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Health Effects Support Document for 1,1-Dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE)

Health Effects Support Document for 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE)

U.S. Environmental Protection Agency
Office of Water (4304T)
Health and Ecological Criteria Division
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FOREWORD

The Safe Drinking Water Act (SDWA), as amended in 1996, requires the Administrator of the Environmental Protection Agency (EPA) to establish a list of contaminants to aid the Agency in regulatory priority setting for the drinking water program. In addition, the SDWA requires EPA to make regulatory determinations for no fewer than five contaminants by August 2001 and every five years thereafter. The criteria used to determine whether or not to regulate a chemical on the Contaminant Candidate List (CCL) are the following:

- The contaminant may have an adverse effect on the health of persons.
- The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern.
- In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The Agency's findings for all three criteria are used in making a determination to regulate a contaminant. The Agency may determine that there is no need for regulation when a contaminant fails to meet one of the criteria. The decision not to regulate is considered a final Agency action and is subject to judicial review.

This document provides the health effects basis for the regulatory determination for DDE. In arriving at the regulatory determination, data on toxicokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology, and mechanisms of toxicity were evaluated. In order to avoid wasteful duplication of effort, information from the following risk assessments by the EPA and other government agencies were used in development of this document.

ATSDR (Agency for Toxic Substances and Disease Registry). 2002. Toxicological profile for DDT, DDE, and DDD (2002 update). Department of Health and Human Services. Available from: <http://www.atsdr.cdc.gov/toxprofiles/tp35.html>. MRLs posted at: <http://www.atsdr.cdc.gov/mrls.html>.

U.S. EPA (United States Environmental Protection Agency). 1988b. Integrated Risk Information System (IRIS): *p,p*'-Dichlorodiphenyldichloroethylene (DDE). Cincinnati, OH. Available from: <http://www.epa.gov/iris/subst/0328.htm>.

WHO (World Health Organization). 2004. DDT and its derivatives in drinking water: Background document for the development of the WHO guideline for drinking water quality. Available from: <http://www.who.int/water_sanitation_health/dwq/chemicals/ddt/en/>.

Information from the published risk assessments was supplemented with information from the primary references for key studies and recent studies of DDE identified by a literature search conducted in 2004.

A reference dose (RfD) is provided as the assessment of long-term toxic effects other than carcinogenicity. RfD determination assumes that thresholds exist for certain toxic effects, such as cellular necrosis, significant body or organ weight changes, blood disorders, etc. It is expressed in terms of milligrams per kilogram per day (mg/kg-day). In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

The carcinogenicity assessment for DDE includes a formal hazard identification and an estimate of tumorigenic potency when available. Hazard identification is a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen via the oral route and of the conditions under which the carcinogenic effects may be expressed.

Development of these hazard identification and dose-response assessments for DDE has followed the general guidelines for risk assessment as set forth by the National Research Council (1983). EPA guidelines that were used in the development of this assessment may include the following: *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986a), *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986b), *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991), *Guidelines for Reproductive Toxicity Risk Assessment* (U.S. EPA, 1996), *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998a), *Guidelines for Carcinogen Assessment* (U.S. EPA 2005a), *Recommendations for and Documentation of Biological Values for Use in Risk Assessment* (U.S. EPA, 1988a), (proposed) *Interim Policy for Particle Size and Limit Concentration Issues in Inhalation Toxicity* (U.S. EPA, 1994a), *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994b), *Use of the Benchmark Dose Approach in Health Risk Assessment* (U.S. EPA, 1995), *Science Policy Council Handbook: Peer Review* (U.S. EPA, 1998b, 2000a), *Science Policy Council Handbook: Risk Characterization* (U.S. EPA, 2000b), *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2000c), *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 2000d), and *A Review of the Reference Dose and Reference Concentration Processes* (U.S. EPA, 2002a).

The chapter on occurrence and exposure to DDE through potable water was developed by the Office of Ground Water and Drinking Water. It is based primarily on first Unregulated Contaminant Monitoring Rule (UCMR 1) data collected under the SDWA. The UCMR 1 data are supplemented with ambient water data, as well as data from the States, and published papers on occurrence in drinking water.

ACKNOWLEDGMENT

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1.0 EXECUTIVE SUMMARY

The U.S. Environmental Protection Agency (EPA) has prepared this Health Effects Support Document for 1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE) to assist in determining whether to regulate DDE with a National Primary Drinking Water Regulation (NPDWR). The available data on occurrence, exposure, and other risk considerations suggest that, because DDE does not occur in public water systems at frequencies and levels of public health concern, regulating DDE will not present a meaningful opportunity to reduce health risk. EPA will present a determination and further analysis in the Federal Register Notice covering the Contaminant Candidate List (CCL) regulatory determinations.

DDE (Chemical Abstracts Services Registry Number 72-55-9) has never been produced commercially, but is a primary environmental and metabolic degradation product of the pesticide DDT. Although all uses of DDT in the U.S. were cancelled on January 1, 1973, DDT and DDE remain in the environment because they are persistent and bioaccumulative. Also, DDT is still used in other parts of the world.

Occurrence data indicate that DDE was not detected at concentrations above the minimum reporting level (MRL; 0.8 µg/L) in any small public water systems. DDE was detected at one monitored large groundwater system. This system represented 0.03% of large public water systems and 0.01% of the population served by them (approximately 18,000 people). Because the MRL for DDE monitoring is greater than half the Health Reference Level (½HRL or 0.1 µg/L) and the full HRL (HRL or 0.2 µg/L), it cannot be stated how many samples may have contained DDE at the HRL or ½ the HRL. DDE has been detected in ambient surface water samples, but none of the detections were greater than ½HRL, or the full HRL. Accordingly, DDE is not likely to occur in public water systems at concentrations of concern. Moreover, based on the occurrence of DDE in food items (at concentrations up to 0.102 ppm) and the estimated DDE intake due to food consumption (up to 0.0441 µg/kg body weight/day), foods are likely a greater source of DDE exposure than drinking water.

Health effects information has identified both cancer and non-cancer effects associated with exposure to DDE. DDE has been associated with reduced body weight gain, and neurological, liver and kidney effects in laboratory animals. DDE has also been found to be an antiandrogenic compound, which may explain a number of reproductive and developmental effects seen in male rats exposed to DDE at various ages. Oral exposure to DDE has been associated with increases in the incidence of liver tumors, including carcinomas, in two strains of mice and in hamsters, as well as nonsignificant increases in the incidence of thyroid tumors in female rats and adrenal tumors in hamsters. There have also been several human epidemiology studies of DDE and cancer, but overall these studies have yielded conflicting results.

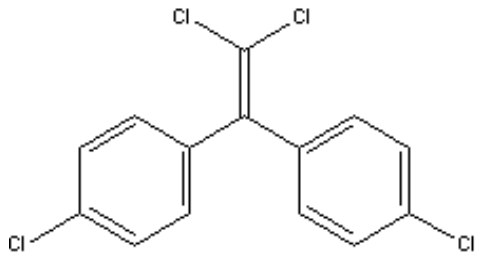
The DDE HRL of 0.2 µg/L is based on female mouse hepatocellular carcinomas data. This number was derived using the oral slope factor of 1.7×10^{-1} $(mg/kg\text{-}day)^{-1}$ and default exposure assumptions of 70 kg body weight and 2 L per day drinking water ingestion.

2.0 IDENTITY: CHEMICAL AND PHYSICAL PROPERTIES

1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethylene, or *p*,*p*'-dichlorodiphenyldichloroethylene (*p*,*p*'-DDE), in its pure form is a white, crystalline solid, soluble in fats and most organic solvents, but practically insoluble in water. DDE was an impurity (up to 4%) in commercial DDT pesticide formulations and never has been produced commercially (NCI, 1978). DDE is also produced as a break-down product of DDT by the environmental degradation or metabolism.

The DDE that was used in the NCI (1978) studies was purchased from Aldrich Chemical Company and was nearly pure *p*,*p*-DDE isomer based on its melting point. Many of the recently published studies of DDE also purchased the chemical from the Aldrich Chemical Company and reported the purity as >99% (You et al., 1999a,b). For the remainder of this document, the abbreviation DDE will refer to the *p*,*p*'-DDE isomer. In cases where a second isomer was utilized (*o*,*p*-DDE), the differing orientation of the chlorines in the molecule will be specified. The chemical structure of *p*,*p*'-dichlorodiphenyldichloroethylene is shown above (Figure 2-1). Its physical and chemical properties, and other reference information are listed in Table 2-1.

Figure 2-1 Chemical Structure of *p*,*p*'-Dichlorodiphenyldichloroethylene



Source: Chemfinder (2004)

Table 2-1 Chemical and Physical Properties of *p,p*'-Dichlorodiphenyldichloroethylene

Property	Information
Chemical Abstracts Registry (CAS) No.	72-55-9
EPA Pesticide Chemical Code	NA
Synonyms	4,4'-DDE *p,p'*-DDE DDE 2,2-bis(4-chlorophenyl)-1,1-dichloroethene 2,2-bis(p-chlorophenyl)-1,1-dichloroethylene DDT Dehydrochloride 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene Dichlorodiphenyldichloroethylene Dichlorodiphenyldichloroethylene, P,p'- 1,1'-dichloroethenylidene)bis(4-chlorobenzene) Ethylene, 1,1-dichloro-2,2-bis(p-chlorophenyl)-
Registered Trade Name(s)	No data
Chemical Formula	$C_{14}H_8Cl_4$
Molecular Weight	318.03
Physical State	Crystalline solid
Boiling Point	336 °C
Melting Point	80-94 °C
Density (at 20 °C)	No data
Vapor Pressure:	
At 20 °C	No data
At 25 °C	6.0×10^{-6} mm Hg
Partition Coefficients:	
Log K_{ow}	6.956 (Range of published literature: 4.88-7.2)
Log K_{oc}	4.70
Solubility in:	
Water	0.12 mg/L at 25 °C (Range of publ. literature: 0.0011-0.12 mg/L)
Other Solvents	lipids and most organic solvents
Conversion Factors (at 25 °C, 1 atm)	1 ppm= 13.01 mg/m^3 1 mg/m^3= 0.077 ppm

Source(s): ATSDR (2002); HSDB (2004); U.S. EPA (1988b); USGS (2001a)

3.0 USES AND ENVIRONMENTAL FATE

3.1 Production and Use

Currently, DDE is not commercially produced in the United States and has no commercial use. It is a degradation product and impurity of the once commercially produced pesticide, DDT (HSDB, 2004). DDE is the product of the dehydrohalogenation of DDT (loss of one molecule of hydrochloric acid). DDT was once widely used in the U.S. as a broad spectrum organochlorine pesticide to control insects in agriculture and insects that carry diseases such as malaria and typhus (Gianessi and Puffer, 1992). Production of DDT in the United States was at its peak in 1962 when 85,000 tons of chemical were produced and 334 agricultural products using DDT were registered (Metcalf, 1995). DDT production in the United States declined from 82 million kg in 1962 to 2 million kg in 1971. On January 1, 1973, all uses of DDT in the United States were canceled, except for emergency public health uses and a few other uses permitted on a case-by-case basis. In smaller quantities, DDT production for export continued as late as the 1980s (ATSDR, 2002; HSDB, 2004). Currently, DDT is not produced commercially in the United States, but is still used in other countries. Until recently, DDT was produced and used in Mexico; however, the production was ended in 1997 and use was phased-out by 2000 under the North American Agreement on Environmental Cooperation (Meister and Sine, 1999; CEC, 2003). Analytical studies have revealed that DDE may be a contaminant in technical grade insecticide dicofol (Risebrough et al., 1986). In addition, DDE can be a product of the degradation of 1,1,2,2-tetrachloro-2,2-bis(*p*-chlorophenyl)ethane, another DDT-related impurity in dicofol (ATSDR, 2002).

3.2 Environmental Release

DDE is found in the environment as a result of contamination or breakdown of DDT. Although DDT is no longer produced or used in the United States, the insecticide is still used in other parts of the world. DDE currently found in the environment may be persistent residues from earlier use of DDT or may be recently deposited following long-range atmospheric transport from areas where DDT is still released to the environment. DDT that has entered the atmosphere via spraying or volatilization can contaminate soils and surface waters by both wet and dry deposition. In soil, DDT biodegrades to DDE under unflooded (generally aerobic) conditions and to DDD (dichlorodiphenyldichloroethane) under flooded (generally anaerobic) conditions (ATSDR, 2002).

Among the 1613 hazardous waste sites in the United States and its territories that have been considered as candidates for inclusion in EPA's National Priorities List (NPL), at least 441 are known to be contaminated with DDT, DDE, and/or DDD. *p,p*'-DDE was found at 219 of these sites. While not specifically targeted, *o,p*'-DDE was also present in at least four sites. Of the 441 hazardous waste sites in which DDT, DDE, or DDD was detected, the contaminants were identified in air samples at 32 sites, in surface water samples at 101 sites, in ground water samples at 247 sites, and in sediment samples at 305 sites (HazDat, 2002).

3.3 Environmental Fate

Air

During its period of agricultural use, DDT was sprayed primarily onto crops, forest lands, surface water, and residential areas. Since DDE is an impurity and degradation product of DDT, application of DDT led to the presence of DDE to the environment. In the atmosphere, DDE may exist in the vapor phase, based on the vapor pressure of $6x10^{-6}$ mm Hg at 25°C, or it can be adsorbed onto particulate matter after release into the atmosphere (HSDB, 2004). In the atmosphere, vapor-phase DDE reacts with photochemically-produced hydroxyl radicals and the estimated half-life ranges from 17 hours to 2 days (Meylan and Howard, 1993). The longer half-life was calculated from its estimated rate constant of $7.4x10^{-12}$ cm^3/molecule-sec at 25°C as determined from a structure estimation method (Meylan and Howard, 1993). The reported atmospheric half-life in sunlight at 40° latitude was calculated to range from 0.9 days in summer to 6.1 days in winter (Callahan et al., 1979; Zepp and Cline, 1977). DDE is expected to undergo direct photolysis since this compound absorbs light at wave lengths greater than 290 nm. Freitag et al. (1979) observed 20% photomineralization of DDE when it was applied to a silica gel irradiated with UV radiation (wavelengths >290 nm) for 7 days.

Particulate-phase DDE may be removed from the air by wet and dry deposition. Particle-phase atmospheric DDE may be subject to long-range transport, which may be responsible for the DDE present at sites distant from where DDT was applied. DDE's vapor pressure of $6x10^{-6}$ mm Hg (Bidleman, 1984) and Henry's Law constant of $4.16x10^{-5}$ atm-m^3/mole (Altschuh, 1999) predict that it will volatilize from moist soils and surface waters; thus, DDE in the atmosphere can be further redistributed by wet or dry deposition throughout the world. This process can be repeated multiple times with volatilization in warm climates and deposition into cooler climates, which is called global distillation. DDE volatilization is expected to be attenuated by adsorption to carbon sources since DDE has high adsorption coefficients, i.e., log K_{oc} values of 4.42 (Ding and Wu, 1995), 4.70 (Sabljic, 1984), and 4.88 (Ding and Wu, 1997). Ding and Wu (1995, 1997) measured empirical K_{oc} values from soil column batches from Taichung, Taiwan. Sabljic (1984) used structural modeling to predict the adsorption coefficient.

Terrestrial

Primarily due to high partition coefficients, DDE, is expected to adsorb strongly onto soil particles. As a result of DDE's strong binding to soil, it will remain mostly on the surface layers of soil (top 1.5-cm layer); small amounts leach into the lower soil layers and groundwater (Callahan et al., 1979). In the process of weathering or aging, DDE becomes sequestered into micropores of soil or sediment, decreasing its bioavailability (ATSDR, 2002). DDE has a low water solubility (0.0011-0.12 mg/L) suggesting limited mobility in soils. In moist soils DDE may volatilize based on the Henry's Law constant, but it is not expected to volatilize from dry soils based on its vapor pressure (HSDB, 2004). Loss of DDE from dryer soil is primarily due to the transport of the particulate mater to which the compound is bound.

Soil dissipation of DDE is much greater in tropical than in temperate regions. In Alabama, a fugacity-based, multilayered soil exchange model predicted that 200-600 kg of DDE is released into the air each year from a $1.23x10^{11}$ m^2 area (the size of Alabama) that has a

geometric mean of 7.9 ng/g dry weight of soil (23 ng/g dry weight of soil arithmetic mean), which is ~50% of the air burden (Harner et al., 2001). Reported half-life in the soil is 1000 days (Mackay et al., 1997). Recent studies report the half-life of ΣDDT (i.e., combined *p,p*'-DDT, DDD, and DDE) and DDE in tropical regions to be between 22 (in Sudan) to 327 (in China) and 151 to 271 days (in Brazil), respectively. The DDE half-lives in temperate regions ranged from 837 to 6,087 days. The half-life of these compounds was also higher in acidic soils (half-life >672 days, pH=4.5), and highest residue levels were found in muck soils and in deeply plowed, unflooded fields (ATSDR, 2002).

Abiotic degradation

DDE is known to undergo photooxidation reactions on the surfaces of soil or 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, 91% of the initial concentration of DDT remained in the soil when not exposed to light (i.e., a dark control); 65% remained for the sample exposed to light (Racke et al., 1997). No information was located on the abiotic mineralization of DDE; UV-irradiation of ^{14}C-*p,p*' -DDT on soil for 10 hours mineralized less than 0.1% of the initial amount (Vollner and Klotz 1994).

Biotic degradation

DDT biodegrades primarily to DDE under aerobic anaerobic conditions due to soil microorganisms including bacteria, fungi, and algae (Arisoy, 1998; U.S. EPA, 1979; Lichtenstein and Schulz, 1959; Menzie, 1980; Stewart and Chisholm, 1971; Verma and Pillai, 1991). Mineralization of DDT and DDE was observed in laboratory experiments using *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). Beyond these limited examples, DDE is often resistant to biodegradation under aerobic and anaerobic conditions (Strompl and Thiele, 1997).

DDT breaks down into DDE and DDD in soil, and the parent-to-metabolite ratio (DDT to DDE or DDD) decreases with time due to weathering of DDT and its metabolites into soil micropores. The parent-to-metabolite ratio may vary considerably with soil type. DDT was much more persistent in muck soils than in dry forest soils. A study of agricultural soils in the corn belt of the central United States found 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). A study of DDT in agricultural soils in British Colombia, Canada reported that over a 19-year period, there was a 70% reduction of DDT in muck soils and a virtual disappearance of DDT from loamy sand soils (Aigner et al., 1998).

Aquatic

DDE may revolatilize if deposited into water; however, it preferentially adsorbs to particulate matter and partitions into the sediment as predicted by the high partitioning

coefficients. The average log K_{oc} value of DDE in lake sediment was 4.58 (van den Hoop, et al., 1999). Lyman et al. (1990) estimated the volatilization half-life of DDE from a model river and model lake to be 2 and 18 days, respectively. When adsorption was considered in a volatilization model performed by EPA's EXAMS II Computer Simulator (U.S. EPA, 1987) the half-life was determined to be 5 years. Hydrolysis is not a major source of degradation; however, photolysis is possible on sunlit water surfaces. The half-life of DDE in irradiated water (310-410 nm) due to photolysis was 15 and 26 hours (Draper, 1985). DDE did not display any sign of degradation after 12 months when exposed to seawater and sediment (Vind et al., 1973).

In laboratory experiments with marine sediment, DDE was shown to be 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). 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 Dünnbier, 1999; Ware et al., 1980).

DDE can bioaccumulate due to its high lipophilicity and long half-life. It biomagnifies up the food chain, i.e., concentrations progressively increase in the tissues of plants and animals in successive trophic levels. It also bioconcentrates in aquatic organisms and bioaccumulates in the food chain (ATSDR, 2002). A field study was conducted where DDE was introduced into a flooded quarry and the water, sediment, and biota were monitored for DDE levels for one year (Callahan et al., 1979). The equilibrium of DDE between water and zooplankton was attained within a day, with a bioconcentration factor (BCF) of $3\text{-}6x10^{+4}$. DDE reached equilibrium between water and bluegill, a resident quarry fish, after 60 days, with a BCF of about $1.1x10^{+5}$; the BCF for trout in this study was obtained after 108 days, and was $1.8x10^{+5}$ (Callahan et al., 1979). Callahan et al. (1979) reported the findings from a terrestrial-aquatic microcosm experiment on the fate of 3.8 ppb DDE in water. The BCFs were calculated to be $3.6x10^{+4}$, $5.9x10^{+4}$, $1.2x10^{+4}$, and $1.1x10^{+4}$ for snail, mosquito larvae, fish, and algae respectively.

DDE BCF values have also been reported in the following aquatic organisms (HSDB, 2004):

- Rainbow trout: 81,000
- Flathead minnow: 51,000
- Fish (Species not reported; static microcosm study): 27,500
- *Gambusia affinis* (3 days): 217
- Zooplankton: 28,600

3.4 Summary

DDE is an impurity and a degradation product of DDT, a pesticide that was manufactured and used in the US, and is still manufactured and used in other parts of the world. Thus, DDE has been released to the environment as a result of the use of DDT as an insecticide. In the air, DDE can exist in both the vapor and particulate phases. Vapor-phase DDE may be degraded by reaction with photochemically-produced hydroxyl radicals; it also may undergo direct photolysis. Particulate-phase DDE may undergo long-distance atmospheric transport and can be removed from the atmosphere by wet and dry deposition.

In the soil, DDE is expected to have limited mobility and bioavailability because it binds to soil particles. Volatilization from moist soil surfaces is expected to be an important environmental fate process; however, adsorption to the soil may attenuate this process. DDE is not expected to volatilize from dry soil surfaces based on its vapor pressure. DDE is resistant to degradation in the soil, and the primary loss of DDE may be due to erosion of the particles to which the compound is bound.

In water, volatilization from water surfaces is expected to be an important environmental fate process, based upon its Henry's Law constant. However, volatilization from water surfaces is expected to be attenuated severely by adsorption to suspended solids and sediment in the water column. Biodegradation of DDE in water is expected to be very slow. DDE bioconcentrates and bioacumulates in the aquatic environment; BCF values of up to 180,000 have been reported in fish, suggesting that bioconcentration in aquatic organisms is very high.

4.0 EXPOSURE FROM DRINKING WATER

4.1 Introduction

EPA used data from several sources to evaluate the potential for occurrence of DDE in Public Water Systems (PWSs). The primary source of drinking water occurrence data for DDE was the first Unregulated Contaminant Monitoring Regulation (UCMR 1) program. The Agency also evaluated ambient water quality data from the United States Geological Survey (USGS).

4.2 Ambient Occurrence

4.2.1 Data Sources and Methods

USGS instituted the National Water Quality Assessment (NAWQA) program in 1991 to examine ambient water quality status and trends in the United States. NAWQA is designed to apply nationally consistent methods to provide a consistent basis for comparisons among study basins across the country and over time. These occurrence assessments serve to facilitate interpretation of natural and anthropogenic factors affecting national water quality. For more detailed information on the NAWQA program design and implementation, please refer to Leahy and Thompson (1994) and Hamilton and colleagues (2004).

Study Unit Monitoring

The NAWQA program conducts monitoring and water quality assessments in significant watersheds and aquifers referred to as "study units." NAWQA's sampling approach is not "statistically" designed (i.e., it does not involve random sampling), but it provides a representative view of the nation's waters in its coverage and scope. Together, the 51 study units monitored between 1991 and 2001 include the aquifers and watersheds that supply more than 60% of the nation's drinking water and water used for agriculture and industry (NRC, 2002). NAWQA monitors the occurrence of chemicals such as pesticides, nutrients, volatile organic compounds (VOCs), trace elements, and radionuclides, and the condition of aquatic habitats and fish, insects, and algal communities (Hamilton et al., 2004).

Monitoring of study units occurs in stages. Between 1991 and 2001, approximately one-third of the study units at a time were studied intensively for a period of three to five years, alternating with a period of less intensive research and monitoring that lasted between five and seven years. Thus all participating study units rotated through intensive assessment in a ten-year cycle (Leahy and Thompson, 1994). The first ten-year cycle was called "Cycle 1." Summary reports are available for the 51 study units that underwent intensive monitoring in Cycle 1 (USGS, 2001a). Cycle 2 monitoring is scheduled to proceed in 42 study units from 2002 to 2012 (Hamilton et al., 2004).

Pesticide National Synthesis

Through a series of National Synthesis efforts, the USGS NAWQA program is preparing comprehensive analyses of data on topics of particular concern. These data are aggregated from the individual study units and other sources to provide a national overview.

