 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.

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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  $^{14}\text{C}$ -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).

#### 3.5.1.3 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  $\text{LD}_{50}$ , 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).

#### 3.5.2 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).

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

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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 parity, children nursed, diet, and cigarette smoking (Bouwman et al. 1990; Bradt and Herrenkohl 1976; Mes et al. 1993; Rogan et al. 1986). 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 6-4 shows levels of DDT and related compounds in breast milk from some recent studies.

LaKind et al. (2000) formulated a model to estimate doses of DDE to nursing infants. Included in the model were nursing variables (duration of breast-feeding, volume of breast milk consumed, percent lipid in breast milk, and milk density), infant variables (percent absorption of chemical, half-life of chemical, and body weight), and maternal depuration rate of the chemical via breast-feeding (time-dependent concentration of the chemical in the mother's milk). Several exposure scenarios were evaluated: 3, 6, 9, and 12 months, and a randomly simulated duration. The concentration of DDE in milk at time zero used in the model was 222.3 ppb (lipid basis), which was the mean value obtained in a Canadian breast milk evaluation of 497 donors from across Canada conducted in 1992 (Newsome et al. 1995). The results showed that, regardless of the exposure scenario simulated, infant body burdens of DDE increase rapidly

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at the start of lactation, but decrease after approximately 5–6 months, even if nursing continues. The maximum mean body burden of DDE was about 70 µg/kg, and by 24 months postpartum, it was <10 µg/kg, regardless of the duration of breast-feeding.

DDT and DDT metabolites have been shown to cross the placenta. A study of 90 mother/infant pairs from Mexico found that all 90 cord blood samples had detectable levels of *p,p'*-DDE, 9 had detectable levels of *o,p'*-DDT, and 44 had measurable levels of *p,p'*-DDT (Waliszewski et al. 2000). The mothers were volunteers from the general population with no known occupational exposure to DDT. The concentrations of the pesticide residues in maternal blood were very similar to those in cord blood. *p,p'*-DDE was the most concentrated (lipid-adjusted means, 4.4 ppm maternal; 4.7 ppm cord blood), followed by *p,p'*-DDT (1.8 ppm maternal, 2.8 ppm cord blood), and *o,p'*-DDT (0.30 ppm maternal, 0.35 ppm cord blood). A study of Spanish women reported a geometric mean of 2.2 ppb (not lipid-adjusted) for *p,p'*-DDE in maternal blood at delivery (n=72) and 0.83 ppb in cord blood (n=69) (Sala et al. 2001). The women in the study lived in the vicinity of an organochlorine-compound factory.

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. (1999b) studied the transplacental and lactational 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 *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 *in utero* had at least two orders of

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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 3.5.5 for a description of physiologically based pharmacokinetic (PBPK) models developed by You et al. (1999b) 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 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.

### 3.5.3 Metabolism

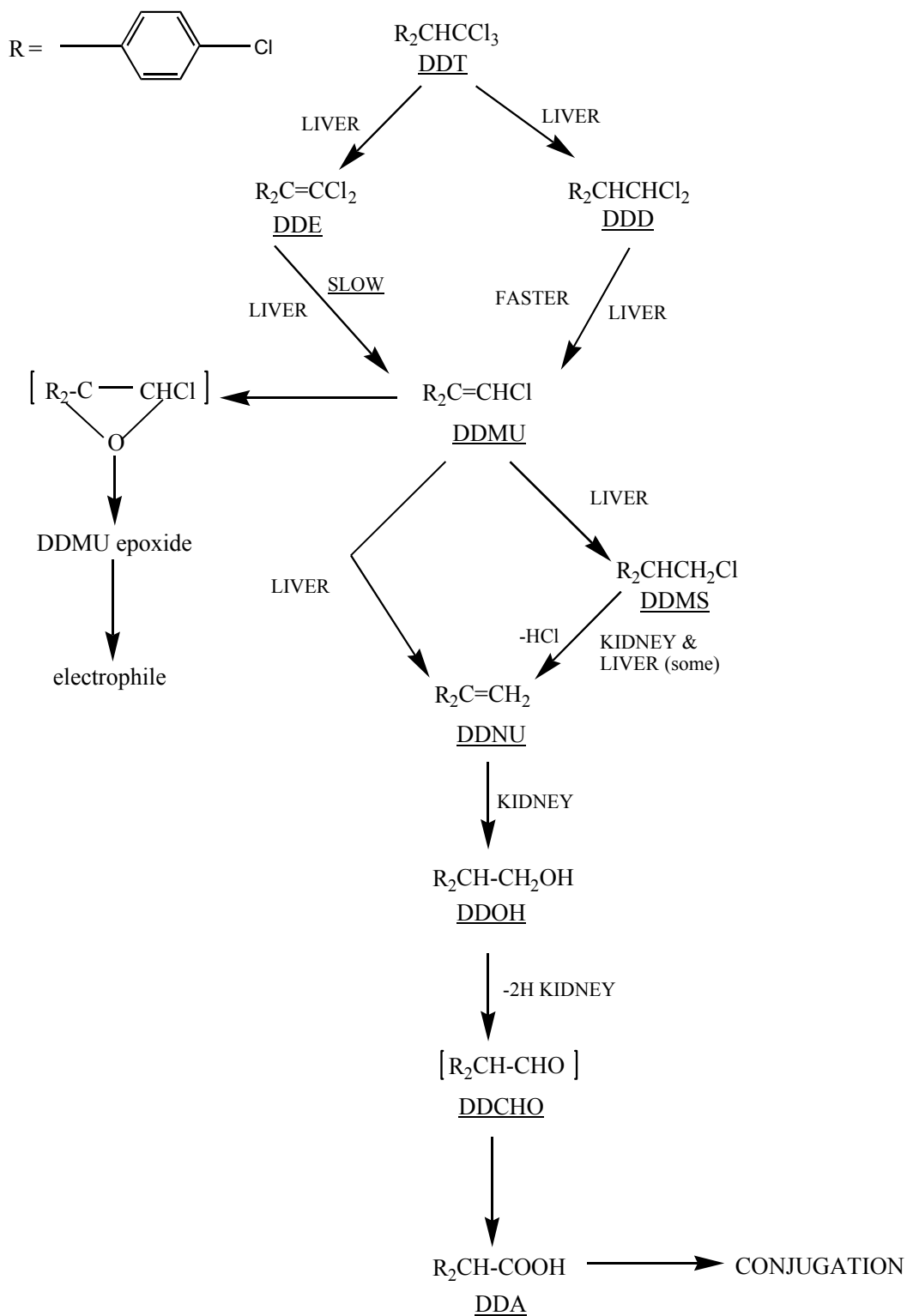
The metabolism of DDT, DDE, and DDD has been studied in humans and a variety of other mammalian species. The metabolism in rats, mice, and hamsters is similar to that in humans; however, not all of the intermediary metabolites identified in animals have been identified in humans. It has been proposed by a number of investigators that in mammals, the major urinary metabolite of DDT, 2,2-*bis*(*p*-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 3-3a), DDT is initially metabolized in

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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-*bis*(*p*-chlorophenyl)ethene (DDMU), and then to DDA in the kidney by way of 1,1-*bis*(*p*-chlorophenyl)ethene (DDNU) (Datta 1970; Datta and Nelson 1970). DDD is rapidly detoxified by way of DDMU to 1-chloro-2,2-*bis*(*p*-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-*bis*(*p*-chlorophenyl)ethanol (DDOH) then to 2,2-*bis*(*p*-chlorophenyl)ethanal (DDCHO) (Suggs et al. 1970), which is further oxidized to DDA (Peterson and Robison 1964).

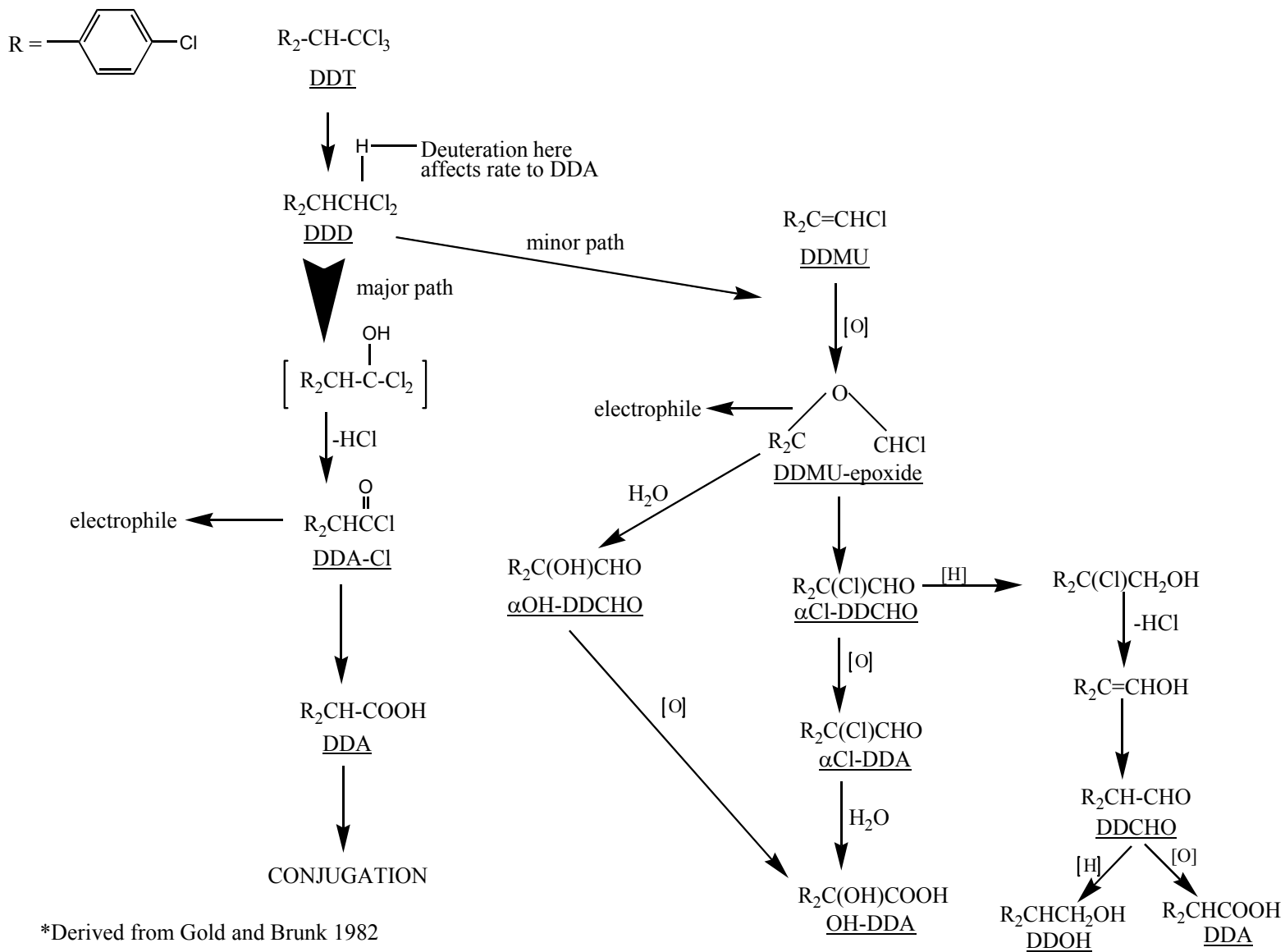
Other evidence in mice and hamsters suggests an alternative metabolic scheme (Gold and Brunk 1982, 1983) (Model II: see Figure 3-3b). In these studies, one dose of radioactively-labeled DDT or DDD was administered by gavage, and urine was collected for 72 hours for analysis. The principal urinary

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**Figure 3-3a. Model I Metabolic Scheme for DDT\***

\*Adapted from Peterson and Robinson 1964

Figure 3-3b. Model II Metabolic Scheme for DDT\*



\*Derived from Gold and Brunk 1982

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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-*bis*(*p*-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 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).

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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 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 Norén 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 methylsulfoxones, which are distributed by the blood (Haraguchi et al. 1989). Figure 3-4 shows the proposed pathway for sulfonyl metabolites. Further information regarding the

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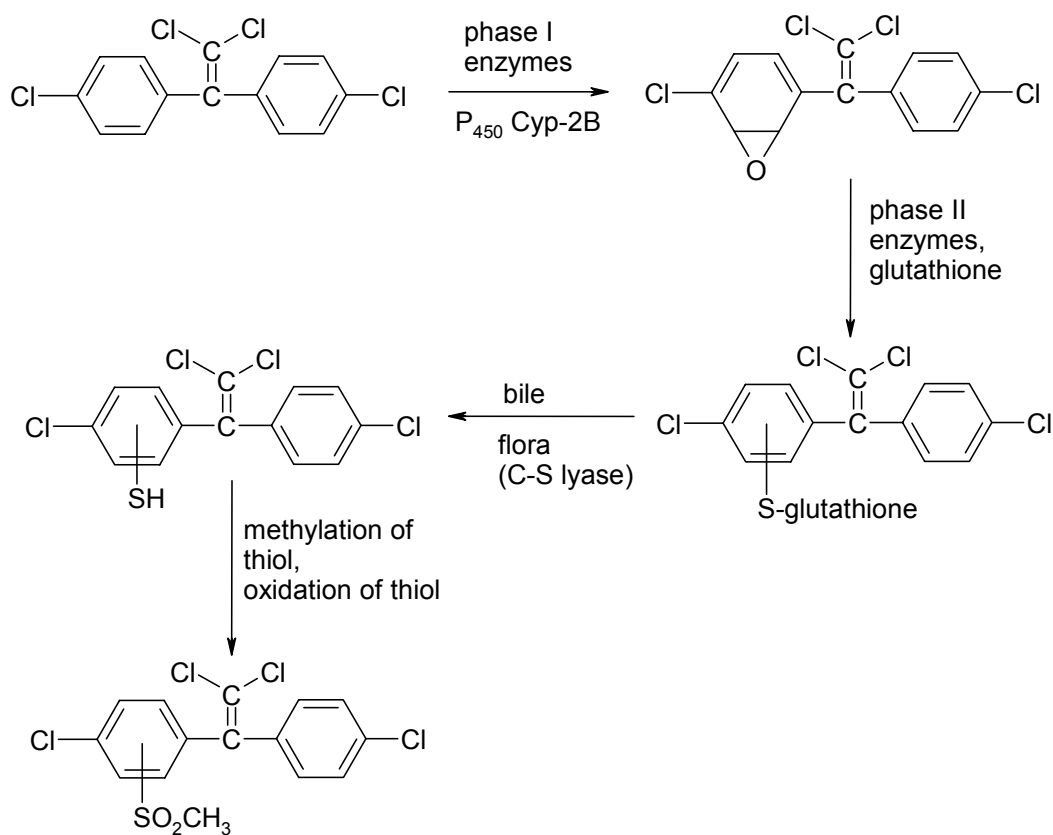
toxicity of this metabolite is presented in Section 3.7, Toxicities Mediated Through the Neuroendocrine Axis.

### 3.5.4 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.

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**Figure 3-4. Proposed Metabolic Pathway for the Conversion of *p,p'*-DDE to its Methylsulfone Derivative**

Source: Bergman et al. 1994; Letcher et al. 1998; Weistrand and Norén 1997

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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.

#### **3.5.5 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 (Clewett and Andersen 1985). Physiologically based

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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

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sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-5 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. (1999b). The You et al. (1999b) 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 3-6 and 3-7 show conceptualized representations of the gestation model and the lactation/nursing models, respectively. Parameters used in the models are shown in Tables 3-5 and 3-6. The gestation model simulates the absorption of an oral dose 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.

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**Table 3-5. Tissue:Blood Partition Coefficients and Pharmacokinetic Constants for Modeling DDE Disposition in the Pregnant Rat<sup>a</sup>**

Tissue:blood partition coefficients	
Liver	7
Fat	450
Poorly-perfused tissues	12
Well-perfused tissues	6
Kidney	6
Uterus	6
Placenta	2
Mammary gland	12
Pharmacokinetic constants	
$K_{AS}$ (L/day) Portal absorption rate constant	24
$K_{LY}$ (L/day) Lymphatic absorption rate constant	74
$K_{FX}$ (L/day) Fecal excretion rate constant	230
$K_B$ (L/day) Biliary excretion rate constant	1.2
$PA_F$ (L/day) Fat diffusion coefficient	5
$PA_1$ (L/day) Placenta-to-embryo/fetus diffusion coefficient	1.6
$PA_2$ (L/day) Embryo/fetus-to-placenta diffusion coefficient	1.9
$K_{12}/K_{21}$ Diffusion to deep fat	1.0/0.1
$T_{del}$ (day) Delay in time	0.1

<sup>a</sup>Adapted from You et al. 1999b

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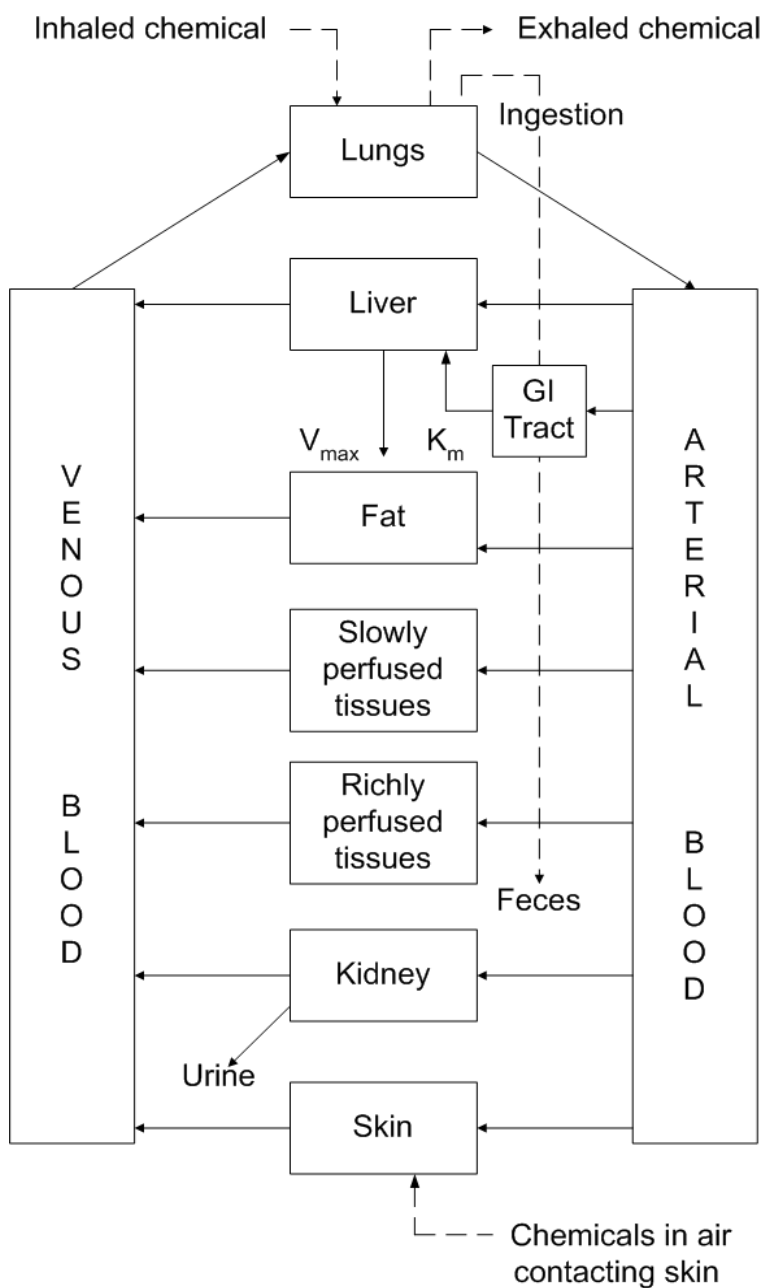
**Table 3-6. Physiological Constants Used in the PBPK Model for the Lactating Dam and the Nursing Pup<sup>a</sup>**

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

<sup>a</sup>Adapted from You et al. 1999b

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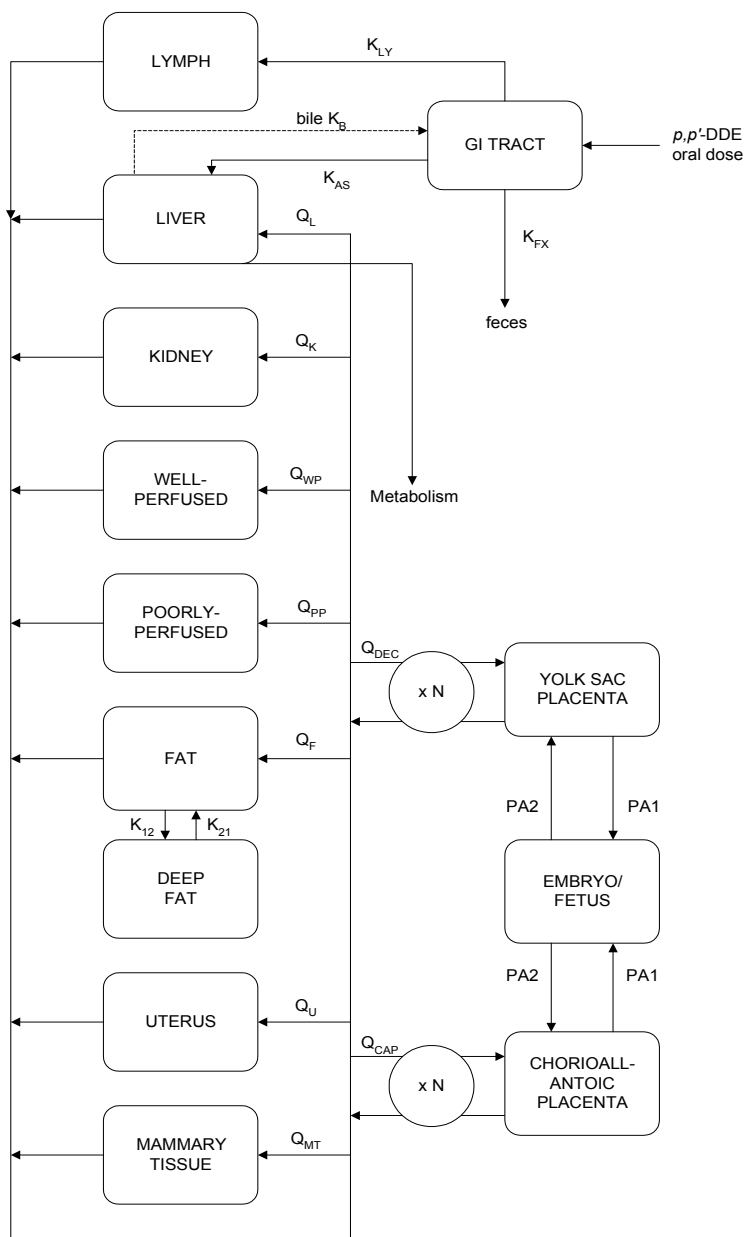
**Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance**



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.

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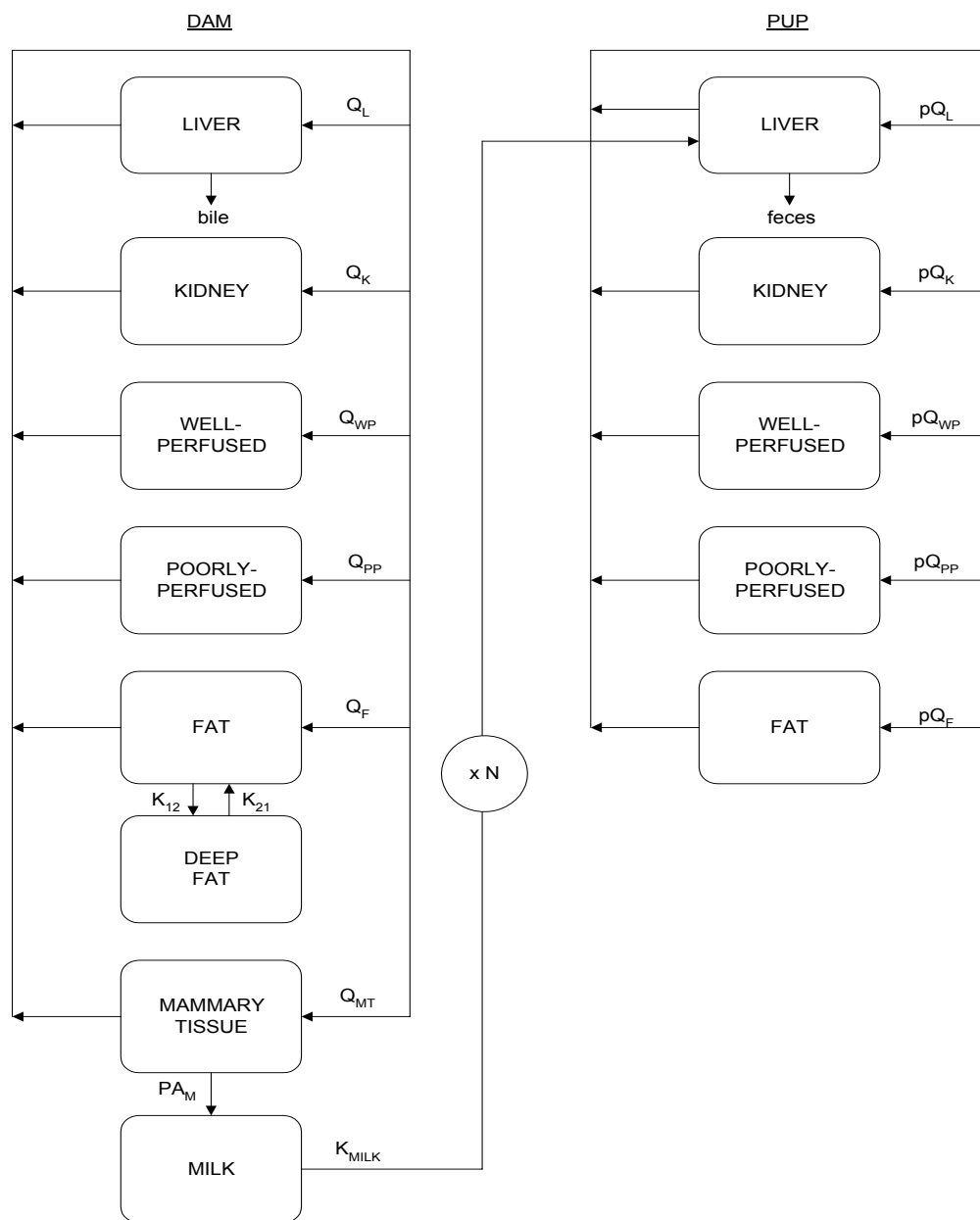
**Figure 3-6. Diagrammatic Representation of the PBPK Model for Gestation\*.**

$N$  = number of concepti

Terms are Defined in Table 3-6 and Table 3-7.

\*Adapted from You et al. 1999b

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**Figure 3-7. Diagrammatic Representation of the PBPK Model for the Lactating Dam and Nursing Pup\*.**

N = number of pups

Portal and lymphatic absorption routes for dams are not shown (see Figure 3-6).

Terms are Defined in Table 3-5 and Table 3-6.

\*Adapted from You et al. 1999b

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**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. (1999b) 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. 1999b)

**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.

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**3.6 MECHANISMS OF ACTION****3.6.1 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.

Studies in humans suggest that DDT and related compounds are 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 (LDL), and very low density lipoproteins (VLDL). 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. In agreement with the findings of Morgan et al. (1972), Norén et al. (1999) found that in blood from humans, *p,p'*-DDE and its methylsulfonyl metabolite, 3-MeSO<sub>2</sub>-DDE, were associated to a great extent (almost 80%) with a fraction containing primarily albumin. In this case, the subjects (three men and two women) had no known occupational exposure to organochlorine compounds. Of the remaining DDE, 12% was recovered associated with LDL, 9% with VLDL, and 6% with high density lipoprotein (HDL). The corresponding figures for 3-MeSO<sub>2</sub>-DDE were 8, 4, and 11%. Results from studies *in vitro* are consistent with findings *in vivo*. Gómez-Catalán et al. (1991) showed that 82.3% of *p,p'*-DDE in human blood was associated with plasma and only 17.7% with cells. In plasma,

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approximately 60% was associated with protein and 9–15% with the various lipid fractions. Similar results were reported by Mohammed et al. (1990) in an *in vitro* study with radiolabeled DDT.