The Pesticide National Synthesis began in 1991. Results from the most recent USGS Pesticide National Synthesis analysis, based on complete Cycle 1 (1991-2001) data from NAWQA study units, are posted on the NAWQA Pesticide National Synthesis website (Martin et al., 2003; Kolpin and Martin, 2003; Nowell, 2003; Nowell and Capel, 2003). USGS considers these results to be provisional. Data for surface water, ground water, bed sediment, and biota are presented separately, and results in each category are subdivided by land use category. Land use categories include agricultural, urban, mixed (deeper aquifers of regional extent in the case of ground water), and undeveloped. The National Synthesis analysis for pesticides is a first step toward the USGS goal of describing the occurrence of pesticides in relation to different land use and land management patterns, and developing a deeper understanding of the relationship between spatial occurrence of contaminants and their fate, transport, persistence, and mobility characteristics.

The surface water summary data presented by USGS in the Pesticide National Synthesis (Martin et al., 2003) only include stream data. Sampling data from a single one-year period, generally the year with the most complete data, were used to represent each stream site. Sites with few data or significant gaps were excluded from the analysis. NAWQA stream sites were sampled repeatedly throughout the year to capture and characterize seasonal and hydrologic variability. In the National Synthesis analysis, the data were time-weighted to provide an estimate of the annual frequency of detection and occurrence at a given concentration.

The USGS Pesticide National Synthesis only analyzed ground water data from wells; data from springs and agricultural tile drains were not included. The sampling regimen used for wells was different than that for surface water. In the National Synthesis analysis (Kolpin and Martin, 2003), USGS uses a single sample to represent each well, generally the earliest sample with complete data for the full suite of analytes.

NAWQA monitored bed sediment and fish tissue at sites considered likely to be contaminated and sites that represent various land uses within each study unit. Most sites were sampled once in each medium. In the case of sites sampled more than once, a single sample was chosen to represent the site in the Pesticide National Synthesis analysis (Nowell, 2003). In the case of multiple bed sediment samples, the earliest one with complete data for key analytes was used to represent the site. In the case of multiple tissue samples, the earliest sample from the first year of sampling that came from the most commonly sampled type of fish in the study unit was selected.

As part of the National Pesticide Synthesis, USGS also analyzed the occurrence of select semivolatile organic compounds (SVOCs) in bed sediment at sites considered likely to be contaminated and sites that represent various land uses within each study unit (Nowell and

Capel, 2003). Most sites were sampled only once. When multiple samples were taken, the earliest one was used to represent the site in the analysis.

Over the course of Cycle 1 (1991-2001), NAWQA analytical methods may have been improved or changed. Hence, reporting levels (RLs) varied over time for some compounds. In the summary tables, the highest RL for each analyte is presented for general perspective. In the ground water, bed sediment, and tissue data analyses, the method of calculating concentration percentiles sometimes varied depending on how much of the data was censored at particular levels by the laboratory (i.e., because of the relatively large number of non-detections in these media).

4.2.2 Results

Surface Water and Ground Water

Under the NAWQA program, USGS monitored DDE (specifically *p,p'*-DDE, the most common isomer) between 1992 and 2001 in representative watersheds and aquifers across the country. Reporting limits in surface water and ground water varied but did not exceed 0.006 µg/L. Results for surface water and ground water are presented in Tables 4-1 and 4-2.

Table 4-1 USGS Pesticide National Synthesis Summary of NAWQA Monitoring of *p,p'*-DDE in Ambient Surface Water, 1992-2001

Land Use Type	No. of Samples (and No. of Sites)	Detection Frequency	50th Percentile (Median) Concentration	95th Percentile Concentration	Maximum Concentration
Agricultural	1,885 (78)	4.84%	<RL	<RL	0.062 µg/L
Mixed	1,021 (47)	6.14%	<RL	<RL	0.009 µg/L
Undeveloped	60 (4)	3.66%	<RL	<RL	0.002 µg/L
Urban	900 (33)	1.68%	<RL	<RL	0.007 µg/L

Source: Martin et al. (2003)
RL = Reporting limit. Reporting limits for *p,p'*-DDE varied, but did not exceed 0.006 µg/L.
The USGS Pesticide National Synthesis used one year of data, generally the year with the most sampling results, to represent each site in this analysis. The sampling results were time-weighted, to eliminate bias from more frequent sampling at certain times of year. Detection Frequencies and Percentile Concentrations can be interpreted as representing annual occurrence. For instance, the detection frequency can be thought of as the percent of the year in which detections are found at a typical site in this land use category, and the 95th percentile concentration can be though of as a concentration that is not exceeded for 95% of the year at a typical site in this land use category.

In surface water (Table 4-1), *p,p'*-DDE was detected at frequencies ranging from 1.68% of samples in urban settings to 3.66% in undeveloped settings, 4.84% in agricultural settings, and 6.14% in mixed land use settings. The 95th percentile concentrations were below the reporting limit in all land use settings. The highest detected concentration, estimated at 0.062 µg/L, occurred in an agricultural setting (Martin et al., 2003).

Table 4-2 USGS Pesticide National Synthesis Summary of NAWQA Monitoring of *p,p'*-DDE in Ambient Ground Water, 1992-2001

Land Use Type	No. of Wells	Detection Frequency	50th Percentile (Median) Concentration	95th Percentile Concentration	Maximum Concentration
Agricultural	1,443	3.26%	<RL	<RL	0.008 µg/L
Mixed (Major Aquifer)	2,716	2.65%	<RL	<RL	0.006 µg/L
Undeveloped	67	7.46%	<RL	<RL	0.002 µg/L
Urban	834	3.96%	<RL	<RL	0.005 µg/L

Source: Kolpin and Martin (2003)

RL = Reporting limit. Reporting limits for *p,p'*-DDE varied, but did not exceed 0.006 µg/L.

The USGS Pesticide National Synthesis considered each well a distinct site in this analysis. Each well was represented by one sample: normally the first one taken, but possibly a later sample if the first sample was not analyzed for the full range of analytes.

Percentile Concentrations were drawn from the range of detects and non-detects. The method for calculating Percentile Concentrations varied depending on how much of the data was censored at particular levels by the laboratory.

In ground water (Table 4-2), *p,p'*-DDE detection frequencies ranged from 2.65% of samples in mixed land use settings (major aquifers) to 3.26% in agricultural settings, 3.96% in urban settings, and 7.46% in undeveloped settings. The 95th percentile concentrations were below the reporting limit in all land use settings. The highest detected concentration, 0.008 µg/L, was found in an agricultural setting (Kolpin and Martin, 2003).

Bed Sediments and Biotic Tissue

The NAWQA program also investigated the occurrence of select organochlorine compounds, including both the most common isomer of DDE, *p,p'*-DDE, and a less common isomer, *o,p'*-DDE, in bed sediments and biotic tissue. Sampling was conducted at 1310 sites from 1992 to 2001. Method detection limits for both isomers were 1 µg/kg dry weight in sediment, and 5 µg/kg wet weight in tissue. Details regarding sampling techniques and analytical methods are described by Nowell (2003). Organochlorines can be present in biotic tissue and in bed sediments of aquatic systems even when they are undetectable in the water column using conventional methods. The occurrence of a toxic compound in stream sediments is pertinent to drinking water concerns because some desorption of the compound from sediments into water, albeit at low rates, may be expected to occur through equilibrium reactions.

Results of monitoring for *p,p'*-DDE in bed sediment and fish tissue are presented in Tables 4-3 and 4-4.

Table 4-3 USGS Pesticide National Synthesis Summary of NAWQA Monitoring of *p,p'*-DDE in Bed Sediment, 1992-2001

Land Use Type	No. of Sites	Detection Frequency in samples	50th Percentile (Median) Concentration	95th Percentile Concentration	Maximum Concentration
Agricultural	282	48%	0.98 µg/kg	28.9 µg/kg	190 µg/kg
Mixed	338	46%	0.81 µg/kg	11.6 µg/kg	440 µg/kg
Undeveloped	224	22%	<RL	3.5 µg/kg	31 µg/kg
Urban	166	70%	2.15 µg/kg	23.9 µg/kg	111 µg/kg

Source: Nowell (2003)
RL = Reporting limit. Reporting limits for *p,p'*-DDE varied, but did not exceed 1 µg/kg.
For sediment, all weights are dry weights.
Most sites were sampled only once. In the case of sites sampled multiple times, USGS used a single sample (the earliest sample with complete data for key analytes) to represent each site in this analysis.
Percentile Concentrations were drawn from the range of detects and non-detects. The method for calculating Percentile Concentrations varied depending on how much of the data was censored at particular levels by the laboratory.

In bed sediment (Table 4-3), *p,p'*-DDE detection frequencies range from 22% of samples in undeveloped settings to 46% in mixed land use settings, 48% in agricultural settings, and 70% in urban settings. The 95th percentile concentrations in bed sediment were found to range from 3.5 µg/kg dry weight (undeveloped settings) to 28.9 µg/kg dry weight (agricultural settings). The highest concentration, 440 µg/kg dry weight, was found in a mixed land use setting (Nowell, 2003).

Table 4-4 USGS Pesticide National Synthesis Summary of NAWQA Monitoring of *p,p'*-DDE in Whole Fish, 1992-2001

Land Use Type	No. of Sites	Detection Frequency	50th Percentile (Median) Concentration	95th Percentile Concentration	Maximum Concentration
Agricultural	205	89%	43.5 µg/kg	2,180 µg/kg	7,300 µg/kg
Mixed	206	93%	42 µg/kg	397 µg/kg	7,200 µg/kg
Undeveloped	162	44%	3.50 µg/kg	128 µg/kg	1,300 µg/kg
Urban	100	89%	36 µg/kg	190 µg/kg	450 µg/kg

Source: Nowell (2003)
RL = Reporting limit. Reporting limits for *p,p'*-DDE varied, but did not exceed 5 µg/kg.
For whole fish, all weights are wet weights.
Most sites were sampled only once. In the case of sites sampled multiple times, USGS used a single sample (from the first year of sampling, the earliest sample of the variety of fish most often sampled in that study unit) to represent each site in this analysis.
Percentile Concentrations were drawn from the range of detects and non-detects. The method for calculating Percentile Concentrations varied depending on how much of the data was censored at particular levels by the laboratory.

NAWQA data indicate that *p,p'*-DDE occurs in fish tissue (Table 4-4) at detection frequencies ranging from 44% of samples in undeveloped settings to 89% in agricultural settings, 89% in urban settings, and 93% in mixed land use settings. The 95th percentile concentrations in fish tissue were found to range from 128 µg/kg wet weight (undeveloped settings) to 2180 µg/kg wet weight (agricultural settings). The highest concentration, 7300 µg/kg wet weight, was found in an agricultural setting (Nowell, 2003).

Results of monitoring for *o,p'*-DDE in bed sediment and fish tissue are presented in Tables 4-5 and 4-6.

Table 4-5 USGS Pesticide National Synthesis Summary of NAWQA Monitoring of *o,p'*-DDE in Bed Sediment, 1992-2001

Land Use Type	No. of Sites	Detection Frequency in samples	50th Percentile (Median) Concentration	95th Percentile Concentration	Maximum Concentration
Agricultural	278	2.6%	<RL	<RL	4.4 µg/kg
Mixed	327	1.6%	<RL	<RL	22 µg/kg
Undeveloped	221	0.0%	<RL	<RL	<RL
Urban	164	3.7%	<RL	<RL	26.7 µg/kg

Source: Nowell (2003)
RL = Reporting limit. Reporting limits for *o,p'*-DDE varied, but did not exceed 1 µg/kg.
For sediment, all weights are dry weights.
Most sites were sampled only once. In the case of sites sampled multiple times, USGS used a single sample (the earliest sample with complete data for key analytes) to represent each site in this analysis.
Percentile Concentrations were drawn from the range of detects and non-detects. The method for calculating Percentile Concentrations varied depending on how much of the data was censored at particular levels by the laboratory.

In bed sediment (Table 4-5), *o,p'*-DDE detection frequencies range from 0% of samples in undeveloped settings to 1.6% in mixed land use settings, 2.6% in agricultural settings, and 3.7% in urban settings. The 95th percentile concentrations in bed sediment were less than the reporting limit in all land use settings. The highest concentration, 26.7 µg/kg dry weight, was found in an urban setting (Nowell, 2003).

Table 4-6 USGS Pesticide National Synthesis Summary of NAWQA Monitoring of *o,p'*-DDE in Whole Fish, 1992-2001

Land Use Type	No. of Sites	Detection Frequency	50th Percentile (Median) Concentration	95th Percentile Concentration	Maximum Concentration
Agricultural	204	7.0%	<RL	10 µg/kg	85 µg/kg
Mixed	206	3.2%	<RL	<RL	130 µg/kg
Undeveloped	162	0.0%	<RL	<RL	<RL
Urban	99	6.4%	<RL	6.9 µg/kg	22 µg/kg

Source: Nowell (2003)
RL = Reporting limit. Reporting limits for *o,p'*-DDE varied, but did not exceed 5 µg/kg.
For whole fish, all weights are wet weights.
Most sites were sampled only once. In the case of sites sampled multiple times, USGS used a single sample (from the first year of sampling, the earliest sample of the variety of fish most often sampled in that study unit) to represent each site in this analysis.
Percentile Concentrations were drawn from the range of detects and non-detects. The method for calculating Percentile Concentrations varied depending on how much of the data was censored at particular levels by the laboratory.

NAWQA data indicate that *o,p'*-DDE occurs in fish tissue (Table 4-6) at detection frequencies ranging from 0.0% of samples in undeveloped settings to 3.2% in mixed land use settings, 6.4% in urban settings, and 7.0% in agricultural settings. The 95th percentile concentrations in fish tissue were found to range from undetectable (undeveloped and mixed land use settings) to 10 µg/kg wet weight (agricultural settings). The highest concentration, 130 µg/kg wet weight, was found in a mixed land use setting (Nowell, 2003).

4.3 Drinking Water Occurrence

4.3.1 Data Sources and Methods

In 1999, EPA developed the UCMR 1 program in coordination with the CCL and the National Drinking Water Contaminant Occurrence Database (NCOD) to provide national occurrence information on unregulated contaminants. EPA designed the UCMR 1 data collection with three parts (or tiers), primarily based on the availability of analytical methods. DDE belonged to the first tier, List 1.

List 1 Assessment Monitoring was performed for a specified number of chemical contaminants for which analytical methods have been developed. With the exception of transient non-community systems and systems that purchase 100% of their water, EPA required all large PWSs (systems serving more than 10,000 people), plus a statistically representative national sample of 800 small PWSs (systems serving 10,000 people or fewer) to conduct Assessment Monitoring. Approximately one-third of the participating small systems were scheduled to monitor for these contaminants during each calendar year from 2001 through 2003. Large systems could conduct one year of monitoring anytime during the 2001-2003 UCMR 1 period. EPA specified a quarterly monitoring schedule for surface water systems and a twice-a-

year, six-month interval monitoring schedule for ground water systems. Although UCMR 1 monitoring was conducted primarily between 2001 and 2003, some results were not collected and reported until as late as 2006.

The objective of the UCMR 1 sampling approach for small systems was to collect contaminant occurrence data from a statistically selected, nationally representative sample of small systems. The small system sample was stratified and population-weighted, and included some other sampling adjustments such as allocating a selection of at least two systems from each state. With contaminant monitoring data from all large PWSs and a statistical, nationally representative sample of small PWSs, the UCMR 1 List 1 Assessment Monitoring program provides a contaminant occurrence data set suitable for national drinking water estimates.

4.3.2 Derivation of the Health Reference Level

To evaluate the systems and populations exposed to DDE through PWSs, the monitoring data were analyzed against the Minimum Reporting Level (MRL) and a benchmark value for health that is termed the Health Reference Level (HRL). Two different approaches were used to derive the HRL, one for chemicals that cause cancer and exhibit a linear response to dose and the other applies to noncarcinogens and carcinogens evaluated using a non-linear approach.

The HRL of 0.2 µg/L for DDE considers the potential carcinogenic effects of DDE (see Section 8.2.4). The HRL is based on the occurrence of liver tumors in mice following chronic exposures (NCI, 1978; please see the Dose-Response Section of this document for more information). No RfD is currently available for DDE.

4.3.3 Results

As a List 1 contaminant, 4,4'-DDE (as the *p,p'*-DDE isomer is also known) was scheduled to be monitored by all large CWSs and NTNCWSs and a statistically representative sample of small CWSs and NTNCWSs. The data presented in this report reflect UCMR 1 analytical samples submitted and quality-checked under the regulation as of March 2006. 4,4'-DDE data were collected and submitted by 797 (99.6 percent) of the 800 small systems selected for the small system sample and 3077 (99.3 percent) of the 3100 large systems defined as eligible for the UCMR 1 large system census. 4,4'-DDE data have been analyzed at the level of simple detections (at or above the minimum reporting level, $\geq$MRL, or $\geq$0.8 µg/L). Since the health reference level (0.2 µg/L) is less than the MRL, the data are not analyzed at the level of the HRL or half the HRL.

EPA set the MRL for UCMR 1 contaminants based on the capability of analytical methods, not anticipated health levels. For many UCMR 1 contaminants, including DDE, the MRL was determined by multiplying by 10 the least sensitive method's minimum detection limit, or, when available, multiplying by 5 the least sensitive method's estimated detection limit (U.S. EPA, 2000e). MRLs were set approximately an order of magnitude higher than detection limits to ensure consistency, accuracy, and reproducibility of results.

For the 1999 UCMR 1, EPA approved three analytical methods for the analysis of DDE. These included EPA Methods 508, 508.1 and 525.2. In setting the minimum reporting limit (MRL) for UCMR 1 contaminants, EPA chose the method detection limit (MDL) for the least sensitive method and multiplied this MDL by a factor of 10. Of the three methods approved for DDE analysis, method 525.2 is the least sensitive. Data from four MDL studies are included in Method 525.2, extraction using either C-18 disk or cartridge with the subsequent analyses performed using either a quadrupole or ion trap mass spectormeter. The MDLs generated using these four options were 0.054, 0.070, 0.070 and 0.075 µg/L. This resulted in an MRL of 0.80 µg/L (i.e., 10 times the MDL of 0.075 µg/L = 0.75 µg/L and then rounded to 0.80 µg/L).

Results of the analysis are presented in Tables 4-7 and 4-8. No detections of 4,4'-DDE were found in any samples from small systems. DDE was detected at a single large system; this ground water system represented 0.03% of large PWSs and 0.01% of the population served by them (approximately 18,000 people). The concentration of the single detection was 3 µg/L.

Table 4-7 Summary UCMR 1 Occurrence Statistics for 4,4'-DDE in Small Systems (Based on Statistically Representative National Sample of Small Systems)

Frequency Factors	UCMR Data - Small Systems		National System & Population Numbers[1]
Total Number of Samples	3,251		--
Percent of Samples with Detections	0.00%		--
99th Percentile Concentration (all samples)	< MRL		--
Health Reference Level (HRL)	0.2 µg/L		--
Minimum Reporting Level (MRL)	0.8 µg/L		--
Maximum Concentration of Detections	< MRL		--
99th Percentile Concentration of Detections	< MRL		--
Median Concentration of Detections	< MRL		--
Total Number of PWSs	797		60,414
Number of GW PWSs	590		56,072
Number of SW PWSs	207		4,342
Total Population	2,760,570		45,414,590
Population of GW PWSs	1,939,815		36,224,336
Population of SW PWSs	820,755		9,190,254
Occurrence by System	**Number**	**Percentage**	**National Extrapolation[2]**
PWSs (GW & SW) with Detections (≥ MRL)	0	0.00%	0
Occurrence by Population Served			
Population Served by PWSs with Detections	0	0.00%	0

1. Total PWS and population numbers are from EPA September 2004 Drinking Water Baseline Handbook, 4th edition.
2. National extrapolations are generated separately for each population-served size stratum and then added to yield the national estimate of GW PWSs with detections (and population served) and SW PWSs with detections (and population served). For intermediate calculations at the level of individual strata, see EPA's UCMR 1 Occurrence Report, entitled "The Analysis of Occurrence Data from the First Unregulated Contaminant Monitoring Regulation (UCMR 1) in Support of Regulatory Determinations for the Second Drinking Water Contaminant Candidate List."

Abbreviations:
PWS = Public Water Systems; GW = Ground Water; SW = Surface Water; N/A = Not Applicable; Total Number of Samples = the total number of samples on record for the contaminant; 99th Percentile Concentration = the concentration in the 99th percentile sample (out of either all samples or just samples with detections); Median Concentration of Detections = the concentration in the median sample (out of samples with detections); Total Number of PWSs = the total number of PWSs for which sampling results are available; Total Population Served = the total population served by PWSs for which sampling results are available; PWSs with detections, PWSs > ½HRL, or PWSs > HRL = PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark, respectively; Population Served by PWSs with detections, by PWSs >½HRL, or by PWSs >HRL = population served by PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark, respectively.

Notes:
-Small systems are those that serve 10,000 persons or fewer.
-Only results at or above the MRL were reported as detections. Concentrations below the MRL are considered non-detects.
-Due to differences between the ratio of GW and SW systems with monitoring results and the national ratio, extrapolated GW and SW figures might not add up to extrapolated totals.
-The HRL used in this analysis is a draft value for working review only.

Table 4-8 Summary UCMR 1 Occurrence Statistics for 4,4'-DDE in Large Systems (Based on the Census of Large Systems)

Frequency Factors	UCMR Data - Large Systems	
Total Number of Samples	30,546	
Percent of Samples with Detections	0.003%	
99th Percentile Concentration (all samples)	< MRL	
Health Reference Level (HRL)	0.2 µg/L	
Minimum Reporting Level (MRL)	0.8 µg/L	
Maximum Concentration of Detections	3 µg/L	
99th Percentile Concentration of Detections	3 µg/L	
Median Concentration of Detections	3 µg/L	
Total Number of PWSs Number of GW PWSs Number of SW PWSs	3,077 1,381 1,696	
Total Population Population of GW PWSs Population of SW PWSs	223,502,113 53,415,745 170,086,368	
Occurrence by System	**Number**	**Percentage**
PWSs (GW & SW) with Detections (≥ MRL) GW PWSs with Detections SW PWSs with Detections	1 1 0	0.03% 0.07% 0.00%
Occurrence by Population Served		
Population Served by PWSs with Detections Pop. Served by GW PWSs with Detections Pop. Served by SW PWSs with Detections	17,670 17,670 0	0.01% 0.03% 0.00%

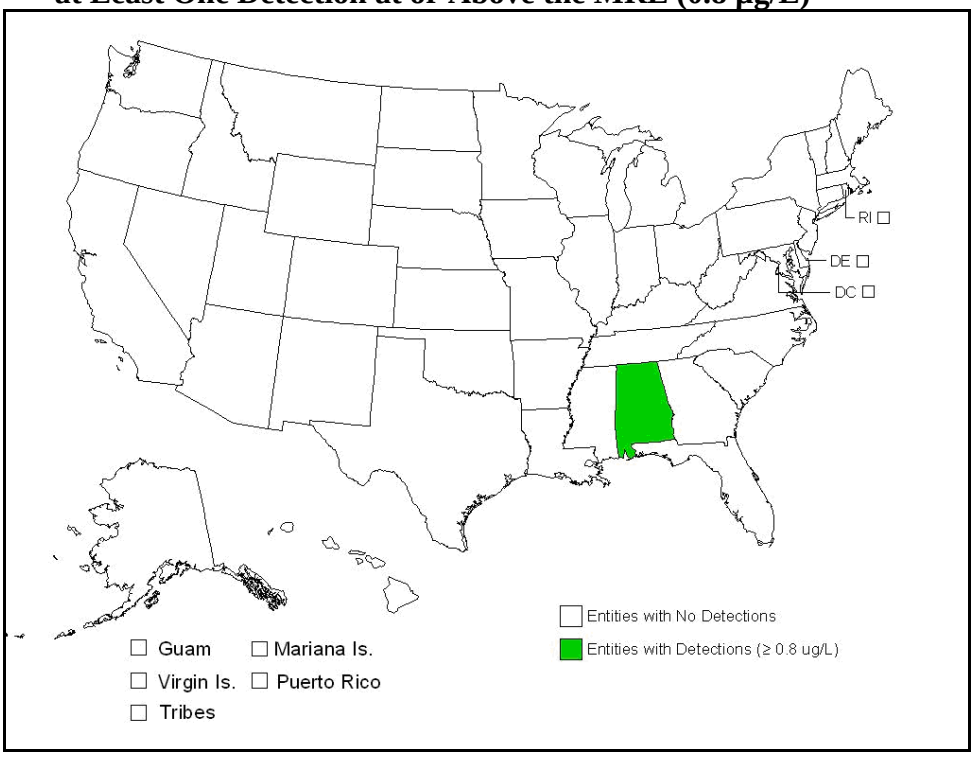
Abbreviations:
PWS = Public Water Systems; GW = Ground Water; SW = Surface Water; N/A = Not Applicable; Total Number of Samples = the total number of samples on record for the contaminant; 99th Percentile Concentration = the concentration in the 99th percentile sample (out of either all samples or just samples with detections); Median Concentration of Detections = the concentration in the median sample (out of samples with detections); Total Number of PWSs = the total number of PWSs for which sampling results are available; Total Population Served = the total population served by PWSs for which sampling results are available; PWSs with detections, PWSs > ½HRL, or PWSs > HRL = PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark, respectively; Population Served by PWSs with detections, by PWSs >½HRL, or by PWSs >HRL = population served by PWSs with at least one sampling result greater than or equal to the MRL, exceeding the ½HRL benchmark, or exceeding the HRL benchmark, respectively.

Notes:
-Large systems are those that serve more than 10,000 persons.
-Only results at or above the MRL were reported as detections. Concentrations below the MRL are considered non-detects.
-The HRL used in this analysis is a draft value for working review only.

Regional Patterns

DDE was only detected in one sample in all of the UCMR 1 sampling. This single detection was in a ground water sample taken in the state of Alabama (see Figure 4-1). Since only one system detected the contaminant, no further spatial analysis of this contaminant is presented.

Figure 4-1 Geographic Distribution of 4,4'-DDE in UCMR 1 Monitoring -- States With at Least One Detection at or Above the MRL (0.8 µg/L)



4.4 Summary

The USGS NAWQA program conducted monitoring of *p,p'*-DDE in ambient surface water, ground water, bed sediment, and fish tissue from 1992 to 2001 (Cycle 1). Four types of land use were considered in this monitoring effort: agricultural, mixed, undeveloped, and urban. Reporting limits varied over the course of the cycle, but did not exceed 0.006 µg/L in water, 1 µg/kg (dry weight) in bed sediment, and 5 µg/kg (wet weight) in whole fish. Summary results are reported in the USGS National Pesticide Synthesis. In none of the 3866 ambient surface water samples or 5060 ambient ground water samples was DDE found at concentrations that exceeded the HRL of 0.2 µg/L. The highest concentrations of *p,p'*-DDE in surface water (0.062 µg/L), ground water (0.008 µg/L) were observed in areas of agricultural land use; however, the highest concentration of *p,p'*-DDE in bed sediment (440 µg/kg dry weight) was observed in an area of mixed land use. Median concentrations in bed sediment ranged from less than the reporting limit to 2.15 µg/kg dry weight in the different land use settings. The median concentrations in surface water and ground water were below the reporting limit. In bed

sediment, it was found most frequently in urban areas (70% of samples). In ground water it was found most frequently in undeveloped areas (7.5% of samples), and in surface water it was found most frequently in areas of mixed land use (6.1% of samples). The NAWQA program also monitored the less common isomer *o,p'*-DDE in bed sediment and fish tissue. The highest concentration of *o,p'*-DDE in bed sediments (26.7 µg/kg dry weight) was found in an urban setting. In bed sediments, *o,p'*-DDE was detected most frequently in urban areas (3.7% of samples).

Under the UCMR 1, DDE was monitored in 33,797 finished drinking water samples from 3077 large and 797 small public water systems in the United States. At the MRL of 0.8 µg/L, no detections of DDE were found in any of the samples from small systems. DDE was detected at a single large system; this ground water system represented 0.03% of large PWSs and 0.01% of the population served by them (approximately 18,000 people). Since the HRL (0.2 µg/L) is less than the MRL (0.8 µg/L), the data are not analyzed at the level of the HRL or half the HRL.

5.0 EXPOSURE FROM MEDIA OTHER THAN WATER

5.1 Exposure from Food

Currently, food provides the primary source of DDE exposure to the general population (ATSDR, 2002). Although DDT is no longer used in the US, it still is used for pest control in some areas of the world (ATSDR, 2002), and depending on use and importation of foods from other countries, there may be some dietary exposure to DDE (Coulston, 1985). DDE is more persistent than DDT and may be expected to remain in animal and human tissues and in commodities for a notably longer time (Ariño, 1995). In addition, DDE bioaccumulates in the environment through terrestrial and aquatic food chains, creating a potential for dietary exposures far greater than environmental levels. Research has found that higher amounts of DDT are consumed by people eating fish from the Great Lakes (Hanrahan et al., 1999; Laden et al., 1999), and that the populations at greatest risk to DDT are the indigenous people in the Arctic who eat traditional foods (e.g., seals, caribou, narwhals, etc.) (Kuhnlein et al., 1995).

As in other media, DDT levels in food generally are declining. Data taken from the Market Basket Surveys between 1965 and 1975 showed an 86% decline in DDT levels in all kinds of food (U.S. EPA, 1980); these studies found decreased DDE levels in all classes of food tested. Detectable quantities of DDE are still present in many commodities. The U.S. FDA's analysis of 13,283 imported agricultural commodities for pesticide residues (1981 to 1986) showed that although no commodities exceeded the EPA tolerance levels for DDT or DDE, 3.1% of the samples had detectable levels of DDT or DDE (Hundley et al., 1988). DDE residues also were found in 41 out of the 6,970 produce samples (0.6%) tested in a 1989 pesticide screening program of produce delivered to supermarkets in Texas (Schattenberg and Hsu, 1992).

5.1.1 Concentration in Non-Fish Food Items

The most recent FDA market basket study summary (1991-2001) found DDE in 157 of 279 food types analyzed (U.S. FDA, 2003). They reported that mean DDE concentrations ranged from 0.0001 ppm (several food types) to 0.0221 ppm (salted butter). The highest mean DDE concentrations were identified in salted butter (0.0221 ppm, n=36), boiled spinach (0.0109 ppm, n=36), baked salmon (0.0079 ppm, n = 16), American cheese (0.0067 ppm, n=36), pan-cooked lamb chop (0.0055 ppm, n=34), and boiled collards (0.0055, n=34). The highest individual sample concentrations of DDE were in salted butter (0.1020 ppm), American cheese (0.0480 ppm), boiled spinach (0.0370 ppm), pan-cooked pork sausage (0.0300 ppm), and pan-cooked lamb chop (0.0300 ppm). Based on these data, it appears that the highest concentrations of DDE can be found in dairy, meat, and leafy greens; fish will be discussed further in the following section.

Data from other recent studies reporting only pesticide occurrences and not the concentration levels are summarized in Table 5-1.

Table 5-1 Percent of food samples with detectable DDE levels

Year(s)	DDE Isomer	% of samples with DDE	Total No. of Samples	Source
1989-1991	*p,p*' -DDE	0.59%	6,970	Schattenberg and Hsu, 1992
1989	DDE	0.99%	13,085	Minyard and Roberts, 1991
	p,p' -DDE	0.25%	13,085	Minyard and Roberts, 1991
1988	DDE	1.5%	13,980	Minyard and Roberts, 1991
	p,p'-DDE	0.18%	13,980	Minyard and Roberts 1991
1984-1986	DDE	23.1%	1,872	Gunderson, 1995b
1981-1986*	DDE	3.1%	13,283	Hundley et al., 1988

*data on imported agricultural commodities

o,p'-DDE was not analyzed in the most recent U.S. Market Basket study; however, in a previous report, this congener was detected only 8 times in 4 different food items at an average concentration of 0.0025 µg/g (while *p,p*'-DDE was detected 1700 times in 142 different food items at an average concentration of 0.0026 µg/g; Kan- Do Office and Pesticide Team, 1995).

Another study of ready to eat foods (Schecter and Lingjun, 1997) measured DDE levels in four types of popular U.S. fast foods. The chemical was detected in all four types of food with concentrations of 3170 pg/g (ppt) in McDonald's Big Mac Hamburger, 650 pg/g in Pizza Hut's Personal Pan Pizza Supreme, 180 pg/g in Kentucky Fried Chicken (KFC) three piece original recipe mixed dark and white meat luncheon package, and 2780 pg/g in Häagen-Daz chocolate-chip ice cream. These and previous data confirm that DDE bioconcentrates in meat and milk as can be predicted from its high K_{oc}. Thus, it is expected that those foods are potentially the biggest source of the DDT metabolite in the human diet. Conventional and "organic" baby foods from grocery stores in Michigan were evaluated for DDE and various other organochlorine pesticide residues (Moore et al., 2000); however, none of the foods contained residues of pesticides. The products tested were applesauce, pears, winter squash, and carrots.

DDE concentration was analyzed 129 samples of various Spanish meat products (Ariño et al., 1995); the frequency of detection for DDE was between 78 and 100%. The mean levels were below 10 µg/kg in all meat products, except for pork bologna where the mean concentration measured was 16 µg/kg (total range: 4 to 30.1 µg/kg). In addition, this study investigated the effect of commercial processing on the DDE residues and found DDE to be resistant to degradation under the conditions of ham ripening, sausage cooking, and pork bologna cooking. Another Spanish study supported the findings that the curing processes had little or no effect on DDE (Bayarri et al.,1998); however, a common bacteria found in meat, *Micrococcus varians*, reduced DDE concentrations by 17.7% in nutrient media. Measured levels of DDE in sausages were as follows: salchión, 2.5-1.8 ng/g lipid; chorizo vela, 5.7-7.4 ng/g lipid; and chorizo de Pamplono, 1.5-2.4 ng/g.

Recent research conducted by the U.S. Department of Agriculture, through its Pesticide Detection Program, found 17% of milk samples contained an average of 0.002 ppm DDE (Benbrook, 2002). Another study noted that mean DDE levels in cow's milk in Southern Ontario, Canada, have declined from 96 ng/g lipid in 1970–1971 to 16 ng/g lipid in 1985–1986 (Frank and Braun, 1989). Waliszewski et al. (1996) detected *p,p*'-DDE in 46% of the 192 samples of cow's milk collected between April and November of 1993 from random farms in the central coastal region of Veracruz, Mexico; the highest concentration measured was 0.107 mg/kg, while the mean was 0.028 mg/kg.

Due to its high lipophilicity DDE selectively partitions into human fatty tissue and breast milk. The fat content of milk fluctuates; therefore, it is more accurate to measure and express DDE content on a lipid basis (i.e., µg/g lipid rather than µg/mL milk), which has become the standard for hydrophobic pollutants. These compounds are usually found in human breast milk in concentrations higher than in cow's milk (human breast milk has a higher fat content than cow's milk) or other infant foods. This leads to generally higher dietary exposure to DDE for breast-fed infants. However, DDE concentrations in human breast milk have been declining steadily across the U.S., Canada, and Western Europe (ATSDR, 2002).

Kalantzi et al. (2001) measured *p,p*'-DDE and *o,p*'-DDE concentrations in butter throughout the world. The eighteen samples taken in the United States yielded an average of 24,070 pg/g lipid and a range of 1620-140,380 pg/g lipid for *p,p*'-DDE; *o,p*'-DDE was not detected in any of those samples. Another study, focusing on DDE concentration in Spanish cheeses, (Bentabol, 1995) reported the following mean (and range) values, estimated from 146 samples of various cheeses: 40.7 µg/kg (4-354 µg/kg) fat basis for *p,p*'-DDE; 6.9 µg/kg (1-101 µg/kg) fat basis for *o,p*'-DDE. DDE concentrations also were measured in Greek cheese (Mallatou et al., 1996). The mean *p,p*'-DDE concentration in 28 samples was 37 ng/g fat, with a range of 20-70 ng/g fat. The same study reported a mean *p,p*'-DDE concentration from 38 samples of bovine milk from Greece to be 22 ng/g fat, with a range of 14-32 ng/g fat.

Mean DDE levels were reported for milk and cheese in Egypt. Abou-Arab (1997) reports mean *p,p*'-DDE concentrations of 64 µg/kg fat in milk and 4 µg/kg fat in cheese as measured from 25 samples collected from different regions. The respective mean *o,p*'-DDE concentrations were 84 and 5 µg/kg fat in milk and cheese.

5.1.2 Concentrations in Fish, Shellfish and Marine Mammals

The high lipid solubility of DDE combined with its extremely long half-life is responsible for its high bioconcentration in aquatic organisms. This results in a progressive biomagnification of DDE in organisms at the top of the food chain. It is possible that humans may be the ultimate consumer of some of these organisms (ATSDR, 2002).

The most recent FDA market basket study summary (1991-2001), analyzed eight fish- and shellfish-based food items for DDE, with mean concentrations ranging from 0.0008 to 0.0079 ppm (U.S. FDA, 2003).

The USGS NAQWA program monitors water quality in more than 50 major river basins and aquifer systems. A summary of their *p,p*'-DDE and *o,p*'-DDE data for whole fish tissue can be found in the preceding section (Tables 4-4 and 4-6). These data constitute a national dataset for DDE fish tissue concentrations; however, the types of fish analyzed in this assessment may not be the same types eaten by humans. Median concentrations in fish tissues ranged from 3.5 to 43.2 µg/kg wet weight.

Giesy et al. (1994) measured the concentrations of the two DDE isomers in fish (8 species, 23 samples) from 3 rivers in Michigan between August and September 1990. They reported a *p,p*'-DDE range of 3.54-627.13 µg/kg wet weight, and *o,p*'-DDE range of 0.15-37.95 µg/kg wet weight. The high ratios of DDE to DDT (5:1 to 758:1) suggested that the DDE accumulation in the fish was a result of direct DDE exposure in the food chain rather than a recent exposure to DDT.

There has been a marked decline in the levels of DDT and related compounds in fish, shellfish, and aquatic mammals since the early 1970s (Addison and Stobo, 2001; Bard, 1999; Lauenstein, 1995; Lieberg-Clark et al., 1995; Odsjo et al., 1997; Schmitt et al., 1990). The National Contaminant Biomonitoring Program (Schmitt et al., 1990) reported that the mean concentration of *p,p*'-DDE has decreased from 260 µg/kg in 1976 to 190 µg/kg in 1984 (fish sampled at 112 locations across the United States).

Recent studies reporting concentrations of DDT and its metabolites in various fish, shellfish, and marine mammals are shown in Table 5-2. Only studies reporting DDE concentrations have been included. Studies reporting combined concentration levels for DDT and its metabolites have been omitted.

Table 5-2 Concentration of DDE in fish, shellfish, and marine mammals*

Species	Location	Year	Mean concentration, (range, if applicable)	Reference
Fish and shellfish				
Clams	San Joaquin River (Orestimba creek)	1992	3,300 ng/g (w.w.)	Pereira et al. (1996a)
Clams	San Joaquin River (Dry creek)	1992	25 ng/g (w.w.)	Pereira et al. (1996a)
Clams	San Joaquin River (Mokelumne River)	1992	13 ng/g (w.w.)	Pereira et al. (1996a)
Clams	San Joaquin River (Stanislaus River)	1992	22 ng/g (w.w.)	Pereira et al. (1996a)
Perch (n=5)	Lake ØrsjØen, Norway, Mid-lake	1994	0.53 ng/g (w.w.), 757 ng/g (f.w.)	Brevik et al. (1996)
Perch (n=5)	Lake ØrsjØen, Norway	1994	2.56 ng/g (w.w.), 5,120 ng/g (f.w.)	Brevik et al. (1996)
Pike (n=5)	Lake ØrsjØen, Norway, Mid-lake	1994	3.5 ng/g (w.w.), 3,888 ng/g (f.w.)	Brevik et al. (1996)

Species	Location	Year	Mean concentration, (range, if applicable)	Reference
Lake trout (n=59)	Lake Ontario	1992	1.159 µg/g (w.w.)	Kiriluk et al. (1995)
Rainbow smelt (n=8)	Lake Ontario	1992	0.256 µg/g (w.w.)	Kiriluk et al. (1995)
Marine Mammals				
Pilot whale (n=7)	North Atlantic	Since 1987	3847 (942-7118) ng/g (f.w.)	Becker et al. (1997)
Harbor Porpoise (n=5)	North Atlantic	Since 1987	3260 (1880-4900) ng/g (f.w.)	Becker et al. (1997)
Beluga whale (n=12)	Arctic	Since 1987	1415 (142-2230) ng/g (f.w.)	Becker et al. (1997)
Beluga whale (n=12)	Cook Inlet	Since 1987	624 (65.9-1630) ng/g (f.w.)	Becker et al. (1997)
Northern fur seal (n=2)	North Pacific	Since 1987	1190 (1050-1330) ng/g (f.w.)	Becker et al. (1997)
Ringed seal (n=4)	Arctic	Since 1987	198 (27-350) ng/g (f.w.)	Becker et al. (1997)
Beluga whale (neonate) (n=1)	St. Lawrence estuary near Quebec	1991	689 ng/g (brain); 2289 ng/g (kidney); 3370 ng/g (liver); 2106 ng/g (fat)	Gauthier et al. (1998)

*Source: ATSDR (2002)
f.w. = fat weight basis; n = number; w.w. = wet weight basis

5.1.3 Intake of DDE from Food

Based on the U.S. FDA Adult Total Diet Study for October 1979-September 1980, the daily intake of DDE was 0.004 µg/kg in 1979 and 0.003 µg/kg body weight/day in 1980 (Gartrell et al., 1986a). This study used the diet of a 16- to 19-year-old male as a basis for the adult intake. Similar studies reported a daily intake of DDE for infants of 0.034 µg/kg body weight/day, and for toddlers of 0.045 µg/kg body weight/day for 1980 (Gartrell et al., 1986b). The dietary DDE intakes for eight population groups determined from more recent U.S. FDA Total Diet Studies (from 1984 to 1991) are summarized in Table 5-3 (Gunderson, 1995a,b).

Table 5-3 Mean Daily Intake of DDE from Food Per Unit Body Weight (µg/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
1984-1986								
o,p'-DDE	0.0002	0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001
p,p'-DDE	0.0468	0.0484	0.01949	0.0207	0.0123	0.0150	0.0105	0.0119

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
1986-1991								
o,p'-DDE	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
p,p'-DDE	0.0441	0.0420	0.0130	0.0151	0.0099	0.0119	0.0082	0.0096

*Source: Gunderson (1995a,b)
F = female; M = male; mo = month; yr = year

5.2 Exposure from Air

Before 1972, when DDT was banned in the United States, it was used extensively as a pesticide and large amounts of the chemical were released to air during agricultural or vector control applications. Release of the chemical also could have resulted from production, transport, and disposal operations. Due to the U.S. ban on DDT, current release in the United States should be negligible (ATSDR, 2002).

However, an analysis of peat cores, as well as rain and snow samples from bogs or peat lands across the mid latitudes of North America, indicated that DDT is still present in the atmosphere (Rapaport et al., 1985). Because these areas receive all of their pollutant input from the atmosphere, these data suggest that DDT still is being released to the atmosphere either from its current production and use in other countries and transport to the U.S., or from the volatilization of residues resulting from previous use in the US (ATSDR, 2002).

The estimated half-life of vapor-phase DDE is 17 hours; however, this estimate does not necessarily reflect the lifetime of the compound in air. DDE can be adsorbed on particulate matter, which slows photooxidation and results in long-range transport. Such long-range transport has been demonstrated for DDT and several of its metabolites (Bard, 1999; Bidleman, et al.,1992; Goldberg, 1975; Ottar, 1981; Wania and MacKay, 1993).

DDT, DDE, or DDD also has been detected in air samples from 32 of the 441 NPL hazardous waste sites where those compounds were detected in some environmental media (HazDat, 2002).

5.2.1 Concentration of DDE in Air

DDE is ubiquitous in the environment due to its persistence. In remote areas away from agriculture DDE can be detected in air samples, over 20 years after the date it was banned in the United States. Hawthorne et al. (1996) measured the DDE concentration in samples from two rural sites between 1992 and 1994 in North Dakota at least 0.4 km from agricultural application of pesticides. They found the chemical concentration ranged from 6 to 200 pg/m^3 (Table 5-4); the detection limit was 0.3 pg/m^3. DDE concentrations varied by month, and levels detected in 1994 were greater than those from 1993.

Table 5-4 DDE Concentrations in North Dakota Air Sampling Collected in 1993 and 1994

1993						
	May 12	**June 22**	**Aug 1**	**Aug 17**	**Sept 21**	**Oct 26**
Temperature (°C)	17	22	14	23	12	1
DDE (pg/m^3)	6.2	18	21	20	8.1	8.9

1994							
	May 18	**July 18**	**Aug 1**	**Aug 11**	**Aug 15**	**Sept 8**	**Sept 22**
Temperature (°C)	26	23	24	22	22	22	8
DDE (pg/m^3)	9.7	120	49	41	50	200	8.8

Source: Hawthorne et al. (1996)

Another study conducted by Harner (2001) in Alabama, a region where DDT was used heavily, DDE median air concentration in 1996 was 10 pg/m^3 with a range of 1-92 pg/m^3.

An air monitoring study in the Arctic region (Fellin et al., 1996) detected mean DDE concentrations of 1.2 pg/m^3 for the warm months (May-September, 1992) where the temperatures ranged from -10 to 15°C (mean -3°C) and 2.9 pg/m^3 cold months (October-April, 1992), with temperature ranges from -45 to -5°C (mean -25°C), respectively. These findings seem counter to other temperature effects on DDE in the atmosphere. The increase of DDE and other POPs in the atmosphere during the colder months in the Arctic are attributed to anthropogenic contaminants from temperate latitudes being transported to the Arctic via semistationary high pressure cells that preside over Eurasia and North America. The advection of these anthropogenic contaminants into the Arctic has been described as "Arctic haze" (Barrie, 1986).

DDE's volatilization is affected by temperature; it is expected that increasing temperatures and moisture lead to higher ambient concentrations. This conclusion is supported by data reported by Iwata et al. (1993) who collected and analyzed 71 samples of air over several oceans (18 sampling locations) from April 1989 to August 1990. The author notes that at a number of sampled locations ΣDDT concentrations were below the detection limit during most of the winter months, while they were the highest during the summer months. An analysis of the Great Lakes region between November 1990 and October 1991 demonstrated that the highest monthly concentrations of DDE in Michigan cities were 63 pg/m^3 in Saginaw (August), 119 pg/m^3 in Sault Ste. Marie (May), and 92 pg/m^3 in Traverse City (July; Monosmith and Hermanson, 1996). The mean concentrations of DDE ranged between 0.3–180 pg/m^3 and the maximum was 180 pg/m^3.

An analysis of the Monosmith and Hermanson (1996) data suggests a correlation between higher DDT and DDE levels and air mass movement from the south, perhaps from areas where DDT was still used (i.e., Central America or Mexico). As a comparison, the DDE level in 1989 was 15 pg/m^3 over Green Bay, Wisconsin and 59 pg/m^3 over the four lower Great Lakes

(McConnell et al., 1998). In this study, however, an analysis of air masses indicated that the atmospheric sources were local or regional volatilization, not long-range transport.

Atmospheric levels of pesticides in the United States were measured during a time of high DDT usage. Stanley et al. (1971) took samples from 9 locations representing both urban and agricultural areas. The group reported maximum *o,p*'-DDT and *p,p*'-DDE levels in the range between 2.4 and 131 ng/m^3, with the highest levels found in the agricultural areas of the South. Periodical monitoring of some agricultural areas in which DDT was extensively used has provided data on the declining levels of the pesticide and its metabolites. DDE concentrations in air over agricultural lands in Mississippi have declined from 2.6-7.1 ng/m^3 as measured in 1967, to 0.13-1.1 ng/m^3, as measured in 1995 (Coupe et al., 2000). However, the authors point out that those results also are evidence for the persistence of the DDT degradation products.

DDE levels were measured in air and rain in Portland, Oregon, in 1984 (Ligocki et al., 1985). The authors did not detect DDE in rain samples; however, it was detected in five of seven samples from the gas phase associated with the rainfall. Levels ranged from not detectable to 420 pg/m^3.

In 1986–1988, EPA assessed non-occupational exposure to pesticides (NOPES) for the residents of two sites, Jacksonville, Florida and Springfield/Chicopee, Massachusetts (Whitmore et al., 1994). The authors report that indoor DDE levels in air were higher than outdoor levels, and that DDE was detected most frequently in the spring in Jacksonville (14%) and in the winter in Springfield/Chicopee (20%). The estimated mean air DDE concentrations were $\leq$1.0 ng/m^3.

5.2.2 Intake of DDE from Air

DDT and its metabolites are fairly ubiquitous in the atmosphere; however, the concentrations are so low that exposure via inhalation is generally negligible when compared to other routes of exposure.

5.3 Exposure from Soil

In the U.S., DDT was primarily used as an agricultural pesticide. Consequently, large amounts of DDT were released to agricultural soils; estimates include 27 million pounds in 1966 and 14 million pounds in 1971, shortly before it was banned (Gianessi et al., 1992). In addition, direct or indirect releases during manufacturing, formulation, storage, or disposal of the chemical have been sources of DDT in soils (ATSDR, 2002).