Extensive information regarding the metabolism of DDT and DDT-related compounds was presented in Section 3.5.3. 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 antiandrogenicity 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.

#### 3.6.2 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 1967). 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.

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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 androgenic 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.

Androgens and estrogens are very lipid soluble and thus, diffuse easily through the cell membrane into the cytosol and nucleus. Unoccupied steroid receptors bound to a complex of molecular chaperones are in dynamic equilibrium between the cytosol and the nucleus (DeFranco 1999). Once a steroid binds to its receptor and the hormone-receptor complex reaches the nucleus, it 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

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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  $\alpha$  (ER $\alpha$ ). Recently, however, a second estrogen receptor, ER $\beta$ , 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 ER $\alpha$  and ER $\beta$ . 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 ER $\alpha$  receptor pairs up with an ER $\beta$  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 ER $\alpha$  with an ER $\alpha$  or an ER $\beta$  with an ER $\beta$ ). 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.

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*p,p'*-DDT (200 mg/kg twice) and *o,p'*-DDD (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 (200 mg/kg once) and *o,p'*-DDT (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 was as efficient as *o,p'*-DDT 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 > technical DDT > *p,p'*-DDT in immature female rats treated intraperitoneally. Singhal et al. (1970) showed that *o,p'*-DDT (100 mg/kg) was much more effective in increasing uterine weight in young rats than *p,p'*-DDT after a single intramuscular injection. Shelby et al. (1996) examined the estrogenicity of *o,p'*-DDT 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 uterotrophic 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 on three consecutive days and determining uterine weight on the fourth day. *o,p'*-DDT gave positive estrogenic responses in the three assays, but with a potency that was several orders of magnitude weaker than 17 $\beta$ -estradiol and diethylstilbestrol (DES). *o,p'*-DDT, *o,p'*-DDD, and *p,p'*-DDT were full estrogenic agonists in the *in vitro* E-screen test, *p,p'*-DDE and *p,p'*-DDD 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<sup>7</sup> times more *o,p'*-DDT, *o,p'*-DDD, *p,p'*-DDT, *p,p'*-DDE, *p,p'*-DDD, and technical DDT was needed to produce maximal cell yields than 17 $\beta$ -estradiol. *p,p'*-DDE also showed partial antagonistic effects on MCF-7 cell proliferation (Soto et al. 1998).

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. *o,p'*-DDT and *o,p'*-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<sub>50</sub> (effective concentration for 50% maximal response) values for *o,p'*-DDT and *o,p'*-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<sub>50</sub> values were 1.8 mM for *o,p'*-DDT (8x10<sup>6</sup> less potent than estradiol) and 3.32 mM for *o,p'*-DDD (15x10<sup>7</sup> less potent than estradiol) compared to an actual estradiol EC<sub>50</sub> of 2.25 nM. *o,p'*-DDE produced

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little apparent response. Sohoni and Sumpter (1998) investigated the ability of *o,p'*-DDT and *p,p'*-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 *o,p'*-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 *p,p'*-DDE even at concentrations as high as 0.5 mM. In a similar study using recombinant receptor-reporter gene assays in stably transfected MCF-7 and HeLa cells, both *o,p'*-DDE and *p,p'*-DDE showed weak estrogenic activity (Balaguer et al. 1999). *o,p'*-DDE was slightly more potent than *p,p'*-DDE, but it was still approximately  $10^6$  times less potent than  $17\beta$ -estradiol on a molar basis. In an additional study using HeLa cells cotransfected with an expression vector containing ER and an RE-responsive chloramphenicol acetyltransferase reporter, *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD showed no appreciable transcriptional induction (Tully et al. 2000). The highest concentration tested was 10  $\mu$ M; for comparison, 0.01 nM  $17\beta$ -estradiol produced approximately a 3-fold induction over the vehicle. Moreover, when the chemicals were tested in binary combinations, the mixtures showed no additional estrogenicity (Tully et al. 2000).

Several investigators have demonstrated that *o,p'*-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 *o,p'*-DDE ( $IC_{50}=40$   $\mu$ M) competed with  $17\beta$ -estradiol ( $IC_{50}=2.7$  nM) for binding to the estrogen receptor in rabbit uterine extracts and *p,p'*-DDT and *p,p'*-DDE were much less effective competitors. Kelce et al. (1995) showed in uterine extracts from immature rats that *o,p'*-DDE ( $IC_{50}=5$   $\mu$ M) competed with  $17\beta$ -estradiol ( $IC_{50}=0.8$  nM) for estrogen receptor binding and that *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD were relatively ineffective competitors ( $IC_{50}>1,000$   $\mu$ M). The observations of the lack estrogenicity of the *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 *p,p'*-DDT, *p,p'*-DDE, *o,p'*-DDT, and *p,p'*-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. *p,p'*-DDE was the greatest competitor with an inhibition constant ( $K_i$ ) of 3.5  $\mu$ 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 *p,p'*-DDE. Based on  $IC_{50}$  values for displacement of the synthetic androgen from the androgen receptor or  $17\beta$ -estradiol from the estrogen receptor, *o,p'*-DDT was 20-fold more effective as a

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competitor of estrogen binding to the estrogen receptor than androgen binding to the androgen receptor. *p,p'*-DDT, *p,p'*-DDD, and *p,p'*-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 antiandrogenic effects of the DDT isomers were not due to their ability to inhibit the conversion of testosterone by 5 $\alpha$ -reductase to 5 $\alpha$ -dihydrotestosterone and 5 $\alpha$ -androstane-3 $\alpha$ -17 $\beta$ -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 17 $\beta$ -estradiol. Danzo (1997) also confirmed that *p,p'*-DDE (IC<sub>50</sub>=6.8  $\mu$ M) could compete with dihydrotestosterone (IC<sub>50</sub>=1.1 nM) for binding to androgen receptors in rat prostate cytosol. In contrast to Kelce, Danzo found that *o,p'*-DDT and *p,p'*-DDT were only slightly less effective than *p,p'*-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'*-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 transduced 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  $\mu$ M *p,p'*-DDE and 1  $\mu$ M hydroxyflutamide were able to inhibit 5 $\alpha$ -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'*-DDE in inhibiting binding to the androgen receptor. In the transient transfection assay, levels of 5 $\alpha$ -dihydrotestosterone were not measured in the wells, so there was no control for whether the DDE could have affected its metabolism. *p,p'*-DDT and *o,p'*-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'*-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'*-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.

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Other investigators have confirmed Kelce's results showing the antiandrogenic 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 *in vitro* in HEPG2 human hepatoma cells transiently transfected with the human androgen receptor and a reporter gene linked to an androgen responsive promoter. These cell were exposed for 24 hours to a maximally inducing dose (0.1  $\mu$ M) 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  $\mu$ M) in inhibiting dihydrotestosterone induced gene transcription. The authors state that *p,p'*-DDE was the most potent inhibitor ( $IC_{50}$ =1.86  $\mu$ M), 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 antiandrogenic 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 antiandrogen flutamide. From graphs, they appeared to have  $IC_{50}$  values on the order of 10  $\mu$ M 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 antiandrogenic 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 3.2.2.5 Reproductive Effects and Section 3.2.2.6 Developmental Effects.

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Alterations in development and reproduction can also be induced by altering the metabolism of sex hormones. For example, in perinatally exposed rats, *p,p'*-DDE was shown to increase liver CYP enzymes systems that hydroxylate testosterone (You et al. 1999c). *p,p'*-DDE was also shown to increase liver aromatase activity in adult male rats (You et al. 2001); aromatase plays a critical role in steroidogenesis by catalyzing the conversion of C19 steroids to estrogens.

DDT and metabolites apparently also exhibit additional 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 *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 E<sub>2</sub> (PGE<sub>2</sub>) from the uterine strips since PGE<sub>2</sub> 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 (50,000–500,000 times lower ) relative to DES; 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

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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. Evidence that the latter may happen was provided by You et al. (1999c) who examined the potential of *in utero* DDE exposure to affect the developmental expression of hepatic CYPs enzymes responsible for testosterone hydroxylations. They treated pregnant Sprague-Dawley rats on gestation days 14–18 and also adult male rats with *p,p'*-DDE and found that the responses of CYP2C11 and CYP2A1 were development-regulated. DDE induced 2A1 in males on postnatal day (PND) 10 but not PND 21; pronounced induction of 2B1 was seen in males and females on both PND 10 and 21 and to a lesser extent of 3A1; there was no induction of 2C11. In adult rats, DDE induced 2B1, 3A1, and 2C11, but not 2A1. Similar results, also in adult Sprague-Dawley rats, but with technical DDT were published by Sierra-Santoyo et al. (2000). Another enzyme involved in steroid metabolism that was affected by *p,p'*-DDE was aromatase (catalyzes the conversion of C19 steroids to estrogens), whose activity was significantly increased in hepatic microsomes from treated adult male rats, as were the levels of aromatase protein in the liver (You et al. 2001).

**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).

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**Adrenal Gland Effects.** The adrenal gland consists of the adrenal medulla, which secretes epinephrine and norepinephrine, 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). *o,p'*-DDD has been used to treat adrenocortical carcinoma and Cushing's disease in humans for almost 4 decades (Bergental 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 and inhibition of cortisol synthesis. The latter is accomplished by inhibiting the intramitochondrial conversion of pregnenolone and the conversion of 11-deoxycortisol to cortisol (Hart and Straw 1971; Hart et al. 1971). Damage to the adrenal gland was first observed in dogs given DDD orally in earlier studies by Nelson and Woodard (1949). Many additional studies in dogs have confirmed the original observations after acute and long-term administration of *o,p'*-DDD to the animals (Kirk and Jensen 1975; Kirk et al. 1974; Powers et al. 1974). Studies *in vitro* 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. This reactive intermediate is thought to be formed by hydroxylation of *o,p'*-DDD at the  $\beta$ -carbon and quick transformation by dehydrochlorination into the acyl chloride. The latter either binds covalently to nucleophiles, or by losing water, is transformed to DDA for renal excretion (Schteingart 2000).

As previously mentioned in Section 3.5.3 Metabolism, methylsulfonyl metabolites of DDT (3-MeSO<sub>2</sub>-DDE and 2-MeSO<sub>2</sub>-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; Norén et al. 1996; Weistrand and Norén 1997). 3-MeSO<sub>2</sub>-DDE is a potent toxicant in the adrenal cortex, particularly of mice, and possibly in humans after local activation by

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cytochrome P-450. For example, whole body autoradiography of  $^{14}\text{C}$ -labeled 3-MeSO<sub>2</sub>-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* 1–12 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<sub>2</sub>-DDE intraperitoneally identified mitochondria in the *zona fasciculata* as the primary targets for 3-MeSO<sub>2</sub>-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 cytochrome P-450s expressed predominantly in the adrenal cortex, P-45011 $\beta$  and P-450SCC, the former (which converts 11-deoxycorticosterone to cortisone) is involved in the metabolic activation of 3-MeSO<sub>2</sub>-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-MeSO<sub>2</sub>-DDE. Intraperitoneal administration of radioactive 3-MeSO<sub>2</sub>-DDE to pregnant or lactating mice resulted in specific accumulation and binding of 3-MeSO<sub>2</sub>-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<sub>2</sub>-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 the 1.5 and 25 mg/kg dose levels, respectively, suggesting that mother's milk may be an important route of exposure of 3-MeSO<sub>2</sub>-DDE in DDT-exposed animals. A later study showed that P-45011 $\beta$  seems to be expressed during gestation days 10–12 in the adrenal cortex in the mouse fetus (Jönsson et al. 1995). 3-MeSO<sub>2</sub>-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-MeSO<sub>2</sub>-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. The bioactivation and mitochondrial toxicity of 3-MeSO<sub>2</sub>-DDE observed *in vivo* has recently been reproduced in an *ex vivo* tissue-slice culture preparation (Lindhe et al. 2001).

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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-MeSO<sub>2</sub>-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-MeSO<sub>2</sub>-DDE and *o,p'*-DDD *in vitro*, and both compounds were adrenotoxic *in vivo*.

**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 3.10). 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

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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  $\text{Ca}^{+2}$  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 *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, 2000; Roseng et al. 1994), rat precision-cut liver slices (de Graaf et al. 2000), mouse skin cells (Jansen and Jongen 1996), bovine oviductal cells (Tiemann and Pöhland 1999), human breast cells (Kang et al. 1996), and human urothelial cells (Morimoto 1996), and *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

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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 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 3.2.2.8, 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  $17\beta$ -estradiol metabolites in favor of the genotoxic  $16\alpha$ -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  $17\beta$ -estradiol.

Another mechanism by which DDT compounds may increase cancer risk is by increasing the production of genotoxic metabolites from the breakdown of  $17\beta$ -estradiol, at the expense of producing nongenotoxic metabolites. Two  $17\beta$ -estradiol metabolites that have been studied extensively are  $16\alpha$ -hydroxyestrone ( $16\alpha$ -OHE1) and 2-hydroxyestrone (2-OHE1), which are formed via two mutually exclusive metabolic pathways.  $16\alpha$ -OHE1 binds covalently to the estrogen receptor in human breast cancer cells (Swanek and Fishman 1988), and has induced genetic and proliferative changes in mouse mammary epithelial cells

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(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  $16\alpha$ -OHE1/2-OHE1, may be predictive of xenoestrogen-induced mammary cancer in humans; as the ratio of  $16\alpha$ -OHE1/2-OHE1 increases, so does the risk of breast cancer.

The ratio of estradiol metabolites  $16\alpha$ -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  $16\alpha$ -OHE1/2-OHE1 ratio in a MCF-7 human cancer cell assay was elevated when the cells were exposed to *o,p'*-DDE, and  $E_2$  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  $16\alpha$ -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  $16\alpha$ -OHE1/2-OHE1 ratio hypothesis is controversial, however. Epidemiology studies of the association of  $16\alpha$ -OHE1 with breast cancer have provided mixed results (Safe 1998). In addition, although  $16\alpha$ -OHE1 induced cell proliferation, a closely related compound,  $16\alpha$ -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.

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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  $\mu$ M concentrations, but appeared to impede the activity at 1 and 10  $\mu$ M concentrations (Shen and Novak 1997b).

#### 3.6.3 Animal-to-Human Extrapolations

In humans and in 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 rates 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.

### 3.7 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Thomas (1992) and again by Colborn (1993), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine

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Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, reproductive, growth, immune, and neurobehavioral functions. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

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 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 Appendix D, 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

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and in other relevant end points; the results have been mixed. For instance, 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). 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 (Saxena et al. 1980, 1981; Wassermann et al. 1982). However, other potentially 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 pre-term delivery (Berkowitz et al. 1996). An earlier study by Procianoy and Schwartsman (1981) found no differences in DDT levels in maternal blood at delivery full-term babies and cases of pre-term delivery; however, they found that umbilical cord blood from pre-term newborns had higher DDT than full-term newborns. A recent study of 361 pre-term infants and 221 small-for-gestational-age cases found that the odds for both outcomes increased steadily with increasing maternal blood concentrations of DDE in samples taken in the third trimester of pregnancy (Longnecker et al. 2001). The association was evident at DDE concentration  $\geq 10$  ppb, but there was essentially no relation at lower DDE concentrations. With regard to cancers of the reproductive tissues, no association was found between risk of endometrial cancer and lipid-corrected blood serum concentrations *p,p'*-DDE and *o,p'*-DDT in a multicenter case-control study of women in the United States, but there was a slight increased risk associated with *p,p'*-DDT (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) or between DDE and death from uterine cancer in a study of women in the United States (Cocco et al. 2000).

Numerous studies have been conducted in the United States and elsewhere that evaluate the association between DDT and related compounds and breast cancer. Although a few studies have found positive associations among some subgroups of women (Aronson et al. 2000; Dewailly et al. 1994; Falck et al. 1992; Güttes et al. 1998; Romieu et al. 2000; Wasserman et al. 1976; Wolff et al. 1993), others have found no association between these chemicals and breast cancer (Demers et al. 2000; Dorgan et al. 1999; Helzlsouer et al. 1999; Laden et al. 2001a; Krieger et al. 1994; Liljegren et al. 1998; Lopez-Carrillo et al. 1997; Mendonca et al. 1999; Moysich et al. 1998; Schecter et al. 1997; Unger et al. 1984; van't Veer et al. 1997; Ward et al. 2000; Wolff et al. 2000a, 2000b; Zheng et al. 1999, 2000). A recently published combined analysis of five U.S. studies that included 1,400 cases and 1,642 controls found no evidence linking breast cancer and DDE body burdens (Laden et al. 2001a). Details of the individual studies about breast, endometrial, testicular, and prostate cancer are presented in Section 3.2.2.8 Cancer.

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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 vitro* test systems. Such tests can be used to assay for estrogenic, antiestrogenic, androgenic, and antiandrogenic 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, 17 $\beta$ -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'*-DDE and *p,p'*-DDT were approximately 16 times less active than *o,p'*-DDT and *o,p'*-DDD was inactive. Clement and Okey (1972) showed that *o,p'*-DDT (200 ppm in the diet) induced premature vaginal opening in Wistar rats. An *in vivo* assay with rats and mink showed that *o,p'*-DDT had uterotrophic 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 3.6.2, 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 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 antiandrogenic 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 (Gray et al. 1999; 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 (Gray et al. 1999; Kelce et al. 1995, 1997; You et al. 1999a). The experimental details of those studies are discussed extensively in Section 3.2.2.5, Reproductive Effects and Section 3.2.2.6, Developmental Effects.

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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 receptors. The type and magnitude of the response varied between assays and was dependent on the concentration of test material, as well as the temporal aspects of the exposure. Reviews of published data suggest that 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 (Balaguer et al. 1999; 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 17 $\beta$ -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 and many have additive effects. 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 antiandrogenic 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 3.6.2, Mechanisms of Toxicity.

### 3.8 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.

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Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children. Children are particularly susceptible to hazardous chemicals due to the fact that many physiological systems, such as the nervous system, are being organized during the childhood years.

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.

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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).

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<sub>50</sub> 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<sub>50</sub> dose was administered daily for 4 days to preweanling and adult rats, both groups had similar 4-day LD<sub>50</sub> values. Lu et al. (1965) suggested that the elimination mechanisms in the preweaning 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.

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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 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. 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 antiandrogenic effects of DDE (Kelce et al. 1995).

Limited information exists regarding developmental effects of DDT on humans (Reproductive effects are discussed in Section 3.2.2.5). A study of 594 children from North Carolina found that height and weight adjusted for height of boys at puberty increased with transplacental exposure to DDE, but there was no association between any measure of DDE exposure (DDE in breast milk, maternal blood, cord blood, placenta) and age at which pubertal stages were attained (Gladen et al. 2000). Children from this cohort has normal birth weight and normal growth in the first year of life. A study of German children found an inverse association between serum DDE levels and height in girls (Karmaus et al. 2002). A study of Inuit infants exposed to *p,p'*-DDE (and other organochlorines) *in utero* revealed no association between immunological parameters (white blood cell counts, lymphocyte subsets, immunoglobulins) and prenatal exposure to organochlorines (Dewailly et al. 2000). However, the authors found that organochlorine exposure was associated with the incidence of infectious diseases and that the risk of contracting otitis media at 7 months of age increased with prenatal exposure to *p,p'*-DDE, hexachlorobenzene, and dieldrin. They also found that the relative risk for 4- to 7-month-old infants in the highest tertile of *p,p'*-DDE exposure was 1.87 (95% CI, 1.07–3.26) compared to infants in the lowest tertile. In addition, the relative risk of otitis media over the entire first year of life also increased with prenatal exposure to *p,p'*-DDE and hexachlorobenzene.

In animals, DDT can cause abnormal development of sex organs, embryotoxicity and fetotoxicity 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;

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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 *in utero*, and also as juveniles (Gray et al. 1999; Kelce et al. 1995, 1997; Loeffler and Peterson 1999; You et al. 1998, 1999a). 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. Gray et al. (1999) and 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. An additional study from the same group showed that prenatal exposure to *p,p'*-DDE was associated with expression of TRPM-2, an androgen-repressed gene (You et al. 1999a). 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 3 $\alpha$ -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

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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 3.2.2.6, 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.

Alterations in learning processes and in other behavioral patterns have also been described in adult mice exposed to DDT perinatally (Craig and Ogilvie 1974; Palanza et al. 1999b; vom Saal et al. 1995) 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 2.3, Minimal Risk Levels. These studies suggest that exposure of the developing fetus or newborn to DDT during critical stages in nervous system development can cause developmental toxicity 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).

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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. Recent studies have suggested that enzymes involved in the metabolism of steroids are development-regulated and can be affected by DDE. For example, You et al. (1999c) examined the effects of *p,p'*-DDE on CYPs enzymes responsible for testosterone hydroxylations. They found that exposure of pregnant Sprague-Dawley rats to *p,p'*-DDE during gestation days 14–18 resulted in induction of CYP2A1 in males on PND 10 but not PND 21; pronounced induction of CYP2B1 was seen in males and females on both PND 10 and 21 and to a lesser extent of CYP3A1; there was no induction of CYP2C11. In contrast, in adult rats, DDE induced 2B1, 3A1, and 2C11, but not 2A1.

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), amniotic fluid (Foster et al. 2000), placenta (Gladen and Rogan 1995; Procianoy and Schwartsman 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. Model estimates of increasing body burden of DDE in infants from breast-feeding milk with a DDE concentration of 222 ppb (lipid basis) predict that maximum body burden (approximately 70 µg/kg) is achieved after approximately 5–6 months of nursing, even if nursing continues, and then gradually decreases to <10 µg/kg by 2 years postpartum (LaKind et al. 2000). Levels of DDT and related compounds in human tissues from recent studies are presented in Table 6-4. 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. 1999b). 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. (1999b). 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,

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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<sub>2</sub>-DDE, to pregnant or lactating mice resulted in specific accumulation and binding of 3-MeSO<sub>2</sub>-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<sub>2</sub>-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<sub>2</sub>-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<sub>2</sub>-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.

### 3.9 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).

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

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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 3.9.1.

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 3.9.2.

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 3.11, Populations That Are Unusually Susceptible.

#### **3.9.1 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 7). Metabolites of DDT have also been measured in body fluids. The major

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urinary metabolite identified in humans is DDA (Gingell 1976), while the *p,p'*-isomers of DDT and DDE as well as *o,p'*-DDT have been detected in breast milk (Takei et al. 1983; Torres-Arreola et al. 1999; see also Table 6-4). 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, and *p,p'*-DDT in whole blood. An earlier study had identified *p,p'*-DDE, *p,p'*-DDD, and *o,p'*-DDT in whole blood (Agarwal et al. 1976). *p,p'*-DDE has also been detected in amniotic fluid (Foster et al. 2000). 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 6-4. 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 when concentrations are expressed on a lipid basis (Hayes et al. 1971; Morgan and Roan 1971; Mussalo-Rauhamaa 1991). On a wet tissue basis, 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 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

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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 6-4 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 3.5.3). 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.

#### **3.9.2 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 3.2.

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**3.10 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 3.5.3. 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 3.5.2). 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 (CCl<sub>4</sub>) (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.

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.

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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 aflatoxin B<sub>1</sub> in mice was inhibited by pretreatment with DDT and by co-treatment with DDT when given throughout aflatoxin B<sub>1</sub> dosing (Rojanapo et al. 1988, 1993). However, DDT acted as a hepatocarcinogenic promoter to aflatoxin B<sub>1</sub> initiation when a 14-week DDT administration followed an 8-week aflatoxin B<sub>1</sub> treatment, or when the DDT administration began halfway through aflatoxin B<sub>1</sub> treatment (Rojanapo et al. 1988, 1993). Also, in groups receiving both aflatoxin B<sub>1</sub> and DDT, in any order, absolute and relative liver weights were significantly increased over both the vehicle control and the group receiving just aflatoxin B<sub>1</sub>; treatment with aflatoxin B<sub>1</sub> 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 3.5.2.

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 3.2.2.4), 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<sup>+</sup> uptake, but they enhance 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.

As previously mentioned, in the United States, exposure of the general population to DDT/DDE/DDD occurs mainly through consumption of contaminated food (i.e., meat, fish, dairy products). Because organochlorines, in general, bioaccumulate in the food chain, it is very likely that there will be also

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simultaneous exposure to several other persistent organochlorine chemicals, many also with hormonal activity. Therefore, interactions at the level of the estrogen and/or androgen receptor may occur, and the final outcome probably represents the summation of effects (positive or negative; linear or non-linear) of chemicals with similar modes of action.

#### 3.11 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 6.7, 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 3.8, Children's Susceptibility.

#### 3.12 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

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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.

#### **3.12.1 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 2002a, 2002b, 2002c, 2002d). 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 2002a, 2002b, 2002c, 2002d). 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 Yearly 1980). At this point, it is unknown whether there are any specific binding or reactive agents that 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 2002a, 2002b, 2002c, 2002d).

#### **3.12.2 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 that 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 that might be worth investigation. Studies of DDT excretion in

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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  $^{14}\text{C}$ -*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 *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 3.4.4). 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 that 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).

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

DDT, DDE, and DDD are stimulants that can cause tremors and convulsions by several postulated mechanisms (Section 3.5.2). The most well accepted mechanism is interference with membrane ion fluxes, which leads to prolongation of the action potential and repetitive firing (Narahashi and Haas 1967). Other contributory mechanisms that may be secondary to interferences 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-anxiety drug diazepam, and the anticonvulsant phenytoin (Herr et al. 1985; HSDB 2002a, 2002b, 2002c, 2002d; 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,

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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 *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.

#### 3.13 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.

##### 3.13.1 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 3-8. 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

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studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

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**Figure 3-8. Existing Information of Health Effects of DDT, DDE, and DDD**

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation										•
Oral	•	•	•	•	•	•	•	•	•	•
Dermal										

**Human**

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation										
Oral	•	•	•	•	•	•	•	•	•	•
Dermal	•	•				•				•

**Animal**

- Existing Studies

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**3.13.2 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 derived based on neurobehavioral effects observed in adult mice following acute perinatal exposure to DDT (Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996; Talts et al. 1998). 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 6.5, 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 (Hayes et al. 1956). The animal studies describe predominantly neurological (Cranmer et al. 1972a; Sanyal et al. 1986), hepatic (Gupta et al. 1989; Laug et al. 1950; Ortega 1956), immunological (Banerjee et al. 1987a, 1995, 1996, 1997a, 1997b), and reproductive/developmental (Clement and Okey 1974; Jonsson et al. 1976; Kelce et al. 1995; Krause 1977; Krause et al. 1977; Lundberg 1974; Wrenn et al. 1971) 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 described in the Laug et al. (1950) study. Because this study was conducted several decades ago, it would be desirable to replicate the findings using modern histopathological techniques and current views on the interpretation of specific liver changes. The immunological studies on DDT are not considered to be adequate for MRL

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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 main target organ following intermediate or chronic oral exposure, but there is little evidence that liver function has been impaired in humans occupationally exposed, although 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; Fitzhugh 1948; NCI 1978; Rossi et al. 1977; Takayama et al. 1999). 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 (Fitzhugh 1948). Because few experimental details were given in the Fitzhugh (1948) report, it may be desirable to replicate the findings using modern histopathological techniques and current views on the physiological meaning of specific liver changes.