DDT and its metabolites are largely insoluble in water, so adsorb strongly to sediments in aquatic systems or soils. The strong binding of DDE to soil particles suggests that it is more likely to remain in the surface layers of soil, with little leaching into the lower soil layers and groundwater (ATSDR, 2002). DDT, DDE, and DDD may revolatilize from soil to the air (especially from moist soils) and then redeposited elsewhere by wet or dry deposition. This

process of revolatilization and redistribution of DDT and its metabolites leads to the occurrence of these compounds in areas where DDT never was used. This process is referred to as "global distillation" and results in redistribution of the compounds from warm source areas to cold polar regions.

As discussed in Chapter 3, the half-life of DDE is shorter in tropical soils than temperate soils. DDT, DDE, or DDD has been detected in soil samples at 305 of the 441 NPL hazardous waste sites where they were detected in the environment (HazDat 2002).

5.3.1 Concentration of DDE in Soil

Sediment

Monitoring - National

As discussed in Section 4 (above), the NAWQA program investigated the occurrence of *p,p*'-DDE and *o,p'*-DDE, in bed sediments (Tables 4-3, 4-5). Sampling was conducted at 1310 sites from 1992 to 2001. The highest concentration of *p,p*'-DDE, 440 µg/kg dry weight, was found in a mixed land use setting; the highest concentration of *o,p*'-DDE, 26.7 µg/kg dry weight, was found in an urban setting (Nowell, 2003).

As part of the Environmental Monitoring and Trends Program (EMAP) 168 sites were sampled along the southeastern coast of the United States in 1994–1995. The maximum concentration of *p,p*'-DDE in sediment was 34.2 µg/kg, while the median concentration was below the detection limit (Hyland et al., 1998). The National Surface Water Monitoring Program monitored DDE in surface water and sediment in 1976–1980. The percent occurrence (and maximum concentrations) of the DDE isomers in sediments was *p,p*'-DDE: 22.7% (163.0 µg/kg), and *o,p*'-DDE: 0.5% (1.3 µg/kg) (Carey and Kutz, 1985).

Mixed use areas - Bays

Between February 1990 and March 1993, Gills et al. (1995) assayed 246 surface and buried sediment samples from Newark Bay, New Jersey, and its major tributaries for the presence and levels of DDT, DDE, and DDD. The mean DDE concentrations in surface sediments ranged from 5 to 111 µg/kg. In addition, the group calculated profiles of mean sediment concentrations by the decade from 1940 to the present. DDE was rarely detected in sediments deposited prior to 1940. Overall, its concentration in sediments deposited after 1970 (when DDT was banned in the United States) was lower (less than 500 µg/kg) than in sediments deposited between 1940 and 1960, the peak time period for production and usage of DDT-containing insecticides in the United States. Although at lower concentrations, DDE occurred more frequently in post-1970 sediments than in layers from the 1950s and 1960s (Gills, 1995).

In 1993, Pereira et al. (1996b) collected and analyzed bed sediments from sixteen sites along the Lauritzen Canal and Richmond Harbor in the San Francisco area. Reported *p,p*'-DDE values ranging from 1.9 to 860 ng/g dry weight of soil and *o,p*'-DDE values ranging from 0.3 to 120 ng/g dry weight. DDE was detected at virtually every site tested (Pereira et al., 1996b). Between 1975 and 1980, the USGS and EPA cooperatively monitored levels of pesticides in

water and sediment at Pesticide Monitoring Network stations. Detectable levels of DDE were recorded for 42 of the 171 stations (approximately 900 samples) monitored (Gilliom, 1984). Between 1980 and 1983, EPA's STORET database listed analytical results for approximately 1,100 samples of sediments for DDE and reported median levels of 0.1 µg/kg dry weight (Staples et al., 1985).

Mixed use areas - Watershed

The concentration of DDE in bed sediment from the San Joaquin River and its tributaries in California (7 sites) in 1992 was 1.4–115 ng/L, respectively (Pereira et al., 1996a). 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 cm; Ford and Hill, 1991). DDE was detected in the upper soil layers at an occurrence of 93%, with a mean concentration of 100 µg/kg (range, non-detectable - 660 µg/kg); in deeper soil layers the occurrence was 79%, with a mean concentration of 40 µg/kg (range, non-detectable - 560 µg/kg).

Mixed use areas - Industrial (DDT production)

Some of the highest levels of DDE isomers in surface sediment (0–2 cm) were measured in the Palos Verdes Shelf, near Los Angeles, where waste from a large DDT manufacturer was discharged via a sewer outfall. The five sites in the area had *o,p*'-DDE and *p,p*'-DDE levels that were between 6-45 mg/kg and 10-327 mg/kg, respectively (Venkatesan et al., 1996).

Soil

Monitoring - National

The U.S. National Soils Monitoring Program monitored the overall pattern of DDT residues in soil, taking approximately 1500 samples each year. The 1970 results for *p,p*'-DDE were 31% occurrence, with a mean concentration of 50 µg/kg (range 10-6820 µg/kg). Those for *o,p*'-DDE were 3% occurrence, with a mean concentration of <10 µg/kg (range non-detectable-510 µg/kg) (Crockett et al., 1974). The mean ΣDDT level in five U.S. cities ranged from 120 to 560 µg/kg in 1971, and generally urban areas had higher pesticide levels than did nearby agricultural areas. The exceptions to this observation were some southern cities that were near areas where the agricultural use of pesticides traditionally was heavy (Carey et al., 1979). The Aberdeen pesticides dumpsite, Moore Country, North Carolina, had some of the highest reported surficial soil levels of DDE that were between 8.5 µg/kg and 2335 µg/kg (Vine, 2000).

Agricultural

Samples of 38 soils collected between 1995–1996 from the corn belt in the mid-central United States where DDT was heavily used, showed a geometric mean concentration for *p,p*'-DDE of 3.75 µg/kg (Aigner et al.,1998). The DDT/DDE ratio was determined in 21 of the samples and ranged from 0.5 to 6.6. Forest soils in Maine, which had been sprayed with DDT in the past, had ΣDDT levels between 270 and 1898 µg/kg, much higher than the maximum concentration of 11 µg/kg in unsprayed locations.

Soil samples taken near Dell City, Texas, in 1980 contained an average of 0.46 mg/kg (dry weight) of DDE (Hitch and Day, 1992). DDT use was extensive in agricultural areas in

Arizona for 18 years until a statewide moratorium on use in January 1969, after which the pesticide and its residues were monitored. Three years later, residues in agricultural soils had decreased by 23%, and the ratio of DDE to DDT was increasing, indicating a transformation of DDT to DDE (Ware et al.,1978). Similar results were reported by Buck et al. (1983) from monitoring these same sites over 12 years following the ban on DDT use. During that 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. Yet another study (Aigner et al., 1998) reports a mean DDE concentration of 3.75 ng/g soil as measured in 38 agricultural and 2 garden samples from Pennsylvania, Ohio, Indiana, and Illinois.

A study measured organochlorine pesticide concentrations in elementary school yards along the Texas-Mexico border. It concluded that DDE was the most frequently detected contaminant, occurring at 69% of the 13 sites examined. Relatively higher concentrations were observed in agricultural areas along the southern border (50-60 ppb in soils from Harlingen, McAllen, Palmview, and San Benito) than in other soils. In contrast, the DDE range from reference soil samples collected from eight national parks was between 4 and 9 ppb (Miersma, 2003). Historical data obtained during the time of DDT use indicate that its concentration in soil ranged from 0.01 to 53 ppm (Miersma, 2003).

5.3.2 Intake of DDE from Soil

Specific studies were not found in the literature reviewed concerning the intake of DDE from soil. An estimate of the intake of *p,p*'-DDE from soil can be derived from the data produced by the U.S. National Monitoring Program, which reported concentrations that ranged between 0.01 to 6.82 mg/kg of soil (Crockett et al., 1974). Intake can be estimated assuming that a 70-kg adult ingests 50 mg of soil daily and a 10-kg child ingests 100 mg (U.S. EPA, 1997a). Based on these data and assumptions, the intake of *p,p*'-DDE from soil for adults ranges between 0.000007 and 0.005 µg/kg-day, and for children it is between 0.0001 and 0.07 µg/kg-day.

5.4 Other Residential Exposures

Monitoring in older homes reveals that carpeting in these homes may have high levels of DDE (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^2 or 5.7 µg/g of ΣDDT (*p,p*'-DDT, DDD, and DDE).

Chlorinated pesticide residues also have been detected in cigarettes. Djordjevic et al. (1995) measured their content in U.S. and foreign cigarettes manufactured between the 1960s and the 1990s. Since 1970, the concentration of DDT analogs has decreased by more than 98%. The levels of *o,p*'-DDD detected in cigarettes manufactured between 1961–1979 were 396-7150 ng/g; by 1983-1994 levels were reduced to levels that were undetectable up to 19.0 ng/g. Levels of *p,p*'-DDE in cigarettes were 58-959 ng/g between 1961–1979; they also were reduced by 1983-1994 to 6.6-15.8 ng/g. The same author also measured the transfer rate of DDE from tobacco into mainstream smoke to be 27%.

ATSDR (HazDat, 2002) reports that DDT, DDE, or DDD have been identified in at least 441 of the 1613 hazardous waste sites proposed for inclusion on the EPA National Priorities List (NPL). The number of sites evaluated for those compounds was not specified, but *p,p*'-DDT, *p,p*'-DDE, and *o,p*'-DDE were detected at 326, 219, and 4 sites respectively (U.S. EPA, 1994c).

5.5 Occupational (Workplace) Exposures

DDT is not produced or used in the United States; therefore little or no occupational exposure to DDT or its degradates, including DDE, is expected via manufacturing or application. In 1971, the estimated respiratory exposure potential for formulating plant workers was 14.1 mg/person/hour (Wolfe and Armstrong, 1971)

5.6 Summary

Due to the persistence of DDE in the environment, exposure is likely to occur through media in addition to water, including exposures through food, air, soil, and residential contact. The general population likely has exposures primarily through food. Because of the persistence of DDT and DDE, it is anticipated that low levels of residues will be present in commodities for decades. In fact, depending on the continued use of DDT and export of commodities that may contain DDT by other countries, levels in the diet may even increase (Coulston, 1985). In domestic commodities, dietary exposure of consumers may result from residues bioaccumulated in some food items, including fish.

DDT and its metabolites are transported globally in the atmosphere but are present in such low concentrations that exposure via inhalation is negligible. Soil levels of DDE have been gradually declining; an estimate for adult *p,p*'-DDE intake from soil ranges between 0.000007 and 0.005 µg/kg-day, and for children it is between 0.0001 and 0.07 µg/kg-day. Other exposures may be residential in origin, including residues found in carpeting and cigarette smoke.

6.0 TOXICOKINETICS

6.1 Absorption

Oral Exposure

No studies were located that quantify the rate or extent of absorption of DDE in either humans or animals after oral exposure. Gastrointestinal absorption, however, can be inferred by measurements in serum and adipose tissues, the presence of metabolites in the urine, and toxic effects observed (ATSDR, 2002; Fawcett et al., 1987; Gold and Brunk, 1982, 1983, 1984; Hayes et al., 1971; Morgan and Roan, 1971, 1974). DDE is preferentially absorbed by the intestinal lymphatic system; however, some absorption into the portal blood also occurs (ATSDR, 2002). DDT has been shown to be absorbed 1.5-10 times more effectively in laboratory animals when administered in digestible oils compared to administration in nonabsorbable solvents (Hayes, 1982); this is likely also true for DDE. Sieber (1976) demonstrated vehicle-related differences in the uptake of DDE into the lymphatic system. Uptake via the chylomicrons was 30% when the DDE was in an aqueous vehicle and 60% when in corn oil.

Dermal Exposure

No studies that quantify the rate or extent of dermal absorption of DDE in either humans or animals were located. However, DDT is poorly absorbed through the skin even in solution (WHO, 1979).

Inhalation Exposure

No studies were located that quantify the rate or extent of absorption of DDE in either humans or animals after inhalation exposure.

6.2 Distribution

Once absorbed, the distribution of DDE is similar regardless of route of exposure. Both the blood and lymph deliver DDE to all body tissues with storage in these tissues generally proportional to the lipid content of the tissue (Morgan and Roan, 1971). DDE was demonstrated to be stored at a greater rate than either DDT, or DDD, a companion DDT metabolite (Morgan and Roan, 1971).

Although DDE transport from the intestines involves distribution to both portal circulation and the lymphatic system, the proportions vary with the nature of the exposure vehicle (oil or water; Sieber, 1976). Systemically less than 18% of DDE is carried in human erythrocytes. Gómez-Catalán et al. (1991) found 82.3% of DDE in human blood associated with plasma and 17.7% with cells. In plasma, 12% of the DDE recovered was associated with low density lipoproteins (LDL), 9% with very low density lipoproteins (VLDL), and 6% with high density lipoproteins (HDL). Norén et al. (1999) found that DDE and its methylsulfonyl metabolite, 3-MeSO_2-DDE, were primarily (80%) in the albumin fraction of human blood. Gómez-Catalán et al. (1991) estimated that about 60% of the DDE in plasma was associated with proteins and 9-15% with lipoproteins.

Because of the high fat content in human breast milk, DDE is selectively partitions into it. DDE was detected in all human breast milk samples collected and tested from 1969 to1970 in a U.S. national human milk study. The mean concentration of DDE in human breast milk was 1.9 ppm (lipid-basis; Takei et al., 1983). Using a model, the body burden of DDE in infants exposed via mother's milk was estimated to increase rapidly at the start of lactation, but decrease after approximately 5-6 months, even with continued nursing under all the exposure scenarios evaluated. Maximum mean body burden of DDE was estimated to be 70 μg/kg with the level reduced to <10 μg/kg by 24 months regardless of the duration of breast-feeding (LaKind et al., 2000).

DDE is distributed to the fetus during pregnancy. In one study, lipid-adjusted mean concentrations were similar in maternal blood and cord blood (4.4 ppm maternal; 4.7 ppm cord blood; Waliszewki et al., 2000). However, O'Leary et al. (1970b) and Schvartsman et al. (1974) found that cord blood levels were lower than the corresponding maternal blood. Sala et al. (2001) reported a geometric mean of 2.2 ppb (not lipid-adjusted) for DDE at delivery in maternal blood of 72 Spanish women, who lived in the vicinity of an organochlorine-compound plant compared to 0.83 ppb in cord blood (n=69).

DDE exposure of pregnant rats demonstrated that very little DDE crossed the placenta. Pregnant rats were administered 10 or 100 mg/kg/day on gestational days (gd) 14-18. In dams sacrificed on gestational day 15 or 17, the concentration of DDE in the placenta was about 3-fold higher than in fetal tissues. Ten-day-old pups exposed only *in utero* to 10 mg/kg/day had no detectable levels of DDE in blood, liver, or brain, while the pups exposure to 100 mg/kg/day had measurable DDE in their livers, but not in their blood or brain (You et al., 1999c).

In the study by You et al. (1999c) some pups were exposed to DDE through combined gestational and lactation exposure or during lactation only. There were no statistically-significant differences between the two groups in the levels of DDE detected in the liver, brain, and blood. By 78 days of age, all three exposure groups had DDE detectable only in fat deposits. Rats exposed only *in utero* had at least 2-fold less DDE in their fat than the other two exposure groups. DDE levels in the tissues and plasma of dams at the end of nursing were approximately a third those observed at the end of gestation, suggesting mobilization of DDE from storage sites during lactation.

Distribution kinetics of intravenously administered DDE (5 mg/kg) demonstrate a redistribution from blood to liver and muscle, to skin, and ultimately to adipose tissue with the entire process appearing to take about 1 day. 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. The tissue/blood concentration ratio 4 to 14 days after injection was 6 for liver and muscle, 35 for skin, and 400 for adipose tissue (Mühlebach et al., 1991).

6.3 Metabolism

Overview of Metabolic Pathways

The metabolism of DDE 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 have been identified in both humans and animals. DDE is metabolized to easily excretable phenols, as well as to m-methylsulfone-*p,p*'-DDE. DDE has been demonstrated to induce hepatic cytochrome P-450 (mainly CYP2B).

Studies of DDE Metabolism in Humans

Studies by Roan et al. (1971) and Morgan and Roan (1971) indicate that in humans little if any DDE is converted to bis(*p*-chlorophenyl)acetic acid (DDA). Part of stored DDE is excreted unchanged in humans; however, because its elimination is promoted by the induction of microsomal enzymes, it appears that it undergoes metabolism to include conjugation.

Animal Studies of DDE Metabolism

It has been proposed that in mammals, including humans, that DDT is initially metabolized to DDE (Mattson et al., 1953; Pearce et al., 1952) and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (DDD) (Klein et al., 1964) in the liver (Figure 6-1). Further metabolism of DDE is apparently slow with DDE retained in adipose tissues (Hayes et al., 1971; Morgan and Roan, 1971). In cases where the initial exposure is to DDE, especially when it is dissolved in corn oil, a considerable portion of the DDE could partition to adipose tissues before reaching the liver for further metabolism since chylomicrons are discharged directly from the lymphatic system to systemic circulation.

In rats, DDE is slowly converted in the liver to 1-chloro-2,2-bis(*p*-chlorophenyl)ethene (DDMU). DDMU is converted to 1,1-bis(*p*-chlorophenyl)ethene (DDNU), which is metabolized in the kidney to 2,2-bis(*p*-chlorophenyl)ethanol (DDOH), followed by 2,2-bis(*p*-chlorophenyl)ethanal (DDCHO) (Suggs et al., 1970), and finally oxidized to DDA (Peterson and Robison, 1964). DDA can then go through conjugation with glycine, bile acid conjugates, serine, aspartic acid, or glucuronic acid prior to elimination (Gingell, 1975; Pinto et al., 1965; Reif and Sinsheimer, 1975). It also has been suggested that conversion to DDA may proceed by way of an acid chloride intermediate (DDA-Cl) in Wistar rats, mice, and hamsters which would be hydrolyzed to form the acid. (Fawcett et al., 1987; Gold and Brunk, 1982, 1983, 1984).

An alternate metabolic option for DDMU is conversion to a DDMU expoxide. It is hypothesized that the epoxide could generate an intermediate with an electrophylic carbon (Datta, 1970; Datta and Nelson, 1970) capable of adding to and modifying DNA or other macromolecules involved in cell cycle control and/or signal transduction.

Methylsulfonyl metabolites also have been identified. Two such metabolites (3- and 2-methylsulfonyl-DDE) have been isolated in the blubber of seals from the Baltic (Jensen and Jansson, 1976), as well as in several other species (Bergman et al., 1994) including humans (Weistrand and Norén, 1997). Figure 6-2 demonstrates metabolism of DDE into its methylsulfonyl metabolites. DDE in the presence of phase I enzymes produces arene oxide,

which then undergoes conjunction with glutathione. Once excreted in the bile into the large intestines, it is cleaved by microbial C-S lyase (Bakke et al., 1982; Preseton, et al., 1984) into a thiol. The thiol is then methylated, reabsorbed, and the sulfur is further oxidized to methylsulfones, which are distributed by the blood (Haraguchi, et al., 1989).

6.4 Excretion

There are limited data on human excretion of DDE. DDE was measured in the bile of 5 male human subjects (Paschal et al., 1974). DDE is eliminated in human breast milk most likely due to its high lipid concentration. Lactational transfer is not an excretory pathway, but does result in removal of DDE from the mother and transfer to the offspring or into the food supply.

DDE has been detected in the urine of mice and hamsters following both acute and chronic exposure to DDT (Gingell, 1976; Gold and Brunk, 1983). Intravenously administered DDE (5 mg/kg) was mainly excreted in the feces (34%) of rats within a 14-day period following a single dose (Mühlebach et al., 1991); 1% was excreted in the urine. Although 10% of the DDE excreted in the feces was unchanged, no unchanged DDE was detected in the urine and no hexane-extractable lipophilic metabolites were detected in the feces. The total body burden half-life for DDE in rats was estimated to be 120 days (Mühlebach et al., 1991) and is longer than that for DDT (ATSDR, 2002).

Figure 6-1 Proposed metabolic pathway for DDT, including further metabolism of DDE (adapted from Peterson and Robinson, 1964 and presented in ATSDR, 2002)

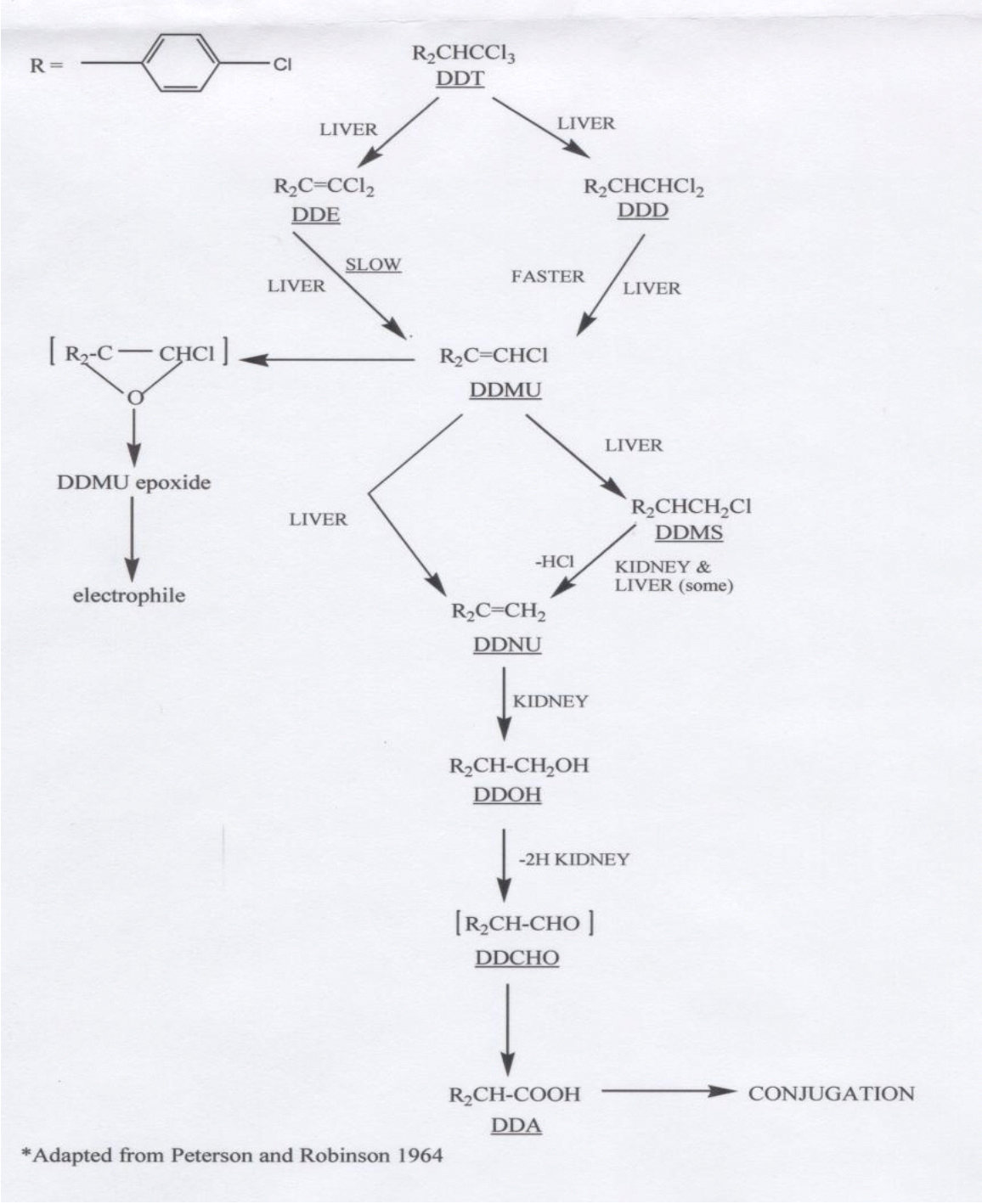
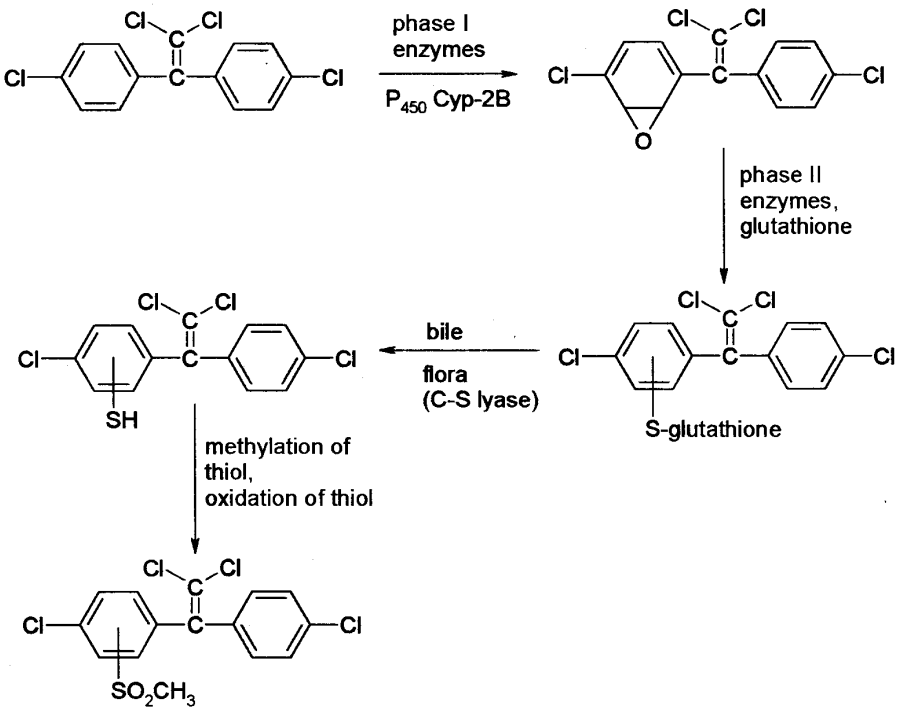


Figure 6-2 Proposed metabolic pathway for the conversion of *p,p'*-DDE to its methylsulfone derivatives (Bergman et al., 1994; Letcher et al., 1998; Weistrand and Norén, 1997)



7.0 HAZARD IDENTIFICATION

7.1 Human Effects

Human exposure to DDE can occur via human metabolism of DDT, the parent pesticide of DDE, or via direct exposure to DDE that has been degraded from DDT in the environment (e.g., through fish consumption). DDE is stored in fat leading to long-term internal exposure. There are commonalities and differences in the health effects associated with DDT and DDE based on experimental studies of both compounds in animal species. In cases where the initial exposure was only to DDT, it is difficult to determine which effects are due to the DDT, DDE or other metabolites.