The possible association between exposure to DDT and various types of cancers in humans has been studied extensively (Aronson et al. 2000; Cocco and Benichou 1998; Cocco et al. 1997a, 1997b, 2000; Demers et al. 2000; Dewailly et al. 1994; Dorgan et al. 1999; Garabrant et al. 1992; Hardell et al. 1996; Helzlsouer et al. 1999; Hoppin et al. 2000; Krieger et al. 1994; Laden et al. 2001a; Liljegren et al. 1998; Lopez-Carrillo et al. 1997; Moysich et al. 1998; Romieu et al. 2000; Schecter et al. 1997; Sturgeon et al. 1998; van't Veer et al. 1997; Ward et al. 2000; Wasserman et al. 1976; Wolff et al. 1993, 2000a; Zheng et al. 1999, 2000). Nearly all of the human studies evaluated the carcinogenicity of either *p,p'*-DDT or *p,p'*-DDE. Cancer end points that have been investigated in humans include respiratory system, pancreatic, endometrial, breast, prostate, liver, and testicular cancers, Hodgkin's and non-Hodgkin's lymphomas, and multiple myeloma. Thus far, there is no conclusive evidence linking DDT and related

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compounds to cancer in humans. It is expected that some of these cohorts will continue to be monitored to ensure that latency is appropriately accounted for. Other areas where data gaps exist include exposure assessment in epidemiological studies; studies on validity and reliability of recall of pesticide use for occupationally and nonoccupationally exposed populations; and information on inert ingredients of pesticide formulations, where specific pesticides are still used, since inert components are not necessarily biologically inert. The finding of Demers et al. (2000) of a potential association between blood DDE levels in breast cancer patients and aggressiveness of the disease requires replication in additional studies to rule it out as artifactual. In addition, further attention should be paid to physiological changes that may occur in cancer patients that could alter the pharmacokinetics of the biomarkers of exposure. This issue was brought up by Hoppin et al. (2000) in their study of patients with pancreatic cancer, a condition in which wasting may greatly diminish the lipid pool and thus give artificially-elevated values of body burden for lipid-soluble chemicals.

Animal data provide sufficient evidence of carcinogenicity via oral exposure. DDT has been shown to be carcinogenic in a number of studies in rodents (Cabral et al. 1982b; Innes et al. 1969; Kashyap et al. 1977; Rossi et al. 1977; Thorpe and Walker 1973). DDT and related compounds caused primarily liver cancer. 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; Silinskis and Okey 1975). Virtually no information was located regarding the carcinogenicity of DDT by the inhalation and dermal routes of exposure, but additional bioassays do not seem necessary at this time.

**Genotoxicity.** There is no conclusive evidence that DDT and related compounds are genotoxic in humans. While some studies of humans exposed occupationally have reported chromosomal aberrations (Rabello et al. 1975; Rupa et al. 1988, 1989; Yoder et al. 1975), the subjects were also exposed to other pesticides and it is unclear whether additional potential confounders were adequately controlled. A recent study of subjects residing near a waste site found no association between serum levels of DDE and the incidence of micronuclei in peripheral lymphocytes (Vine et al. 2001). Two high-dose oral studies in

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rodents, one in rats (Palmer et al. 1973) and the other in mice (Clark 1974), reported increases in dominant lethality. In general, the results from standard gene mutation tests in bacteria did not show mutagenicity (Fahrig 1974; Fluck et al. 1976; McCann et al. 1975; Shirasu et al. 1976) and conflicting results have been obtained in tests for chromosomal aberrations in cultured rodent and human cells (Kelly-Garvert and Legator 1973; Palmer et al. 1972; Probst et al. 1981; Tong et al. 1981; Tsuchimoto et al. 1983). It is unlikely that further studies will provide new key information.

**Reproductive Toxicity.** Several studies in humans have examined possible associations between body burdens of DDT and analogues and alterations of some aspects of reproduction. Duration of lactation was found to be inversely related to the concentration of *p,p'*-DDE in breast milk in two studies (Gladen and Rogan 1995; Rogan et al. 1987). Some studies also found weak associations between blood DDT/DDE levels and miscarriages (Gerhardt et al. 1998) and infertility (Gerhardt et al. 1999), but these findings need to be confirmed. Additional studies have examined associations between body burdens of DDT, DDE, and DDD and premature infants and abortions (Saxena et al. 1980, 1981; Wassermann et al. 1982), but the possible role of other chemicals, such as PCBs and other chlorinated pesticides, could not be ruled out. A recent study in the United States found increased odds of having pre-term infants and small-for-gestational-age infants in women having blood concentrations of DDE  $\geq 10$  ppb in samples taken in the third trimester of pregnancy (Longnecker et al. 2001). There was essentially no relation at lower DDE concentrations. Overall, there is no conclusive evidence that body burdens of DDT/DDE/DDD currently found in the general U.S. population represent a reproductive hazard, but adverse reproductive outcomes may be a concern for women in countries where these chemicals are still used.

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 antiandrogenic effects of *p,p'*-DDE (Kelce et al. 1995, 1997). One study *in vitro* showed that all DDT/DDE/DDD isomers can exhibit some degree of antiandrogenicity (Maness et al. 1998), but it is not known whether isomers other than *p,p'*-DDE have antiandrogenic properties *in vivo*. Also, it would be useful to determine whether the persistent DDT metabolite, 3-MeSO<sub>2</sub>-DDE, functions as an androgen antagonist in both *in vitro* binding assays and gene expression assays, and how its potency compares to that of DDE itself.

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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 1.5 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.

**Developmental Toxicity.** There are limited data on developmental effects of DDT and analogues in humans. A study of children from North Carolina found that transplacental exposure of DDE was associated with increased height and weight adjusted for height in boys at puberty (Gladen et al. 2000). A study of German children found an inverse association between serum DDE levels and height in girls (Karmaus et al. 2002). Also, a study of Inuit infants found that prenatal exposure to DDE and other chemicals may have been associated with increased risk of otitis media during the first year of life (Dewailly et al. 2000).

While the limited data in humans do not allow for definite conclusions to be drawn, data in animals indicate that perinatal exposure to DDT/DDE/DDD (Craig and Ogilvie 1974; Fabro et al. 1984; Gellert and Heinrichs 1975; Gray et al. 1999; Hart et al. 1971, 1972; Kelce et al. 1995; Loeffler and Peterson

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1999; You et al. 1998, 1999a) or neonatal exposure to DDT (Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996; Talts et al. 1998) can cause adverse developmental effects in the offspring. These effects depend on the dose administered, the timing of exposure during or after gestation, and the specific isomer administered. The *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 antiandrogenic 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 versus lactational exposure to *p,p'*-DDE in relation to delays in the onset of puberty. Standardization of both *in vivo* (pre and postnatal exposures) and *in vitro* tests for estrogenicity and antiandrogenicity 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 *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.

**Immunotoxicity.** Evidence of immunotoxicity in humans is inconclusive and is limited to a study with only 3 volunteers (Shiplov et al. 1972), a study of 12 fish-consumers in Sweden (Svensson et al. 1994) and a more recent study of subjects who resided near a waste site (Vine et al. 2001). 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

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(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 acutely exposed to relatively high oral doses (Hayes 1982; Hsieh 1954; Velbinger 1947a, 1947b), there is limited information on effects of chronic exposure. Two studies, one in workers (Ortelee 1958) and one in volunteers (Hayes et al. 1956), found no evidence of adverse neurological effects among the subjects studied. However, a recent small study of retired malaria-control workers in Costa Rica found mildly impaired neurological functions among the workers relative to a control group (van Wendel de Joode et al. 2001). Evaluation of further cohorts from countries where DDT is still used may provide relevant information.

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

### 3. HEALTH EFFECTS

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. Based on the known estrogenic effects of the *o,p'*-isomers and antiandrogenic properties of *p,p'*-DDE in animals, monitoring these chemicals in human tissues seems important. Identification and follow-up of cohorts who may have been exposed to DDT before its ban would be useful for evaluation of health conditions that have long latency, such as cancer. Also of interest is the assessment of long-term low level exposure as well as potential delayed effects of acute high exposure. 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, amniotic fluid, 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

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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 enzymes. Studies designed to identify specific biomarkers of effect for DDT, DDE, and DDD would be useful.

**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

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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 2002a, 2002b, 2002c, 2002d). Studies that examine the efficacy of gastric lavage with mannitol versus 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

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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 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 3.5). 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 nonspecific 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; Gray et al. 1999; Kelce et al. 1995, 1997; Loeffler and Peterson 1999; Singhal et al. 1970; You et al. 1998, 1999a). 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. Important information was recently published on estimates of body burden of DDE that result from nursing by using a model that incorporates a wide array of variables (LaKind et al. 2000). The only existing PBPK model for DDT is that of You et al. (1999b), 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

### 3. HEALTH EFFECTS

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; Talts et al. 1998). 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.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

#### **3.13.3 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 2001) database and are listed in Table 3-7.

## 3. HEALTH EFFECTS

**Table 3-7. Ongoing Studies on the Health Effects of DDT and DDT Analogues**

Investigator	Affiliation <sup>a</sup>	Research description	Sponsor
Bhatia, R	Public Health Institute, Berkeley, CA	DDT and other organochlorine pesticides and male genital anomalies	NIEHS
Charles, MJ	University of California, Environmental Toxicology Center, Berkeley, CA	Exploration of linkages among organochlorines (DDT, DDE), oxidative DNA damage and breast cancer	USDA
Clark, DR	Columbia Environmental Research Center Columbia, MO	Ecotoxicological investigations of effects of DDT on native wildlife species	USGS
Cohn, BA	Public Health Institute, Berkeley, CA	Breast cancer and organochlorines	NCI
Cohn, BA	Public Health Institute, Berkeley, CA	Prenatal exposure to organochlorine and fecundity	NIEHS
Darvill, T	SUNY at Oswego, Oswego, NY	Prenatal exposure to PCBs, DDE and other contaminants on cognitive development in school-age children	NIEHS
Denslow, ND	University of Florida, Gainesville, FL	Chlorinated hydrocarbons and non ionic surfactants effect on endocrine functions	NIEHS
Fraser, PA	Center for Blood Research, Boston, MA	Genes and chemical exposure associated with SLE risk	NIEHS
Gammon, MD	Columbia University Health Sciences, New York, NY	Breast cancer and the environment on Long Island	NCI
Gross, TS	University of Florida, Gainesville, FL	Endocrine, reproductive, and developmental disrupting effects of chlorinated hydrocarbons on wildlife	USGS

## 3. HEALTH EFFECTS

**Table 3-7. Ongoing Studies on the Health Effects of DDT and DDT Analogues (*continued*)**

Investigator	Affiliation	Research description	Sponsor
Gross, TS	Florida Caribbean Science Center Gainesville, FL	Immuno-toxicity and endocrine disruption in Lake Apopka alligator neonates	USGS
Gurpide, E	Mount Sinai School of Medicine of CUNY, New York, NY	Hormonal activity of chlorinated hydrocarbons from New York harbor sediments	NIEHS
Hauser, RB	Harvard University, School of Public Health, Boston, MA	Environmental organochlorines and semen quality	NIEHS
Henny, CJ	Forest and Rangeland Ecosystem Science Center Corvallis, OR	Effects of persistent organochlorines on nesting success of Osprey along the Columbia River system	USGS
Hothem, R	Western Ecological Research Center Sacramento, CA	Contaminant residues and their effects on reproductive success of aquatic birds nesting at Edwards Air Force Base	USGS
Hothem, R	Western Ecological Research Center Sacramento, CA	Reproduction by black-crowned night-herons and snowy egrets on Alcatraz Island, California	USGS
Korrick, SA	Harvard University, School of Public Health, Boston, MA	In utero PCB, pesticide and metal exposure and childhood cognition	NIEHS
Landrigan, PJ	Mount Sinai School of Medicine of CUNY, New York, NY	Environmental distribution and toxic effects on human health of PCBs and DDT in New York City	NIEHS
Longnecker, MP	NIEHS	Human health effects of exposure to organochlorine compounds	NIEHS
Matsumura, F	University of California, Davis, CA	Mechanism of insecticides on the development of prostate cancer	USDA
Remington, P	University of Wisconsin Madison, Madison, WI	Regional variation of breast cancer rates in Wisconsin	NCI
Rice, RH	University of California, Environmental Toxicology Center, Davis, CA	Toxic and mutagenic responses of keratinocytes to heterocyclic amines and polycyclic aromatic hydrocarbons	USDA

## 3. HEALTH EFFECTS

**Table 3-7. Ongoing Studies on the Health Effects of DDT and DDT Analogues (*continued*)**

Investigator	Affiliation	Research description	Sponsor
Rogan, WJ	NIH, NIEHS	Human exposure to halogenated aromatic compounds	NIEHS
Schwartz, S	Fred Hutchinson Cancer Research Center, Seattle, WA	Risk associated with exposure to phytoestrogens, organochlorines, and fibroids	NIEHS
Seegal, RF	Wadsworth Center, Albany, NY	Developmental effects of fish borne toxicants in the rat	NIEHS
Stellman, SD	American Health Foundation, Valhalla, NY	Epidemiology of breast cancer	NCI
Terranova, PF	University of Kansas Medical Center, Kansas City, KS	Effects of dioxin, xenoestrogen, and estradiol on reproductive processes	NSF
Trosko, JE	Michigan State University, East Lansing, MI	Cell-cell communication carcinogenesis	NCI
Trosko, JE	Michigan State University, East Lansing, MI	Epigenic effects of environmental toxicants on cellular communication pathways	NIEHS
Weston, A	Mount Sinai School of Medicine of CUNY, New York	Effects of PCB-containing river sediments on carcinogen metabolism	NIEHS
Windham, GC	Public Health Institute, Berkeley, CA	Organochlorine compounds and menstrual cycle function	NIEHS
Wolff, MS	Mount Sinai School of Medicine of CUNY, New York	PBC and DDE body burden and breast cancer	NIEHS

<sup>a</sup>Post office state abbreviations used

DNA = deoxyribonucleic acid; NCI = National Cancer Institute; NIEHS = National Institute of Environmental Health Sciences; NSF = National Science Foundation; PCB = polychlorinated biphenyl; USDA = United States Department of Agriculture; USGS = United States Geological Survey



## 4. CHEMICAL AND PHYSICAL INFORMATION

### 4.1 CHEMICAL IDENTITY

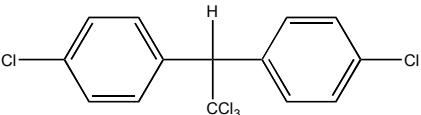
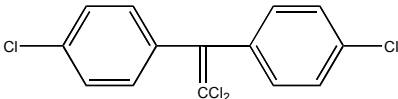
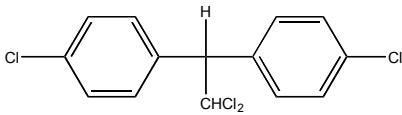
When we refer to DDT, we are generally referring to *p,p'*-DDT, which was produced and used for its insecticidal properties. However, technical grade DDT, the grade that was generally used as an insecticide, was composed of up to fourteen chemical compounds, of which only 65–80% was the active ingredient, *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 4-1. The latter five compounds are either impurities or metabolites of technical DDT.

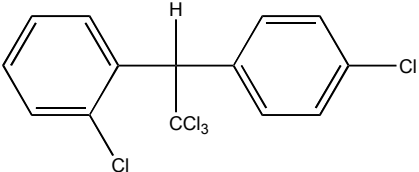
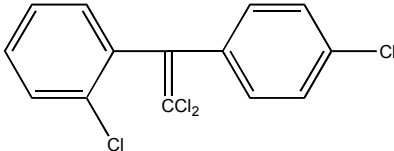
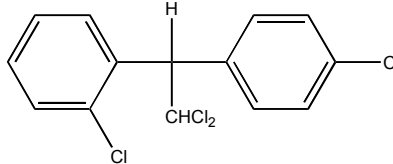
### 4.2 PHYSICAL AND CHEMICAL PROPERTIES

Technical DDT is a white amorphous powder that melts over the range of 80–94 EC (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 4-2.

**Table 4-1. Chemical Identity of *p,p'*- and *o,p'*-DDT, DDE, and DDD<sup>a</sup>**

Characteristic	<i>p,p'</i> -DDT	<i>p,p'</i> -DDE	<i>p,p'</i> -DDD
Synonym(s)	4,4'-DDT; 1,1,1-trichloro-2,2-bis( <i>p</i> -chlorophenyl)ethane; dichlorodiphenyl trichloroethane; DDT; 1,1'-(2,2,2-trichloroethylidene)bis(4-chlorobenzene); $\alpha$ - $\alpha$ -bis( <i>p</i> -chlorophenyl)- $\beta$ , $\beta$ , $\beta$ -trichloroethane	4,4'-DDE; dichlorodiphenyl-dichloroethane; 1,1-dichloro-2,2-bis( <i>p</i> -chlorophenyl) ethylene; 1,1'-(2,2-dichloroethylidene)bis(4-chlorobenzene); DDE	4,4'-DDD; DDD; 1,1-dichloro-2,2-bis( <i>p</i> -chlorophenyl)ethane; 1,1-bis(4-chlorophenyl)-2,2-dichloroethane; TDE; tetrachlorodiphenylethane
Registered trade name(s)	Genitox, Anofex, Detoxan, Neocid, Gesarol, Pentachlorin, Dicophane, Chlorophenothane <sup>b</sup>	No data	DDD; Rothane; Dilene, TDE
Chemical formula	C <sub>14</sub> H <sub>9</sub> Cl <sub>5</sub>	C <sub>14</sub> H <sub>8</sub> Cl <sub>4</sub>	C <sub>14</sub> H <sub>10</sub> Cl <sub>4</sub>
Chemical structure			
Identification numbers:			
CAS registry	50-29-3	72-55-9	72-54-8
NIOSH RTECS	KJ3325000	KV9450000	KI0700000
EPA hazardous waste	U061	No data	U060
OHM/TADS	7216510	No data	7215098
DOT/UN/NA/IMCO shipping	IMCO 6.1; UN2761	No data	NA2761; TDE
HSDB	200	1625	285
NCI	C00465	C00555	C00475

**Table 4-1. Chemical Identity of *p,p'*- and *o,p'*-DDT, DDE, and DDD<sup>a</sup> (continued)**

Characteristic	<i>o,p'</i> -DDT	<i>o,p'</i> -DDE	<i>o,p'</i> -DDD
Synonym(s)	4,4'-DDT; 1,1,1-trichloro-2-( <i>o</i> -chlorophenyl)-2-( <i>p</i> -chlorophenyl)-ethane; <i>o,p'</i> -dichlorodiphenyltrichloroethane	2,4'-DDE; 1,1-dichloro-2-( <i>o</i> -chlorophenyl)-2-( <i>p</i> -chlorophenyl)ethylene; 1-chloro-2-(2,2-dichloro-1-(4-chlorophenyl)ethenyl)benzene	2,4'-DDD; Mitotane; <i>o,p'</i> -DDD; 1,1-dichloro-2-( <i>o</i> -chlorophenyl)-2-( <i>p</i> -chlorophenyl)ethane; <i>o,p'</i> -TDE; Choditane; 2-( <i>o</i> -chlorophenyl)-2-( <i>p</i> -chlorophenyl)-1,1-dichloroethane
Registered trade name(s)	No data	No data	Lysodren
Chemical formula	C <sub>14</sub> H <sub>9</sub> Cl <sub>5</sub>	C <sub>14</sub> H <sub>8</sub> Cl <sub>4</sub>	C <sub>14</sub> H <sub>10</sub> Cl <sub>4</sub>
Chemical structure			
Identification numbers:			
CAS registry	789-02-6	3424-82-6	53-19-0
NIOSH RTECS	No data	No data	KH7880000
EPA hazardous waste	No data	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	No data
HSDB	No data	No data	3240
NCI	No data	No data	C04933

<sup>a</sup>All information obtained from HSDB 1999a, 1999b, 1999c, 1999d, or Howard and Neal 1992 except where noted.

<sup>b</sup>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

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of *p,p'*- and *o,p'*-DDT, DDE, and DDD<sup>a</sup>**

Property	<i>p,p'</i> -DDT	<i>p,p'</i> -DDE	<i>p,p'</i> -DDD
Molecular weight	354.49 <sup>b</sup>	318.03 <sup>b</sup>	320.05 <sup>b</sup>
Color	Colorless crystals, white powder <sup>c</sup>	White	Colorless crystals, white powder
Physical state	Solid <sup>d</sup>	Crystalline solid	Solid
Melting point	109 EC <sup>b</sup>	89 EC <sup>b</sup>	109–110 EC <sup>b</sup>
Boiling point	Decomposes	336 EC <sup>b</sup>	350 EC <sup>b</sup>
Density	0.98–0.99 g/cm <sup>3</sup>	No data	1.385 g/cm <sup>3</sup>
Odor	Odorless or weak aromatic odor <sup>e</sup>	No data	Odorless
Odor threshold:			
Water	0.35 mg/kg <sup>c</sup>	No data	No data
Air	No data	No data	No data
Solubility:			
Water	0.025 mg/L at 25 EC <sup>b</sup>	0.12 mg/L at 25 EC <sup>b</sup>	0.090 mg/L at 25 EC <sup>b</sup>
Organic solvents	Slightly soluble in ethanol, very soluble in ethyl ether and acetone <sup>f</sup>	Lipids and most organic solvents	No data <sup>g</sup>
Partition coefficients:			
Log K <sub>ow</sub>	6.91 <sup>b</sup>	6.51 <sup>b</sup>	6.02 <sup>b</sup>
Log K <sub>oc</sub>	5.18 <sup>h</sup>	4.70 <sup>i</sup>	5.18 <sup>i</sup>
Vapor pressure	1.60x10 <sup>-7</sup> at 20 EC, torr <sup>b</sup>	6.0x10 <sup>-6</sup> at 25 EC, torr <sup>b</sup>	1.35x10 <sup>-6</sup> at 25 EC, torr <sup>b</sup>
Henry's law constant	8.3x10 <sup>-6</sup> atm-m <sup>3</sup> /mol <sup>b</sup>	2.1x10 <sup>-5</sup> atm-m <sup>3</sup> /mol <sup>b</sup>	4.0x10 <sup>-6</sup> atm-m <sup>3</sup> /mol <sup>b</sup>
Autoignition temperature	No data	No data	No data
Flashpoint	72.2–77.2 EC	No data	No data
Flammability limits	No data	No data	No data
Conversion factors			
ppm(v/v) to mg/m <sup>3</sup> in air at 20 EC	Not applicable <sup>k</sup>	Not applicable <sup>k</sup>	Not applicable <sup>k</sup>
mg/m <sup>3</sup> to ppm(v/v) in air at 20 EC	Not applicable	Not applicable	Not applicable
Explosive limits	No data	No data	No data

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of *p,p'*- and *o,p'*-DDT, DDE, and DDD<sup>a</sup> (continued)**

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

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



## 5. 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*-chlorophenyl)-2,2,2-trichloroethanol (Metcalf 1995).

### 5.1 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-tetrachloro-2,2-bis(*p*-chlorophenyl)ethane, has been shown to degrade to *p,p'*-DDE.

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

**5.2 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.

**5.3 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 in the United States has been limited to the control of emergency public health problems. In some regions of the world where malaria is endemic, such as South Africa, Swaziland, and Madagascar, DDT is sprayed onto the interior surfaces of homes to decrease the incidence and spread of the disease by controlling mosquitoes (Attaran et al. 2000; Roberts et al. 1997). Not only is DDT a contact toxin for mosquitoes, it is also a contact irritant and repellent. As such, DDT has been shown to be effective in controlling malaria by not only limiting the survival of the mosquito, but also decreasing the odds of an individual being bitten within the sprayed homes. *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.

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

**5.4 DISPOSAL**

Under current federal guidelines, DDT and DDD are potential candidates for incineration in a rotary kiln at 820–1,600 EC. Disposal of DDT formulated in 5% oil solution or other solutions is mainly by using liquid injection incineration at 878–1,260 EC, 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 EC, 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 EC (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.



## 6. 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.

### 6.1 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. DDT and its metabolites also enter the atmosphere through 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.

When 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.

## 6. POTENTIAL FOR HUMAN EXPOSURE

However, based on the ability of DDT, DDE, and DDD to undergo long range global transport, these estimated half-lives do not adequately reflect the actual lifetimes of these chemicals in the atmosphere.

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.  $\Sigma$ DDT 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.  $\Sigma$ DDT levels rapidly rose in invertebrates, reaching equilibrium in 5 days and then declining as the  $\Sigma$ DDT content of the water declined. Degradation of DDT is altered by invertebrates, with the conversion of DDT to DDMU.  $\Sigma$ DDT levels in fish rose rapidly and reached a high equilibrium level. In a study of a fresh water lake, DDT was found to accumulate to higher concentrations in fattier fish occupying high trophic levels than in leaner species occupying lower trophic levels (Kidd et al. 2001). Also, accumulation of DDT was significantly higher in the pelagic food web than in the benthic food web.

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 (e.g., aerobic) and to DDD under flooded (e.g., anaerobic) 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  $\Sigma$ DDT 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

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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 degradation product of DDT, ranged from 151 to 271 days. In another 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 (Dimond and Owen 1996). 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 (Arthur et al. 1977; Boul et al. 1994; Van Metre and Callender 1997; Van Metre et al. 1997; Ware et al. 1978). For example, the concentration of DDT in lake sediments has decreased by 93% from 1965 to 1994 and declined by 70% in silt loam between 1960 and 1980 (Boul et al. 1994; Van Metre and Callender 1997; Van Metre et al. 1997). GDDT levels in sea lions have decreased by 2 orders of magnitude between 1970 and 1992 (Lieberg-Clark et al. 1995). The Market Basket Surveys have shown a 86% decline in DDT levels measured in all classes of food from 1965 to 1975 (EPA 1980a). However,

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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 (Hanrahan et al. 1999; Laden et al. 1999), but as DDT levels in Great Lakes fish continue to decline, exposure from consuming fish should also decline (Anderson et al. 1998; Hanrahan et al. 1999; 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, caribou, narwhal whales, etc.) (Kuhnlein et al. 1995).

DDT, DDE, or DDD have been identified in at least 441 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2002). However, the number of sites evaluated for DDT, DDE, and DDD is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 438 are located in the United States, 1 is located in Guam (not shown), 1 is located in 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).

**Figure 6-1. Frequency of NPL Sites with DDT, DDE, and DDD Contamination**



## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.2 RELEASES TO THE ENVIRONMENT****6.2.1 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 32 of the 441 NPL hazardous waste sites where it was detected in some in some environmental media (HazDat 2002).

**6.2.2 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  $\Sigma$ DDT 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).

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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 101 sites and groundwater collected at 247 of the 441 NPL hazardous waste sites where it was detected in some environmental (HazDat 2002).

**6.2.3 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).

DDT, DDE, or DDD have been identified in soil samples collected from 776 sites and sediment samples at 305 of the 441 NPL hazardous waste sites where it was detected in some environmental media (HazDat 2002).

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**6.3 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 6.3.1) and 'Transformation and Degradation' (Section 6.3.2). These studies are discussed in Section 6.3.2 with the understanding that 'degradation' may only account for part of the reported loss.

**6.3.1 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 particulate matter to which these compounds are bound. For example, DDT and its metabolites have been found to fractionate and concentrate on the organic material that is transported with the clay fraction of the washload in runoff (Masters and Inman 2000). 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 (Kratzer 1999). 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.

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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  $>0.7\ \mu\text{m}$ ) (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  $\Sigma\text{DDT}$  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). The 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.

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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 (Bard 1999; Bidleman et al. 1992; Goldberg 1975; Ottar 1981; Wania and MacKay 1993). 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 (Anthony et al. 1999; 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<sup>3</sup>/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 <sup>14</sup>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 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 EC (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

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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 and Dobbs 1984; Geyer et al. 1982; Metcalf 1973a; Reish et al. 1978; Veith et al. 1979). 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).

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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,p'*-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 four 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,p'*-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,p'*-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 [<sup>14</sup>C]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

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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.

### 6.3.2 Transformation and Degradation

#### 6.3.2.1 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  $3.44 \times 10^{-12}$  cm<sup>3</sup>/molecule-sec determined from a fragment constant estimation method (Meylan and Howard 1993). Assuming an average hydroxyl radical concentration of  $1.5 \times 10^6$  per cm<sup>3</sup>, its half-life is estimated to 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.

It should be noted that the estimated half-lives for vapor-phase DDT, DDE, and DDD do not necessarily reflect the lifetimes of these compounds in air. DDT, DDE, and DDD can be adsorbed on particulate matter, where they are not expected to undergo rapid photooxidation, and therefore, may be subject to long-range transport. Indeed, long-range transport through the atmosphere has been demonstrated for DDT and several of its metabolites (Bard 1999; Bidleman et al. 1992; Goldberg 1975; Ottar 1981; Wania and MacKay 1993). The work of Bidleman (1988) suggests that 50% of DDT in the atmosphere is adsorbed to particulate matter. Further, 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).

#### 6.3.2.2 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 >150 years (EPA 1979c). Direct photolysis of DDE will vary as a function of photoperiod and brightness, resulting in different half-lives depending on the season and latitude. Over the United States, the direct photolysis of DDE results in a

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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. Studies with DDT at shorter wavelengths suggest that the initial reaction results in the dissociation of the  $\text{Cl}_2\text{C}-\text{Cl}$  bond. Some information exists on the indirect photolysis of DDT; 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).

### 6.3.2.3 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 1971; Verma and Pillai 1991b). Since biodegradation studies generally focus on the loss of the parent

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compound rather than complete degradation or mineralization, and since DDT initially biodegrades to DDD or DDE, there still may be dangerous compounds remaining 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 and DDE was even observed in laboratory experiments using a member of this group of fungi, *Phanerochaete chrysosporium* (a white rot fungus) (Aislabie et al. 1997; Singh et al. 1999). Other soil microorganisms, such as *Aerobacter aerogenes*, *Pseudomonas fluorescens*, *E. coli*, and *Klebsiella pneumoniae*, have also been shown to have the capability to degrade DDT under both aerobic and anaerobic conditions, forming 4-chlorobenzoic acid and DDE, respectively (Singh et al. 1999). 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). In laboratory experiments with marine sediments, DDT has been shown to degrade to DDE and DDD under anaerobic and anaerobic conditions, respectively (Kale et al. 1999). In these same experiments, it was shown that extensive degradation of DDT occurred in clams, converting DDT to DDMU. 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). The rate of DDE dechlorination to DDMU was found to be dependent on the presence of sulfate and temperature (Quensen et al. 2001). DDD is also converted to DDMU, but at a much slower rate. DDMU degrades further under anaerobic conditions to 2,2-bis(chlorophenyl)acetonitrile (DDNU) and other subsequent degradation species, such as 2,2-bis(chlorophenyl)ethanol (DDOH) and 2,2-bis(chlorophenyl)acetic acid (DDA), through chemical action (Heberer and Dünnebier 1999; Ware et al. 1980). 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 (e.g., Al, Ba, Cd, Co, Cr, Fe, and K were the major metals examined) degrade DDT to DDE much more slowly than do soils with high metal content.

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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 6.3.1. 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  $\Sigma$ DDT 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 with 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 (Dimond and Owen 1996). DDT was much more persistent in muck soils than in dry forest soils. A study of DDT in agricultural soils in British Columbia, 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 6.3.1, 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

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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.

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  $^{14}\text{C}$ -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).

## 6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

### 6.4.1 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<sup>3</sup>,

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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<sup>3</sup> of DDT, with a range of 10–78 pg/m<sup>3</sup> (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<sup>3</sup>, 180 pg/m<sup>3</sup>; *o,p'*-DDT, 0.3–180 pg/m<sup>3</sup>, 420 pg/m<sup>3</sup>; *p,p'*-DDT, 1.2–220 pg/m<sup>3</sup>, 590 pg/m<sup>3</sup>; and  $\Sigma$ DDT, 2.4–580 pg/m<sup>3</sup>, 1,000 pg/m<sup>3</sup>. 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 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<sup>3</sup> in Saginaw (August), 31 pg/m<sup>3</sup> in Sault Ste. Marie (May), and 21 pg/m<sup>3</sup> in Traverse City (July). The corresponding highs for *p,p'*-DDE were 63 pg/m<sup>3</sup> (August), 119 pg/m<sup>3</sup> (May), and 92 pg/m<sup>3</sup> (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<sup>3</sup>, and those over the four lower Great Lakes obtained during a cruise were 38 and 59 pg/m<sup>3</sup> (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<sup>3</sup> in Iowa City, Iowa to 1,560 ng/m<sup>3</sup> in Orlando Florida. Maximum levels of *o,p'*-DDT and *p,p'*-DDE ranged from 2.4 to 131 ng/m<sup>3</sup>. 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

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7.5 ng/m<sup>3</sup>, compared to 11.9 ng/m<sup>3</sup> 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. In a comparison of the results from a 1995 study of the occurrence and temporal distribution of pesticides in Mississippi with the results obtained in 1967, a decline in the concentration of *p,p'*-DDE in air over agricultural lands was also noted (Coupe et al. 2000). Concentrations of *p,p'*-DDE in air were lower in the 1995 measurements, ranging from 0.13 to 1.1 ng/m<sup>3</sup>, as compared to a range of 2.6–7.1 ng/m<sup>3</sup> obtained in 1967. However, these results also attest to the persistence of *p,p'*-DDT degradation products after >2 decades since the ban on DDT use in the United States (Coupe et al. 2000).

*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 1.5–30 times higher in DDT, DDE, and DDD concentration 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/m<sup>3</sup>. In another study, 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. In rainwater samples taken from a forested region in northeast Bavaria in 1999, *p,p'*-DDT and *p,p'*-DDE were detected in three of six and four of six rainwater samples, respectively, ranging in concentration from not detected to 12.9 ng/L and not detected to 13.3 ng/L, respectively. In the vapour phase, *p,p'*-DDT and *p,p'*-DDE were detected in two of five and three of five air samples, respectively, ranging in concentration from not detected to 0.03 ng/m<sup>3</sup> and from not detected to 0.055 ng/m<sup>3</sup>, respectively (Streck and Herrmann 2000).

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**6.4.2 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 0.000 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 detectable 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 6.4.3).

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 not detectable 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 (Singh et al. 1999; Wolfe and Seiber 1993). The authors have suggested an unusually long half-life for DDT in Yakima basin soils, which would enter the river through runoff to explain the higher than expected *p,p'*-DDT/*p,p'*-DDE ratios.

In the Malheur watershed, DDT was found to be persistent in the watershed, with estimated concentrations for ΣDDT ranging from 0.13–0.34 ng/L in rural regions of the watershed to 3.0–4.7 ng/L

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in urbanized areas of the Malheur River near Ontario, Oregon (Anderson and Johnson 2001). Unlike the relative concentrations of DDT and DDE in the Yakima River, the concentrations of DDE in water samples were higher than those measured for DDT (ranges from 0.03–0.25 and 0.07–0.14 ng/L for DDE and DDT, respectively, in rural areas and 1.9–4.3 and 0.25–0.61 ng/L near Ontario, respectively), indicating that although DDT was still persistent in this watershed, it was undergoing the expected environmental degradation.

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). In a study of Maryland drinking water during the September 1995, *p,p'*-DDE was detected in 22 out of 394 (5.6%) water samples, ranging in concentration from 0.039 to 0.133 µg/L (MacIntosh et al. 1999).

Concentrations of *p,p'*-DDT and *p,p'*-DDD could not be measured above their limits of detection of 0.021 and 0.028 ppb, respectively. 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 ΣDDT, 0.3–16 pg/L, 41 pg/L. The highest concentrations of DDT-related compounds were in the

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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. Even at sites where the surficial soil concentrations of *p,p'*-DDT are extremely high (29–959 mg/kg), the concentration of *p,p'*-DDT and its metabolites, *p,p'*-DDE and *p,p'*-DDD, in groundwater were close to their detection limits (#0.05 µg/L) (Vine et al. 2000). *p,p'*-DDE was detected in monitoring wells (depth range of 20–110 feet) set up around orchards and row crop fields in the Columbia Basin Irrigation Project, but was not detected in shallow domestic wells (depth range of 80–250 feet) that were within 100 feet of these agricultural sites (Jones and Roberts 1999).

#### 6.4.3 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 6.4.2). 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:

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Compound	Depth (cm)	Occurrence	Concentration (µg/kg)	
			Mean	Range
<i>p,p'</i> -DDD	2.54–7.62	86%	40	ND–410
<i>p,p'</i> -DDD	25.40–30.48	64%	20	ND–390
<i>p,p'</i> -DDE	2.54–7.62	93%	100	ND–660
<i>p,p'</i> -DDE	25.40–30.48	79%	40	ND–560
<i>p,p'</i> -DDT	2.54–7.62	79%	30	ND–600
<i>p,p'</i> -DDT	25.40–30.48	64%	20	ND–860

ND = not detected

River bed sediment samples collected in 1985 from the Yakima River basin in Washington contained 0.1–234 µg/kg (dry weight) of  $\Sigma$ DDT 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  $\Sigma$ DDT 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. Runoff that occurs during winter storms and the irrigation season contributes significant amounts of DDT-laden sediment into the San Joaquin River and its tributaries (Kratzer 1999). For example, during the 1994 irrigation season, it was estimated that approximately 136 g/day of  $\Sigma$ DDT entered the river and its tributaries from runoff, totaling around 5,190–8,920 g of  $\Sigma$ DDT for the season. Additionally, winter storm runoff can input large amounts of DDT within sediments into these surface waters in short periods of time. For example, a winter storm in January 1995 sent sediment-laden runoff into the river and its tributaries, carrying upwards of 4,500 g/day of  $\Sigma$ DDT into these surface waters for a total contribution of 1,750–2,620 g of  $\Sigma$ DDT from this one storm alone.

Total DDT in surface sediment collected in eight remote lakes in Canada along a midcontinental transect from 49 EN to 82 EN 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

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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  $\Sigma$ DDT in sediment in the Newark Bay Estuary, New Jersey collected between February 1990 and March 1993 ranged from about 100 to 300  $\mu\text{g/kg}$  except for the Arthur Kill, where the mean concentrations exceeded 700  $\mu\text{g/kg}$  (Gillis et al. 1995). These levels may pose a potential threat to aquatic organisms. The maximum concentrations of *p,p'*-DDD, *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  $\mu\text{g/kg}$ , 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  $\mu\text{g/kg}$ ; *o,p'*-DDT, 2.9%, 7.2  $\mu\text{g/kg}$ ; *p,p'*-DDE, 22.7%, 163.0  $\mu\text{g/kg}$ ; and *o,p'*-DDE, 0.5%, 1.3  $\mu\text{g/kg}$  (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  $\Sigma$ DDT (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  $\Sigma$ DDT in sediment above the discharge point averaged less than 1 mg/kg dry weight. Remaining stations showed a decreasing gradient of  $\Sigma$ DDT with annual means ranging from 2,730 mg/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,p'*-DDD, *o,p'*-DDT, and *o,p'*-DDE. The frequency of detection of *o,p'*-DDT and *o,p'*-DDE was below 5%. Sediments can act as repositories for DDT and its metabolites, serving as sources for these compounds for long periods of time, given the long half-lives of these compounds and their resistance to biodegradation (Sanger et al. 1999). Because DDT and its metabolites will fractionate and concentrate in organic material, the sediments of some waterways, such as salt marshes, that receive a large amount of organic content in washloads discharged from sources of water originating from urban and agricultural areas can act as potential DDT repositories (Masters and Inman 2000). Also, the concentrations of DDT and its metabolites are high enough in some sediments to exceed the threshold effects level (TEL),

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probable effects level (PEL), and the effects range low and median (ER-L, ER-M) for specific biota in marine and estuarine environments (Carr et al. 2000; Long et al. 1995).

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):

Substance	Occurrence	Concentration (: g/kg)	
		Mean	Range
<i>p,p'</i> -DDT	20%	180	10–69,300
<i>o,p'</i> -DDT	14%	40	10–11,700
<i>p,p'</i> -DDE	31%	50	10–6,820
<i>o,p'</i> -DDE	3%	<10	ND–510
ΣDDT	23%	300	10–113,090

ND = not detectable

The mean ΣDDT level in five U.S. cities ranged from 120 to 560 µg/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, ΣDDT varied from below quantitation to 11,846 µg/kg, with a geometric mean value of 9.63 µg/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 µg/kg, respectively. At least one DDT analog was found in 33 of the soils. Nine of the samples contained ΣDDT above 200 µg/kg, while the concentrations in the rest of the samples were below 40 µg/kg. Two garden soils had ΣDDT 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

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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  $\Sigma$ DDT levels ranging from 270 to 1,898  $\mu\text{g/kg}$  compared with a maximum concentration of 11  $\mu\text{g/kg}$  in unsprayed locations. A study of DDT in agricultural soils in British Columbia, Canada report that  $\Sigma$ DDT levels ranged from 194 to 763  $\mu\text{g/kg}$  in silt loam soils and from 2,984 to 7,162  $\mu\text{g/kg}$  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,

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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.

#### 6.4.4 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 (Giesy et al. 1994). 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

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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  $\Sigma$ DDT in plankton was 11.8 ng/g dry weight (43.5  $\mu$ g/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  $\Sigma$ DDT concentrations of <57, 299, and 3,769  $\mu$ g/kg dry weight (<347, 1,594, and 12,511  $\mu$ g/kg lipid), respectively. Pelagic fish contained a mean  $\Sigma$ DDT of 200  $\mu$ g/kg lipid, while abyssal fish (2,075 m) contained 819  $\mu$ g/kg dry weight (1,465  $\mu$ g/kg lipid). Similar comparisons have also been conducted on surface and deep-sea fish caught in the North and South Atlantic oceans and northwest Pacific ocean off California, showing higher concentrations of  $\Sigma$ DDT in deep-sea fish (Atlantic 175–1,090  $\mu$ g/kg lipid; Pacific 2,380–2,420  $\mu$ g/kg lipid) in comparison to surface fish (Atlantic 59–125  $\mu$ g/kg lipid; Pacific 1,260–1,875  $\mu$ g/kg lipid) (Looser et al. 2000). 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 (Bard 1999). The ringed neck seal (n=19) and polar bear (n=10) had mean  $\Sigma$ DDT concentrations of 1,482 and 266  $\mu$ g/kg (lipid basis) (Muir et al. 1988). Beluga whales, ringed neck seals, and walrus near Baffin Island in the eastern Arctic had mean  $\Sigma$ DDT levels (wet weight) of 3.16, 0.33, and 1.42  $\mu$ g/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 received 1,000,000 kg of DDT discharged into the Bight from the Montrose Chemical Company and also receives a large amount of sewage outfall from the southern California region (Zeng et al. 1999). Historically, DDT levels in these fish exceeded the Food and Drug Administration (FDA) action level of 5 mg/kg wet

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weight of fish tissue, and fish intended for human consumption were confiscated to prevent human exposure to DDT (NOAA 1988).

Levels of  $\Sigma$ DDT have declined markedly since the early 1970s in fish, shellfish, and aquatic mammals (Addison and Stobo 2001; Bard 1999; 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  $\Sigma$ DDT decreased from 50, 260, 80, and 370  $\mu\text{g/kg}$ , respectively, in 1976 to 30, 190, 60, and 260  $\mu\text{g/kg}$ , respectively, in 1984. A follow-up study of DDT in California sea lions reported a decrease in  $\Sigma$ DDT and DDE of over two orders of magnitude between 1970 and 1992 (Lieberg-Clark et al. 1995).  $\Sigma$ DDT concentrations in maternal grey seals decreased from 12  $\mu\text{g/g}$  lipid in 1974 to 0.5  $\mu\text{g/g}$  lipid in 1994;  $\Sigma$ DDT concentrations in seal pups were lower (60% of maternal concentrations) and decreased at similar rates over the same 20-year period (Addison and Stobo 2001).  $\Sigma$ DDT 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  $\Sigma$ DDT concentration for mussels and oysters at 51 sites of 20  $\mu\text{g/kg}$  dry weight, down from a high of 53  $\mu\text{g/kg}$  in 1977 (Lauenstein 1995). Over 90% of the  $\Sigma$ DDT present was as metabolites rather than the parent compounds (*p,p'*- and *o,p'*-DDT).

Among the metabolites of DDT are two methylsulfonyl metabolites of DDE, 2-methylsulfonyl-DDE (2-MeSO<sub>2</sub>-DDE) and 3-methylsulfonyl-DDE (3-MeSO<sub>2</sub>-DDE). These DDE metabolites are known to be persistent and have been measured in several species of mammals, including humans (for example, Bergman et al. 1994). The methylsulfonyl derivatives of DDE are formed through the action of phase I and II enzymes in the liver and the mercapturic acid pathway, as shown in Figure 3-4 of Chapter 3 (Letcher et al. 1998; Weistrand and Norén 1997). DDE is converted to an arene oxide through the action of the phase I cytochrome (CYP) P450 2B-type enzymes, followed by the conjugation of the arene oxide with glutathione as part of the phase II reactions. As part of the mercapturic acid pathway, the glutathione function is converted to a cysteine residue, which is then cleaved by C-S lyase to form the thiol-substituted intermediates, 2-SH-DDE or 3-SH-DDE. These thiolated DDE derivatives are methylated by adenosyl-methionine and then oxidized to the methylsulfonyl derivatives of DDE. The ratio of 2-MeSO<sub>2</sub>-DDE to 3-MeSO<sub>2</sub>-DDE varies between species and tissue site (Bergman et al. 1994).

The two sulfonyl DDE metabolites have been measured in fat and various tissues of arctic mammals and in humans (Bergman et al. 1994; Haraguchi et al. 1989; Letcher et al. 1998; Norén et al. 1996;

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Weinstrand and Norén 1997). In pooled adipose tissue of polar bears from 12 arctic regions, the concentration of 3-MeSO<sub>2</sub>-DDE ranged from 0.60 to 11 µg/kg lipids, and the ratio of methylsulfone to DDE ranged from 0.009 to 0.056 with a mean of 0.033 (Letcher et al. 1995). These ratios may be the result of both biotransformation of DDE to methylsulfonyl-DDE in the animal and bioaccumulation (Letcher et al. 1998). In the polar bear food chain, lipid adjusted concentrations of 3-MeSO<sub>2</sub>-DDE in arctic cod (<0.01 ng/g, in whole body pools), ringed seal (0.4 ng/g, in blubber) and polar bear (2.0 ng/g, in fat tissue) were measured, showing an increase in the concentration of 3-MeSO<sub>2</sub>-DDE as a function of the trophic level (Letcher et al. 1998). In humans, methylsulfonyl-DDE has been measured in liver, lung, and adipose tissue at respective concentrations of 1.1, 0.3, and 6.8 ppb, wet weight (Haraguchi et al. 1989). In plasma, the concentration of 3-MeSO<sub>2</sub>-DDE (0.1–2 ng/g lipid) was 2–3 orders of magnitude lower than the concentration of DDE (0.11–0.88 µg/g lipid) (Norén et al. 1999). In a comparison of the concentrations of the two methylsulfonyl-DDE isomers in paired human liver and adipose tissues, 3-MeSO<sub>2</sub>-DDE is the most abundant of the two isomers in these tissues (Weinstrand and Norén 1997). In human breast milk, the concentration of 3-MeSO<sub>2</sub>-DDE has been found to range between 0.4 and 5 ng/g lipid (Norén et al. 1996).

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. High concentrations have been noted in animals from areas of historically high DDT use. Mean GDDT concentrations were 1,362 µg/kg in spring peeper frogs living in southern Ontario, Canada (Russell et al. 1995). These concentrations exceed the suggested maximum concentration of 1,000 µg/kg proposed by the Great Lakes Water Quality Agreement of 1978. 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 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 6-1.

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Even with the reduction in the levels of DDT in the environment, there are still areas of concern where heavy applications of DDT during past legal uses of the pesticide have resulted in high concentrations of residual DDT and its metabolites that can, in turn, have potentially adverse effects on wildlife. For example, the transfer of DDT, DDE, and DDD from fruit orchard soils to American robins had been investigated in Okanagan, British Columbia, and Ontario, Canada, showing increasing concentrations of these compounds in soil, earthworm, and robin eggs (Harris et al. 2000). In Okanagan, high average concentrations (mg/kg, dry weight) of DDE and DDT in soil (5.5 and 9.2), earthworms (52 and 21) and robin eggs (484 and 73) were consistent with the recorded contamination of this area. These concentrations are comparable to those where mortality or reproductive effects have been observed to occur in field studies. These results also illustrate one way in which DDT and its metabolites in soil can

**Table 6-1. Concentrations of DDT and Metabolites in Biota**

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

**Table 6-1. Concentrations of DDT and Metabolites in Biota (*continued*)**

Species	Location	Year	Concentration	Type	Reference
Beluga whale (neonate) (n=1)	St. Lawrence estuary near Quebec	1991	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); 3,370 ng/g (liver); 2,106 ng/g (fat) [DDE] ND (brain); ND (kidney); 15 ng/g (liver); 17 ng/g (fat) [DDD]		Gauthier et al. 1998
<u>Terrestrial mammals</u>					
Polar bear (n=320)	Arctic (16 regions)	1989–1993	219 µg/kg (f.w.) [DDE] 52–560 µg/kg (f.w.) [DDE]	median range of geomeans	Norstrom et al. 1998
Arctic ground squirrel (n=13)	Elusive Lake	1991–1993	6.13 (0.34–34.08) µg/kg (w.w.) (liver) [ΣDDT] 1.51 (0.33–5.57) µg/kg (w.w.) (liver) [DDE]	mean (range)	Allen-Gil et al. 1997
Arctic ground squirrel (n=6)	Feniak Lake	1991–1992	1.43 (0.19–5.16) µg/kg (w.w.) (liver) [ΣDDT] 0.86 (0.19–3.10) µg/kg (w.w.) (liver) [DDE]	mean (range)	Allen-Gil et al. 1997
Arctic ground squirrel (n=17)	Schrader Lake	1992–1993	12.25 (0.12–39.76) µg/kg (w.w.) (liver) [ΣDDT] 4.47 (0.12–13.63) µg/kg (w.w.) (liver) [DDE]	mean (range)	Allen-Gil et al. 1997
<u>Birds</u>					
Bald eagle chicks (n=51)	Great Lakes region	1990–1996	ND–0.0171 mg/kg (plasma) [DDT] 0.0036–0.1484 mg/kg (plasma) [DDE]	range	Donaldson et al. 1999
Bald eagle eggs (n=6)	Lake Erie	1974–1980	24.4 (13.8–35.8) mg/kg [DDE]	mean (range)	Donaldson et al. 1999
Bald eagle eggs (n=6)	Lake Erie	1989–1994	10.8 (2.7–22.2) mg/kg [DDE]	mean (range)	Donaldson et al. 1999
Bald eagle eggs (n=7)	Lake of the Woods, Canada	1993–1996	3.3 (0.9–12.6) mg/kg [DDE]	mean (range)	Donaldson et al. 1999

**Table 6-1. Concentrations of DDT and Metabolites in Biota (*continued*)**

Species	Location	Year	Concentration	Type	Reference
Blue heron eggs (n=10)	Southern Lake Michigan	1993	0.02 (ND–0.12) (µg/g) (w.w.) [DDT] 1.58 (0.23–13.00) (µg/g) (w.w.) [DDE] 0.03 (ND–0.12) (µg/g) (w.w.) [DDD]	mean (range)	Custer et al. 1998
<u>Fish and shellfish</u>					
Mussels and oysters	United States (51 sites)	1992	0.51–1,400 ng/g (d.w.) [ΣDDT] 20 ng/g (d.w.) [ΣDDT]	range of sites geomean	Lauenstein 1995
Clams	San Joaquin River (Orestimba Creek)	1992	4,350 ng/g (w.w.) [ΣDDT] 3,300 ng/g (w.w.) [DDE] 390 ng/g (w.w.) [DDD]	mean	Pereira et al. 1996
Clams	San Joaquin River (Dry Creek)	1992	29 ng/g (w.w.) [ΣDDT] 25 ng/g (w.w.) [DDE] 0.5 ng/g (w.w.) [DDD]	mean	Pereira et al. 1996
Clams	San Joaquin River (Mokelumne River)	1992	15 ng/g (w.w.) [ΣDDT] 13 ng/g (w.w.) [DDE] 0.5 ng/g (w.w.) [DDD]	mean	Pereira et al. 1996
Clams	San Joaquin River (Stanis- laus River)	1992	24 ng/g (w.w.) [ΣDDT] 22 ng/g (w.w.) [DDE] <0.5 ng/g (w.w.) [DDD]	mean	Pereira et al. 1996
Mountain whitefish (10 composites from 7 sites)	Yakima River Basin, Washington	1989– 1991	0.10–1.7 mg/kg (w.w.) (whole fish) [ΣDDT]	range of composites	Marien and Laflamme 1995

**Table 6-1. Concentrations of DDT and Metabolites in Biota (*continued*)**

Species	Location	Year	Concentration	Type	Reference
Largescale sucker (18 composites from 13 sites)	Yakima River Basin, Washington	1989– 1991	0.05–4.37 mg/kg (w.w.) (whole fish) [ΣDDT]	range of composites	Marien and Laflamme 1995
Perch (n=5)	Lake Ørsjøen, Norway Mid-lake	1994	1.15 ng/g (w.w.), 1,643 ng/g (f.w.) [ΣDDT] 0.53 ng/g (w.w.), 757 ng/g (f.w.) [DDE] 0.26 ng/g (w.w.), 371 ng/g (f.w.) [DDD] 0.28 ng/g (w.w.), 400 ng/g (f.w.) [DDT]	mean	Brevik et al. 1996
Perch (n=5)	Lake Ørsjøen, Norway.	1994	5.59 ng/g (w.w.), 11,180 ng/g (f.w.) [ΣDDT] 2.56 ng/g (w.w.), 5,120 ng/g (f.w.) [DDE] 1.48 ng/g (w.w.), 2,960 ng/g (f.w.) [DDD] 1.15 ng/g (w.w.), 2,300 ng/g (f.w.) [DDT]	mean	Brevik et al. 1996
Pike (n=5)	Lake Ørsjøen, Norway Mid-lake	1994	7.3 ng/g (w.w.), 8,111 ng/g (f.w.) [ΣDDT] 3.5 ng/g (w.w.), 3,888 ng/g (f.w.) [DDE] 1.5 ng/g (w.w.), 1,667 ng/g (f.w.) [DDD] 1.8 ng/g (w.w.), 2,000 ng/g (f.w.) [DDT]	mean	Brevik et al. 1996
Lake trout (n=59)	Lake Ontario	1992	1.159 µg/g (w.w.) [DDE]	mean	Kiriluk et al. 1995
Rainbow smelt (n=8)	Lake Ontario	1992	0.256 µg/g (w.w.) [DDE]	mean	Kiriluk et al. 1995

<sup>a</sup>U.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

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be mobilized and bioaccumulated by soil organisms which, in turn, are further accumulated in higher trophic levels.

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 6-2. 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 (15%) items analyzed (FDA 1995). In the 1999 FDA Total Diet Study, DDT was found in 255 out of 1,040 (22%) items analyzed (FDA 1999). In a recent FDA study, the mean concentrations of *p,p*-DDT and *o,p*-DDT ranged from 0.0002 to 0.005 ppm. The mean concentrations of *p,p*-DDE ranged from 0.0001 to 0.0257 ppm, with the highest values found in dairy, fish and vegetable products (FDA 2001). 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).

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**Table 6-2. Average Residues in Food Groups and Average Daily Intake from U.S. FDA Total Diet Studies**

Food Group	October 1979 – September 1980 <sup>a</sup>				October 1980 – March 1982 <sup>b</sup>			
	DDE		DDT		DDE		DDT	
	Residue (ppb)	Intake (µg/day)	Residue (ppb)	Intake (µg/day)	Residue (ppb)	Intake (µg/day)	Residue (ppb)	Intake (µg/day)
Dairy products	0.9	0.626	0	0	1.5	1.05	0	0
Meat, fish, and poultry	4.8	1.28	0.8	0.219	3.0	0.777	0	0
Grains and cereal	0	0	0	0	0	0	0	0
Potatoes	0.5	0.0847	<0.1	0.0079	0.5	0.0864	0	0
Leafy vegetables	1.7	0.0954	0.2	0.0137	2.4	0.132	0	0.0195
Legumes	0	0	0	0	<0.1	0.0014	0.4	0
Root vegetables	1.0	0.0309	0	0	4.6	0.146	0	0.0192
Garden vegetables	0.2	0.0185	0	0	0.1	0.0095	0.6	0
Fruits	0	0	0	0	<0.1	0.0081	0	0
Oils and fats	<0.1	0.0028	0	0	<0.1	0.0018	0	0
Sugar	<0.1	0.0042	0	0	<0.1	0.0018	0	0
Beverages	0	0	0	0	0	0	0	0

<sup>a</sup>Adapted from Gartrell et al. 1985<sup>b</sup>Adapted from Gartrell et al. 1986b

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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 whether residues are lost as a result of volatilization or decomposition or carried away in fat runoff.