7.1.1 Short-Term Studies and Case Reports

General Population

Intentional and Accidental Acute Ingestion

No studies of acute intentional or accidental ingestion of DDE in humans were found. However, data on DDT can be useful in hazard identification for DDE. The only documented case of human fatality following DDT ingestion occurred when a 1-year-old child ingested one ounce of 5% DDT in kerosene (Hill and Robinson, 1945). In other reports, doses as high as 285 mg DDT/kg body weight have been accidentally ingested without fatality (Garrett, 1947).

Oral exposure of doses up to approximately 22 mg DDT/kg in an oil solution caused neurological effects including prickling sensation of the area in and around the mouth, disturbance of sensitivity to the lower part of the face, uncertain gait, malaise, cold moist skin, hypersensitivity to contact, disturbance of equilibrium, dizziness, confusion, tremors, headache, fatigue, and severe vomiting within 10 hours of exposure. By 24 hours after exposure, most symptoms were no longer evident (Velbinger, 1947a,b). Perspiration, headache, and nausea were reported following a single oral exposure to 6 mg DDT/kg (Hayes, 1982). Convulsions have been reported in humans exposed to 16mg DDT/kg or higher (Hsieh, 1954). Similar symptoms have been reported after accidental or uncontrolled intentional ingestion of DDT (ATSDR, 2002).

To examine immunological effects, three volunteers were administered 5 mg DDT/day (0.07 mg/kg) for 20 days, and then challenged with an injection of *Salmonella typhimurium* vaccine. Volunteers receiving DDT had significantly higher serum agglutinin titers than volunteers receiving vaccine alone; immunoglobulin levels were unchanged. There were no apparent side effects associated with the DDT exposure (Shiplov et al., 1972).

7.1.2 Long-Term and Epidemiological Studies

No longer-term intentional dosing studies in humans were identified for DDE; however, a 12-18 month study of DDT administration to humans was identified (Hayes et al., 1956). In this study doses of 3.5 or 35 mg DDT/day were administered to 51 male volunteers and no

neurological (e.g., loss of coordination, tremor, etc.), cardiac (e.g., blood pressure, heart rate, etc.), or body weight effects were reported.

A number of occupational and general population epidemiology studies have explored the relationship of serum DDE levels and various physiological conditions or endpoints. The majority of the studies examined cancer endpoints or those associated with reproduction and development. Summaries of these studies and their findings follow.

General Populations

Noncancer Systemic Effects

In a case-control study of patients with chronic, debilitating fatigue lasting at least 6 months, the mean concentration of DDE in blood serum was significantly higher in cases (11.9 ppb; n=14) than in controls (5.2 ppb; n=23) (Dunstan et al., 1996). The 37 subjects were pooled and then re-divided according to their serum DDE levels (high being >6 ppb and low being <6 ppb). There was greater variability in the width of the erythrocyte cells in the high DDE group compared to the low DDE group; no differences were observed in other hematological parameters. Variability in the width of the erythrocyte cells can be a sign of anemia; unresolved anemia is one factor that is often associated with chronic fatigue.

Bohannon et al. (2000) hypothesized that high levels of DDE would be associated with lower bone density in peri- and post-menopausal women than in premenopausal women due to its (and DDT's) estrogen- and androgen-like properties. Women (50 black and 53 white) from the Mount Sinai Medical Center Longitudinal Normative Bone Density Study (1984-1987), were studied to examine the relationship between serum levels of DDE and bone mineral density. The study found that black women had significantly higher serum DDE levels than white women (mean 13.9 ppb vs. 8.4 ppb, respectively), but it did not find a correlation between DDE and either bone density or the rate of bone loss in the lumbar spine over a 2-year period.

In a study of 68 sedentary Australian women (45-64 years of age), an association was found between bone mineral (lumbar spine) and serum DDE levels >2 ppb. Only about 7.24% of the variance, however, was attributed to DDE with a stronger correlation found between bone mineral density and age (Beard et al., 2000). A study of 115 Swedish men aged 40-75 did not find a correlation between serum DDE levels and bone mineral density (Glynn, 2000).

Immunotoxicity

Vine et al. (2001) measured immunological parameters in 302 individuals (residing near a waste site) with a median of 2 ppb blood DDE (32 ppb blood DDE maximum). Parameters included white blood cell counts, lymphocyte phenotypes, immunoglobulin, mitogen-induced lymphoproliferative activity, and a skin test to evaluate delayed-type hypersensitivity. Although 20 organochlorines were targeted by the analysis, DDE was the only one detected. Results indicated that subjects with higher blood DDE levels had lower mitogen-induced lymphoproliferative activity (concanavalin A) and slightly increased total lymphocyte immunoglobulin A levels. The other parameters studied were unaffected; the authors concluded

that relatively low blood DDE levels were associated with changes in immune markers, but the changes were of uncertain clinical significance.

Reproductive and Developmental Endpoints

Infants of 23 women with preterm deliveries had higher DDE blood levels (19-22.1 ppb) than the full-term infants (4.9-6.1 ppb DDE) of 44 women. DDE was the only organochlorine monitored (O'Leary et al., 1970a).

A dose-related trend ($p<0.0001$) was observed between DDE concentrations in maternal blood and odds of pre-term birth among 2380 children born between 1959 and 1966 (Longnecker et al., 2001). The study cohort included 361 pre-term deliveries and 221 children who were small-for-gestational-age. Serum samples were obtained from mothers during the third trimester and stored at -20°C until 1997-1999 when the serum samples were analyzed. The median serum DDE was 25 ppb (range of 3-178 ppb). Quadratic spline models showed that the odds of pre-term birth began to increase at a blood DDE concentration of 10 ppb. Adjusted odds for small-for-gestational-age births also increased, but the trend was less consistent ($p=0.04$); the association of DDE with small-for-gestational-age births remained even with the exclusion of pre-term births. The authors noted that because pre-term births are a major contributor to infant mortality, inclusion of only children who survived may have lead to an underestimate of DDE's effects.

DDE levels in maternal milk were not associated with birth weight, head circumference, or neonatal jaundice; however, DDE at levels >4 ppm in maternal milk was associated with decreased reflex reactions in infants (Rogan, 1986). The same authors found an inverse relationship between the levels of DDE in maternal milk and lactation duration in women in the United States and Mexico (Rogan, 1987). Gladen and Rogan (1995) examined the relationship between DDE and lactation duration in Tlahualilo, Mexico and found an inverse relationship between DDE and duration of lactation only applied to women with prior breast-feeding experience and not in women breast feeding for the first time. A statistically-significant decrease in median lactation duration was observed in women with $\geq$12 ppm (lipid-adjusted; 3 months of lactation) compared to women with 0-2.5 ppm (7.5 months of lactation). The observed effects on lactation may be due to the ability of DDE to disrupt normal hormonal regulation of lactation (Guyton, 2000).

A prospective longitudinal study was performed to examine the relationship between prenatal or lactational exposure to background levels of DDE (or polychlorinated biphenyl, PCB) and pubertal growth and development. Exposure was estimated for 856 children by measuring DDE in maternal milk, maternal blood, cord blood, and placenta. These children had normal birth weights and normal growth during their first year of life. Five hundred and ninety-four (316 girls and 278 boys) were available at puberty for follow-up. The transplacental DDE index ranged from 0.3 to 23.8 ppm (median 2.4 ppm) and the lactational DDE index ranged from 0.2 to 96.3 mg (median 6.2 mg). Transplacental exposure to DDE was associated with increased height and weight of boys at puberty. Boys with the highest exposures to transplacental DDE (a median index of 2.4 ppm) were 6.3 cm taller and 6.9 kg larger than boys from the lowest

exposure (0-1 ppm). These effects were not observed in the girls. No effects on the age at which pubertal stages were attained were observed (Gladen et al., 2000).

Karmaus et al. (2002) studied the association of serum DDE levels in children at 8 years of age with weight and height through age 10. Medical records were used to obtain the height and weight of the children from birth to 4 years of age. While there were 323 children with weights and heights measured at birth, there were only 202 at 43-48 months. Measurements at 8, 9, and 10 years of age were performed by the investigators (the number of children at each age was not provided in ATSDR, 2002). Blood was collected and analyzed only at 8 years of age. Results indicate that, after controlling for relevant confounders, DDE was a significant predictor of height in girls from 1.3 months until 8 years of age. Girls in the highest DDE quartile (0.44-40.4 ppb) were 1.8 cm shorter than girls in the lowest quartile (0.08-0.2 ppb). At 10 years of age, no association was found.

An evaluation of Inuit infants' *in utero* exposure to DDE (and other organochlorines) revealed no association with immunological parameters, but there was a relative risk of 1.87 (95% CI, 1.07-3.26) for increased otitis media for 4- to7-month old infants in the highest tertile of DDE exposure when compared to the lowest tertile (Dewailly, 2000). The organochlorine concentration in breast milk was used as an index of the infants' exposure. The authors of this study noted that there the organochlorine exposures in this population originate from the same few food items, such that the concentrations of the various chemicals (DDE, hexachlorobenzene, etc.) are correlated with each other.

Cancer Endpoints

A positive correlation was made between DDE and breast cancer in New York City women attending a mammography clinic between 1985 and 1991. Serum DDE (not lipid-corrected) was measured in archived blood samples of 58 women who were diagnosed with breast cancer within 6 months of entering the study and in matched (by menopausal status, age, number and dates of blood donations, and day of menstrual cycle at time of first blood drawing) with cancer-free control women from the same cohort (n=171). Case patients had a significantly ($p=0.031$) higher mean serum DDE (11.0 ppb) than the control subjects (7.7 ppb). The adjusted odds ratio for breast cancer in the highest quintile of serum DDE was 3.68 (95% Confidence Interval [CI]=1.01-13.50) using the lowest quintile as the referent group. A positive trend ($p=0.035$) was observed in the odds ratio for breast cancer and increasing quintile, and a positive trend ($p=0.0037$) was observed between the odds ratio and serum DDE when serum DDE was elevated as a continuous variable using conditional multiple logistic regression. The odds ratios were adjusted for confounders, such as first-degree family history of breast cancer, lifetime months of lactation, age at first full-term pregnancy, age at menarche, history of benign breast disease, history of tobacco and alcohol use, and race (Wolff et al., 1993).

Age-adjusted serum DDE levels were significantly related to breast cancer risk in 120 cases (3.84 ppm) compared to 126 controls (2.51 ppm) living in Mexico City. There was a marginally significant ($p=0.06$) positive trend between DDE levels and the risk of breast cancer ($OR_{Q1-Q4}=2.16$; 95% CI=0.85-5.50) even after adjusting for age at menarche, duration of breast feeding, quetelet index (as a measure of obesity), and menopausal status. The association was

strongest in menopausal women, with no association found in premenopausal women. Serum DDT levels did not have the same association. Major predictors of DDE levels included DDT levels, age, duration of lactation, parity, and socioeconomic level (Romieu et al., 2000).

A few studies found an increase in DDE levels in malignant breast tissue in comparison to adjacent "normal" breast tissue or to benign breast disease; however the difference in DDE levels generally was not significant (Dewailly et al., 1994; Falck et al., 1992; Wasserman et al., 1976). A case-control study in German women performed in 1993-1994 found a 62% ($p=0.017$) higher level of DDE in malignant breast tissue of recently masectomized women ($n=45$) compared to age-adjusted geometric mean DDE concentration in benign breast tissue in the control group ($n=20$). A significant difference was not observed in the concentrations of DDT (Güttes et al., 1998).

A hospital-based case-control study of Canadian woman found a weak association between DDE in breast adipose tissue and breast cancer. The geometric mean of DDE in the 217 cases was 693 ppb compared to 596 ppb in the 213 benign controls. The increased risk was observed when current hormone replacement therapy users were excluded. The odds ratio of DDE was higher for the risk of estrogen receptor-negative breast cancers than for estrogen-positive breast cancer (Aronson et al., 2000; Woolcott et al., 2001).

Although there are several studies associating DDE with breast cancer, there are also many showing no association, even when the studies were performed by the same authors. These studies adjusted for confounders, had matched controls, used current or past (up to 19 years prior) DDE levels, used serum or adipose DDE concentrations, and had sufficient numbers of cases (Demers et al., 2000; Helzlsouer et al., 1999; Høyer et al., 1998; Hunter et al., 1997; Laden et al., 2001a; Liljegren et al., 1998; Lopez-Carrillo et al., 1997; Matuo et al., 2000; Mendonca et al., 1999; Moysich et al., 1998; Schecter et al., 1997; Unger et al., 1984; Ward et al., 2000; Wolff et al., 2000a,b; Zheng et al., 1999, 2000).

Hunter et al. (1997) performed a prospective study on the health of 121,700 married nurses in the United States. Cholesterol-adjusted plasma DDE was determined in blood samples collected from 1989 to 1990. There was no significant difference in historical plasma DDE (1989-1990) in women who developed breast cancer before June 1992 ($n=236$) and pair-wise matched control women who did not develop breast cancer. This lack of association was observed regardless of menopausal status, age, age at menarche, age at birth of first child, number of children, and history of lactation. A follow-up report added 143 postmenopausal cases and controls, and adjusted for plasma organochlorines and for triglycerides in addition to cholesterol (Laden, 2001b). Median (lipid-adjusted) concentrations of DDE in cases and controls were 0.768 and 0.817 ppm, respectively. Again, no association between breast cancer and DDE was observed 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. The multivariate relative risk of breast cancer for women in the highest quintile of DDE (1.5-6.0 ppm) compared to women in the lowest DDE quintile (0.007-0.43 ppm) was 0.82 (95% CI=0.49-1.37).

Krieger et al. (1994) did not find an association between serum DDE levels and breast cancer in 150 cases (50 each of Caucasian, African-American, and Asian women) compared to 150 matched controls (43.1 vs. 43.3 ppb; not lipid adjusted) in a prospective nested case-control study. Blood was collected between 1964 and 1971 from women in northern California. Controls did not develop breast cancer through the end of 1990. When the ethnic groups were examined separately, however, high serum DDE concentrations were associated with breast cancer incidence in Caucasian and African-American women (not significant), but not Asian American women. Black women with breast cancer had an average of 5.7 ppb higher levels of serum DDE than paired controls, but the difference was not statistically significant (95% CI on the difference ranging from -3.3 to 14.8). It also should be noted that serum DDE concentrations were higher in black and Asian women compared to white women.

A case-control study nested within a prospective cohort study was conducted in residents of Washington County, Maryland, to examine the association between breast cancer and serum DDE (both lipid-adjusted and unadjusted) from blood samples collected in 1974 (20,305 samples) or 1989 (25,080 samples). The cases consisted of 346 women diagnosed with breast cancer by June 1994. Controls (n=346) were cancer-free women matched for age, race, menopausal status, and date of blood donation. Lipid-adjusted DDE concentrations were higher (nonsignificantly) in the controls than in the cases. Risk analyses conducted on quintiles (1974 samples) or tertiles (1989 samples) showed no association between DDE (lipid-adjusted) and breast cancer (Helzlsouer et al., 1999).

Wolff et al. (2000a) investigated breast cancer risk associated with organochlorine exposure in a hospital-based, case-control study using 175 cancer patients, 181 control patients with benign breast disease, and 175 women in a second hospital control. Overall 57% of the subjects were Caucasian, 21% hispanic, and 22% African-American. Several organochlorines were measured in blood serum, which generally was obtained before surgery and no more than 2 months after surgery and measured for 4 tumor markers (estrogen, progesterone, p53, and erbB-2). Results demonstrated that African-American woman had significantly higher lipid-adjusted DDE levels (geometric mean of 1.0 ppm) than Hispanic (0.71 ppm) and Caucasian (0.48) women. Organochlorine levels were not associated with breast cancer risk, including tumor stage or tumor markers. Higher DDE levels were associated with increasing body mass index (BMI), as well as, decreasing level of education, frequency of nulliparity, and frequency of family history of breast cancer. The findings were attributed to historical patterns of exposure and to metabolic differences in organochlorines related to BMI.

In a re-evaluation of the data from their 1993 report, the same investigators (Wolff et al., 2000b) did not find the same results. In the re-evaluation, the authors were interested in assessing the half-lives of DDE and PCBs; therefore, the study was restricted to cases with at least three yearly blood donations after the first year of serum analysis. Lipid measurements were available in 110 cases and 213 controls, and DDE half-life was calculated for 84 cases and 196 controls. Odds ratios were calculated with conditional logistic regression analysis using DDE (as well as PCB) as both quartile or tertiles and continuous variables. DDE levels were similar in the cases (geometric mean 977 ppb, lipid-adjusted) and controls (1097 ppb) regardless of whether the concentration was lipid-adjusted or not. Differences were not noted when

estrogen receptor status of tumors, age at menarche, number of full-term pregnancies, age at first full-term pregnancy, first degree family history of breast cancer, months of lactation, and height were considered. The half-life of DDE, but not serum level, was correlated with BMI.

A nested case-control study of 240 breast cancer patients and 477 control subjects from a prospective heart study of 7712 women in Denmark found that odds ratios for breast cancer were not increased in the upper quartiles of lipid-adjusted serum DDE (Høyer, 1998). Breast cancer diagnosis occurred up to 17 years following the collection of blood samples. The analysis considered the following confounders: weight, height, number of full term pregnancies, alcohol consumption, smoking, physical activity, menopausal status, household income, marital status, and education.

Ward et al. (2000) also did not find an association between breast cancer and serum DDE using 150 breast cancer cases and 150 controls from Norway. Blood was collected 2 to 18.2 years (mean of 8.8 years) prior to diagnosis. Mean lipid-adjusted DDE concentrations were 1230 and 1260 ppb in cases and controls, respectively (corresponding DDT concentrations were 120 and 138 ppb, respectively). When the data was stratified by age at diagnosis, the interval between blood collection and diagnosis, and estrogen and progesterone receptor status, DDE was found to be higher in women with breast cancer who were 50 years of age or older at diagnosis and who had $\geq$10 years between blood sample and diagnosis. The results, however, were not statistically significant.

In a nested case-control study of 105 breast cancer cases and 208 matched controls (subjects were participating in a prospective breast cancer study), risk ratios were found not to be elevated for breast cancer in the highest quartile of lipid adjusted-serum DDE (Dorgan, 1999). Breast cancer diagnoses were made up to 9.5 years after the collection of blood samples.

A case-control study examining postmenopausal women in western New York State (154 cases and 192 controls) found no association between breast cancer risk and current age- or lipid-corrected serum DDE concentrations. Blood samples were collected within several months of diagnosis between 1986 and 1991. Confounding factors considered included age, education, familial breast cancer, parity, quetelet index (as a measure of obesity), age at first birth, duration of lactation, years since last pregnancy, fruit and vegetable intake, and serum lipids (Moysich et al., 1998).

Age-adjusted mean serum DDE levels (lipid-adjusted) in 475 case and 502 control women in Connecticut were comparable (460 and 456 ppb, respectively), even when controlling for menopausal status, parity, lactation, and by cases' estrogen receptor status. Patients (n=389) with early stage disease had a slightly higher (not statistically significant) level of serum DDE than the 20 patients with later stage disease (456 vs. 402 ppb, respectively; Zheng et al., 2000).

In Mexico City, DDT has been used in the recent past for malaria control. Between 1994 and 1996, hospital patients did not demonstrate a significant association between the level of serum DDE (either wet weight or lipid weight basis using arithmetic or geometric mean) and breast cancer risk. Cases consisted of 141 women with breast cancer. Age-matched control

women were obtained from other areas in the hospital (excluding oncology and gynecology). No association was found when menopausal status (using an odds ratio analysis adjusted for age), quetelet index (as a measure of obesity), breast feeding with first birth, parity, family history of breast cancer, and time elapsed since first birth were controlled (Lopez-Carrillo et al., 1997).

There was no association between current (1994) plasma DDE (or DDT) concentrations (nonlipid-adjusted) and newly diagnosed breast cancer (n=21) in northern Vietnamese women. The relative risk for breast cancer was not elevated significantly for subjects in the higher tertile of plasma DDE, DDT, or total DDT (DDT plus molar-adjusted DDE) compared to the lowest tertile. Women were similar with respect to age, age at menarche, age at first pregnancy, parity, history of lactation, and maximum attained body weight (Schecter et al., 1997).

Mendonca et al (1999) found no association between breast cancer incidence and serum DDE concentrations in women from Brazil. The study examined 177 cases of invasive breast cancer and 350 controls from a large metropolitan region. Cases had a mean and median serum DDE of 5.1 and 3.1 ppb, respectively, compared to 4.8 and 3.1 ppb, respectively, in controls. The age-adjusted odds ratio for breast cancer in the upper quintile compared to the lowest quintile was 0.90 (95% CI=0.47-1.73).

A study of DDE concentrations in breast adipose tissue from 73 breast cancer cases and 73 breast reduction surgery patients revealed that DDE levels were significantly elevated in cases relative to controls; however, when adjusted for age the significance was lost (Bagga, 2000). Another case-control study of postmenopausal European women showed no significant difference in current DDE concentrations in buttocks adipose for 265 women with breast cancer (1.35 ppm) and 341 controls matched on age and study center (1.51 ppm; Van't Veer, 1997).

Laden et al. (2001a) performed a combined meta analysis from 5 studies (Helzlsouer et al., 1999; Laden et al., 2001; Moysich et al., 1998; Wolff et al, 2000a; Zheng et al., 2000) comparing women in the fifth quintile of lipid adjusted DDE values with the first quintile. The multivariate pooled odds ratio for breast cancer was 0.99 (95% CI=0.77-1.27), indicating no association between breast cancer risk and serum DDE concentrations. This analysis included 1400 case patients and 1642 controls.

Liljegren et al. (1998) found no association between malignant breast cancer and the concentration of DDE in breast tissue fat. Forty-three cases of malignant breast cancer were compared to 35 controls with benign breast disease. Fat samples were collected during surgery after diagnosis from 1993-1995. Results did not change when the study groups were divided into pre- and postmenopausal women or estrogen-receptor (ER-positive) subgroups. The Liljegren et al. (1998) results were supported by Zheng et al. (1999), which also did not find a significant association between breast adipose DDE concentrations and breast cancer. This study included 304 cases of breast cancer and 186 benign breast disease controls in Connecticut. The age-adjusted geometric mean of breast adipose DDE concentration was 737 and 784 in cases and controls, respectively (DDT concentrations were 52 and 56 ppb, respectively).