*p,p'*-DDT (but not *p,p'*-DDE or *p,p'*-DDD) decomposes on heating (see Table 4-2). Concentrations of *p,p'*-DDT in tomatoes could be reduced by between 11.5 and 33.7% by washing the fruit with acetic acid and sodium chloride solutions; the concentrations of *p,p'*-DDT, *o,p'*-DDE, *p,p'*-DDD, and *o,p'*-DDD residues in tomatoes could be reduced by up to approximately 80% from the fruit by simply removing the peel (Abou-Arab 1999). Production of tomato paste through home-canning methods reduced *p,p'*-DDT concentrations by 30.7%.

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; and *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, which was believed to be at least 25 years old, contained up to 10.8 µg/m<sup>2</sup> or 5.7 µg/g of ΣDDT (*p,p'*-DDT, DDD, and DDE).

Organochlorine pesticides have been detected and quantified in composting feedstocks and finished compost (Büyüksönmez et al. 2000). Although banned for several decades, DDT and its metabolites have been detected in lawn trimmings and municipal waste compost as recently as 1990–1996, with concentrations of DDT, DDE, and DDD at 0.01–0.21, 0.01–0.11, and 0.007–0.13 ppm, respectively. The concentrations of the DDT, DDE, and DDD have been found to typically decrease as composting feedstocks are converted to finished compost. For example, DDT and DDE concentrations in lawn trimmings were found to decrease from 0.0466 and 0.0143 ppm to 0.0159 and 0.0108 ppm, respectively, after 90 days of composting. However, under some composting conditions, DDE concentrations have been observed to increase in the finished compost (mean concentration of 0.0807 ppm, maximum value of

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0.483 ppm) compared to the initial feedstock (mean concentration of 0.0516 ppm, maximum value of 0.201 ppm) (Strom 2000).

**6.5 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). ΣDDT 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 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

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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  $<0.001$   $\mu\text{g/kg}$  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 (not determined), and ND  $\mu\text{g/kg}$  body weight/day for infants and 0.049, 0.045, 0.002, and 0.002  $\mu\text{g/kg}$  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 6-3 (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  $\mu\text{g/day}$  for 1978–1979, 1979–1980, 1984–1986, and 1986–1991, respectively. The acceptable daily intake of DDT established by WHO/FAO is 20  $\mu\text{g/kg/day}$  (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).

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  $\Sigma$ DDT intake of 24.2 to 27.8  $\mu\text{g/day}$  for the eastern Arctic community and 0.51 to 1.0  $\mu\text{g/day}$  for the western Arctic communities (Kuhnlein et al. 1995). The foods with the highest  $\Sigma$ DDT concentrations were raw Beluga whale blubber (316  $\mu\text{g/g}$  wet weight) and aged Narwhal whale blubber (273  $\mu\text{g/g}$  wet weight) in the eastern Arctic, and baked Loch (species of fish) liver (1.85  $\mu\text{g/g}$  wet weight) and smoked Canada goose meat (1.47  $\mu\text{g/g}$  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

**Table 6-3. Mean Daily Intake of DDT Per Unit Body Weight ( $\mu\text{g}/\text{kg}$  body weight/day)  
for Various Age Groups in the United States**

Analyte	6–11 mo	2 yr	14–16 yr F	14–16 yr M	25–30 yr F	25–30 yr M	60–65 yr F	60–65 yr M
<u>1984–1986</u>								
$\Sigma\text{DDT}$	0.0485	0.0499	0.0154	0.0213	0.0128	0.0155	0.0111	0.0124
<i>o,p'</i> -DDE	0.0002	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001
<i>p,p'</i> -DDE	0.0468	0.0484	0.0149	0.0207	0.0123	0.0150	0.0105	0.0119
<i>p,p'</i> -DDT	0.0004	0.0010	0.0003	0.0004	0.0003	0.0003	0.0003	0.0003
<i>p,p'</i> -DDD	0.0011	0.0004	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
<u>1986–1991</u>								
$\Sigma\text{DDT}^1$	0.0448	0.0438	0.0138	0.0139	0.0106	0.0127	0.0090	0.0104
<i>o,p'</i> -DDE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
<i>p,p'</i> -DDE	0.0441	0.0420	0.0130	0.0151	0.0099	0.0119	0.0082	0.0096
<i>o,p'</i> -DDT	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
<i>p,p'</i> -DDT	0.0004	0.0011	0.0005	0.0005	0.0005	0.0005	0.0006	0.0006
<i>p,p'</i> -DDD	0.0003	0.0007	0.0003	0.0003	0.0002	0.0003	0.0002	0.0002

Source: Gunderson 1995a, 1995b

<sup>1</sup>The average daily  $\Sigma\text{DDT}$  intake of 0.8 : g/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. The data presented in the table were derived from the June 1984 through April 1991 FDA Total Diet Studies.

F = female; M = male; mo = month; yr = year

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the spring in Jacksonville (14%) and in the winter in Springfield/Chicopee (20%), with estimated mean air DDE and DDT concentrations of  $\approx 1.0 \text{ ng/m}^3$ . Mean  $\Sigma$ DDT 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  $\Sigma$ DDT with median and mean levels of 0.7 and 1.2  $\mu\text{g/g}$ , 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  $1 \times 10^{-7}$  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  $\mu\text{g}$  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

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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'*-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.

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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 respective mean and maximum levels of *p,p'*-DDE at 811 and 6,070 ng/g and *p,p'*-DDT at 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  $\Sigma$ DDT, 1,031 ng/g. The  $\Sigma$ DDT 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 6.6. Levels of DDE and DDT in human milk, blood, and tissue appear in Table 6-4. Correlations in the concentrations of DDT and its metabolites in human milk, adipose tissue, and blood serum have been observed. The lipid adjusted mean concentrations of *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD in human milk (0.65, 4.00, and 0.01 mg/kg, respectively) have been shown to correlate well ( $r^2=0.95$ , 0.89, and 0.75, respectively) with concentrations in adipose tissue (1.22, 4.36, and 0.02 mg/kg, respectively) (Waliszewski et al. 2001). The lipid adjusted serum concentrations of *p,p'*-DDE were observed to correlate with concentrations of this compound in breast adipose tissue (Dorea et al. 2001). The concentrations of *p,p'*-DDT and *p,p'*-DDE in blood serum taken from mothers in Veracruz, Mexico (1.848 and 4.378 mg/kg fat, respectively) have also been observed to correlate ( $r^2=0.854$  and 0.779, respectively) with concentrations in umbilical cord blood (2.800 and 4.676 mg/kg fat, respectively) (Waliszewski et al. 2000).

**Table 6-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies**

DDT compound	Population	Tissue	Mean <sup>a</sup> concentration	Units as reported	Reference
<u>Milk</u>					
<i>p,p'</i> -DDT	Maternity patients in Mexico City, Cuernavaca and rural Morelos	Milk fat	0.71, 1.69, 4.84 <sup>b</sup>	mg/kg	Elvia et al. 2000
<i>p,p'</i> -DDT	Mothers in Sweden	Milk fat	14	µg/g	Norén and Meironyté 2000
<i>p,p'</i> -DDT	Maternity patients in Mexico City	Milk fat	0.162	mg/kg	Torres-Arreola et al. 1999
<i>p,p'</i> -DDT	Women in Germany	Milk fat	0.7 (estimated from graph)	mg/kg	Scheele et al. 1995
<i>o,p'</i> -DDT	Maternity patients in Mexico City	Milk fat	0.138	mg/kg	Torres-Arreola et al. 1999
<i>p,p'</i> -DDE	Maternity patients in Mexico City, Cuernavaca and rural Morelos	Milk fat	3.85, 6.51, 16.52 <sup>b</sup>	mg/kg	Elvia et al. 2000
<i>p,p'</i> -DDE	Mothers in Sweden	Milk fat	129	µg/g	Norén and Meironyté 2000
<i>p,p'</i> -DDE	Inuit women in Canada	Milk fat	962	µg/kg	Dewailly et al. 2000
<i>p,p'</i> -DDE	Quebec women between 1989 and 1990 (n=536)	Milk fat	0.34	mg/kg	Dewailly et al. 1996
<i>p,p'</i> -DDE	Maternity patients in Mexico City	Milk fat	0.594	mg/kg	Torres-Arreola et al. 1999
<i>p,p'</i> -DDE	Maternity patients in Veracruz, Mexico	Milk fat	5.302	mg/kg	Pardio et al. 1998

**Table 6-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies (*continued*)**

DDT compound	Population	Tissue	Mean <sup>a</sup> concentration	Units as reported	Reference
<i>p,p'</i> -DDE	Mothers of hospitalized children in Zagreb, Croatia	Milk fat	0.318	mg/kg	Krauthaker et al. 1998
ΣDDT	Canadian women - 1986 (n=412)	Milk fat	0.385	mg/kg	Smith 1999
ΣDDT	Arkansas women - 1986 (n=536)	Milk fat	0.99	mg/kg	Smith 1999
<u>Blood</u>					
<i>p,p'</i> -DDT	Workers in Sao Paulo, Brazil	Serum	13.5 (DDT applicers) 1.5 (unexposed)	µg/L	Minelli and Ribeiro 1996
<i>o,p'</i> -DDT	Workers in Sao Paulo, Brazil	Serum	<0.7–4.7 (range; DDT applicers)	µg/L	Minelli and Ribeiro 1996
<i>p,p'</i> -DDE	Workers in Sao Paulo, Brazil	Serum	64.3 (DDT applicers) 14.3 (unexposed)	µg/L	Minelli and Ribeiro 1996
<i>p,p'</i> -DDT	Men in southeast Sweden	Blood plasma	0.11 (lipid adjusted)	ng/g	Asplund et al. 1994
<i>p,p'</i> -DDE	Woman hospital patients in New Haven, Connecticut	Serum (lipid-adjusted)	967 (median), <1.0–2261.5 (range) (n=36)	ng/g	Archibeque-Engle et al. 1997
<i>p,p'</i> -DDE	Iowa and North Carolina farmers and spouses	Serum	0.39–6.51 (range)	µg/L	Brock et al. 1998
<i>o,p'</i> -DDE	Iowa and North Carolina farmers and spouses	Serum	0.71–2.31 (range)	µg/L	Brock et al. 1998

**Table 6-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies (*continued*)**

DDT compound	Population	Tissue	Mean <sup>a</sup> concentration	Units as reported	Reference
<i>p,p'</i> -DDE	Women without breast cancer in Long Island	Serum	4.7	µg/L	Stellman et al. 1998
<i>p,p'</i> -DDE	New York University Women's Health Study (1985 to 1991)	Serum	11.0±9.1 in cancer patients (n=58) 7.7±6.8 controls (n=171)	µg/L	Wolff et al. 1993
<i>p,p'</i> -DDE	Female hospital patients in New York City	Plasma	6.93–7.29 (range of mean values)	µg/L	Gammon et al. 1997
<i>p,p'</i> -DDE	Female hospital patients in New York City	Plasma (lipid-adjusted)	0.963–0.997 (range of mean values)	µg/mL	Gammon et al. 1997
<i>p,p'</i> -DDE	Mothers in Veracruz, Mexico	Serum	14.5	ng/mL	Waliszewski et al. 2001
<i>p,p'</i> -DDE	Men in southeast Sweden	Plasma	2.4–14 (range of mean values among groups of men with different levels of fish consumption)	ng/g	Asplund et al. 1994
<i>p,p'</i> -DDE	Men in southeast Sweden	Plasma (lipid-adjusted)	750–4500 (range of mean values among groups of men with different levels of fish consumption)	ng/g	Asplund et al. 1994
DDE	Controls in a case-control study nested within the Nurses Health Study (n=240)	Plasma	7.09	ppb <sup>c</sup>	Laden et al. 1999
<i>p,p'</i> -DDE	Four groups of refugees from Asia, 'USSR', Africa, 'Yugoslavia' (n=103); Controls from Germany (n=34)	Plasma	2.30–16.90 (range of median values) 12.20–93.00 (range of maximum values) (refugees) 1.14 (median), 4.97 (maximum) (controls)	µg/L	Schmid et al. 1997

**Table 6-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies (*continued*)**

DDT compound	Population	Tissue	Mean <sup>a</sup> concentration	Units as reported	Reference
<i>p,p'</i> -DDT	Residents of Nainital, India	Serum	4.46 (mean), range (0.78–14.29)	mg/L	Dua et al. 2001
<i>p,p'</i> -DDE	Residents of Nainital, India	Serum	1.55 (mean), range (0.14–4.10)	mg/L	Dua et al. 2001
<i>p,p'</i> -DDD	Residents of Nainital, India	Serum	0.91 (mean), range (ND–2.82)	mg/L	Dua et al. 2001
<i>p,p'</i> -DDE	New Bedford area infants	Cord blood	0.493	ng/g serum	Korrick et al. 2000a
<i>p,p'</i> -DDE	Maternity patients in Veracruz, Mexico	Cord blood	6.0	ng/mL	Waliszewski et al. 2001
<i>p,p'</i> -DDE	Maternity patients in Nicaragua	Venous blood (lipid-adjusted)	7.12 (mean), range (0–35.23) (n=52)	ng/g	Dorea et al. 2001
<i>p,p'</i> -DDE	Maternity patients in Nicaragua	Cord blood (lipid-adjusted)	6.39 (mean), range (0–9.35) (n=52)	ng/g	Dorea et al. 2001
<i>p,p'</i> -DDT	Great Lakes fishermen (n=30); Controls (n=180)	Serum	0.3 (median), 0.05–0.8 (range) ND (controls)	ppb <sup>c</sup>	Anderson et al. 1998
<i>o,p'</i> -DDT	Great Lakes fishermen (n=30); Controls (n=180)	Serum	0.06 (median), 0.03–0.3 (range) ND (controls)	ppb <sup>c</sup>	Anderson et al. 1998
<i>p,p'</i> -DDE	Great Lakes fishermen (n=30); Controls (n=180)	Serum	5.2 (median), 0.6–23.9 (range) 2.8 (median), ND–38.5 (range) (controls)	ppb <sup>c</sup>	Anderson et al. 1998

**Table 6-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies (*continued*)**

DDT compound	Population	Tissue	Mean <sup>a</sup> concentration	Units as reported	Reference
DDE	Frequent GLSCF (Lake Michigan) males (n=98); females (n=83); male controls (n=23); female controls (n=22)	Serum	6.9 (males), 2.9 (females), 2.6 (controls, males), 1.4 (controls, females) (geometric means)	ppb <sup>c</sup>	Hanrahan et al. 1999
DDE	Frequent GLSCF (Lake Huron) males (n=65); females (n=37); male controls (n=3); female controls (n=3)	Serum	3.5 (males), 2.3 (females), 2.6 (controls, males), 0.6 (controls, females) (geometric means)	ppb <sup>c</sup>	Hanrahan et al. 1999
DDE	Frequent GLSCF (Lake Erie) males (n=89); females (n=67); males controls (n=31); female controls (n=17)	Serum	3.8 (males), 2.0 (females), 2.0 (controls, males), 1.7 (controls, females) (geometric means)	ppb <sup>c</sup>	Hanrahan et al. 1999
ΣDDT	1982 Great Lakes fish eaters (n=572); controls (n=419)	Serum	28.8 10.6 (controls)	ppb <sup>c</sup>	Hovinga et al. 1992
ΣDDT	1982 Southern Great Lakes fish eaters (n=115); controls (n=95)	Serum	25.8 9.6 (controls)	ppb <sup>c</sup>	Hovinga et al. 1992
ΣDDT	1989 Southern Great Lakes fish eaters <sup>d</sup> (n=115); controls (n=95)	Serum	15.6 6.8 (controls)	ppb <sup>c</sup>	Hovinga et al. 1992
<u>Adipose and other tissue</u>					
<i>p,p'</i> -DDT	Children in Germany	Adipose	0.6 (estimated from graph)	mg/kg	Scheele et al. 1995

**Table 6-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies (*continued*)**

DDT compound	Population	Tissue	Mean <sup>a</sup> concentration	Units as reported	Reference
<i>p,p'</i> -DDT	Children in Germany	Bone marrow (lipid-adjusted)	1.75 (estimated from graph)	mg/kg	Scheele et al. 1995
<i>p,p'</i> -DDT	Woman hospital patients in New Haven, Connecticut	Adipose, breast (lipid-adjusted)	132.2 (median), 54.0–418.2 (range) (n=36)	ng/g	Archibeque-Engle et al. 1997
<i>p,p'</i> -DDT	Maternity patients in Veracruz, Mexico	Adipose, abdominal (lipid-adjusted)	1.22 (mean), 0.01–9.03 (range) (n=60)	mg/kg	Waliszewski et al. 2001
<i>p,p'</i> -DDE	Maternity patients in Veracruz, Mexico	Adipose, abdominal (lipid-adjusted)	4.36 (mean), 0.31–16.04 (range) (n=60)	mg/kg	Waliszewski et al. 2001
<i>p,p'</i> -DDD	Maternity patients in Veracruz, Mexico	Adipose, abdominal (lipid-adjusted)	0.02 (mean), ND–0.25 (range) (n=60)	mg/kg	Waliszewski et al. 2001
<i>p,p'</i> -DDE	Woman hospital patients in New Haven, Connecticut	Adipose, breast (lipid-adjusted)	970 (median), 240.0–2,644.1 (range) (n=36)	ng/g	Archibeque-Engle et al. 1997
<i>p,p'</i> -DDT	Adults in Germany	Bone marrow (dry lipid-adjusted)	0.364	ppm <sup>c</sup>	Scheele 1998
<i>p,p'</i> -DDE	Adults in Germany	Bone marrow (dry lipid-adjusted)	1.689	ppm <sup>c</sup>	Scheele 1998
<i>p,p'</i> -DDE	Women without breast cancer in Long Island	Adipose	546.7	ng/g	Stellman et al. 1998
<i>p,p'</i> -DDE	Adults in Sweden who suffered sudden death	Liver (lipid-adjusted)	836	ng/g	Weistrand and Norén 1998

**Table 6-4. Levels of DDT Compounds in Human Milk, Blood, and Tissues — Recent Studies (*continued*)**

DDT compound	Population	Tissue	Mean <sup>a</sup> concentration	Units as reported	Reference
<i>p,p'</i> -DDE	Adults in Sweden who suffered sudden death	Adipose, abdominal	788	ng/g	Weistrand and Norén 1998
<i>p,p'</i> -DDE	FY1986 National Adipose Tissue Survey Composite samples (n=50, from 671 specimens)	Adipose	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)	ng/g	Lordo et al. 1996
<i>p,p'</i> -DDT	FY1986 National Adipose Tissue Survey Composite samples (n=50, from 671 specimens)	Adipose	177 (SE 11%) (nation) 73.0 (SE 36%) (0–14 years) 177 (SE 16%) (15–44 years) 252 (SE 13%) (45+ years)	ng/g	Lordo et al. 1996
<i>p,p'</i> -DDE	Women patients at Hartford Hospital, Hartford, Connecticut	Adipose, breast (lipid basis)	2,200±1,470 cancer patients (n=20) 1,487±842 controls (n=20)	ng/g	Falck et al. 1992
<i>p,p'</i> -DDT	Women patients at Hartford Hospital, Hartford, Connecticut	Adipose, breast (lipid-adjusted)	216±174 cancer patients (n=20) 148±75 controls (n=20)	ng/g	Falck et al. 1992

<sup>a</sup>Arithmetic mean concentrations are reported unless otherwise specified.

<sup>b</sup>Geometric mean concentrations

<sup>c</sup>ppm=μg/g; ppb=ng/g

<sup>d</sup>Same Southern Great Lakes fish eaters that participated in the 1982 study.

FY = fiscal year; ND = not detected; SE = standard error

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Comparison of the concentrations of DDT and its metabolites in breast tissues and serum have been conducted in women with breast cancer in comparison to control subjects. The mean concentrations (unadjusted for age) of *p,p'*-DDT and *p,p'*-DDD in breast tissues of U.S. women with breast cancer (261.6 and 9.8 ng/g lipid, respectively) did not statistically differ ( $p=0.23$  and  $0.79$ ) from those measured in control subjects (267.3 and 24.0 ng/g lipid); however, the concentration of *p,p'*-DDE was statistically higher ( $p=0.006$ ) in breast cancer patients (800.0 ng/g lipid) than in control subjects (709.1 ng/g lipid) (Bagga et al. 2000). When the mean concentrations for *p,p'*-DDT, *p,p'*-DDE, and *p,p'*-DDD were adjusted for age, there was no statistical difference ( $p\#0.001$ ) between cases and controls for all three compounds. Statistically higher concentrations ( $p<0.05$ ) of *p,p'*-DDE in serum were observed in both premenopausal (2.40  $\mu\text{g/g}$  lipid) and postmenopausal (5.10  $\mu\text{g/g}$  lipid) breast cancer patients from Mexico City, Mexico, in comparison to controls (1.93 and 3.12  $\mu\text{g/g}$  lipid, respectively) (Romieu et al. 2000). The increased concentrations of *p,p'*-DDE in breast tissues of cancer patients has been attributed to increased exposures of these women to *p,p'*-DDE rather than to differences in the metabolism of *p,p'*-DDE by cancer cells (Romieu et al. 2000). However, in a study of breast cancer patients and control subjects in the New York University Women's Health Study, there was no statistical difference between the geometric means of the *p,p'*-DDE concentrations in serum (1,097 ng/g lipid in patients versus 977 ng/g lipid in controls) obtained from these two groups of women (Wolff et al. 2000b). A number of other studies have also found no statistical differences in the mean concentrations of DDT and/or its metabolites in serum or adipose tissue between cancer cases and controls (Demers et al. 2000; Dorgan et al. 1999; Helzlsouer et al. 1999; Krieger et al. 1994; Laden et al. 2001a; Liljegren et al. 1998; Lopez-Carrillo et al. 1997; Mendonca et al. 1999; Moysich et al. 1998; Schechter et al. 1997; Unger et al. 1984; van't Veer et al. 1997; Ward et al. 2000; Wolff et al. 2000; Zheng et al. 1999, 2000).

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 (Norén et al. 1996). In that time, levels declined from 5.05 to 0.46 ng/g lipids and the ratio of the 3-methylsulfone metabolite to *p,p'*-DDE remained constant at 0.002.

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

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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. Residents living near a pesticide dump site in Aberdeen, North Carolina, known to contain high concentrations of DDT, have been shown to have age-adjusted mean levels of DDE in their blood of 4.05 ppb, which is higher than the mean value of 2.95 ppb obtained from residents of neighboring communities (Vine et al. 2000).

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 Schvartsman 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 ( $\mu\text{g/g}$ ):  $\Sigma\text{DDT}$ , 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  $\mu\text{g/g}$  was predicted for the population of 331 workers, 80% of whom were employed in the sanitation campaign for 20 years. Mean  $\Sigma\text{DDT}$  serum level in a group of 26 malaria control sprayers in Brazil was 76.9  $\mu\text{g/L}$  and ranged from 7.5 to 473.5  $\mu\text{g/L}$ , whereas 16 unexposed workers had mean serum levels of 16.1  $\mu\text{g/L}$  (range: 5.1–32.9  $\mu\text{g/L}$ ) (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  $\mu\text{g/L}$ , respectively.

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**6.6 EXPOSURES OF CHILDREN**

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.8 Children's Susceptibility.

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

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  $\mu\text{g/kg}$  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 6-3).

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.,  $\mu\text{g/g}$  lipid rather than  $\mu\text{g/mL}$  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 (Bard 1999; 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

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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 (Norén 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% (Norén 1993). In another study conducted between 1972 and 1992, this same group of investigators noted a similar decline in *p,p'*-DDE and *p,p'*-DDT concentrations in human milk in Sweden; the rates at which the concentration of these two compounds have been declining has also been progressively decreasing with time during this same period (Norén et al. 1996). 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 U.S. mainland (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 ΣDDT 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

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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 6-4 (Lordo et al. 1996).

**6.7 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 6.6 Exposures of Children.

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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 441 of the 1,613 hazardous waste sites that have been proposed for inclusion on the EPA NPL (HazDat 2002).

## 6.8 ADEQUACY OF THE DATABASE

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

### 6.8.1 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 D-1). 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 world wide. This type of information is important for estimating the potential for environmental releases from

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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

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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). 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 (Fuhremann 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, especially in regions where DDT is currently used in vector control for malaria and as an agricultural pesticide.

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.

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**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 6-4.

**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 3.13.2, Identification of Data Needs: Children's Susceptibility.

**Exposure Registries.** No exposure registries for DDT, 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.

### 6.8.2 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.

The remediation of soil and sediments contaminated with select organic contaminants, like DDT and its metabolites, is being investigated by several groups. A study of the bioremediation of soil through the action of coryneform bacteria in metabolizing chlorinated hydrocarbon insecticides, as compared to faster-growing pseudomonad bacteria is being investigated by D.D. Focht and colleagues at the University of California at Riverside. This group is examining the substrate specificity of a biphenyl-A gene (bphA) in the metabolism of chlorinated hydrocarbon insecticides and are also looking at the role of surfactants in uptake and catabolism of chlorinated hydrocarbon pesticides. Laboratory investigations into the feasibility of remediation of sediments contaminated with select organic contaminants, like DDT,

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are currently being undertaken by W.L. Mauck and colleagues at the Columbia Environmental Research Center in Columbia, Missouri.

An investigation of the phytoremediation of soils to remove persistent organics like *p,p'*-DDE is being conducted by J.C. White and colleagues at the Connecticut Agriculture Experiment Station in New Haven, Connecticut. In this research, the investigators plan to identify plants that are able to intercept and actively remove *p,p'*-DDE and other compounds from soils through the use of such techniques as chelating agents to open up soil and the addition of surfactants to mobilize recalcitrant compounds in soil. These investigators also propose to identify and test organisms in rhizosphere and nonrhizosphere zones in soil that effectively degrade pesticide-contaminants and then inoculate the most tolerant and effective degraders into rhizosphere of plants to stimulate the effectiveness of phytoremediation.

Exposures of persistent organochlorine compounds, like DDT, to wildlife in the deep sea, in remote, pristine environments and in the Columbia River system are ongoing. D.C. Kadkoto and R.G. Zika at the University of Miami, and C.R. Smith at the University of Hawaii, are investigating the exposure of deep-sea whale-fall communities in the Santa Catalina Basin to persistent organic compounds, like DDT, through the measurement of these compounds in the skeletal remains of whales. J.E. Estes and colleagues at the Western Ecological Research Center in Santa Cruz, California, are monitoring endocrine-disrupting compounds in Adak Island, Alaska, measuring environmental concentrations of select compounds, like DDT, in species (e.g., bald eagles, fish, mussels, seabirds, otters) and abiotic media, gaining both temporal and spatial assessments of contamination. Monitoring of persistent compounds (dioxins, furans, and PCBs) in Columbia River system and the relationship of the presence of these compounds to the nesting success of Osprey is being investigated by C.J. Henny and colleagues at the Forest and Rangeland Ecosystem Science Center in Corvallis, Oregon.

A study of dietary human exposure to select contaminants, such as *p,p'*-DDE, is being conducted by D.L. Macintosh and colleagues in the Department of Environmental Health Sciences, University of Georgia, Athens, Georgia. Associations will be drawn between contaminant levels in biological fluids, such as blood, and urine, drawn from study participants to concentrations of these contaminants in environmental samples such as food products, air, water, and soil, with the purpose of identifying various exposure pathways with regard to total exposure. These investigators will also investigate temporal (e.g., time of year), spatial (e.g., region of country), and demographic (e.g., socioeconomic status) factors on the magnitude and sources of exposure.

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An analytical methodology has been developed to quantitate pesticides in carpet and surface dust and is now being used to assess exposure of agricultural workers, and their families, or families in agricultural regions, to pesticides, with an emphasis on children's exposures to select pesticides, like DDT. A.T. Lemley, S.M. Snedeker and colleagues at Cornell University will use this information, in conjunction with information available in the literature, to assess cancer risk and to identify risk reduction procedures.

A number of research groups are investigating the levels of DDT and its metabolites in humans and the association of these levels with specific human health end points. R. Bhatia and colleagues at the Public Health Institute, Berkley, California, are examining DDT concentrations in the cord blood of a subset of 50 infants from the Children's Health and Development Studies cohort to determine if maternal levels of DDT have an effect on the incidence of male genital anomalies. Another group headed by S. Korrick at the School of Public Health, Harvard University, is measuring DDE and other compounds in cord serum and/or breast milk in children/women living near a PCB-contaminated harbor (Superfund site) in Massachusetts to ascertain the effect that these compounds may have on childhood cognitive function. In the Oswego Newborn and Infant Development Project, T. Darvill and colleagues are tracking newborns of women who did or did not consume Great Lakes fish during pregnancy, analyzing cord blood and placental tissues to determine the effect persistent compounds, such as DDT, have on cognitive function in children. Breast cancer risk as a function of exposure to DDT and other xenoestrogens, as measured in blood samples, collected from women in Wisconsin is being investigated by P.L. Remington at the University of Wisconsin at Madison.

## 7. 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.

### 7.1 BIOLOGICAL MATERIALS

Table 7-1 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. GC methodology provides high resolution and a reproducibility of retention time, which is ideal for distinguishing between the *p,p'*- and *o,p'*-isomers of the compounds, especially when using GC capillary columns (Mukherjee and Gopal 1996). The GC separation method has been historically coupled with electron capture detection (ECD) quantitative techniques (Fishbein 1974). For example, the GC/ECD methodology proposed by Cranmer et al. (1972b) has detected DDT, DDE, and DDD in human urine at levels as low as 50 pg/sample. In human serum, detection limits of between 2 and 7 pg/g serum for DDT, DDE, and DDD have been reported for the GC/ECD quantitative method (Atume and Aune 1999). With the wider availability of gas chromatography-mass spectrometry (GC/MS) instrumentation in analytical laboratories, GC/MS detection methods have been used to quantify DDT and its metabolites (Akiyama et al. 2000; Gill et al. 1996). Both the GC/ECD and GC/MS analytical methods are suitable for the analysis of DDT, DDE, and DDD. However, the GC/ECD method typically provides greater detection sensitivity, whereas the GC/MS method has the advantage of providing qualitative information to determine the specificity of the analysis. Various authors cited in Table 7-1 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

**Table 7-1. Analytical Methods for Determining DDT, DDE, and DDD in Biological Samples**

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Blood/plasma/serum	Extract with hexane	GC/ECD	2 ppb (DDT); 1ppb (DDE); 2 ppb (DDD)	>90% (DDT); 100–110% (DDE); No data (DDD)	EPA 1980b; Nachman et al. 1972
Blood/plasma/serum	Extract with methanol and hexane-ethyl ethers; cleanup with Florisil	GC/ECD	0.8 ppb (DDE); No data (DDT, DDD)	90–100% (DDE); No data (DDT, DDD)	McKinney et al. 1984
Blood	Extract with hexane; concentrate to 5 mL	GC/ECD HERL_004	No data	No data	EMMI 1997
Serum	Extract with hexane; cleanup with Florisil	GC/ECD	91 pg/g serum (DDE)	83.1–85.5% (PCB)	Greizerstein et al. 1997
Semen	Extract with acetone; cleanup with Florisil	GC/ECD	No data	96–97% (DDT); 91.4% (DDE); 91.4% (DDD)	Waliszewski and Syzmeczneki 1983
Urine	Extract with acetic acid in hexane followed by methylation	HPLC/NAA	0.01 mg/mL (DDT); No data (DDE, DDD)	No data	Opelanio et al. 1983
Urine	Extract with hexane	GC/ECD	2 pg (DDE); No data (DDT, DDD)	93.2–106.2% (DDE); No data (DDT, DDD)	Muhlebach et al. 1985
Liver, kidney, human milk	Macerate sample with acetonitrile; cleanup with Florisil	GC/ECD	No data	81% (DDD); No data (DDT, DDD)	Ando 1979; EPA 1980b

**Table 7-1. Analytical Methods for Determining DDT, DDE, and DDD in Biological Samples (*continued*)**

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Muscle	Homogenized and extracted with hexane	GC/ECD	2 pg (DDE); No data (DDT, DDD)	93.2–106.2% (DDE); No data (DDT, DDD)	Muhlebach et al. 1985
Human milk	Triple solvent extraction with ethanol, hexane, and hexane-ethyl ether; Florisil cleanup	GC/ECD	2 ppb (DDE); No data (DDT, DDD)	81–108% (DDE); No data (DDT, DDD)	McKinney et al. 1984
Human milk	Extract with hexane; cleanup with Florisil	GC/MS	2 ppb (DDT); 1.5 ppb (DDD); No data (DDE)	80–100% (DDD); No data (DDT, DDE)	Krauthacker et al. 1980
Human milk	Head-space solid-phase extraction; desorption from solid phase in GC injector	GC/ECD	0.08 µg/L ( <i>p,p'</i> -DDT) 2.79 µg/L ( <i>o,p'</i> -DDT) 1.92 µg/L ( <i>p,p'</i> -DDE) 1.36 µg/L ( <i>o,p'</i> -DDE) 1.62 µg/L ( <i>p,p'</i> -DDD) 1.85 µg/L ( <i>o,p'</i> -DDD)	No data	Röhrig and Meisch 2000
Milk	Remove proteins with ethanol; extract with hexane; cleanup with Florisil	GC/ECD	6 pg/g serum (DDE)	95.1% (PCB)	Greizerstein et al. 1997
Milk/adipose tissue	Extract with hexane and petroleum ether; cleanup with GPC	GC/ECD HERL_026	No data	No data	EMMI 1997
Adipose tissue	Digest with perchloric-acetic acid; extract with n-hexane	GC/ECD	2 pg (DDE); No data (DDT, DDD)	93.2–106.2% (DDE); No data (DDT, DDD)	Muhlebach et al. 1985

**Table 7-1. Analytical Methods for Determining DDT, DDE, and DDD in Biological Samples (*continued*)**

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Adipose tissue	Extract with petroleum ether, cleanup with Florisil	GC/ECD	No data	85–100% (DDT); No data (DDD, DDE)	EPA 1980b
Feces	Hexane extraction; evaporate and reconstitute with isooctane	GC/ECD	20 ppb (DDT, DDE); No data (DDD)	92–111% (DDT); 96–109% (DDE); No data (DDD)	Saady et al. 1992
Lymph	Co-extract with ether; final extraction with cyclopentanone	HPLC	No data	96.4% (DDT); No data (DDE, DDD)	Noguchi et al. 1985
Skin lipids	Purify with GPC, wash with sulfuric acid	GC/ECD	No data	96–109% (DDE); No data (DDT, DDD)	Sasaki et al. 1991b
Milk (MeSO <sub>2</sub> -DDE <sup>a</sup> )	Liquid-gel partitioning followed by adsorption and GPC cleanup	capillary GC/MS	No data	80%, mean (MeSO <sub>2</sub> -DDE)	Noren et al. 1996
Lung, blubber, liver (MeSO <sub>2</sub> -DDE)	Extraction with GPC cleanup	GC/ECD GC/AED	No data	No data	Janak et al. 1998

<sup>a</sup>DDE 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; PCB = polychlorinated biphenyls

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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; Phillips et al. 1989).

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/MS or GC/ECD (Janak et al. 1998; Norén et al. 1996), although gas chromatography-tandem mass spectrometry is the preferred instrumental technique for the analysis of 3-methyl sulfonyl 2,2-bis(4-chlorophenyl)-1,1-dichloroethene in complex biological matrices (Letcher and Norstrom 1995). However, the use of atomic emission detection significantly improves its determination (Janak et al. 1998). While methods exist for measuring DDT, DDE, and DDD in liver, breast milk, and adipose tissue, the most frequently used sampling techniques utilize samples of blood, urine, and semen 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.

## 7.2 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 7-2). 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

**Table 7-2. Analytical Methods for Determining DDT, DDE, and DDD in Environmental Samples**

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Air	Separate with silicic acid column	GC/ECD	0.20 ng/m <sup>3</sup> (DDE); 0.16 ng/m <sup>3</sup> (DDT)	104–106% (DDT); 100% (DDE); No data (DDD)	Bidleman et al. 1978
Air	Filter collection and iso-octane extraction	GC	0.49–2.60 mg/m <sup>3</sup> (DDT); No data (DDD, DDE)	No data	NIOSH 1977
Air	Sample collection on glass fiber filter; Soxhlet extraction; cleanup with alumina	GC/ECD AREAL Method TO-4	No data	No data	EMMI 1997
Water	Extract using hexane followed by acetonitrile	GC	No data	85% (DDT); No data (DDD, DDE)	Kurtz 1977
Water	Extract using methylene chloride cleanup with Florisil	GC/ECD EPA Method 608	0.012 µg/L (DDT); 0.004 µg/L (DDE); 0.011 µg/L (DDD)	92% (DDT, DDD); 89% (DDE)	EPA 1982
Water	Extract at neutral pH with methylene chloride	GC/ECD or GC/ELCD EPA Method 8081B	0.081 µg/L (DDT); 0.058 µg/L (DDE); 0.050 µg/L (DDD).	121.1% (4,4'-DDT); 98.0% (4,4'-DDE); 86.8% (4,4'-DDD)	EMMI 1997; EPA 1998j
Water	Digest with chromic acid; extract with hexane	GC	No data	100% (DDT, DDE); No data (DDD)	Driscoll et al. 1991
Water	Extract with methylene chloride	MID GC/MS	0.012 µg/L (DDT); 0.007 µg/L (DDE); 0.008 µg/L (DDD)	93–110% (DDT); 73–110% (DDE); 76–110% (DDD)	Behzadi and Lalancette 1991
Water	Immersion solid-phase extraction, desorption from solid-phase in GC injector	GC/ECD	0.30 ng/L (DDT) 0.20 ng/L (DDE) No data (DDD)	32.3% (DDT); 103.8% (DDE); 113.6% (DDD)	Aguilar et al. 1999

**Table 7-2. Analytical Methods for Determining DDT, DDE, and DDD in Environmental Samples (*continued*)**

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Solid-phase extraction, eluted with methylene chloride/methanol (80:20)	GC/Ion trap MS	0.16 µg/L (DDT) 0.07 µg/L (DDE) No data (DDD)	24–77% (DDT); 27–51% (DDE); No data (DDD)	Eitzer and Chevalier 1999
Finished drinking water and groundwater	Extract with methylene chloride; solvent exchange to methyl <i>tert</i> -butyl ether	GC/ECD EPA Method 508	0.060 µg/L (DDT); 0.010 µg/L (DDE); 0.003 µg/L (DDD)	No data	EMMI 1997
Landfill leachate	Head-space solid-phase microextraction, desorption from solid-phase in GC injector	GC/ECD	0.1 µg/L	78.5% (DDT,DDE, and DDD)	Brás et al. 2000
Soil	Extract with hexane/acetone; cleanup with Florisil	GC/ECD AOAC 970.52	No data	No data	Helrich 1990
Soil	Extract with hexane/acetone; cleanup with Florisil	GC/ECD	No data	No data	Williams 1984
Soil	Extract with hexane-acetone or methylene chloride-acetone, cleanup by appropriate method.	GC/ECD or GC/ELCD EPA Method 8081B	0.0036 µg/kg (DDT); 0.0025 µg/kg (DDD); 0.0042 µg/kg (DDE)	121.1% (DDT); 98.0% (DDE); 86.8% (DDD)	EMMI 1997; EPA 1998j
Soil	Extraction with methylene chloride	GC/MS EPA Method 8270D	No Data	111–134% (DDT)	EPA 1998k
Soil	Extraction with methylene chloride	MID GC/MS	0.4 µg/kg (DDT); 0.3 µg/kg (DDD); 0.3 µg/kg (DDE)	91–109% (DDT); 90–116% (DDD); 93–104% (DDE)	Behzadi and Lalancette 1991

**Table 7-2. Analytical Methods for Determining DDT, DDE, and DDD in Environmental Samples (*continued*)**

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Food	Extract with acetonitrile into petroleum ether; cleanup with Florisil	GC/ECD	No data	>80%	McMahon and Burke 1978; Williams 1984
Food	Soxhlet extraction using redistilled hexane	on-line SEC-GC	10–50 µg/kg (DDE); No data (DDT, DDD)	No data	Grob and Kalin 1991
Food	Extract with n-hexane; cleanup with Florisil	GC-ECD/NPDMS	0.50–10 µg/kg (DDT, DDE); No data (DDD)	68–95% (DDT, DDE); No data (DDD)	Rodriguez et al. 1991
Food	Mixed ether extraction; cleanup with Florisil	DC-GC/ECD	0.05–1.5 ng (DDT, DDE); No data (DDD)	No data	Hopper 1991
Food	Mix sample with dried potassium bromide powder	IR/UV-SP	No data	No data	Gore et al. 1971
Milk	Solid-phase extraction, eluted with hexane, cleanup on neutral alumina, eluted with hexane	GC/ECD	0.12 µg/L ( <i>p,p'</i> -DDT) 0.12 µg/L ( <i>o,p'</i> -DDT) 0.07 µg/L ( <i>p,p'</i> -DDE) 0.05 µg/L ( <i>o,p'</i> -DDE) 0.07 µg/L ( <i>p,p'</i> -DDD) 0.12 µg/L ( <i>o,p'</i> -DDD)	100% ( <i>p,p'</i> -DDT); 104% ( <i>o,p'</i> -DDT); 93% ( <i>p,p'</i> -DDE); 97% ( <i>o,p'</i> -DDE); 106% ( <i>p,p'</i> -DDD); 83% ( <i>o,p'</i> -DDD); (spiked at 1 µg/L)	Yagüe et al. 2001
Animal fat	Extract with methylene chloride/cyclohexane; separation by GPC	GC/ECD AOAC 984.21	No data	No data	Helrich 1990
Plants	Extract with hexane/methanol/acetone	SP	No data	92–99% (DDT); No data (DDD, DDE)	Verma and Pillai 1991a
Plants	Extract with methylene chloride; organic phase concentrated	GC/HECD AOAC 985.22	No data	No data	Helrich 1990

**Table 7-2. Analytical Methods for Determining DDT, DDE, and DDD in Environmental Samples (*continued*)**

Sample matrix	Sample preparation	Analytical method	Sample detection limit	Percent recovery	Reference
Fish	Soxhlet extraction with hexane; cleanup with Florisil	GC/ECD	10 µg/kg	No data	Ford and Hill 1991
Fish	Extract with petroleum ether; cleanup with Florisil	GC/ECD AOAC 983.21	No data	No data	Helrich 1990

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

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1991; Long et al. 1991b; Lott and Barker 1993). The use of silica acid column chromatography purification methods in conjunction with GC/ECD quantitative techniques has provided a detection limit for DDT in air of 0.16 ng/m<sup>3</sup> (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.

Alternative approaches are being developed to improve sample recoveries, speed analysis time, or lower detection sensitivities in the analysis of DDT, DDE, and DDD. Sample extraction techniques such as supercritical fluid extraction (SFE), pressurized liquid extraction (PLE), and microwave extraction techniques have been applied to the analysis of DDT, DDE, and DDD to improve extraction of these compounds from soil (de Andrea et al. 2001; Fitzpatrick et al. 2000; Glazkov et al. 1999). SFE has been shown to improve recoveries of organochlorines from water samples over standard liquid/liquid extraction techniques (Glazkov et al. 1999). Solid-phase microextraction techniques can aid in improving sample clean-up and detection sensitivities (Aguilar et al. 1999; Brás et al. 2000; de Jager and Andrews 2000; Röhrig and Meisch 2000). In this technique, fiber-based solid-phase extractants can either directly extract DDT, DDE, and DDD through immersion in water or other aqueous samples (e.g., milk), or extract DDT, DDE, and DDD from the head-space over a sample as it is heated (Aguilar et al. 1999). Once the compounds have been adsorbed into the solid-phase fibers, the compounds are directly desorbed from the fibers in a GC injector and then detected using either electron-capture or mass spectrometric detection techniques. In addition to the instrumental analytical techniques, immunoassays offer good detection sensitivities (<0.1 µg/L) of DDT compounds in complex matrices, although the assay is not specific to one specific DDT compound (Abad et al. 1997; Beasley et al. 1998). These newer analytical methods show much promise towards improving the analysis DDT, DDE, and DDD in complex environmental and biological samples (Röhrig and Meisch 2000).

### 7.3 ADEQUACY OF THE DATABASE

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

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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.

### 7.3.1 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.

**Effect.** No specific biomarkers of effect have been determined. Until these biomarkers are determined, methodology needed to identify them cannot be established.

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**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.

**7.3.2 Ongoing Studies**

No ongoing studies were located on the analytical methods of DDT, DDE, or DDD.

## 8. 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 8-1.

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; Talts et al. 1998). An intermediate-duration oral MRL of  $5 \times 10^{-4}$  mg/kg/day was derived based on hepatic histologic changes in rats (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 2001a).

EPA assigned DDT, DDE, and DDD a weight-of-evidence classification of B2, probable human carcinogens (IRIS 2001a, 2001b, 2001c). 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 2001c) derived an inhalation unit risk of  $9.7 \times 10^{-5} \text{ (}\mu\text{g/m}^3\text{)}^{-1}$  for DDT. EPA (IRIS 2001c) derived an oral slope factor of  $0.34 \text{ (mg/kg/day)}^{-1}$  for DDE based on observed lesions as neoplastic liver nodules or hepatocellular tumors in mice and hamster studies (NCI 1978; Rossi et al. 1983; Tomatis et al. 1974). 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 2002). The Department of Health and Human Services (DHHS) has determined that DDT may reasonably be anticipated to be a human carcinogen (NTP 2002).

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).

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to DDT/DDE/DDD**

Agency	Description	Information	References
<u>INTERNATIONAL</u> Guidelines:			
IARC	Carcinogenicity classification—DDT	Group 2B <sup>a</sup>	IARC 2002
WHO	Acceptable daily intake—DDT	0.02 mg/kg-bw	WHO 2002
	Drinking water guideline—DDT and metabolites	2 µg/L	WHO 2002
<u>NATIONAL</u> Regulations and guidelines:			
a. Air			
ACGIH	TLV–TWA (8-hour)—DDT	1 mg/m <sup>3</sup>	ACGIH 2001
NIOSH	REL (10-hour TWA)—DDT <sup>b,c</sup> IDLH—DDT	0.5 mg/m <sup>3</sup> 500 mg/m <sup>3</sup>	NIOSH 2002
OSHA	PEL (8-hour TWA) for general industry—DDT <sup>c</sup>	1 mg/m <sup>3</sup>	OSHA 2001b 29CFR1910.1000
	PEL (8-hour TWA) for construction industry—DDT <sup>c</sup>	1 mg/m <sup>3</sup>	OSHA 2001c 29CFR1926.55
	PEL (8-hour TWA) for shipyard industry—DDT <sup>c</sup>	1 mg/m <sup>3</sup>	OSHA 2001a 29CFR1915.1000
USC	Hazardous air pollutant—DDE		USC 2001 42 USC 7412
b. Water			
EPA	Designated as a hazardous substance in accordance with Section 311(b)(2)(A) of the Clean Water Act—DDT and DDD		EPA 2001e 40CFR116.4
	Effluent guidelines and standards; designated as a toxic pollutant pursuant to Section 307(a)(1) of the Clean Water Act—DDT and metabolites		EPA 2002e 40CFR401.15
	Reportable quantities for hazardous substances designated pursuant to Section 311 of the Clean Water Act—DDT and DDE	1 pound	EPA 2002b 40CFR117.3

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to DDT/DDE/DDD (continued)**

Agency	Description	Information		References
NATIONAL (cont.)				
EPA	Groundwater monitoring	Suggested method	PQL (µg/L)	EPA 2001a 40CFR264, Appendix IX
	DDT and DDD	8080	0.1	
		8270	10	
	DDE	8080	0.05	
		8270	10	
	Human health consumption of:			EPA 1999a
	DDT/DDE			
	Water and organism	5.9x10 <sup>-4</sup> µg/L <sup>d,e</sup>		
	Organism only	5.9x10 <sup>-4</sup> µg/L <sup>d,e</sup>		
	DDD			
	Water and organism	8.3x10 <sup>-4</sup> µg/L <sup>d,e</sup>		
	Organism only	8.4x10 <sup>-4</sup> µg/L <sup>d,e</sup>		
	Toxic pollutant effluent standard; ambient water criterion in navigable waters—DDT/DDE/DDD	0.001 µg/L		EPA 2002i 40CFR129.101
	Toxic pollutant effluent standard; toxic pollutant subject to regulations under provisions of this subpart—DDT/DDE/DDD			EPA 2002d 40CFR129.4(b)
c. Food				
FDA	Action levels (ppm)—DDT/DDE/DDD			FDA 2002a
	Fat of meat (cattle, goats, hogs, horses, sheep), fish	5		
	Carrots	3		
	Manufactured dairy products	1.25		
	Beans (cocoa, whole raw), peppermint oil, potatoes, soya bean oil (crude), spearmint oil, sweet potatoes	1.0		
	Artichokes, asparagus, barley grain (food, feed), broccoli, Brussels' sprouts, cabbage, cauliflower, celery, collards, eggs, endives (escarole), hay, kale, kohlrabi, lettuce, maize grain (food, feed)	0.5		

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to DDT/DDE/DDD (*continued*)**

Agency	Description	Information	References
<b>NATIONAL (<i>cont.</i>)</b>			
FDA ( <i>cont.</i> )	Action levels (ppm)— DDT/DDE/DDD		FDA 2002a
	Milo sorghum grain (food, feed), mushrooms, mustard greens, oat grain (food, feed), peppermint hay, rice grain (food, feed), rye grain (food, feed), spearmint hay, spinach, Swiss chard, tomato pomace (dried, for use in dog and cat food), wheat grain (food, feed)	0.5	
	Apricots, avocados, beans, beans (dried), beets (roots, tops), cherries, guavas, mangoes, nectarines, okra, onions (dry bulb), papayas, parsnips (roots, tops), peaches, peanuts, peas, pineapples, plums (fresh prunes), radishes (roots, tops), rutabagas (roots, tops), soya beans (dry), turnips (roots, tops)	0.2	
	Apples, blackberries, blueberries (huckleberries), boysenberries, citrus fruit, maize (fresh sweet plus cob with husk removed), cottonseed, cranberries, cucumbers, currants, dewberries, eggplant, gooseberries, hops (fresh), loganberries, melons, pears, peppers, pumpkins, quinces, raspberries, squash, squash (summer), strawberries, youngberries	0.1	
	Grapes, hops (dried), tomatoes, lettuces	0.05	

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**Table 8-1. Regulations and Guidelines Applicable to DDT/DDE/DDD (*continued*)**

Agency	Description	Information		References
NATIONAL (cont.)				
FDA	Drug products containing certain active ingredients offered over-the-counter for certain uses; as there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for their specified uses	Pediculicide (lice) drug products		FDA 2002b 21CFR310.545 (a)(25)
USDA	Labeling treated seed; commonly accepted abbreviated chemical names—DDT			USDA 2001 7CFR201.31a(b)
d. Other				
ACGIH	Carcinogenicity classification—DDT	A3 <sup>f</sup>		ACGIH 2001
EPA	DDT			IRIS 2001c
	Carcinogenicity classification	B2 <sup>g</sup>		
	Inhalation unit risk	9.7x10 <sup>-5</sup> (µg/m <sup>3</sup> ) <sup>-1</sup>		
	Oral slope factor	0.34 (mg/kg/day) <sup>-1</sup>		
	RfD	5x10 <sup>-4</sup> mg/kg/day		
	DDE			IRIS 2001b
	Carcinogenicity classification	B2 <sup>g</sup>		
	Inhalation unit risk	No data		
	Oral slope factor	0.34 (mg/kg/day) <sup>-1</sup>		
	RfD	No data		
	DDD			IRIS 2001a
	Carcinogenicity classification	B2 <sup>g</sup>		
	Inhalation unit risk	No data		
Oral slope factor	0.24 (mg/kg/day) <sup>-1</sup>			
RfD	No data			
	Criteria for municipal solid waste landfills; listed as a hazardous constituent	Suggested method	PQL (µg/L)	EPA 2002g 40CFR258, Appendix II
	DDT and DDD	8080	0.1	
		8270	10	
	DDE	8080	0.05	
		8270	10	
	Health based limits for exclusion of waste-derived residues; concentration limit for residues—DDT	1x10 <sup>-3</sup> mg/kg		EPA 2001b 40CFR266, Appendix VII

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to DDT/DDE/DDD (continued)**

Agency	Description	Information	References
<b>NATIONAL (cont.)</b>			
EPA	Identification and listing of hazardous waste; hazardous waste number		EPA 2002f 40CFR261.33(f)
	DDT	U061	
	DDD	U060	
	Land disposal restrictions; universal treatment standards		EPA 2001c 40CFR268.48(a)
	Wastewater standard		
	DDT	0.023 mg/L <sup>2</sup>	
	DDE	0.031 mg/L <sup>2</sup>	
	DDD	0.0039 mg/L <sup>2</sup>	
	Non-wastewater standard		
	DDT/DDE/DDD	0.087 mg/kg <sup>3</sup>	
	Pesticide effluent limitation guidelines and standards—DDT/DDE/DDD		EPA 2002c 40CFR455.20(b)
	Pesticide residue tolerances on agricultural commodities—DDT/DDD	Class of chlorinated organic pesticides	EPA 2001d 40CFR180.3(e)(4)
NTP	Reportable quantity designated as a CERCLA hazardous substance under Sections 311(b)(4) and 307(a) of the Clean Water Act and Section 3001 of RCRA—DDT and DDD	1 pound	EPA 2002a 40CFR302.4
	Reportable quantity designated as a CERCLA hazardous substance under Section 307(a) of the Clean Water Act and Section 112 of the Clean Air Act—DDE	1 pound <sup>h</sup>	EPA 2002a 40CFR302.4
	Standards for the management of specific hazardous wastes		EPA 2002h 40CFR266, Appendix V
	Unit risk	9.7x10 <sup>-5</sup> (µg/m <sup>3</sup> ) <sup>-1</sup>	
	Risk specific dose	1.0x10 <sup>-1</sup> µg/m <sup>3</sup>	
	TSCA significant new use subject to reporting—DDT	Manufacture, import, or process 10,000 pounds or more per year per facility for any use	EPA 2002j 40CFR721.2287
NTP	Reasonably anticipated to be a human carcinogen—DDT		NTP 2002

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to DDT/DDE/DDD (*continued*)**

Agency	Description	Information	References
<u>STATE</u> Regulations and guidelines:			
a. Air			
Hawaii	Hazardous air pollutant—DDE		BNA 2001
Idaho	DDT Unit risk factor Emissions level AACC (annual average)	$9.7 \times 10^{-5} (\mu\text{g}/\text{m}^3)^{-1}$ $6.8 \times 10^{-5}$ pounds/hour $1 \times 10^{-2} \mu\text{g}/\text{m}^3$	UATW 1999d
Illinois	Toxic air contaminant— DDT/DDE/DDD		BNA 2001
Kansas	Hazardous air pollutant—DDE		BNA 2001
Kentucky	Hazardous air pollutant—DDE		BNA 2001
Maryland	Toxic air pollutant—DDT		BNA 2001
Minnesota	Hazardous air pollutant threshold; <i>de minimis</i> level—DDE	0.01 tons/year	BNA 2001
Nebraska	Hazardous air pollutant—DDE		BNA 2001
New Hampshire	Regulated toxic air pollutant; occupational exposure level— DDT	1 mg/m <sup>3</sup>	BNA 2001
New Mexico	Toxic air pollutant—DDT OEL Emissions	1.00 mg/m <sup>3</sup> 0.0667 pounds/hour	BNA 2001
Rhode Island	Hazardous air pollutant—DDE		BNA 2001
South Carolina	Toxic air emissions—DDE	High toxicity, may cause chronic effects that result in death or permanent injury after very short exposure to small quantities	BNA 2001
Vermont	Hazardous air contaminant—DDE		BNA 2001
Washington	Threshold for hazardous air pollutants—DDE	0.005 tons/year	BNA 2001

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to DDT/DDE/DDD (continued)**

Agency	Description	Information	References
<u>STATE (cont.)</u>			
b. Water			
Alabama	Aquatic life criteria—DDT Freshwater Acute Chronic Marine Acute Chronic	1.1 µg/L 0.001 µg/L  0.13 µg/L 0.001 µg/L	UATW 1999b
Arizona	Drinking water guideline—DDT	0.1 µg/L	HSDB 2001
Colorado	Human health based standards DDT/DDE Water supply Water and fish DDD Water supply Water and fish	0.1 µg/L 5.9x10 <sup>-4</sup> µg/L  No data 8.3x10 <sup>-4</sup> µg/L	UATW 1999a
Florida	Drinking water guideline— DDT/DDD/DDE	0.1 µg/L	HSDB 2001
Hawaii	Water quality criteria—DDT and metabolite DDD Freshwater Acute Chronic Saltwater Acute Chronic Fish consumption	1.1 µg/L 0.001 µg/L  0.013 µg/L 0.001 µg/L 8x10 <sup>-6</sup> µg/L	UATW 1999c
Illinois	Drinking water standard—DDT	50 µg/L	HSDB 2001
Maine	Drinking water guideline—DDT	0.83 µg/L	HSDB 2001
Minnesota	Drinking water guideline— DDT/DDD/DDE	1 µg/L	HSDB 2001
New Hampshire	Drinking water guideline—DDT	0.1 µg/L	HSDB 2001
c. Food			
Oklahoma	Alert level in fish tissues Concern levels in fish tissue Water column criteria to protect for the consumption of fish flesh	5.0 mg/kg 2.5 mg/kg 5.9x10 <sup>-3</sup> µg/L	FSTRAC 1999

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to DDT/DDE/DDD (continued)**

Agency	Description	Information	References
<u>STATE</u> (cont.)			
Alabama	Fish and Wildlife Advisory for DDT/DDE/DDD	Fish	EPA 1999b
Alaska		Fish	
Arizona		Fish and turtles	
California		Fish	
Georgia		Fish	
Massachusetts		Fish	
Michigan		Fish	
New York		Fish and waterfowl	
Oklahoma		Fish	
Oregon		Fish	
Texas		Fish	
Washington	Fish		
d. Other			
California	Chemicals known to the state to cause cancer— DDT/DDD/DDE		BNA 2001
Hawaii	Restricted use pesticide— DDT/DDE	All concentrations	BNA 2001

<sup>a</sup>Group 2B: possibly carcinogenic to humans

<sup>b</sup>Potential occupational carcinogen

<sup>c</sup>Skin designation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors or, of probable greater significance, by direct skin contact with the substance

<sup>d</sup>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.