Hoppin et al. (2000) examined serum levels of DDE (as well as other organochlorine compounds) in 108 subjects with pancreatic cancer and 82 controls (matched to cases by age and sex) in a population-based study in the San Francisco Bay area. Cases had higher median lipid-adjusted DDE concentrations (1.3 ppm) than the controls (1.0 ppm). The odds ratio for the highest tertile compared to the lowest tertile was 2.1 (95% CI = 0.9-4.7), but it did not achieve statistical significance. The odds ratio was reduced to 1.1 after controlling for PCB levels. As part of this same study, Slebos et al. (2000) measured K-*ras* oncogene and *p*53 tumor suppressor gene (two tumor-related molecular markers) and organochlorine levels in 61 subjects newly diagnosed with pancreatic cancer. Patients with K-*ras* positive tumors tended to have lower serum levels of DDE than those with K-*ras* negative tumors (significance not reported in ATSDR, 2002), but there were no significant differences noted between *p*53 positive and negative patients. Porta et al. (2000), however, determined that serum DDE (as well as DDT) was significantly higher in 51 subjects with pancreatic cancer than in 26 controls (selection of subjects not noted in ATSDR, 2002). The serum DDE levels (nonlipid adjusted) in the 17 patients with wild-type K-*ras* tumors did not differ from the control, however, the serum DDE levels (nonlipid adjusted) in the 34 patients with mutated K-*ras* tumors were about double those in controls. The study did not make comparisons using lipid-adjusted concentrations.

Hardell et al. (1996) did not find an association between DDE concentrations in abdominal adipose tissue and non-Hodgkin's lymphoma. The mean DDE concentration in 28 newly diagnosed patients in Sweden was 1.4 ppm (lipid based) compared to 1.1 ppm in 17 surgical controls; however, nearly all of the 34 PCB congeners analyzed were significantly higher in the cases relative to controls.

No association was found between lipid-corrected blood serum DDE concentration and endometrial cancer in a multicenter case-control study of 180 women in the United States (Sturgeon et al., 1998). Cases and controls both had median blood lipid-adjusted DDE concentrations of approximately 1.4 ppm.

Cocco and Benichou (1998) used an ecological study design with multivariate statistical techniques to examine the relationship between DDE concentration in subcutaneous fat, or levels in tree bark (as a measure of environmental levels), and mortality from prostate and testicular cancers in a number of States. The adipose samples for people in 22 states were collected from the U.S. Department of Health, Education and Welfare's 1968 Human Monitoring Program; data on DDE in tree bark were available for 18 states from 1992-1995. The age-adjusted mortality rates from prostate and testicular cancers by state from 1971-1994 were obtained from the National Center for Health Statistics. African Americans had a higher (74%) mean adipose DDE concentration than whites, so separate analyses were performed for the two races. Numerous demographic factors were considered possible confounders. The authors concluded that the results did not support an association between prostate and testicular cancer and DDE exposure.

A separate study by Cocco et al. (2000) used the same methods discussed above, but examined the association between DDE levels in adipose tissue (collected in 1968) and several additional diseases. They examined DDE's association with age-adjusted mortality rates between 1975 and 1994 for multiple myeloma, non-Hodgkin's lymphoma, and breast, uterus,

liver, and pancreas cancer in 22 U.S. states. Separate analyses were conducted for gender and race. No association was noted between DDE concentrations and pancreatic cancer or multiple myeloma. There was an inverse correlation between adipose DDE and breast cancer mortality in both white and African American women. An inverse correlation (statistically significant) also was observed for uterine cancer in white women, but not in African American women. There was no association observed for non-Hodgkin's lymphoma in either whites or African Americans (men and women). Liver cancer mortality in white males and females was significantly increased with adipose DDE concentrations ($p<0.05$), however, the same results were not observed in African Americans. It should be noted that the number of subjects affects the sensitivity of statistical analyses to find a significant effect.

7.2 Animal Studies

7.2.1 Acute Toxicity

LD_{50} studies of DDE are indicative of moderate toxicity. An LD_{50} of 880 mg/kg was reported for male Sherman rats (Gaines, 1969). For *o,p*'-DDE 810 mg/kg was lethal in female mice and 845.9 mg/kg in male mice (Tomatis et al., 1974).

As mentioned previously, DDE exposure is predominantly a result of its formation as a metabolite of DDT. Accordingly, most studies of acute toxicity have examined the parent compound, rather than the metabolite, and are not considered in this assessment.

7.2.2 Short-Term Studies

DDE mixed in corn oil and incorporated into the basal diet at concentrations of 316, 562, 1000, 1780, or 3160 ppm was administered to Osborne-Mendel rats (5/sex/group) for 6 weeks followed by a 2-week observation period (NCI, 1978). These concentrations are equivalent to doses of 0, 16, 28, 50, 89 or 158 mg/kg/day based on a food intake factor of 0.05 kg diet per kg body weight (U.S. EPA, 1986d). This study was done as a range-finding exercise to help in establishing the dose levels for the NCI cancer bioassay and did not examine a full complement of standard toxicological endpoints. The only published version of the study results is in the background section of the bioassay report, and include only information on the body weight and mortality findings.

Body weight gain was reduced in male rats of all treatment groups. Male rats administered a dose of 1000 ppm had body weights 11% lower than the control group and those administered 1780 ppm were 22% lower than the control group. There were no exposure-related changes in body weight for the females. One female rat administered 1000 ppm died, and all female rats administered 1780 ppm or 3160 ppm died by the end of the 6-week treatment period. The only deaths (number not specified) for the male rats occurred in the 3160-ppm group (NCI, 1978).

The same protocol was used with groups of B6C3F1 mice (5/sex/dose). DDE was mixed in corn oil and incorporated into the basal diet at concentrations of 139, 193, 269, 373, or 519

ppm (NCI, 1978). Using a food intake factor of 0.13 kg diet per kg body weight (U.S. EPA, 1986d), these concentrations are equivalent to doses of 0, 18, 25, 35, 47, and 68 mg/kg/day. There were no changes in body weight associated with treatment. One control male and one male in the 269-ppm dose group died. Four male mice and two female mice administered 373-ppm dose group died (NCI, 1978).

Humoral (significantly increased serum albumin/globulin ratio, suppressed serum IgM, IgG after ovalbumin immunization, and decreased antibody titer) and cell-mediated (increased inhibition of leucocyte and macrophage migration, and decreased footpad thickness) immune responses were adversely affected in male Wistar rats (8-12 per group). The effects occurred after they were administered diets containing 200 ppm DDE, which was estimated to be equivalent to 22.2 mg/kg/day, for 6 weeks. In addition, mean relative liver weight was increased compared to the controls (Banerjee et al., 1996).

7.2.3 Subchronic Studies

No standard subchronic (13-week) oral studies for DDE were identified; however, subchronic studies are available for DDT, the parent compound of DDE. A study of DDT administered in the diet for 3 months suggests that the liver may be a target organ for DDE as well as DDT. In this study a dose of 2.5 mg DDT/kg/day caused minor hepatocyte vacuolation in male rats and a dose of 10 mg DDT/kg/day caused liver hypertrophy in females (Ortega, 1956). Chowdhury et al. (1990) administered 0.2 mg DDT/kg/day by gavage for 120 days to rats. Atrophy of the adrenal gland in all zones except the *zona glomerulosa* was observed. In male rats, the body weight gain was 30% lower in treated animals compared to the controls.

In another study, weanling rats (25/sex/group) were fed commercial DDT (81% *p,p*' isomer and 19% *o,p*' isomer) at levels of 0, 1, 5, 10 or 50 ppm for 15-27 weeks (Laug et al., 1950). Increasing hepatocellular hypertrophy, especially in the centrilobular region, increased cytoplasmic staining with an acid dye, and peripheral basophilic cytoplasmic granules were observed at dose levels of 5 ppm and above. The response was dose-related becoming more pronounced in the 10- and 50-ppm groups. No effects were reported for the 1-ppm concentration (0.05 mg/kg/day), and this was identified as the no observed adverse effect level (NOAEL). The authors stated that the effect seen at 5 ppm (0.25 mg/kg/day) seemed to represent the smallest detectable morphologic effect, based on extensive observations of the rat liver as affected by a variety of chemicals. The NOAEL from this study was used as the basis for the DDT RfD (U.S. EPA, 1986e).

Affects on the immune response also have been observed after subchronic exposure to DDT. Dietary administration of 1.9 or 19 mg DDT/kg/day for 31 days caused a decrease in the severity of the anaphylactic response and the number of mast cells producing histamine after a challenge with diphtheria toxoid compared to the control group (Gabliks et al., 1975). Adult mice administered 0.06 or 0.63 mg DDT/kg/day for 16 weeks had a significant increase in the

primary IgM response to sheep red blood cells (SRBC) and lymphoproliferative response to LPS-coated (*Escherichia coli* lipopolysaccharide) SRBC; however, exposure for 20 or 24 weeks caused a sharp reduction in both responses. A dose of 0.006 mg DDT/kg/day did not have an effect (Rehana and Rao, 1992).

7.2.4 Neurotoxicity

No studies of DDE neurotoxicity are available; however, behavioral effects have been observed in longer term bioassays. Minimal signs of neurotoxicity were reported in both the rats and the mice during the National Toxicology Program (NTP) (1978) bioassay (full details of this study are provided in Section 7.2.6 and 7.2.7). During the period of compound administration, the male rats receiving 675- or 1350-ppm dietary concentrations (30 or 49 mg/kg/day) and female rats receiving the 375- or 750-ppm concentrations (16 or 32 mg/kg/day) reportedly displayed a hunched posture beginning after 8 weeks of treatment and continuing for the remainder of the dosing period. The highest incidence occurred in the high-dose males. During week 24, the dose levels were decreased and the incidence of hunched appearance decreased dramatically in treated rats. Some of the control rats also exhibited a hunched posture during the study but the incidence and severity were lower than that in the dosed rats.

Sixty to 85% of male B6C3F1 mice administered 150 or 300 ppm reportedly had a hunched appearance after 22 weeks of treatment. The frequency and intensity of this effect varied as dosing was altered within the same group during the study, strengthening its association with dose. The doses within groups were not constant across the 78-week exposure period as explained in Section 7.2.6. During the post-dosing observation period there was no discernable difference between the exposed and control animals (NCI, 1978).

Rossi et al. (1983) conducted a chronic dietary exposure study (128 weeks) in groups of 40 to 47 male or female Syrian golden hamsters using concentrations of 0, 500 or 1000 ppm DDE. No signs of neurotoxicity, such as tremors or convulsions were noted; the authors make no reference to any possible changes in animal posture during the dosing period.

7.2.5 Developmental/Reproductive Toxicity

In the NCI (1978) chronic bioassay, DDE administered to Osborne-Mendel rats in the diet at time-weighted-average concentrations of 0, 437, or 839 ppm for male rats or 0, 242, or 462 ppm for female rats for 78-weeks did not cause significant adverse effects on the ovaries, uterus, mammary gland, testes, or prostate as revealed via routine histological examination of these tissues. The same was true for B6C3F1 mice administered time-weighted-average concentrations of 0, 148, or 261 ppm. There was, however, a dose-dependent, but not statistically significant, increase in endometrial stromal polyps (0, 5, and 13%, respectively) in female rats. Reproductive function was not evaluated in the NCI (1978) study.

DDE administered to rats for 5 weeks prior to mating and during gestation and lactation at a dose of 10 mg/kg/day did not affect reproduction as measured by percent sperm positive,

percent pregnant, gestation length, litter size, sex ratio of pups, and milk production and composition (Kornbrust et al., 1986).

Reduced seminal vesicle and ventral prostate weights were observed when 200 mg/kg/day of DDE were administered for 4 or 5 consecutive days via gavage to male Long-Evans rats (Kelce et al., 1995, 1997).

Exposure to 100 mg/kg/day during gestational days 14-18 in Sprague-Dawley rats resulted in a significant decrease in ventral prostate weight in males at 15 months of age. Similar exposure caused a decrease in weights of glans penis, ventral prostate, and epididymis in Long-Evans males when they were 10 months old. Reduced anogenital distance and increased mean number of retained nipples also were observed in the Long-Evans rats when they were newborn (Gray et al., 1999).

Anogenital distance at birth was reduced in male Long-Evans pups exposed transplacentally to 100 mg/kg/day during gestational days 14-18. Because of the long half-life of DDE and its incorporation into milk, the prenatal exposure of the dams would have also led to unquantified pup exposure during lactation. The animals also had retained thoracic nipples on postnatal day 13. A significant delay in the onset of puberty (measured by the age of preputial separation) was reported in male rats treated with 100 mg/kg/day from weaning (either day 21 or 25; ATSDR states that the specific day is unclear in text) until day 57 of age. Puberty was delayed by 5 days, but was not accompanied by a change in serum testosterone levels (Kelce et al., 1995, 1997).

A study by You et al. (1998) compared the effects of DDE on male sexual development in offspring of Sprague-Dawley and Long-Evans rats. Gavage doses were administered to pregnant dams at 10 or 100 mg/kg from gestation day 14 to 18. Reduced anogenital distance developed in Long-Evans male rats, but the same effect was not noted in the Sprague-Dawley rats. A dose of 10 mg/kg/day did not reduce the anogenital distance in males; anogenital distance was not affected in females of either strain. Retention of thoracic nipples in Sprague-Dawley pups was observed in the 10 mg/kg/day dose, but in Long-Evans pups this effect was observed only with the 100 mg/kg/day dose. An apparent reduction of androgen receptor expression (as measured by immunochemical staining) in male sex organs was noted in 100-mg/kg/day Sprague-Dawley pups. Androgen receptor steady state messenger ribonucleic acid (mRNA) was unaffected in Sprague-Dawley rats, but was increased 2-fold in Long-Evans rats administered 100 mg/kg/day. The onset of puberty was unaffected in either strain with either dose. The 10 mg/kg/day dose was an NOAEL in Long-Evans rats, but was the lowest observed adverse effect level (LOAEL) in Sprague-Dawley rats.

Prenatal exposure to 10 and 100 mg/kg/day lead to nonsignificantly reduced prostate ventral weights in males at 85 days of age, but did not affect the weights of the testes, epididymis, or seminal vesicles. In addition, no change was noted in serum testosterone or LH levels; however, DDE was associated with TRPM-2 (an androgen-repressed gene) expression (You et al., 1999a).

Holtzman rats exposed during gestational days 14-18 with doses of 1 to 200 mg/kg/day (exposure also occurred via mothers' milk from stored DDE) had a reduced anogenital distance in males on postnatal day 1 and reduced relative ventral prostate weight on postnatal day 21 with doses $\geq$50 mg/kg/day. Anogenital distance was still reduced on postnatal day 4 only in male exposed to 200 mg/kg/day. Nipple retention on postnatal day 13 was significantly increased with doses of 100 and 200 mg/kg/day. A delay in puberty of less than 2 days was noted in males exposed to 200 mg/kg/day. On postnatal day 21, androgen receptor staining in the ventral prostate was reduced in the 100 mg/kg/day dose, which was the only dose tested. Cauda epididymal sperm number was reduced by 17% (relative to the control) on postnatal day 63 in the 100 mg/kg/day dose group. Serum testosterone and 3α-diol androgens were not altered at any time measured, nor were mRNA levels of androgen regulated genes from either the ventral or dorsolateral prostate affected on postnatal day 21. The DDE body burden was not measured at any point in the study. The LOAEL for this study was 50 mg/kg/day and the NOAEL was 10 mg/kg/day (Loeffler and Peterson, 1999).

7.2.6 Chronic Toxicity

In the NCI (1978) bioassay, DDE was administered to Osborne-Mendel rats in the diet at time-weighted average concentrations of 0, 437, or 839 ppm in males and 0, 242, or 462 ppm in females for 78 weeks. These concentrations are equivalent to approximately 0, 30, and 59 mg/kg/day respectively for males and 0, 16, and 32 mg/kg/day for females using the body weight and food consumption values from U.S. EPA (1988a)[1]. For the first 23 weeks of treatment (rats were 7 weeks of age at the beginning of treatment), concentrations were 0, 675, or 1350 ppm in males and 0, 375, or 750 ppm in females. Due to signs of toxicity the levels were reduced to 0, 338, or 675 ppm for males and 0, 187, or 375 ppm for females. In the low-dose group this concentration was constant until week 78. In the high-dose group, this level was constant for 32 (females) or 36 (males) weeks; after this time, the high-dose group was cyclically administered with 1 week free of treatment followed by 4 weeks of treatment (for a total of 15 weeks of treatment and 4 weeks of no treatment for males and 18 weeks of treatment and 5 weeks of no treatment for females). After 78 weeks of exposure (including the off weeks), rats were observed for an additional 33-34 weeks. Body weight, food consumption, appearance, behavior, clinical signs, and the incidence, size, and location of tumor masses were recorded. The skin, subcutaneous tissue, lungs and bronchi, trachea, spleen, lymph nodes, thymus, heart, salivary glands, liver, pancreas, esophagus, stomach, small and large intestines, pituitary, kidney, urinary bladder, adrenal, thyroid, parathyroid, testis, prostate, brain, muscle, uterus, mammary gland, ovaries and any tissue masses were routinely examined histologically.

The lowest dose administered caused a decrease in body weight gain in both males and females. Mortality was 0, 16, and 28%, respectively, in females and 20, 32, and 48%,

[1] U.S. EPA (1988a) does not provide food consumption information for Osborne Mendel rats. The values used were those for mature Sprague Dawley rats because of similarities in average body weights and those of Osborne Mendel rats. The body weights used for the dose calculation were estimated from the graphs of the average body weights provided in the NCI (1978) report. Body weights over the second half of the study period provided the basis for the body weight estimate.

respectively, in males. Hunched or thin appearance was observed in dosed rats after 8 weeks of treatment with the greatest incidence occurring in the high-dose males. During week 24, the dose levels were decreased and the incidence of hunched appearance decreased dramatically, but were still noted at a greater rate in treated rats than in the controls. Once DDE was completely removed from the diet during week 78, control and treated rats had similar incidences of hunched appearance. Fatty metamorphosis and centrilobular necrosis occurred in the liver of both males and females with the incidence related to dose. There was no significant increase in the incidence of any tumors (See Section 7.2.7). The LOAEL for this study was 16 mg/kg/day for females and 30 mg/kg/day for males. The LOAEL was the lowest dose tested.

The NCI (1978) bioassay, also administered DDE to B6C3F1 mice in the diet at time-weighted average concentrations of 0, 148, or 261 ppm in males and females for 78 weeks. These doses were equivalent to approximately 0, 28, and 51 mg /kg/day in males, respectively, and 0, 29, and 53 mg/kg/day in females, respectively. For the first 7 weeks of treatment (mice were 6 weeks of age at the beginning of treatment) concentrations were 0, 125, or 250 ppm. Concentrations were increased to 0, 150, or 300 ppm after 7 weeks since the previous doses were well tolerated. These concentrations were administered for the remaining 71 weeks in the low-dose group. These concentrations were constant in the high-dose group until week 33; after that time the high-dose group was cyclically administered with 1 week free of treatment followed by 4 weeks of treatment for a total of 33 weeks on treatment and 9 weeks off treatment. After 78 weeks of treatment, the mice were observed for an additional 14 weeks. Body weight, food consumption, appearance, behavior, signs of toxic effects, and the incidence, size, and location of tumor masses were recorded. The skin, subcutaneous tissue, lungs and bronchi, trachea, spleen, lymph nodes, thymus, heart, salivary glands, liver, pancreas, esophagus, stomach, gall bladder, small and large intestines, pituitary, kidney, urinary bladder, adrenal, thyroid, parathyroid, testis, prostate, brain, muscle, uterus, mammary gland, ovaries and any tissue masses were routinely examined histologically.

There was a dose-dependent decrease in body weight in females as early as 10 weeks. Although male body weights were similar to those for the controls throughout the study, final body weights were decreased in a dose-dependent manner. Mortality was 5, 6, and 44%, respectively, in females and 75, 30, and 38%, respectively, in males. Sixty to 85% of male B6C3F1 mice administered 150 or 300 ppm reportedly had a hunched appearance after 22 weeks of treatment. There was a dose-dependent increase in the incidence of chronic inflammation of the kidneys in males. Low-dose females also had an increase incidence of chronic inflammation of the kidneys. A significant increase in tumor incidence was noted (See Section 7.2.7). The lowest dose tested (28 mg/kg/day for males and 29 mg/kg/day for females) was the LOAEL due to effects on the kidneys and body weight gain (females). There was no NOAEL in the study.

Rossi et al. (1983) administered 500 or 1000 ppm DDE to groups of 40 to 47 male or female Syrian golden hamsters in their diet beginning at 5 weeks and continuing until they were 128 weeks old. These concentrations are equivalent to 0, 56 or 122 mg/kg/day for males and 0, 51, or 114 mg/kg/day for females based on the food intake values for mature hamsters provided in U.S. EPA (1988a) and average body weights from weeks 40 to 80 estimated from the graphic presentations in the published paper. Survival did not appear to be affected by treatment

although the numbers of males that died between weeks 50 to 100 in the high dose group was greater than that for the controls. A dose-related reduction in body weight gain was reported for the high dose males throughout the study and for the high dose females over weeks 50 to 80. Body weight measurements were not made after week 80. Average body weights decreased from weeks 50 to 80 for both males and females in the high dose group. Food consumption was reported to be similar for all groups. In addition to an increase in liver tumors, hamsters administered 1000 ppm developed focal or diffuse liver necrosis, fatty and cystic degeneration, and hyperplastic foci of the liver. Liver necrosis, to a lesser extent, also was reported in 500-ppm hamsters. An increase in adrenal tumors also was noted in male hamsters. The low-dose group (56 mg/kg/day for males and 51 mg/kg/day for females) was an LOAEL for noncancer effects based on the observation of liver necrosis.

Tomatis et al. (1974) administered 250 ppm DDE or a combination of 125 ppm DDE with 125 ppm DDD via the diet to CF-1 (minimally inbred) mice from 6 to 7 weeks of age until survivors were sacrificed at 130 weeks of age. These concentrations are equivalent to 0 or 33 mg/kg/day for DDE and 16 mg DDE/kg/day plus 16 mg DDD/kg/day 84 mg/kg/day for the DDE/DDD mixture based on the food intake factors provided in U.S. EPA (1988a). Mortality was greater in mice administered DDE alone compared to both the control and DDE plus DDD group. All mice administered DDE died by 120 weeks. Survival in the DDE plus DDD group was also lower than the control after 100 weeks. DDE and DDE plus DDD administration were associated with lower body weights in males throughout the study. In females, only the DDE plus DDD group had body weights lower than the control. Myocardial necrosis and diffuse hemorrhage, leukocyte infiltration, and fibroblastic reaction were common in DDE treated mice (22 of 60 males; 1 of 60 females). This also occurred in mice treated with DDE plus DDD, but at a lower incidence (11 of 60 males) with no occurrence reported in the controls.

7.2.7 Carcinogenicity

In the NCI (1978) bioassay, DDE was administered to Osborne-Mendel rats in the diet at time-weighted average concentrations of 0, 437, or 839 for males (0, 30, and 59 mg/kg/day) and 0, 242, or 462 ppm for females (0, 16, and 32 mg/kg/day). The methods of this study are described in detail in the preceding Section 7.2.6. There was a slight, but not significant, dose-related increase in thyroid tumors (follicular-cell adenomas and carcinomas in control, low-, and high-dose groups were 11, 19, and 25%, respectively) in females. There was also a slight increase in the males that was not related to dose (15, 24, and 21%, respectively). NCI, however, did not consider there to be convincing evidence of carcinogenicity at these doses to Osborne-Mendel rats.

The NCI (1978) bioassay, also administered DDE to B6C3F1 mice in the diet at time-weighted average concentrations of 0, 148, or 261 ppm in males and females (equivalent to approximately 0, 28, and 51 mg/kg/day in males and 0, 29, and 53 mg/kg/day in females). The methods of this study are described in detail in the preceding Section 7.2.6. Hepatocellular carcinomas occurred at a greater rate in treated mice (0, 17, and 36% in males, respectively; 0, 40, and 71% in females, respectively). The dose-related trend was statistically-significant in

both males and females with high-dose males and both female treatment groups having a significantly higher incidence compared to the control.

Rossi et al. (1983) administered 0, 500, or 1000 ppm DDE (0, 56 or 122 mg/kg/day for males and 0, 51, or 114 mg/kg/day for females) to Syrian golden hamsters in their diet from 5 weeks of age until 128 weeks of age. Tumors were first observed in females after 28 weeks and in males after 55 weeks. The first liver tumors did not appear until 76 weeks in the high dose and 94 weeks for the low-dose females. The fist liver tumors did not appear until 105 weeks in the low- and high-dose males. Table 7-1 provides a summary of the tumor data from this study.

Table 7-1 Tumors observed in the Rossi et al. (1983) study in Syrian Golden Hamsters

Dose ppm	Initial Animals		All Tumors*		Liver Tumors**		Adrenal Tumors*	
	M	F	M	F	M	F	M	F
0	45	46	15/31	13/42	0/10	0/31	8/31	2/42
500	47	45	11/30	13/39	7/15	4/26	5/30	7/39
1000	40	43	20/39	16/39	8/24	5/24	17/39	8/39

* Based on number of animals when tumors first observed
** Based on the number of animals when liver tumors first observed

The total number of tumors and the number of hamsters with more than one tumor was increased in 500-ppm females and 1000-ppm males and females. DDE treated hamsters were found to have a greater incidence of liver tumors (0, 15.4, and 20.8%, respectively, in females; 0, 46.7, and 33.3%, respectively, in males). There was a dose-dependent increase in the average number of liver nodules per animal and the average size of nodules accompanied by a decrease in the time to first observation in females, but not in males. The liver tumors were described as nodules on the surface of the liver that showed a loss of cellular architecture and compression of the surrounding parenchyma. In addition to the tumors, eight of the high dose animals (3 females and 5 males) had hepatic hyperplastic foci. There was an increase in adrenal tumors as well (5, 18, and 21%, respectively, in females; 26, 17, and 44%, respectively, in males), but the results were not statistically significant.

Tomatis et al. (1974) administered 250 ppm DDE (33 mg/kg/day) or a combination of 125 ppm DDE with 125 ppm DDD (16 mg/kg/day of each compound) via the diet to CF-1 (minimally inbred) mice from 6 to 7 weeks of age until survivors were sacrificed at 130 weeks of age. A statistically significant increase in incidence of hepatomas was observed in both males and females in comparison with controls. In females, 98% of the 55 surviving exposed animals developed hepatomas, compared to 1% of the surviving controls. In males, 74% of the animals developed hepatomas as compared to 34% of the control animals. The appearance of the liver tumors in CF-1 mice was similar to those associated with DDT exposure. Microscopically they were either well-defined nodules, traebecular carcinomas or growths with mixtures of both

characteristics. Some had pseudoglandular formations, particularly in the DDE-treated rats. Four metastases to the lungs occurred in the DDE-treated female rats and two among the male control rats.

7.3 Other Key Data

7.3.1 Mutagenicity and Genotoxicity

The direct studies of the mutagenicity and/or genotoxicity of DDE are limited. DDE was mutagenic in mouse lymphoma (L5178Y) cells and Chinese hamster (V79) cells, but was negative in *Salmonella* (ICPEMC, 1984). Testicular DNA synthesis was not inhibited in male mice administered a single oral dose of 50 mg DDE/kg (Seiler, 1977).

DDE was reported to induce chromosomal damage *in vitro* in the B14F28 Chinese hamster cell line (Mahr and Miltenburger, 1976). Chinese hamster V79 cells exposed to DDE with activation had a significant increase in chromosomal aberrations. DDT did not cause the same effect (Kelly-Garvert and Legator, 1973). Positive results for chromosomal aberrations were also reported for kangaroo rat (*Potorus tridactylis*) cells by Palmer et al. (1972).

NTP (2005) reported mixed results in genetic toxicity testing assays (Table 7-2).

Table 7-2 Summary of NTP (2005) Genetic Toxicology Results

in vitro Cytogenetics	Negative (chromosome aberrations) Weakly Positive (sister chromatid exchanges)
Drosophila	Positive (sex-linked recessive lethal) Negative (reciprocal translocation)
Mouse Lymphoma	Positive
Salmonella	Negative (2 tests)

7.3.2 Immunotoxicity

Humoral and cell-mediated immune responses were adversely affected in male Wistar rats (8-12 per group) administered diets containing 200 ppm DDE, which was estimated to be equivalent to 22.2 mg/kg/day, for 6 weeks. Humoral responses included significantly increased serum albumin/globulin ratio, suppressed serum IgM, IgG after ovalbumin immunization, and decreased antibody titer. Cell-mediated responses included increased inhibition of leucocyte and macrophage migration, and decreased footpad thickness (Banerjee et al., 1996).

NCI (1978; see Section 7.2.6 for study description) showed no treatment-related adverse effects on the thymus, spleen or lymph nodes in either rats or mice. Immunocompetence was not evaluated in this study.

7.3.3 Hormonal Disruption

DDE has been shown to have weak estrogenic activity when tested at doses up to 0.5 mM in yeast expressing the human estrogen receptor, MCF-7 and HeLa cells. *o,p*'-DDE was slightly more potent than *p,p*'-DDE, but both were approximately 10^6 times less potent than 17β-estradiol on a molar basis (Balaguer et al., 1999; Sohoni and Sumpter, 1998; Tully et al., 2000). The *in vitro* E-screen test indicated that *p,p*'-DDE was a partial estrogenic agonist, but that 10^7 times more DDE was needed to produce maximal results as compared to 17β-estradiol (Soto et al., 1998). Using yeast, Gaido et al. (1997) found *o,p*'-DDE produced little response in expression of the estrogen receptor, a reporter gene regulated by two estrogen receptor response elements, or a yeast gene that is supposed to enhance steroid receptor mediated transcription.

It has been shown that *o,p*'-DDE competes with 17β-estradiol for binding to the estrogen receptor in rabbit uterine extracts (concentration that inhibited specific binding by 50% = $[IC]_{50}$=40 μM for DDE; IC_{50}=2.7 nM for 17β-estradiol; Danzo, 1997) and immature rats (IC_{50}=5 μM for DDE; IC_{50}=0.8 nM for 17β-estradiol; Kelce et al., 1995). The *p,p*'-DDE isomer was found to be a relatively ineffective competitor, which is consistent with the observation of earlier *in vitro* studies (Bitman and Cecil, 1970; Gellert et al., 1972; Nelson, 1974).

The interaction of DDE with the androgen receptor has also been studied. In a competitive androgen receptor binding assay in rat ventral prostate cytosol using a radiolabeled synthetic androgen (R1881), DDE had an inhibition constant of 3.5 μM, which was similar to that of diethylstilbesterol (DES) and about 30 times weaker than 17β-estradiol. DDE bound to the androgen receptor 200 times more efficiently than the estrogen receptor (in uterine cytosolic extracts from immature rats) (Kelce et al., 1995).

DDE was 20-fold less effective than DES or 17β-estradiol in inhibiting the conversion of testosterone by 5α-reductase to 5α-dihydrotestosterone and 5α-androstan-3α-17β-diol in microsomes isolated from the adult rat caput and corpus epididymis. The study also confirmed that DDE (IC_{50}=6.8 μM) could compete with dihydrotestosterone (IC_{50}=1.1 nM) for binding to androgen receptors in rat prostate cytosol. The study, however, also found *o,p*'-DDE to only be slightly less effective than *p,p*'-DDE in competing with dihydrotestosterone for androgen receptor binding (Danzo, 1997).

Castrated adult (120 days old) male rats implanted with testosterone-containing Silastic capsules to maintain a constant serum testosterone level were administered 200 mg/kg/day DDE for 4 days. A significant reduction in androgen-dependent seminal vesicle and ventral prostate weight relative to the control were reported. 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 the control (Kelce et al., 1995). Similar results were reported by Kelce et al. (1997) after 5 days of administering the same dose of DDE; however, they reported that testosterone metabolism was not affected.

Immunohistochemical staining of androgen receptor in epididymal nuclei of adult rats administered 200 mg/kg/day for 5 days was significantly reduced compared to the control. TRPM-2 was significantly increased and testosterone-induced C3 was significantly decreased. In addition, the weights of the seminal vesicle and ventral prostate weight were significantly reduced (Kelce et al., 1997).

Kelce et al. (1995) transiently transvected monkey kidney cells with an androgen receptor expression vector and a reporter gene containing the MMTV promoter, which contains binding sites for the androgen receptor. Both 0.2 μM *p,p*'-DDE and 1 μM hydroxyflutamide inhibited 5α-dihydrotestosterone (0.1 nM) induced transcription by about 50%. In contrast, in lysates of rat ventral prostate, the androgen antagonist hydroxyflutamide was 10 times more effective than *p,p*'-DDE in inhibiting binding to the androgen receptor. The authors 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.

DDE has been found to inhibit *in vitro* androgen receptor regulated gene expression in HEPG2 human hepatoma cells transiently transected with the human androgen receptor and a reporter gene linked to an androgen responsive promotor. These cells were exposed for 24 hours to dihydrotestosterone (up to 0.1 μM) with various doses of DDE (doses not specified in ATSDR, 2002). Graphical presentation of the data indicates that both DDE isomers were equipotent in inhibiting dihydrotestosterone induced gene transcription. The authors state that DDE was the most potent inhibitor (DDT and DDD also were tested) with an IC_{50} of 1.86 μM, but statistical significance is not mentioned. The study did not sample the cells or media to determine if the metabolism of dihydrotestosterone was affected (Maness et al., 1998).

DDE was shown to inhibit dihydrotestosterone responsive gene expression in yeast expressing the human androgen receptor plus a secreted reported gene controlled by androgen response elements. A 4-day incubation with 1.25 nM dihydrotestosterone (a submaximally inducing dose) appeared to have an IC_{50} value of approximately 10 μM; however, after 5 or 6 days of incubation dihydrotestosterone appeared to partially overcome the inhibition. The effect of DDE on dihydrotestosterone metabolism was not examined (Sohoni and Sumpter, 1998).

Based on these results, DDE has been demonstrated as an androgen receptor antagonist by its ability to inhibit the androgen receptor from either appropriately inducing or repressing transcription from androgen responsive genes (Kelce et al., 1995, 1997; Maness et al., 1998; Sohoni and Sumpter, 1998). The androgen antagonist mechanism demonstrated in these studies would explain a number of reproductive and developmental effects seen in male rats exposed to DDE at various ages.

7.3.4 Physiological or Mechanistic Studies

DDE, like DDT, seems to cause to liver toxicity. Fatty metamorphosis and centrilobular necrosis were seen in both male and female rats in the NCI (1978) study. Male and female mice had a statistically significant, dose-related increase in the incidence of hepatic tumors in this

same study. In concert with these observations, there were several studies of liver enzymes, including cytochrome P450s that illustrate biochemical responses to DDE exposure.

Nims et al. (1998) observed increases in CYP2B, CYP3A1 and CYP3A2, which were accompanied by a significant increase in relative liver weight in rats administered DDE in the diet (0.15 to 36 mg/kg/day) for 14 days. The NOEL for CYP2B induction was 0.17 mg/kg/day, while the liver weight was significantly increased with a dose of $\geq$4.1 mg/kg/day. Rats exposed to two gavage doses of 350 mg DDE/kg exhibited an increase in ornithine decarboxylase and cytochrome P-450 levels (Kitchin and Brown, 1988). CF1 mice administered 42.9 mg/kg/day via gavage for 7 days had increased liver weight (29% increase in absolute liver weight), microsomal P450, cytochrome-C reductase, and serum total protein (Pasha, 1981). Adult rats administered 100 mg/kg/day for 7 days had elevated hepatic aromatase (an enzyme involved in steroid metabolism; You et al., 2001). The most sensitive of these responses is the induction of CYP2B at a dose of 0.17 mg/kg/day. The CYP2B family is involved in the metabolism of xenobiotic compounds.

You et al. (1999b) examined the potential of *in utero* DDE exposure to affect the developmental expression of hepatic CYPs enzymes responsible for testosterone hydroxylation. Pregnant Sprague-Dawley rats were treated with DDE (0, 10, or 100 mg/kg/day) on gestational days 14-18. Adult male rats also were treated for comparison. The results indicate that responses of CYP2C11 and CYP2A1 are regulated differently in relationship to developmental stages. DDE induced 2A1 in males on postnatal day 10, but not on postnatal day 21. Pronounced induction of 2B1 was observed in both males and females on postnatal days 10 and 21. 3A1 was induced to a lesser extent, and 2C11 was not induced. DDE induced 2B1, 3A1, and 2C11 in the adult males, but 2A1 was not induced. You et al. (2001) found that aromatase, which catalyzes the conversion of C19 steroids to estrogen, was increased in hepatic microsomes of treated adult male rats, as were the levels of aromatase protein in the liver. Adult rats administered 100 mg/kg/day for 7 days had elevated hepatic aromatase (an enzyme involved in steroid metabolism), which is a potential mechanism by which DDE could affect reproduction and/or sexual maturation (You et al., 2001).

In cultures of ER-positive MCF-7 human breast cancer cells exposed to *o,p*'-DDE (dose not specified in ATSDR, 2002), the ratio of estradiol metabolites 16α-OHE1/2-OHE1 was increased over controls. It also was found that $E_2$2-hydroxylation was reduced compared to the control group. It was noted, however, that the ratio did not consistently predict known mammary carcinogens in the same assay. *o,p*'-DDE (dose not specified in ATSDR, 2002) did not induce significant changes in either C2 or 16α-hydroylation of estradiol in ER-negative MCF-10 or MDA-MB-231 cell lines, suggesting an estrogenic mechanism pathway (Bradlow et al., 1995, 1997; McDougal and Safe, 1998).

As discussed above (Section 7.3.3), the mechanism DDE's endocrine action appears to be via antagonism at the androgen receptor. This mechanism could explain a number of reproductive and developmental effects seen in male rats exposed to DDE at various ages.

7.3.5 Structure-Activity Relationship

No studies were identified that examined the structure-activity relationship of DDE and other aromatic organochlorine compounds. However, DDT, DDE and DDD are related compounds that differ only in their degree of chlorination or saturation. DDT differs from DDD in that it has three chlorine atoms bound to the terminal carbon on the aliphatic potion of the molecule in place of two, and DDE differs from DDD in that the aliphatic side chain is unsaturated (includes a double bond). DDE and DDD are degradation products and metabolites of DDT. According, it is likely that the three compounds will have a number of properties in common.

7.4 Hazard Characterization

7.4.1 Synthesis and Evaluation of Major Noncancer Effects

DDE has been demonstrated to reduce body weight gain in Osborne-Mendel rats, B6C3F1 mice, CF-1 mice and Syrian hamsters. While neurological effects were noted in both rats and mice, they were not noted in the hamster. In rats and hamsters, the liver was a target organ. Rats developed fatty metamorphosis and centrilobular necrosis in the livers of both males and females with the incidence related to dose. Hamsters developed focal or diffuse liver necrosis, fatty and cystic degeneration, and foci of hyperplastic cells of the liver. In mice, the kidney was a target organ. There was a dose-dependent increase in the incidence of chronic inflammation of the kidneys in males; low-dose females also had an increase incidence of chronic inflammation of the kidneys (there was greater than 7-fold higher mortality in the high-dose females, which may be related to the lack of findings in this group).

DDE has been found to be an antiandrogenic compound, which may explain a number of reproductive and developmental effects seen in male rats exposed to DDE at various ages. Humoral and cell-mediated immune responses were adversely affected in male Wistar rats (22.2 mg/kg/day, for 6 weeks), and subjects with higher blood DDE levels were demonstrated to have lower mitogen (concanavalin A)-induced lymphoproliferative activity and slightly increased total lymphocytes immunoglobulin A levels have been observed as immune-related effects.

The potential influence of DDE body burden on health effects is not well understood, but is an important consideration given the potential for accumulation in lipid tissues. Similarly, the health effects associated with the combined exposure to DDT, DDE, and other related metabolites have not been addressed.

7.4.2 Synthesis and Evaluation of Carcinogenic Effects

In animals treated with DDE via the diet, increases in the incidence of liver tumors, including carcinomas, were observed in two strains of mice and in hamsters; there were also nonsignificant increases in the incidence of thyroid tumors in female rats and adrenal tumors in hamsters.

Human epidemiology studies have not established any conclusive link between any specific type of cancer and DDE exposure. Although there have been several studies that observed an association between DDE levels in serum or adipose tissues and breast cancer, there are numerous other studies that did not find such an association.

7.4.3 Mode of Action and Implications in Cancer Assessment

DDE has been demonstrated to cause chromosomal damage or aberrations in several cell types but was only mutagenic in the mouse lymphoma and chinese hamster cell assays. There also is some evidence that DDE alters the immune system, which is a feature that can facilitate the tumorigenic process. However, a mode of action and sequence of key events in DDE carcinogenesis has not been established.

7.4.4 Weight of Evidence Evaluation for Carcinogenicity

DDE is *likely to be carcinogenic to humans*. This conclusion is based on increases in the incidence of liver tumors, including carcinomas, in two strains of mice (B6C3F1 and CF-1) and in hamsters (NCI, 1978; Rossi et al., 1983; Tomatis et al., 1974). The incidence of thyroid tumors was increased in female rats after dietary exposure to DDE (NCI, 1978); however, the NTP did not consider the increase to be significant and concluded that the evidence did not support carcinogenicity in male and female Osborne-Mendel rats. The evidence of carcinogenicity from human epidemiology studies is inconclusive.

7.4.5 Potentially Sensitive Populations

Potential Gender Sensitivity

In the cancer bioassay (NCI, 1978) females had a stronger tumor (liver carcinomas in mice, thyroid follicular-cell adenomas and carcinomas in rats) response to dose than did the males. In the short-term study by NCI (1978), males were more susceptible to body weight effects, and females to mortality, after exposure to DDE.

DDE's potency as an antiandrogenic agent is stronger than its estrogenic properties. This androgen antagonism or antiandrogenic activity could explain a number of reproductive and developmental effects seen in male rats of various ages. Observed effects in the male animals 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).

Neonates, Infants, and Fetuses

There is some evidence in humans that DDE may have adverse effects on reproductive outcome. Prenatal exposure may affect parturition timing, as observed in two epidemiologic studies. The levels of DDE found in the blood of women who had early deliveries were higher

than that for women who delivered at term (O'Leary et al., 1970a). Quadratic spline models were used to examine 2830 birth records relative to maternal serum levels of DDE and found that the odds of pre-term birth began to increase at a DDE concentration of 10 ppb (Longnecker et al., 2001).

Due to its high K_{ow}, DDE selectively partitions into human breast milk. Infants exposed to DDE in maternal milk at levels >4 ppm had poorer reflect reactions than children exposed to lower levels (Rogan et al., 1986, 1987). The same authors found an inverse relationship between the levels of DDE in maternal milk and lactation duration in women in the United States and Mexico. Gladen and Rogan (1995) examined the relationship between DDE and lactation duration in Mexico and found that the inverse relationship between DDE and duration of lactation only applied to women with prior breast-feeding experience. ΣDDT concentrations (which includes DDE) in human breast milk have been declining steadily across the U.S., Canada, and Western Europe (approximately one half in 4.2-5.6 years for ΣDDT; ATSDR, 2002).

Some of the epidemiological studies discussed in Section 7.1.2 have suggested that DDE may adversely affect growth in children. Serum samples collected from 2380 pregnant women with a median DDE concentration of 25 ppb (range 3-178 ppm), showed that the adjusted odds for small-for-gestational-age births was increased at a blood DDE concentration of 10 ppb (Longnecker et al., 2001). Karmaus et al. (2002) found that girls between 1.3 months and 8 years of age exposed to 0.44-40.4 ppb of DDE were almost 2 cm shorter than those exposed to lower concentrations; the decrement in height was not observed in these same girls at age 10. Prenatal exposure to DDE has also been associated with increased height and weight in boys at puberty (Gladen et al., 2000).

As discussed in Section 7.2.5, animal studies also reveal susceptibility to DDE during development, particularly in males. In rats, exposure to 100 mg/kg/day during gestation resulted in a significant decrease in ventral prostate weight in males at 15 months of age and a decrease in weights of glans penis, ventral prostate, and epididymis at 10 months old; reduced anogenital distance and increased mean number of retained nipples also were observed in the newborns (Gray et al., 1999). Anogenital distance at birth was reduced in male rat pups exposed transplacentally to 100 mg/kg/day during gestational (and also unquantified pup exposure during lactation); the animals also had retained thoracic nipples on postnatal day 13 and a significant delay in the onset of puberty was reported (Kelce et al., 1995, 1997).

You (1998) administered doses of 10 or 100 mg/kg to Long-Evans and Sprague-Dawley rats from gestation day 14 to 18. Reduced anogenital distance developed in the Long-Evans male rat. Retention of thoracic nipples in Sprague-Dawley pups was observed in the 10 mg/kg/day dose, but in Long-Evans pups this effect was observed only with the 100 mg/kg/day dose. An apparent reduction of androgen receptor expression (as measured by immunochemical staining) in male sex organs was noted in 100 mg/kg/day Sprague-Dawley pups; androgen receptor steady state messenger ribonucleic acid (mRNA) was increased 2-fold in the Long-Evans. Prenatal exposure to 10 or 100 mg/kg/day lead to nonsignificantly reduced prostate

ventral weights in males at 85 days of age and was associated with TRPM-2 (an androgen-repressed gene) expression (You et al., 1999a).

Holtzman rats exposed during gestational days 14-18 with doses of 1 to 200 mg/kg/day (exposure also occurred via mothers' milk from stored DDE) had a reduced anogenital distance in males on postnatal day 1 and 4, reduced relative ventral prostate weight on postnatal day 21, significantly increased nipple retention on postnatal day 13, and delayed puberty (of less than 2 days in males). On postnatal day 21, androgen receptor staining in the ventral prostate was reduced, and Cauda epididymal sperm number was reduced on postnatal day 63 (Loeffler and Peterson, 1999).

Early-life exposure to DDT, the parent compound of DDE, has been associated with an increased tumor incidence (U.S. EPA, 2005b). Vesselinovitch et al. (1979) assessed early-life exposures to DDT and resulting liver tumors in $B6C3F_1$ mice. The analysis performed by the U.S. EPA in the *Supplemental Guidance for Assessing Susceptibility from Early Life Exposure to Carcinogens* found that the median ratio of juvenile to adult potency for DDT is 2.5 (male mice; U.S. EPA, 2005b). Similar data are not available for DDE in order to assess the potential for early-life exposure effects. The *Supplemental Guidance* did not establish default adjustments (to be used when chemical-specific data are not available) for chemicals with nonmutagenic modes of action, such as DDT.

8.0 DOSE-RESPONSE ASSESSMENT

8.1 Dose-Response for Noncancer Effects

A limited number of conventional dose-response studies are available to assess the dose-response of DDE. Limited data on DDE, mostly from the NCI (1978) bioassay, suggest that the liver is a target organ in mammalian species. Hormonal effects on reproduction and sexual development are also important aspects of DDE toxicity. A reference dose (RfD) has not been developed for DDE; however, there is an RfD for the parent pesticide DDT of 0.0005 mg/kg/day (based on an NOAEL of 0.05 mg/kg/day from a dietary subchronic study; U.S. EPA, 1986e). In this study, liver lesions were identified at an LOAEL of 0.25 mg/kg/day. This RfD has relevance to DDE because: 1) DDE is the principle persistent metabolite of DDT; and 2) both compounds have a number of similar effects. An RfD is estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

ATSDR has established acute and intermediate-term Minimum Risk Levels (MRLs) for DDT's noncancer effects (ATSDR, 2002). The DDT oral acute MRL is 0.0005 mg/kg/day, based on developmental effects and applying and uncertainty factor of 1000. The in oral intermediate-term MRL for DDT is also 0.0005 mg/kg/day, but is based on hepatic effects and the application of a 100-fold uncertainty factor.

The World Health Organization (2004) recently established a Provisional Tolerable Daily Intake (TDI) value for DDT and its derivatives of 0.01 mg/kg/day based on an NOAEL of 1 mg/kg/day for developmental effects in rats and applying a 100-fold uncertainty factor.

8.2 Dose-Response for Cancer Effects

8.2.1 Choice of Study

There are three studies that demonstrate the carcinogenic potential of DDE in animals. Table 8-1 provides a summary of the dose and response information from these three studies. The NCI (1978) study was chosen as the principal study because it provided the best dose-response data and because the mice appear to be more sensitive to the carcinogenic effects of DDE than the hamster.

The NCI (1978) bioassay, administered DDE to B6C3F1 mice in the diet at time-weighted average concentrations of 0, 148, or 261 ppm in males and females (equivalent to approximately 0, 28, and 51 mg/kg/day in males and 0, 29, and 53 mg/kg/day in females). The methods of this study are described in detail in the preceding Section 7.2.6. Hepatocellular carcinomas occurred at a greater rate in treated mice (0, 17, and 36% in males, respectively; 0, 40, and 71% in females, respectively). The dose-related trend was statistically-significant in both males and females, with high-dose males and both female treatment groups having a significantly higher incidence compared to the control.