<sup>e</sup>This criterion is based on carcinogenicity of 10<sup>-6</sup> risk. Alternate risk levels may be obtained by moving the decimal point (e.g., for a risk level of 10<sup>-5</sup>, move the decimal point in the recommended criterion one place to the right).

<sup>f</sup>A3: confirmed animal carcinogen with unknown relevance to humans

<sup>g</sup>B2; probable human carcinogen

<sup>h</sup>The 1-pound reportable quantity is a Section 102 CERCLA statutory reportable quantity

AACC = acceptable ambient concentrations for carcinogens; ACGIH = American Conference of Governmental Industrial Hygienists; BNA = Bureau of National Affairs; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FSTRAC = Federal-State Toxicology and Risk Analysis Committee; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; NIOSH = National Institute of Occupational Safety and Health; NTP = National Toxicology Program; OEL = occupational exposure limit; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limits; RCRA = Resource Conservation Recovery Act; REL = recommended exposure limit; RfD = oral reference dose; TLV = threshold limit value; TSCA = Toxic Substances Control Act; TWA = time-weighted average; UATW = Unified Air Toxics Website; USC = United States Code; USDA = U.S. Department of Agriculture; WHO = World Health Organization



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## 10. GLOSSARY

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

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

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

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

**Adsorption Ratio ( $K_d$ )**—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.

**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.

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**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.

**Genotoxicity**—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

**Half-life**—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

**Immediately Dangerous to Life or Health (IDLH)**—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

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**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.

**Immunologic Toxicity**—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

**Immunological Effects**—Functional changes in the immune response.

***In Vitro***—Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo***—Occurring within the living organism.

**Lethal Concentration<sub>(LO)</sub> (LC<sub>LO</sub>)**—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**—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<sub>(LO)</sub> (LD<sub>LO</sub>)**—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<sub>(50)</sub> (LD<sub>50</sub>)**—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**—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.

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**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.

**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

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points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

**Physiologically Based Pharmacokinetic (PBPK) Model**—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

**Prevalence**—The number of cases of a disease or condition in a population at one point in time.

**Prospective Study**—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

**$q_1^*$** —The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The  $q_1^*$  can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually  $\mu\text{g/L}$  for water,  $\text{mg/kg/day}$  for food, and  $\mu\text{g/m}^3$  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  $\text{mg/m}^3$  or ppm.

**Reference Dose (RfD)**—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the no-observed-adverse-effect level (NOAEL—from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

**Reportable Quantity (RQ)**—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity**—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

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**Retrospective Study**—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

**Risk**—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

**Risk Factor**—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

**Risk Ratio**—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

**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)**—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

**Target Organ Toxicity**—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen**—A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)**—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

**Time-Weighted Average (TWA)**—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

**Toxic Dose<sub>(50)</sub> (TD<sub>50</sub>)**—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.

## 10. GLOSSARY

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.

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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 a hundredfold 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.

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**MINIMAL RISK LEVEL WORKSHEET**

Chemical Name: DDT  
CAS Number: 50-29-3  
Date: September 2002  
Profile Status: Third Draft Post Public  
Route: ☐ Inhalation ☒ Oral  
Duration: ☒ Acute ☐ Intermediate ☐ Chronic  
Graph Key: 47m  
Species: Mice

Minimal Risk Level: 0.0005 ☒ mg/kg/day ☐ ppm

Reference: Eriksson and Nordberg 1986; Eriksson et al. 1990a, 1990b, 1992, 1993; Johansson et al. 1995, 1996; Talts et al. 1998.

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<sup>+</sup>-stimulated ACh release from cerebral cortex slices. In addition, five 10-day-old mice were administered 0.5 mg <sup>14</sup>C-DDT and the radioactivity in the brain was assayed 24 hours, 7 days, or 1 month after dosing. The results showed that K<sup>+</sup>-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 M<sub>1</sub> 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

## APPENDIX A

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). Also, treatment with DDT followed by bioallethrin significantly increased the density of muscarinic receptors in the cerebral cortex relative to DDT alone. This increase was later attributed to increased expression of muscarinic receptor m4 mRNA (Talts et al. 1998). 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.

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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

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**MINIMAL RISK LEVEL WORKSHEET**

Chemical Name: DDT  
CAS Number: 50-29-3  
Date: September 2002  
Profile Status: Third Draft Post Public  
Route: ☐ Inhalation ☒ Oral  
Duration: ☐ Acute ☒ Intermediate ☐ Chronic  
Graph Key: 60r  
Species: Rat

Minimal Risk Level: 0.0005 ☒ 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).

Reference: Fitzhugh and Nelson 1947; Laug et al. 1950

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

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maximum at 19–23 weeks; age did not affect the rate of DDT-accumulation; about 50–75% 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

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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  $F$  = kg food/day and  $W$  = body weight in kilograms

For chronic duration, the average body weight of male and female Osborne-Mendel rats is 0.452 kg, yielding an  $F=0.033$  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 body weight = 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  $F=0.0213$  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

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

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 2001a). The Fitzhugh and Nelson (1947) study is considered supportive for the RfD.

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**MINIMAL RISK LEVEL WORKSHEET**

Chemical Name: DDT  
CAS Number: 50-29-3  
Date: September 2002  
Profile Status: Third Draft Post Public  
Route: ☐ Inhalation ☒ Oral  
Duration: ☐ Acute ☐ Intermediate ☒ Chronic  
Graph Key: N/A  
Species: N/A

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 be 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): Obaid Faroon



## APPENDIX B

### USER'S GUIDE

#### Chapter 1

##### Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

#### Chapter 2

##### Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order 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 chapter. 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 Chapter 3 Data Needs section.

## APPENDIX B

**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, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3, Section 3.10, "Interactions with Other Substances," and Section 3.11, "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 end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest 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.

**Chapter 3****Health Effects****Tables and Figures for Levels of Significant Exposure (LSE)**

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) 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).

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The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

**LEGEND****See LSE Table 3-1**

- (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 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.
- (2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).
- (5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.5, "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.

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- (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 end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL A 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 3-1**

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/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL Key number 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.

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- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ( $q_1^*$ ).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

# SAMPLE

1 6

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

	Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
						Less serious (ppm)	Serious (ppm)	
2	6	INTERMEDIATE EXPOSURE						
		5	6	7	8	9		10
3	6	Systemic	9	9	9	9		9
4	6	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)	Nitschke et al. 1981
<hr/>								
CHRONIC EXPOSURE								
							11	
							9	

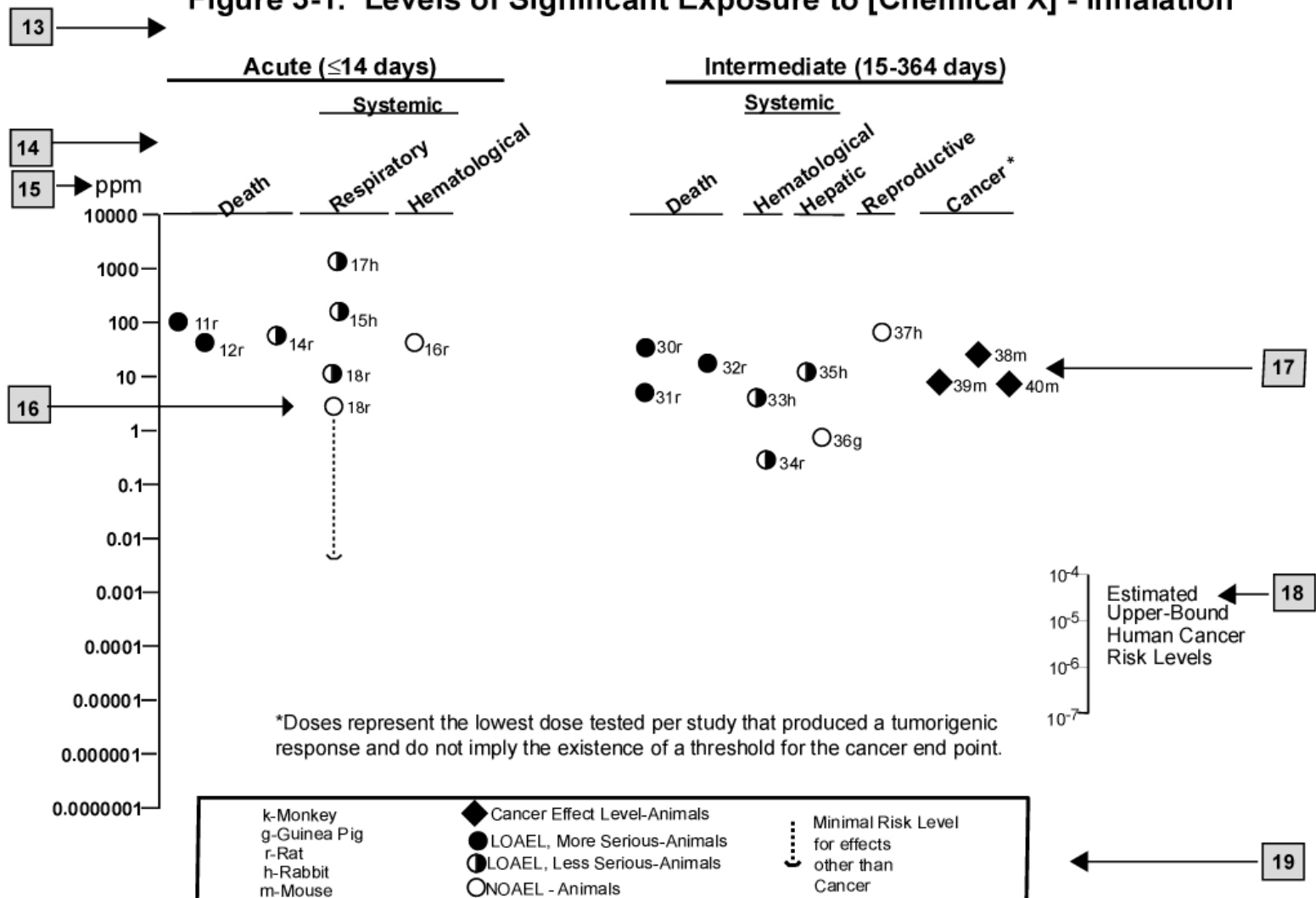
<sup>a</sup> The number corresponds to entries in Figure 3-1.

12 6

<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).

# SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation





## APPENDIX C

### ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACOEM	American College of Occupational and Environmental Medicine
ACGIH	American Conference of Governmental Industrial Hygienists
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AOEC	Association of Occupational and Environmental Clinics
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation

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DOT/UN/	Department of Transportation/United Nations/
NA/IMCO	North America/International Maritime Dangerous Goods Code
DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F <sub>1</sub>	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	<i>Federal Register</i>
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K <sub>d</sub>	adsorption ratio
kg	kilogram
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>Lo</sub>	lethal concentration, low
LC <sub>50</sub>	lethal concentration, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LD <sub>50</sub>	lethal dose, 50% kill
LDH	lactic dehydrogenase
LH	lutinizing hormone
LT <sub>50</sub>	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal

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MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
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
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic

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PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	reportable quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD <sub>50</sub>	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
\$	greater than or equal to
=	equal to
<	less than

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#	less than or equal to
%	percent
$\alpha$	alpha
$\beta$	beta
$\gamma$	gamma
$\delta$	delta
$\mu\text{m}$	micrometer
$\mu\text{g}$	microgram
$q_1^*$	cancer slope factor
—	negative
+	positive
(+)	weakly positive result
(—)	weakly negative result



## APPENDIX D

### D. 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 3.6.2, Mechanisms of Toxicity. Environmental monitoring studies have shown that DDT, DDE, and DDD are also highly persistent in the environment (see Section 6.3, 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 Appendix D, Health Effects in Wildlife Potentially Relevant to Human Health, closely parallels that of Section 3.2, 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, Florida. 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 ( $p \leq 0.05$ ) 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 3.2, 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

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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 platyrhynchos*), 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, testicular feminization).

A hazard identification table (Table D-1) 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 D-1 for the ambiguous results. Not every significant effect reported in the text received a unique entry in Table D-1. 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 D-1 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 D-1 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.

## D.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

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\$95 mg/kg body weight; the estimated LD<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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 (*Callipepla californica*), DDT (unspecified isomeric

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composition) in 3-month-old Mallard ducks (*Anas platyrhynchos*), 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<sub>50</sub> 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<sub>50</sub> of 1,612 mg/kg diet for *p,p'*-DDT after a 5-day exposure was reported in 10-week-old clapper rails (*Rallus longirostris*) (Van Veltzen and Kreitzer 1975). Dietary LC<sub>50</sub> values for technical-grade DDT after 5-day exposures in immature bobwhite quail, cardinal (*Richmondia 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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<sub>50</sub> 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 (*Haliaeetus 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 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

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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 ppm 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 42 ppm (Jefferies and Walker 1966).

## D.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.

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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 (Jefferies and French 1971), increased thyroid weights with decreased thyroidal colloid (Jefferies and French 1969, 1971), and increased adrenal weights (Jefferies et al. 1971). These effects are discussed further below under Endocrine 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 (Jefferies 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 (Jefferies 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 (Jefferies 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 (Jefferies 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” (Jefferies 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.

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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 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). 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

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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 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 <sup>14</sup>C-labelled progesterone to metabolites *in vitro* than microsomal extracts from untreated female quail;

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microsomal enzyme extracts from DDT-treated male quail did not produce a significant increase in mean testosterone conversion *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 (Greichus 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 (Greichus 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 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 (creatinine 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

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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 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 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 mg *p,p'*-DDT, 15 mg *p,p'*-DDD, and 15 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 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 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 mg *o,p'*-DDT or by nine oral administrations of 10 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 mg/kg/day technical-grade DDT (Fourie and Hattingh 1979).

Significantly depressed serum protein was 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). Blood total protein 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). Plasma protein was not significantly affected 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 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 8<sup>th</sup> 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*

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*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  $I^{131}$  uptake or no change in two studies at #25 ppm DDT, and increased  $I^{131}$  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 3.6.2, 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 platyrhynchos*) 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

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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.

Uptake of  $I^{131}$  into the thyroid was decreased (not significantly) in juvenile male mallards (*Anas platyrhynchos*) 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 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). 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).

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 platyrhynchos*) fed technical-grade DDT at 2.5–250 ppm in the diet for 30 days (Peterle et al. 1973).

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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 8<sup>th</sup> 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<sub>50</sub> levels of 5651 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 (*Haliaeetus 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

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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 (*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 (*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 (*Streptopelia risoria*) fed *p,p'*-DDE at 10 or 50 ppm in the diet for 63 days (Haegele 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 (*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).

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**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  $p\text{CO}_2$  after acute oral exposures, although the significance of this is uncertain.

**Mammals.** Metabolic rate as measured by  $\text{O}_2$  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 EC, except at thermal neutrality at 30 EC, 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 EC (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 responses that have been attributed to neurotoxicity have been observed in several other studies of energy-stressed birds (Appendix D.4, 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 8<sup>th</sup> 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

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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<sub>2</sub> (partial pressure of CO<sub>2</sub> 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 pCO<sub>2</sub>, but no significant effect on pO<sub>2</sub> 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 osmolality. 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 8<sup>th</sup> 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,  $\alpha$ -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  $\mu$ g *p,p'*-DDT administered in equal daily doses over a 12-day period (Karlsson et al. 1974).

### D.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.

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**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).

#### D.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 3.6.2, 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 LC<sub>50</sub> of 1,784 ppm)

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(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 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 (*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 (*Bufo bufo*), and smooth newts (*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 (*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 (*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 (*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 (*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). A significant negative correlation was seen between neurotransmitter levels and DDE residues in the brain (Heinz et al. 1980).

Bald eagles (*Haliaeetus 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 to 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).

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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 (*Richmondia 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 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 ppm technical-grade DDT (Hill et al. 1971). Balance disturbances were seen in house sparrows, cardinals (*Richmondia 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 (Mahoney 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 (Haegle 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

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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).

## D.5 Reproductive Effects

Little information is available concerning reproductive effects in reptiles, amphibians, and wild mammals from exposure to DDT/DDE/DDD. 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 Appendix D.6, Eggshell Thinning in Birds). Egg production, fertility, and hatchability were largely unaffected in numerous studies in a variety of bird species. However, increased embryo lethality, 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). Similar to the associations made between DDT and preterm deliveries in humans (Saxena et al. 1980, 1981; Wassermann et al. 1982), premature births in California sea lions (*Zalophus californianus californianus*) are associated with elevated DDT concentrations (DeLong et al. 1973). Mean blubber DDT in sea lions delivering preterm was 824.4 ppm, whereas blubber DDT in full term individuals averaged 103.2 ppm. However, the effect of preterm delivery could not be causally isolated to DDT, as PCBs were also significantly elevated in individuals having preterm deliveries.

**Reptiles.** Organochlorine contaminants, in general, and *p,p'*-DDE specifically, are thought to influence sexual dimorphism in the common snapping turtle (*Chelydra serpentina*) (de Solla et al. 1998). In normal snapping turtles, the cloaca of the female is located very close to the plastron when compared to males. However, snapping turtles in Ontario, Canada, with high *p,p'*-DDE concentrations (mean concentrations of 10.1 ppm at one site and 21.7 ppm at another site) lacked such sexual dimorphism in the distance between cloaca and plastron. De Solla et al. (1998) attributed this lack of sexual dimorphism to the antiandrogenic effects of *p,p'*-DDE.

**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 (*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, FSH and 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 (*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 (*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'*-DDT, *p,p'*-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 (*Anas platyrhynchos*) exposed to 40 ppm *p,p'*-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 (*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).

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'*-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). Egg production was significantly decreased in Japanese quail that were on restricted diets for approximately 10 days prior to dietary exposure to \$700 ppm (lowest level tested) of

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*p,p'*-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'*-DDE for up to 74 days, but not in those fed 100 ppm *p,p'*-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'*-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 (*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 (*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 (Haegele 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 (*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 (*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 compounds) in the diet for up to 10 weeks (Scott et al. 1975). There was no consistent effect on egg

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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 turtle doves fed diets containing 40 ppm of *p,p'*-DDE for 126 days (Haegele and Hudson 1973).

Compared to controls, significantly increased embryo lethality 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 ppm *p,p'*-DDE for 2–3 weeks or for over 1 year; no significant effect on embryo lethality was seen in ducks fed *p,p'*-DDT or technical-grade DDD for over 1 year (Heath et al. 1969). Embryo lethality in intact eggs was 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).

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 *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 *ad libitum* (Keith and Mitchell 1993). See Appendix D.7, Developmental Effects, 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 (*Haliaeetus 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

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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 17 $\beta$ -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.

## D.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<sub>3</sub> – 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

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(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 Appendix D.2, 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  $\text{Ca}^{+2}$  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). The leading 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  $\text{E}_2$  acts as a signal for calcium ATP-ase transport of  $\text{Ca}^{+2}$  (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 (*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 vs. 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 platyrhynchos*) fed 25 ppm *p,p'*-DDT in the diet or 10 ppm *p,p'*-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 or in ducks fed 10 ppm DDT (Heath et al. 1969). Egg breakage, due to significantly decreased eggshell thickness, was increased compared to untreated controls in Mallards (*Anas platyrhynchos*) 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

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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 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 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 (Haeghele and Hudson 1973). Significantly reduced deposition of calcium in eggs (as measured by <sup>45</sup>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 <sup>45</sup>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 platyrhynchos*) fed diets containing 250 ppm DDE for 10 days; no other exposure levels were tested (Peakall et al. 1975).

## D.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 (Crain et al. 1997; Guillette et al. 1995), abnormal ovarian morphology and plasma 17 $\beta$ -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

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hormonal imbalance in Lake Apopka alligators, causing the observed effects (Guillette and Crain 1996). 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 general, reptiles may be particularly susceptible to the endocrine-altering effects of DDT/DDE/DDD, as many reptiles have environmental sex-determining mechanisms compared to the genetic sex-determining mechanisms in birds and mammals (Crain and Guillette 1998).

In birds, the most consistently reported developmental effect is 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 include a decreased ability to thermoregulate and behavioral alterations in chicks of treated parental birds, a reduced testicular development in chicks directly administered DDT, and development of ovarian tissue and oviducts in genetically male sea gulls exposed to DDT in the egg. 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.

**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).

**Reptiles.** Recently, vitellogenin has been used as a biomarker for exposure to estrogenic contaminants (Folmar et al. 1996). 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). 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). 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 µg *p,p'*-DDE/kg of egg painted onto the eggshell; no significant effects were seen in alligators pooled from groups exposed to 0.3 µg *p,p'*-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 ppm), but not in the high exposure group (1 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 warrants further investigation into the dose-response of gender alterations. Treatment (topical application) of eggs of the green sea turtle (*Chelonia mydas*) with *p,p'*-DDE in doses that resulted in up to

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543 ng DDE/g egg (ppb) did not alter the sex ratio from what was expected based on temperature alone (Podreka et al. 1998). Furthermore, incubation time, hatching success, incidence of body deformities, hatching size, and weight were not significantly affected.

**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 platyrhynchos*) 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 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 (Haeghele 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 4<sup>th</sup> 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 platyrhynchos*) 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

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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 8<sup>th</sup> 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).

Fry and Toone (1981) exposed sea gulls (*Larus californicus*), which are much more susceptible to the effects of estrogenic contaminants than domesticated chickens and quail, to different congeners of DDT and DDE. *o,p'*-DDT induced feminization (development of ovaries and oviduct) at all dosages tested (2–100 ppm) in genetically male gulls. *p,p'*-DDE induced such feminization only at high concentrations (20–100 ppm), whereas *p,p'*-DDT caused no abnormalities. Thus, the estrogenic action of *o,p'*-DDT has a gender-reversing effect in birds.

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 4<sup>th</sup> 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).

## D.8 Genotoxic Effects

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

## D.9 Cancer

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

**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife**

Adverse biological effect	<u>Wild mammals, reptiles, and amphibians</u>										
	Short-tailed shrew	Free-tailed bats	Big brown bat	Pipistrelle bat	Common frog	Bull frog	Common toad	Smooth newt	African clawed frog	Red-eared turtle	American alligator
<u>Mortality</u>											
immature					$O_{A,I}^1$						
mature	$O_A^1$	$O_I^5$	$O_A^3$	$O_A^1$		$O_A^1$					
<u>Systemic Effects</u>											
Respiratory											
Cardiovascular											
Gastrointestinal											
Hematological											
Musculoskeletal											
Hepatic liver weight	$NO_I^4$										
Renal											
Endocrine induction of vitellogenin in males									$O_A^2$	$O_A^2$	
Dermal/ocular											
Body weight loss or reduced gain	$NO_{A,I}^4$	$O_I^7$			$O_A^1$						
Metabolic $O_2$ consumption	$O_A^4$ $NO_I^4$										

**TABLE KEY:**

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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 D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

<u>Wild mammals, reptiles, and amphibians (<i>continued</i>)</u>											
Adverse biological effect	Short-tailed shrew	Free-tailed bats	Big brown bat	Pipistrelle bat	Common frog	Bull frog	Common toad	Smooth newt	African clawed frog	Red-eared turtle	American alligator
<u>Immunological/Lymphoreticular</u>											
<u>Neurological/Behavioral</u>											
tremors	O <sub>A</sub> <sup>1</sup>	O <sub>I</sub> <sup>7</sup>	O <sub>A</sub> <sup>3</sup>	O <sub>A</sub> <sup>1</sup>	O <sub>A,I</sub> <sup>4</sup>						
convulsions	O <sub>A</sub> <sup>1</sup>				O <sub>A</sub> <sup>1,4</sup>						
hyperactivity	O <sub>A</sub> <sup>1</sup>				O <sub>I</sub> <sup>4</sup>		O <sub>A</sub> <sup>4</sup>	O <sub>A</sub> <sup>4</sup>			
uncoordinated movement					O <sub>A,I</sub> <sup>1,4</sup> O <sub>I</sub> <sup>4</sup>		O <sub>A</sub> <sup>4</sup>	O <sub>A</sub> <sup>4</sup>			
<u>Reproductive</u>											
testis weight	NO <sub>I</sub> <sup>4</sup>										
<u>Developmental</u>											
facial features					O <sub>A</sub> <sup>1</sup>						
spinal abnormalities					O <sub>I</sub> <sup>1</sup>						
hatchling sex ratio											O <sub>A</sub> <sup>5</sup>
penis size											O <sub>A</sub> <sup>5</sup>
clitoris size											O <sub>A</sub> <sup>5</sup>
induction of vitellogenin in males											NO <sub>A</sub> <sup>5,6</sup>
delayed development					O <sub>I</sub> <sup>1</sup> O <sub>A</sub> <sup>4</sup>						
<u>Genotoxic</u>											
<u>Cancer</u>											

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7 = unspecified DDE;  
8 = p,p'-DDD;  
9 = o,p'-DDD;  
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11 = unspecified DDD;  
12 = DDT/DDE/DDD mixture

**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

<u>Birds: raptors, wading birds, water birds</u>													
Adverse biological effect	Bald eagle	White pelican	American kestrel	Double-crested cormorant	Puffin	Mallard duck	Clapper Rail	Sandhill crane	White Pekin duck	Black duck	Barn owl	Red-tailed hawks	Gull
<u>Mortality</u>													
immature	O <sub>I</sub> <sup>3</sup>		O <sub>C</sub> <sup>5</sup>			O <sub>A,I</sub> <sup>4</sup> O <sub>A</sub> <sup>1,5,10,11</sup>	O <sub>A</sub> <sup>1</sup>						
mature	O <sub>I</sub> <sup>3</sup>		O <sub>C</sub> <sup>5</sup>			O <sub>A,I</sub> <sup>4</sup> O <sub>A</sub> <sup>1</sup>		O <sub>A</sub> <sup>1</sup>			NO <sub>C</sub> <sup>7</sup>		
<u>Systemic Effects</u>													
Respiratory													
Cardiovascular heart weight		NO <sub>I</sub> <sup>12</sup>		NO <sub>I</sub> <sup>12</sup>									
Gastrointestinal													
Hematological hematocrit				NO <sub>I</sub> <sup>12</sup>									
hemoglobin				NO <sub>I</sub> <sup>12</sup>									
Musculoskeletal													
Hepatic													
liver weight		O <sub>I</sub> <sup>12</sup>		O <sub>I</sub> <sup>12</sup>	NO <sub>I</sub> <sup>7</sup>								
vitamin A level		O <sub>I</sub> <sup>12</sup>		O <sub>I</sub> <sup>12</sup>									
microsomal MFO induction			O <sub>C</sub> <sup>7</sup>										
liver carotene level		NO <sub>I</sub> <sup>12</sup>		NO <sub>I</sub> <sup>12</sup>									
serum protein		O <sub>I</sub> <sup>12</sup>		NO <sub>I</sub> <sup>12</sup>									
Renal													
kidney weight		NO <sub>I</sub> <sup>12</sup>											

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7 = unspecified DDE;  
8 = p,p'-DDD;  
9 = o,p'-DDD;  
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11 = unspecified DDD;  
12 = DDT/DDE/DDD mixture

**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

Birds: raptors, wading birds, water birds ( <i>continued</i> )													
Adverse biological effect	Bald eagle	White pelican	American kestrel	Double-crested cormorant	Puffin	Mallard duck	Clapper Rail	Sandhill crane	White Pekin duck	Black duck	Barn owl	Red-tailed hawks	Gull
Endocrine													
adrenal weight						NO <sub>I</sub> <sup>3</sup>							
adrenal cortico-medullary ratio						NO <sub>I</sub> <sup>3</sup>							
thyroid weight						O <sub>I</sub> <sup>3</sup>							
thyroid iodine uptake						O <sub>I</sub> <sup>3</sup>							
plasma cortico-sterone level						NO <sub>I</sub> <sup>3</sup>							
Dermal/ocular													
Body weight loss or reduced gain	O <sub>I</sub> <sup>3</sup>	NO <sub>I</sub> <sup>12</sup>	O <sub>C</sub> <sup>5</sup>			NO <sub>A</sub> <sup>1</sup> O <sub>A</sub> <sup>4</sup>							
Metabolic													
blood urea		NO <sub>I</sub> <sup>12</sup>		NO <sub>I</sub> <sup>12</sup>									
blood K <sup>+</sup>		O <sub>I</sub> <sup>12</sup>								NO <sub>I</sub> <sup>7</sup>			
blood Na <sup>+</sup>		NO <sub>I</sub> <sup>12</sup>		NO <sub>I</sub> <sup>12</sup>						O <sub>I</sub> <sup>7</sup>			
blood phosphorus		NO <sub>I</sub> <sup>12</sup>		NO <sub>I</sub> <sup>12</sup>									
blood Mg <sup>+2</sup>		NO <sub>I</sub> <sup>12</sup>											
blood Ca <sup>+2</sup>		NO <sub>I</sub> <sup>12</sup>		NO <sub>I</sub> <sup>12</sup>						NO <sub>A</sub> <sup>7</sup>			
plasma osmolality										O <sub>I</sub> <sup>7</sup>			
Other													
nasal gland secretion rate						O <sub>A</sub> <sup>7</sup>				NO <sub>A</sub> <sup>7</sup>			

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7 = unspecified DDE;  
8 = p,p'-DDD;  
9 = o,p'-DDD;  
10 = technical grade DDD;  
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12 = DDT/DDE/DDD mixture

**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

Birds: raptors, wading birds, water birds ( <i>continued</i> )													
Adverse biological effect	Bald eagle	White pelican	American kestrel	Double-crested cormorant	Puffin	Mallard duck	Clapper Rail	Sandhill crane	White Pekin duck	Black duck	Barn owl	Red-tailed hawks	Gull
<u>Immunological/Lymphoreticular</u> hepatitis susceptibility spleen weight serum immuno-globulins		NO <sub>I</sub> <sup>12</sup>  NO <sub>I</sub> <sup>12</sup>		NO <sub>I</sub> <sup>12</sup>		NO <sub>A</sub> <sup>1</sup>							
<u>Neurological/Behavioral</u> tremors brain weight convulsions predatory behavior social peck dominance	O <sub>I</sub> <sup>3</sup>	NO <sub>I</sub> <sup>12</sup>	O <sub>C</sub> <sup>5</sup>  NO <sub>I</sub> <sup>5</sup>	O <sub>I</sub> <sup>12</sup> NO <sub>I</sub> <sup>12</sup> O <sub>I</sub> <sup>12</sup>		NO <sub>I</sub> <sup>3</sup>							
<u>Reproductive</u> egg production  egg size/weight embryo survival  spermatogenesis testicular lesions egg lipid content egg fertility timing of oviposition egg hatchability	NO <sub>I</sub> <sup>3</sup> O <sub>I</sub> <sup>3</sup>		NO <sub>I,C</sub> <sup>4</sup>  O <sub>I,C</sub> <sup>4</sup>  NO <sub>I,C</sub> <sup>4</sup>  O <sub>I,C</sub> <sup>4</sup>			NO <sub>C</sub> <sup>1,3,5,10</sup> NO <sub>I</sub> <sup>1,5,7,10</sup>  NO <sub>I,C</sub> <sup>1,10</sup> O <sub>I,C</sub> <sup>5</sup>  O <sub>I</sub> <sup>7</sup> O <sub>I</sub> <sup>7</sup>				NO <sub>I</sub> <sup>5</sup>  O <sub>I</sub> <sup>5</sup>	O <sub>I,C</sub> <sup>7</sup>  NO <sub>I,C</sub> <sup>7</sup>  NO <sub>I,C</sub> <sup>7</sup>		

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8 = p,p'-DDD;  
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11 = unspecified DDD;  
12 = DDT/DDE/DDD mixture

**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

Birds: raptors, wading birds, water birds ( <i>continued</i> )													
Adverse biological effect	Bald eagle	White pelican	American kestrel	Double-crested cormorant	Puffin	Mallard duck	Clapper Rail	Sandhill crane	White Pekin duck	Black duck	Barn owl	Red-tailed hawks	Gull
<u>Eggshell Thinning</u>													
egg breakage			O <sub>i,c</sub> <sup>4</sup>			O <sub>i,c</sub> <sup>1,5</sup> NO <sub>c</sub> <sup>10</sup>				O <sub>i</sub> <sup>5</sup>	O <sub>i,c</sub> <sup>7</sup>		
eggshell thickness			O <sub>i,c</sub> <sup>4</sup>			O <sub>c</sub> <sup>1,5</sup> O <sub>i</sub> <sup>1,5,7</sup> NO <sub>c</sub> <sup>10</sup>			O <sub>A</sub> <sup>7</sup>	O <sub>i</sub> <sup>5</sup>	O <sub>i,c</sub> <sup>7</sup>		
<u>Developmental</u>													
chick behavior						O <sub>i</sub> <sup>5</sup>							
chick early survival			O <sub>i,c</sub> <sup>4</sup>			NO <sub>i,c</sub> <sup>5,10</sup> O <sub>i,c</sub> <sup>1</sup> O <sub>i</sub> <sup>7</sup> O <sub>i</sub> <sup>7</sup>				O <sub>i</sub> <sup>5</sup>			
nestling weight												NO <sub>i</sub> <sup>3</sup>	
nestling foot pad growth												NO <sub>i</sub> <sup>3</sup>	
nestling plumage development												NO <sub>i</sub> <sup>3</sup>	
chick thermo regulation						O <sub>i</sub> <sup>7</sup>							
testicular feminization													O <sub>i</sub> <sup>2,12</sup>
abnormal oviducts													O <sub>i</sub> <sup>2,12</sup>
<u>Genotoxic</u>													
<u>Cancer</u>													

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8 = p,p'-DDD;  
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12 = DDT/DDE/DDD mixture

**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

Adverse Biological Effect	Birds: gallinaceous birds						
	Bobwhite quail	Japanese quail	California quail	Pharol D-1 quail	Crowned Guinea fowl	Domestic fowl	Ring-necked pheasant
<u>Mortality</u>							
immature	O <sub>I</sub> <sup>4,5</sup> O <sub>A</sub> <sup>3,4,5,10</sup>	NO <sub>C</sub> <sup>4</sup> O <sub>A</sub> <sup>4,5,10</sup>	O <sub>A</sub> <sup>3,11</sup>				O <sub>I</sub> <sup>4,5</sup> O <sub>A</sub> <sup>1,4,5,10,11</sup>
mature	O <sub>A</sub> <sup>3,4</sup> O <sub>I</sub> <sup>4,5</sup> NO <sub>I</sub> <sup>4</sup>	O <sub>A</sub> <sup>1,2</sup> O <sub>I</sub> <sup>1</sup> NO <sub>C</sub> <sup>4</sup>					O <sub>A</sub> <sup>4</sup> O <sub>I</sub> <sup>3,4,5</sup>
<u>Systemic Effects</u>							
Respiratory gross lung lesions							NO <sub>I</sub> <sup>3</sup>
Cardiovascular gross heart lesions							NO <sub>I</sub> <sup>3</sup>
Gastrointestinal							
Hematological hemoglobin RBC count		NO <sub>I</sub> <sup>5</sup>			O <sub>A</sub> <sup>3</sup> O <sub>A</sub> <sup>3</sup>	NO <sub>I</sub> <sup>4</sup> O <sub>I</sub> <sup>4</sup> NO <sub>I</sub> <sup>4</sup>	
hematocrit	O <sub>I</sub> <sup>3</sup>	NO <sub>I</sub> <sup>5</sup>			O <sub>A</sub> <sup>3</sup>	NO <sub>I</sub> <sup>4</sup>	
Musculoskeletal gross muscle lesions							NO <sub>I</sub> <sup>3</sup>

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6 = o,p'-DDE;

7 = unspecified DDE;  
8 = p,p'-DDD;  
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12 = DDT/DDE/DDD mixture

**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

<u>Birds: gallinaceous birds (<i>continued</i>)</u>							
Adverse Biological Effect	Bobwhite quail	Japanese quail	California quail	Pharol D-1 quail	Crowned Guinea fowl	Domestic fowl	Ring-necked pheasant
Hepatic							
liver weight	O <sub>I</sub> <sup>3</sup>	NO <sub>I</sub> <sup>1,2,4,5,8</sup>				NO <sub>I</sub> <sup>1</sup>	
plasma hepatic enzyme activity		O <sub>I</sub> <sup>5</sup>				NO <sub>A</sub> <sup>3</sup>	
liver microsomal enzyme activity		O <sub>I</sub> <sup>5</sup>			O <sub>A</sub> <sup>3</sup>		
microsomal protein level		O <sub>A</sub> <sup>1,2,5,6,8,9</sup>				O <sub>A,I</sub> <sup>3</sup>	
liver lipid		O <sub>I</sub> <sup>1,4,5,8</sup>					
liver microscopic lesions		NO <sub>I</sub> <sup>3</sup>					
blood cholesterol		NO <sub>I</sub> <sup>4</sup>				NO <sub>A</sub> <sup>3</sup>	
serum lipid	O <sub>I</sub> <sup>3</sup>						NO <sub>I</sub> <sup>3</sup>
serum protein		NO <sub>A,I</sub> <sup>2</sup>			O <sub>A</sub> <sup>3</sup>	O <sub>A</sub> <sup>9</sup>	
fibrinogen level					NO <sub>A</sub> <sup>3</sup>	NO <sub>I</sub> <sup>4</sup>	
prothrombin time						NO <sub>I</sub> <sup>4</sup>	
microsomal hormone metabolism	O <sub>I</sub> <sup>3</sup>					O <sub>A,I</sub> <sup>3</sup>	
Renal							
gross kidney lesions							NO <sub>I</sub> <sup>3</sup>
Endocrine							
adrenal weight	NO <sub>I</sub> <sup>3</sup>					NO <sub>I</sub> <sup>1</sup>	
adrenal microscopic lesions	O <sub>I</sub> <sup>3</sup>					O <sub>A</sub> <sup>9</sup>	
thyroid weight	O <sub>I</sub> <sup>3</sup>						
thyroid iodine uptake	O <sub>I</sub> <sup>3</sup>						
adrenal histology	O <sub>I</sub> <sup>3</sup>						
blood sugar level					O <sub>A</sub> <sup>3</sup>	NO <sub>I</sub> <sup>4</sup>	
Dermal/ocular							

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12 = DDT/DDE/DDD mixture

**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

<u>Birds: gallinaceous birds (<i>continued</i>)</u>							
Adverse Biological Effect	Bobwhite quail	Japanese quail	California quail	Pharol D-1 quail	Crowned Guinea fowl	Domestic fowl	Ring-necked pheasant
Body weight loss or reduced gain	NO <sub>I</sub> <sup>4</sup> O <sub>A</sub> <sup>3</sup>	NO <sub>I</sub> <sup>1,2,5</sup> O <sub>A</sub> <sup>2</sup> NO <sub>C</sub> <sup>4</sup>				NO <sub>I</sub> <sup>1,4</sup> O <sub>A</sub> <sup>3</sup>	O <sub>I</sub> <sup>4</sup>
decreased food consumption						O <sub>A</sub> <sup>3</sup>	
Metabolic							
oxygen consumption	NO <sub>I</sub> <sup>3</sup>				O <sub>A</sub> <sup>3</sup>		
blood urea					O <sub>A</sub> <sup>3</sup>		
blood K <sup>+</sup>							
blood calcium	O <sub>I</sub> <sup>4</sup>	NO <sub>A,I</sub> <sup>2</sup>				NO <sub>I</sub> <sup>4</sup> NO <sub>A</sub> <sup>3</sup>	
blood Na <sup>+</sup>					NO <sub>A</sub> <sup>3</sup>		
blood lactic acid					NO <sub>A</sub> <sup>3</sup>		
blood osmolarity							
blood phosphorous						NO <sub>I</sub> <sup>4</sup>	
blood pCO <sub>2</sub>		O <sub>I</sub> <sup>3</sup>			O <sub>A</sub> <sup>3</sup>		
blood pO <sub>2</sub>					NO <sub>A</sub> <sup>3</sup>		
blood pH					NO <sub>A</sub> <sup>3</sup>		
<u>Immunological/Lymphoreticular</u>							
spleen weight						NO <sub>I</sub> <sup>1</sup>	
bursa weight						NO <sub>I</sub> <sup>1</sup>	
bursal lesions						O <sub>I</sub> <sup>1</sup>	
BSA antibody formation						O <sub>I</sub> <sup>1</sup>	
SRBC plaque-forming cells						NO <sub>I</sub> <sup>1</sup>	
serum immunoglobulins						O <sub>I</sub> <sup>1</sup>	
phagocytic index						NO <sub>I</sub> <sup>1</sup>	

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**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

Adverse Biological Effect	<u>Birds: gallinaceous birds (<i>continued</i>)</u>						
	Bobwhite quail	Japanese quail	California quail	Pharol D-1 quail	Crowned Guinea fowl	Domestic fowl	Ring-necked pheasant
<u>Neurological/Behavioral</u>							
tremors	O <sub>A</sub> <sup>3</sup>	NO <sub>I</sub> <sup>5</sup> O <sub>I</sub> <sup>1</sup> O <sub>A</sub> <sup>4</sup>		O <sub>I</sub> <sup>1</sup>			O <sub>I</sub> <sup>3</sup>
convulsions	O <sub>A</sub> <sup>3</sup>	NO <sub>I</sub> <sup>5</sup>				O <sub>A,I</sub> <sup>1</sup>	
ataxia							
loss of balance	O <sub>A</sub> <sup>3</sup>						
gross brain lesions							NO <sub>I</sub> <sup>3</sup>
uncoordinated movement							O <sub>I</sub> <sup>3</sup>

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**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

<u>Birds: gallinaceous birds (<i>continued</i>)</u>							
Adverse Biological Effect	Bobwhite quail	Japanese quail	California quail	Pharol D-1 quail	Crowned Guinea fowl	Domestic fowl	Ring-necked pheasant
<u>Reproductive</u>							
egg hatchability	O <sub>I</sub> <sup>4</sup>	NO <sub>A</sub> <sup>3</sup> NO <sub>I</sub> <sup>12</sup> NO <sub>C</sub> <sup>4</sup>				NO <sub>I</sub> <sup>12</sup>	NO <sub>I</sub> <sup>3</sup>
egg production	NO <sub>I</sub> <sup>4</sup>	O <sub>I</sub> <sup>1,3,5</sup> NO <sub>I</sub> <sup>1,5,12</sup> NO <sub>C</sub> <sup>4</sup>		NO <sub>I</sub> <sup>1</sup>		NO <sub>I</sub> <sup>1</sup> NO <sub>A</sub> <sup>3</sup>	NO <sub>I</sub> <sup>3</sup>
egg size/weight	O <sub>I</sub> <sup>4</sup>					NO <sub>I</sub> <sup>1</sup>	
egg fertility	O <sub>I</sub> <sup>4</sup>	NO <sub>C</sub> <sup>4</sup>					NO <sub>I</sub> <sup>3</sup>
timing of oviposition		O <sub>I</sub> <sup>1,3,5</sup>					
ovary weight		O <sub>I</sub> <sup>1</sup>					
oviduct weight		NO <sub>A</sub> <sup>2</sup> NO <sub>A</sub> <sup>2</sup>				O <sub>A</sub> <sup>2</sup>	
testis weight		O <sub>A</sub> <sup>2</sup> NO <sub>I</sub> <sup>2</sup> O <sub>I</sub> <sup>1</sup>				O <sub>I</sub> <sup>4</sup>	
testicular atrophy						O <sub>I</sub> <sup>4</sup>	
semen volume						O <sub>I</sub> <sup>4</sup>	
percentage viable sperm						O <sub>I</sub> <sup>4</sup>	
sperm motility						O <sub>I</sub> <sup>4</sup>	
sperm concentration						O <sub>I</sub> <sup>4</sup>	
semen cholesterol						O <sub>I</sub> <sup>4</sup>	
testicular microscopic lesions						O <sub>I</sub> <sup>4</sup>	
gross gonad lesions							NO <sub>I</sub> <sup>3</sup>
decreased plasma estrogen						O <sub>A</sub> <sup>3</sup> O <sub>A</sub> <sup>2</sup>	
uterine glycogen		O <sub>A</sub> <sup>2</sup> NO <sub>A</sub> <sup>1</sup>				NO <sub>A</sub> <sup>1</sup>	

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**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

<u>Birds: gallinaceous birds (<i>continued</i>)</u>							
Adverse Biological Effect	Bobwhite quail	Japanese quail	California quail	Pharol D-1 quail	Crowned Guinea fowl	Domestic fowl	Ring-necked pheasant
<u>Eggshell Thinning</u>							
eggshell calcium		O <sub>I</sub> <sup>1</sup>				NO <sub>I</sub> <sup>1</sup>	
eggshell thickness	O <sub>I</sub> <sup>4</sup>	NO <sub>I</sub> <sup>5</sup> NO <sub>I</sub> <sup>1,5</sup>		NO <sub>I</sub> <sup>1</sup>		NO <sub>I</sub> <sup>1</sup> NO <sub>A</sub> <sup>3</sup> NO <sub>I</sub> <sup>1</sup>	
eggshell weight		NO <sub>I</sub> <sup>1,5</sup> O <sub>I</sub> <sup>3</sup>		NO <sub>I</sub> <sup>1</sup>		NO <sub>I</sub> <sup>12</sup>	
egg breakage		NO <sub>I</sub> <sup>1,5,12</sup>					
egg membrane thickness	O <sub>I</sub> <sup>4</sup>						
<u>Developmental</u>							
chick survival		O <sub>A</sub> <sup>3</sup> NO <sub>C</sub> <sup>4</sup>					O <sub>I</sub> <sup>3,4</sup>
testis development						O <sub>I</sub> <sup>4</sup>	
secondary sex characteristics						O <sub>I</sub> <sup>4</sup>	
chick weight	NO <sub>I</sub> <sup>4</sup>	NO <sub>C</sub> <sup>4</sup>					
<u>Genotoxic</u>							
<u>Cancer</u>							

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**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

<u>Birds: passerines and non-passerine ground birds</u>											
Adverse biological effect	House sparrow	Cowbird	Red-winged blackbird	Blue jay	Cardinal	Ringed turtle dove	Rock dove	Pigeons (homing and white king)	Bengalese finch	Redstart	White-throated sparrow
<u>Mortality</u>											
immature	O <sub>A</sub> <sup>3</sup>			O <sub>A</sub> <sup>3</sup>	O <sub>A</sub> <sup>3</sup>						
mature	O <sub>A</sub> <sup>4</sup>	O <sub>A</sub> <sup>1</sup>	O <sub>A,I</sub> <sup>4</sup>				O <sub>A</sub> <sup>4</sup>		O <sub>I</sub> <sup>1</sup>		
<u>Systemic Effects</u>											
<u>Respiratory</u>											
Cardiovascular											
pulse rate								O <sub>I</sub> <sup>1</sup>	O <sub>I</sub> <sup>1</sup>		
ventricular beat								O <sub>I</sub> <sup>1</sup>	NO <sub>I</sub> <sup>1</sup>		
amplitude								O <sub>I</sub> <sup>1,5</sup>	O <sub>I</sub> <sup>1</sup>		
heart weight								O <sub>I</sub> <sup>5</sup>			
heart muscle tone											
<u>Gastrointestinal</u>											
Hematological											
hematocrit							O <sub>I</sub> <sup>7</sup>				
Musculoskeletal											
soft skull								O <sub>I</sub> <sup>5</sup>			
calcium uptake in bone							O <sub>I</sub> <sup>1</sup>				
<u>Hepatic</u>											
liver weight						O <sub>I</sub> <sup>7</sup>		O <sub>I</sub> <sup>1,5</sup>		NO <sub>A</sub> <sup>1</sup>	
plasma aspartate aminotransferase						O <sub>I</sub> <sup>7</sup>					
vitamin A storage								O <sub>I</sub> <sup>1</sup>			
hypertrophy								O <sub>I</sub> <sup>1</sup>			
microsomal hormone metabolism						O <sub>I</sub> <sup>1,3</sup>		O <sub>A</sub> <sup>1</sup>			
<u>Renal</u>											
kidney weight										NO <sub>A</sub> <sup>1</sup>	

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<u>Birds: passerines and non-passerine ground birds (<i>continued</i>)</u>											
Adverse biological effect	House sparrow	Cowbird	Red- winged blackbird	Blue jay	Cardinal	Ringed turtle dove	Rock dove	Pigeons (homing and white king)	Bengalese finch	Redstart	White- throated sparrow
Endocrine											
adrenal weights								O <sub>I</sub> <sup>1,5</sup>			
thyroid weight								O <sub>I</sub> <sup>1</sup>			
hyperplasia of thyroid follicular epithelium								O <sub>I</sub> <sup>1</sup>			
decreased follicular colloid								O <sub>I</sub> <sup>1</sup>			
Dermal/ocular											
Body weight											
loss or reduced gain	O <sub>A</sub> <sup>3</sup>					NO <sub>I</sub> <sup>7</sup>		O <sub>I</sub> <sup>5</sup>		NO <sub>A</sub> <sup>1</sup>	O <sub>I</sub> <sup>3</sup> NO <sub>I</sub> <sup>5</sup>
decreased body fat											O <sub>I</sub> <sup>3</sup> NO <sub>I</sub> <sup>5</sup>
Metabolic rate											
body temperature								O <sub>I</sub> <sup>1</sup>			
oxygen consumption rate								O <sub>I</sub> <sup>1</sup>			
blood Na <sup>+</sup>						O <sub>I</sub> <sup>7</sup>					
blood K <sup>+</sup>						NO <sub>I</sub> <sup>7</sup>					
blood Ca <sup>+2</sup>						NO <sub>I</sub> <sup>7</sup>					
Other											
activity of various dehydrogenases in various tissues										NO <sub>A</sub> <sup>1</sup>	
Immunological/ Lymphoreticular											

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<u>Birds: passerines and non-passerine ground birds (<i>continued</i>)</u>											
Adverse biological effect	House sparrow	Cowbird	Red-winged blackbird	Blue jay	Cardinal	Ringed turtle dove	Rock dove	Pigeons (homing and white king)	Bengalese finch	Redstart	White-throated sparrow
<u>Neurological/Behavioral</u>											
tremors	O <sub>A</sub> <sup>3,4</sup>	O <sub>A</sub> <sup>1</sup>		O <sub>A</sub> <sup>3</sup>	O <sub>A</sub> <sup>3</sup>			O <sub>I</sub> <sup>1,5</sup>			
balance disturbance	O <sub>A</sub> <sup>3</sup>			O <sub>A</sub> <sup>3</sup>	O <sub>A</sub> <sup>3</sup>						
affected courtship behavior						O <sub>I</sub> <sup>5</sup>					
brain dopamine						NO <sub>I</sub> <sup>5</sup>					
brain norepinephrine						O <sub>I</sub> <sup>7</sup>					
brain weight						O <sub>I</sub> <sup>7</sup>				NO <sub>A</sub> <sup>1</sup>	
migratory behavior											O <sub>I</sub> <sup>3,7</sup>
nesting behavior						O <sub>I</sub> <sup>5</sup>					
activity pattern										NO <sub>A</sub> <sup>1</sup>	
<u>Reproductive</u>											
egg hatchability						NO <sub>I</sub> <sup>5</sup>					
egg production						O <sub>I</sub> <sup>5</sup>					
testis weight						NO <sub>I</sub> <sup>5</sup>					
clutch size						NO <sub>I</sub> <sup>5</sup>					
ovary weight						O <sub>I</sub> <sup>5</sup>			NO <sub>I</sub> <sup>1</sup>		
oviduct weight						O <sub>I</sub> <sup>5</sup>			NO <sub>I</sub> <sup>1</sup>		
timing of oviposition						O <sub>I</sub> <sup>1,5</sup>					
egg size/weight						O <sub>I</sub> <sup>1</sup>			O <sub>I</sub> <sup>1</sup>		
serum LH levels						O <sub>I</sub> <sup>5</sup>					
blood estradiol levels						O <sub>I</sub> <sup>1</sup>					
<u>Eggshell Thinning</u>											
eggshell weight						O <sub>A</sub> <sup>5</sup>					
eggshell thickness						O <sub>I</sub> <sup>5,7</sup>					
<sup>45</sup> Ca deposition in egg						O <sub>I</sub> <sup>1</sup>					
oviduct carbonic anhydrase activity						O <sub>A</sub> <sup>5</sup>					

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**Table D-1. DDT/DDE/DDD Hazard Identification in Wildlife: Health Effects Observed in Experimental Toxicological Studies in Wildlife (*continued*)**

<u>Birds: passerines and non-passerine ground birds (<i>continued</i>)</u>											
Adverse biological effect	House sparrow	Cowbird	Red-winged blackbird	Blue jay	Cardinal	Ringed turtle dove	Rock dove	Pigeons (homing and white king)	Bengalese finch	Redstart	White-throated sparrow
<u>Developmental</u> chick early survival						O <sub>I</sub> <sup>5</sup>					
<u>Genotoxic</u>											
<u>Cancer</u>											

**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

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