Table 8-1 Dose Response Data for the Carcinogenicity of DDE

Administered Concentration mg/kg/day[1]	Tumor Incidence		Reference
	female	male	
Mouse/B6C3F1; hepatocellular carcinomas			
0	0/19	0/19	NCI, 1978
28 M/ 29 F	19/47	7/41	
51 M/ 53 F	34/48	17/47	
Mouse/CF-1; hepatomas			
0	1/90	33/98	Tomatis et al., 1974
33	54/55	39/53	
Hamsters/Syrian Golden; neoplastic nodules (hepatomas)			
0	0/31	0/42	Rossi et al., 1983
54	4/26	7/15	
118	5/24	8/24	

1. Doses derived from experimental body weights and food intake values from U.S. EPA (1988a)

Tomatis et al. (1974) administered 250 ppm DDE (33 mg/kg/day) via the diet to CF-1 mice from 6 to 7 weeks of age until survivors were sacrificed at 130 weeks of age. A statistically significant increase in incidence of hepatomas was observed in both males and females in comparison with controls. In females, 98% of the 55 surviving exposed animals developed hepatomas, compared to 1% of the surviving controls, however, this study used only one dose and is not appropriate for dose-response modeling.

Rossi et al. (1983) administered 0, 500, or 1000 ppm DDE (0, 54, or 118 mg/kg/day average doses) to Syrian hamsters in their diet from 5 weeks of age until 128 weeks of age. Although the number of tumor-bearing hamsters was the same regardless of treatment, the total number of tumors and the number of hamsters with more than one tumor was increased in 500-ppm females and 1000-ppm males and females. DDE treated hamsters were found to have a greater incidence of liver tumors (0, 15.4, and 20.8%, respectively, in females; 0, 46.7, and 33.3%, respectively, in males). There was a dose-dependent increase in the average number of liver nodules per animal and the average size of nodules accompanied by a decrease in the time to first observation in females, but not in males. There was an increase in adrenal tumors as well (5, 18, and 21%, respectively, in females; 26, 17, and 44%, respectively, in males), but the results were not statistically significant.

For the current assessment, the tumor data from the mice in the NCI (1978) study were used for quantification. Both the NCI (1978) and the Rossi et al (1983) study in hamsters included a control and two dose groups. However, the mice appeared to be more sensitive to the tumorigenic effects of DDE than hamsters. The Tomatis et al. (1974) study could not be used because it employs a single dose and, therefore, cannot be used for dose-response modeling following to the U.S. EPA (2005a) guidelines for carcinogen risk assessment. The hepatomas observed in the hamsters are important to the risk assessment because they demonstrate that the carcinogenic effects of DDE are not limited to mice.

8.2.2 Dose-Response Characterization

Groups of male and female B6C3F1 mice (50/sex/treated mice and 20/sex/control group) were administered commercially available DDE in corn oil incorporated into the diet at time-weighted concentrations of 0, 148 and 261 ppm. Normalized-time-weighted-average (TWA) daily doses were approximately 0, 28 and 51 mg/kg/day, respectively, in males and 0, 29, and 53 mg/kg/day, respectively, in females. Effects in treated animals were compared to the untreated control animals. A highly significant dose-related trend in the incidence of hepatocellular carcinomas was observed in males and females that received the chemical when compared to the respective controls (Table 8-2). These tumors also appeared earlier in mice administered the higher dose. Slightly decreased body weight gain and increased mortality also were observed in exposed female mice, but were not observed in the male mice. There were no apparent increases in the incidences of non-neoplastic lesions (NCI, 1978).

Table 8-2 Summary of Liver Tumor Incidence, 78-Week Study in Mice

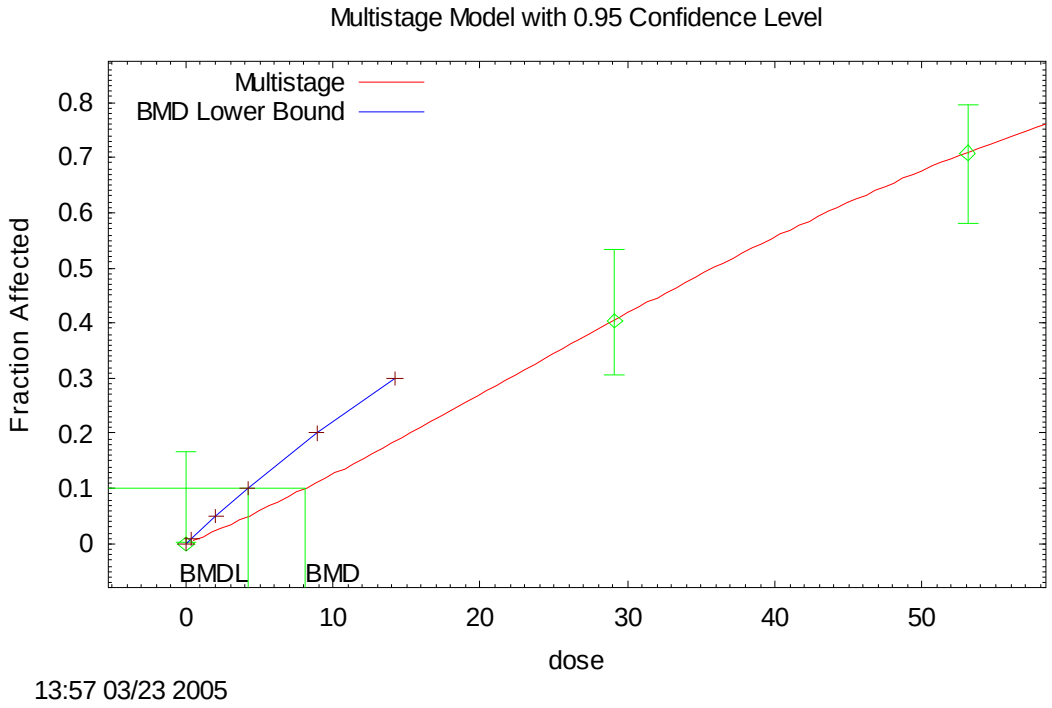
	Dietary Concentration (ppm)	Normalized-time-weighted-average dose (mg/kg/day)	Liver Tumor Incidence
Male	0	0	0/19
	148	22	7/41
	261	51	17/47*
Female	0	0	0/19
	148	29	19/47*
	261	53	34/48*

Source: NCI (1978)
*Significantly increased compared to control, $p<0.05$

8.2.3 Extrapolation Models and Rationale

The data from the NCI (1978) study in mice were analyzed using the EPA Benchmark Dose Software (BMDS) Version 1.3.2, and results are summarized in Appendix B. For female mice, the multistage (2) model, extra risk, was used, yielding an ED_{10} of 8.09 mg/kg-day and a LED_{10} of 4.19 mg/kg-day; the LED_{10} was selected as the point of departure for the cancer analysis and a linear extrapolation was applied. A linear low-dose extrapolation is appropriate for the assessment of a carcinogen lacking a demonstrated mode-of-action. Figure 8-1 shows the fit of the multistage (2) model to the data for the female mice.

Figure 8-1 Multistage (2) Model with 0.95 Confidence Interval for the Female Mice Data from the NCI (1978) Tumor Bioassay



8.2.4 Cancer Potency and Unit Risk

Oral

The NCI (1978) female mouse hepatocellular carcinomas data were BMD modeled, yielding an ED_{10} of 8.09 mg/kg-day and LED_{10} of 4.19 mg/kg-day, which were used as the points of departure in the derivation of central tendency and lower bound slope factors for DDE. The rodent ED_{10} and LED_{10} values were converted to human equivalent doses (HED) by applying a 3/4-power body weight adjustment, as recommended by the U.S. EPA Guidelines for Carcinogen Risk Assessment Guidelines (U.S. EPA, 2005a). This resulted in HED ED_{10} and HED LED_{10} values of 1.16 and 0.60 mg/kg/day, respectively. The central tendency and lower bound slope factor estimates for carcinogenicity are calculated from these values as follows:

Central Tendency Estimate:

$$\text{Slope Factor (SF)} = \frac{\text{Response}}{ED_{10}} = \frac{0.1}{1.16 \text{ mg/kg/day}} = 8.6 \times 10^{-2} \text{ (mg/kg-day)}^{-1}$$

Lower Bound Estimate:

$$\text{Slope Factor} = \frac{\text{Response}}{LED_{10}} = \frac{0.1}{0.60 \text{ mg/kg/day}} = 1.7 \times 10^{-1} \text{ (mg/kg-day)}^{-1}$$

The Health Reference Level (HRL) serves as the benchmark for examining the occurrence data for DDE in the Regulatory Determination process. It is the concentration in drinking water equivalent to a one-in-a million risk (10^{-6}) of cancer above back ground. For DDE, the 10^{-6} risk is calculated as follows:

$$10^{-6}\ \text{risk} = \frac{\text{risk x body weight}}{\text{SF x drinking water intake}} = \frac{0.000001 \times 70\ \text{kg}}{0.17\ (\text{mg/kg/day})^{-1} \times 2\text{L/day}} = 2.1 \times 10^{-4}\ \text{mg/L}$$

The HRL is rounded to one significant figure and becomes 0.2 µg/L

Prior Cancer Slope Factor

EPA evaluated the carcinogenicity for DDE under the Guidelines for Cancer Risk Assessment (U.S. EPA, 1986c) using the linear multistage model. The oral slope factor using this approach is 3.4×10^{-1} per (mg/kg-day) using administered doses that were adjusted for frequency and length of exposure, and human equivalent dose (U.S. EPA, 1988b; see Table 8-3). The HRL calculated from the IRIS slope factor is 0.1 µg/L.

Table 8-3 Factors Used to Derive the Previous Oral Slope Factor for DDE

Administered Dose (ppm)	Human Equivalent Dose (mg/kg-day)	Tumor Incidence (Female mice)
0	0	0/19
148	0.9	19/47
261	1.58	34/48

Source: U.S. EPA (1988b)

The U.S. EPA (1988b) assessment on IRIS differs from the revised assessment presented in this document in a number of respects. The differences in the approach are summarized as follows:

- The 1988 HED was determined using a body weight raised to the 2/3-power as recommended by the EPA Guidelines for Cancer Risk assessment (1986a). The new assessment uses body weight raised to the 3/4-power as recommended by the EPA Guidelines for Carcinogen Risk Assessment (U. S. EPA, 2005a).

- Different dose conversion factors were used in the conversion from ppm to mg/kg-d. The new assessment applied strain-specific food consumption parameters (U.S. EPA, 1988a) and body weights derived from growth curves in the study publication (NCI, 1978).

- The linear multistage model was used for the 1988 IRIS assessment. The multistage (2) model from BMDS Version 1.3.2 was used in the current assessment.

- The linear multistage model derived a slope by fitting the dose-response data to a straight line that passes through the zero point for the X and Y axises. The Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005a) determine the slope factor by drawing a straight line from the lower bound on the 10 percent response level (e.g., LED_{10}) to zero.

Despite the difference in cancer risk assessment approaches listed above, the findings are remarkably similar. The revised and legacy IRIS slope factors are 1.7×10^{-1} and 3.4×10^{-1} $(mg/kg\text{-}day)^{-1}$, respectively. The revised and legacy IRIS HRL values are 0.2 µg/L and 0.1 µg/L, respectively.

9.0 REGULATORY DETERMINATION AND CHARACTERIZATION OF RISK FROM DRINKING WATER

9.1 Regulatory Determination for Chemicals on the CCL

The Safe Drinking Water Act (SDWA), as amended in 1996, required the Environmental Protection Agency (U.S. EPA) to establish a list of contaminants to aid the Agency in regulatory priority setting for the drinking water program. EPA published a draft of the first Contaminant Candidate List (CCL) on October 6, 1997 (62 FR 52193, U.S. EPA, 1997b). After review of and response to comments, the final CCL was published on March 2, 1998 (63 FR 10273, U.S. EPA, 1998c).

On July 18, 2003, EPA announced final Regulatory Determinations for one microbe and 8 chemicals (68 FR 42897, U.S. EPA, 2003) after proposing those determinations on June 3, 2002 (67 FR 38222, U.S. EPA, 2002b). The remaining 41 chemicals and ten microbial agents from the first CCL became CCL 2 and were published in the Federal Register on April 2, 2004 (69 FR 17406, U.S. EPA, 2004).

EPA proposed Regulatory Determinations for 11 chemicals from CCL2 on May 1, 2007 (72FR 24016) (U.S. EPA, 2007). Determinations for all 11 chemicals were negative based on a lack of national occurrence at levels of health concern. The Agency is given the freedom to determine that there is no need for a regulation if a chemical on the CCL fails to meet one of three criteria established by the SDWA and described in section 9.1.1. After review of public comments and submitted data, the negative determinations for the 11 contaminants have been retained. Each contaminant will be considered in the development of future CCLs if there are changes in health effects and/or occurrence.

9.1.1 Criteria for Regulatory Determination

These are the three criteria used to determine whether or not to regulate a chemical on the CCL:

- The contaminant may have an adverse effect on the health of persons.
- The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern.
- In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.

The findings for all criteria are used in making a determination to regulate a contaminant. As required by the SDWA, a decision to regulate commits the EPA to publication of a Maximum Contaminant Level Goal (MCLG) and promulgation of a National Primary Drinking Water

Regulation (NPDWR) for that contaminant. The Agency may determine that there is no need for a regulation when a contaminant fails to meet one of the criteria. A decision not to regulate is considered a final Agency action and is subject to judicial review. The Agency can choose to publish a Health Advisory (a nonregulatory action) or other guidance for any contaminant on the CCL independent of the regulatory determination.

9.1.2 National Drinking Water Advisory Council Recommendations

In March 2000, the EPA convened a Working Group under the National Drinking Water Advisory Council (NDWAC) to help develop an approach for making regulatory determinations. The Working Group developed a protocol for analyzing and presenting the available scientific data and recommended methods to identify and document the rationale supporting a regulatory determination decision. The NDWAC Working Group report was presented to and accepted by the entire NDWAC in July 2000.

Because of the intrinsic difference between microbial and chemical contaminants, the Working Group developed separate but similar protocols for microorganisms and chemicals. The approach for chemicals was based on an assessment of the impact of acute, chronic, and lifetime exposures, as well as a risk assessment that includes evaluation of occurrence, fate, and dose-response. The NDWAC protocol for chemicals is a semi-quantitative tool for addressing each of the three CCL criteria. The NDWAC requested that the Agency use good judgment in balancing the many factors that need to be considered in making a regulatory determination.

The EPA modified the semi-quantitative NDWAC suggestions for evaluating chemicals against the regulatory determination criteria and applied them in decision-making. The quantitative and qualitative factors for DDE that were considered for each of the three criteria are presented in the sections that follow.

9.2 Health Effects

The first criterion asks if the contaminant may have an adverse effect on the health of persons. Because all chemicals have adverse effects at some level of exposure, the challenge is to define the dose at which adverse health effects are likely to occur, and estimate a dose at which adverse health effects are either not likely to occur (threshold toxicant), or have a low probability for occurrence (non-threshold toxicant). The key elements that must be considered in evaluating the first criterion are the mode of action, the critical effect(s), the dose-response for critical effect(s), RfD for threshold effects, and the slope factor for non-threshold effects.

A full description of the health effects associated with exposure to DDE is presented in Chapter 7 of this document and summarized below in Section 9.2.2. Chapter 8 and Section 9.2.3 present dose-response information.

9.2.1 Health Criterion Conclusion

The available toxicological data indicate that DDE has the potential to cause adverse health effects in humans and animals. DDE toxicity is manifested in a variety of effects impacting the liver, nervous system, reproductive system, and possibly the immunological system; however, toxicity varies depending on the species. There are limited human and animal studies examining noncancer effects of chronic DDE exposure. The health reference level (HRL; 0.2 µg/L) for DDE is based on the occurrence of liver tumors in mice following chronic exposures (NCI, 1978). There is no RfD for DDE; however, there is an RfD of 0.0005 mg/kg/day for DDT that is relevant to DDE as a derivative of DDT. Based on these considerations, the evaluation of the first criterion for DDE is positive: DDE may have an adverse effect on human health.

9.2.2 Hazard Characterization and Mode of Action Implications

DDE is not produced as a commercial product. This has limited the numbers of conventional studies that have been performed to assess toxicological properties. Limited data on DDE, mostly from the National Cancer Institute (NCI) bioassay, suggest that the liver is the principle target organ in mammalian species. However, the NCI study did not evaluate a full array of noncancer endpoints. Data on DDT identify effects on the nervous and endocrine systems as adverse effects that might also be seen with DDE because it is one of DDT's principal metabolites. The limited data for DDE suggest that any effects on the nervous system are less severe than those observed with DDT. Endocrine effects from DDE are discussed in this section.

Based on animal studies DDE is likely to be carcinogenic to humans. This classification is based on increases in the incidence of liver tumors, including carcinomas, in two strains of mice and in hamsters after dietary exposure to DDE. Some epidemiological studies suggest a possible association of the levels of DDE in serum with breast cancer. However, other studies with similar methodologies do not show any association. DDE was mutagenic in mouse lymphoma L5178Y and Chinese hamster V79 cells but negative in the Ames assay.

There are some indications that DDE has an adverse impact on the immune system (Banerjee et al., 1996). Oral exposures to 22 mg/kg/day for six weeks suppressed serum immunoglobin levels and antibody titers. Inhibition of leucocytes and macrophage migration were observed at the cellular level. Considerable evidence exists that DDE can act as an endocrine disruptor since it binds to the estrogen and androgen receptors. DDE has a stronger affinity for the androgen receptor than for the estrogen receptor. It competes with testicular hormones for the androgen receptor leading to receptor-related changes in gene expression (Kelce et al., 1995).

EPA evaluated whether health information is available regarding the potential effects on children and other sensitive populations. Children and adolescents may be sensitive populations for exposure to DDE due to its endocrine disruption properties. Some data suggest that DDE can delay puberty in males (ATSDR, 2003).

9.2.3 Dose-Response Characterization and Implications in Risk Assessment

There is an RfD of 0.0005 mg/kg/day for the parent pesticide DDT based on an NOAEL of 0.05 mg/kg/day from a dietary subchronic study (U.S. EPA, 1988b). In this study, liver lesions were identified at an LOAEL of 0.25 mg/kg/day.

In the 1988 IRIS, EPA calculated an oral slope factor of 0.34 $(mg/kg/day)^{-1}$ for DDE. For regulatory determination, EPA calculated an oral slope factor from the same data set (from the 1988 IRIS) using the EPA 2005 Cancer Guidelines (U.S. EPA, 2005a). The revised slope factor is 1.67×10^{-1} $(mg/kg/day)^{-1}$ resulting in a one-in-a-million cancer-risk (HRL) of 0.2 µg/L when using exposure factors of 2 L/day drinking water ingestion and 70 kg body weight.

9.3 Occurrence in Public Water Systems

The second criterion asks if the contaminant is known to occur or if there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern. In order to address this question the following information was considered:

- Monitoring data from public water systems
- Ambient water concentrations and releases to the environment
- Environmental fate

Data on the occurrence of DDE in public drinking water systems were the most important determinants in evaluating the second criterion. EPA looked at the total number of systems that reported detections of DDE, as well those that reported concentrations of DDE above an estimated drinking-water HRL. For noncarcinogens, the estimated HRL level was calculated from the RfD assuming that 20% of the total exposure would come from drinking water. For carcinogens, the HRL was the 10^{-6} risk level (i.e., the probability of 1 excess tumor in a population of a million people). The HRLs are benchmark values that were used in evaluating the occurrence data while the risk assessments for the contaminants were being developed.

The available monitoring data, including indications of whether or not the contaminant is a national or a regional problem, are included in Chapter 4 of this document and summarized below. Additional information on production, use, and fate is found in Chapters 2 and 3.

9.3.1 Occurrence Criterion Conclusion

DDE is a metabolite, degradation product, and impurity of DDT and is not commercially used or produced. Although DDT was once widely used as a broad spectrum organochlorine pesticide, it has been banned in the U.S. since January 1, 1973 and is not currently produced in the U.S. Some areas of the world still produce and use DDT. DDE is persistent in the

environment and mainly adheres to soil and sediments. Although DDE concentrations are decreasing in the environment, monitoring data continue to show DDE in environmental media.

DDE has been analyzed in surface and ground water and in monitoring studies of ambient water. At the MRL of 0.8 µg/L, it was not detected in 3251 samples collected from 797 small systems under the UCMR 1. Of the 3077 large systems monitored, DDE was detected at one large groundwater system, which represented 0.03% of large public water systems and 0.01% of the population served by them (approximately 18,000 people). The MRL of 0.8 µg/L was greater than the HRL and ½ the HRL. However, the MRL is equivalent to a risk of 4×10^{-6}, and thus, falls within the 10^{-4} to 10^{-6} risk that is the targeted in establishing a Maximum Contaminant Level for a carcinogen. DDE also has been measured in sediment (maximum concentration 31-440 µg/kg) and in whole fish (maximum concentrations 450-7300 µg/kg).

Because the MRL was greater than the HRL, it is possible that DDE occurs in public water systems at the HRL or ½ the HRL. However, this is considered unlikely due to the low maximum levels observed in NAQWA ambient water monitoring where the detection limit and the maximum concentration detected were below the HRL. Accordingly, the finding for the second criterion is negative: DDE does not occur in public water systems at levels of concern.

9.3.2 Monitoring Data

Drinking Water

Occurrence data for DDE were collected through the UCMR 1 program. The first cycle extended from 2001 to 2006. The minimum reporting level (MRL) is 0.8 µg/L. A total of 797 small public water systems (590 ground water and 207 surface water) were tested with 3251 samples obtained. Among the small systems, DDE was not detected in any system. A total of 3077 large public water systems (1381 ground water and 1696 surface water) were tested with 30,546 samples obtained. Among the large systems, DDE was detected in a single ground water system that represented 0.03% of large public water systems and 0.01% of the population served by them (approximately 18,000 people). Because the minimum reporting level is greater than half the Health Reference Level (½HRL or 0.1 µg/L) and the full HRL (HRL or 0.2 µg/L), it cannot be stated how many samples may have contained DDE at the HRL or ½ the HRL.

Ambient Water

Occurrence data for DDE were collected with the NAWQA program from 1992 to 2001 (Cycle 1) in representative watersheds and aquifers across the country. Reporting limits varied over the course of the cycle, but the level of detection did not exceed 0.006 µg/L. In agricultural areas, 1885 samples from 78 ambient surface water sites were collected and analyzed; the detection frequency was 4.84%. Samples were also collected from 1443 ambient ground water wells and analyzed; the detection frequency was 3.26%. The maximum concentration was 0.062 µg/L in ambient surface water and 0.008 µg/L in ambient ground water. In mixed land use areas, 1021 samples from 47 ambient surface water sites were tested with a detection frequency of 6.14% and 2716 samples from ambient ground water wells were tested with a detection frequency of 2.65%. The maximum concentration was 0.009 µg/L in ambient surface water and 0.006 µg/L in ambient ground water. In undeveloped areas, 60 samples from 4 ambient surface

water sites were tested with a detection frequency of 3.66% and 67 ambient ground water wells were tested with a detection frequency of 7.46%. The maximum concentration was 0.002 µg/L in ambient surface water and in ambient ground water. In urban areas, 900 samples from 33 ambient surface water sites were tested with a detection frequency of 1.68% and 834 ambient ground water wells were tested with a detection frequency of 3.96%. The maximum concentration was 0.007 µg/L in ambient surface water and 0.005 µg/L in ambient ground water. The median and 95th percentile concentrations were below the reporting limit and well below the HRL and ½ the HRL.

9.3.3 Use and Fate Data

DDE has no commercial use and is currently not commercially produced in the United States. It is a degradation product and impurity of the once commercially produced pesticide, DDT. DDT was once widely used as a broad spectrum organochlorine pesticide that controls insects in agriculture and those that carry diseases such as malaria and typhus (Gianessi and Puffer, 1992). Production of DDT in the United States was at its peak in 1962. On January 1, 1973, DDT use in the United States was banned. Analytical studies have revealed that DDE may be a contaminant in technical grade insecticide dicofol (Risebrough et al., 1986). In addition, DDE can be a product of the degradation of 1,1,2,2-tetrachloro-2,2-bis(*p*-chlorophenyl)ethane, another DDT-related impurity in dicofol (ATSDR, 2002).

DDE has high partition coefficients. Therefore, it is expected to adsorb strongly onto organic matter such as soils, sediment, and suspended particulate matter. As a result of DDE's strong binding to soil, it will remain mostly on the surface layers of soil (top 1.5 cm layer); small amounts leach into the lower soil layers and groundwater (Callahan et al., 1979). Soils and sediments are the environmental sink for DDE. DDE has a low water solubility ($\leq$0.12 mg/L).

DDE can bioaccumulate due to its high lipophilicity and long half-life, and may biomagnify up the food chain. Callahan et al. (1979) reported the findings from a terrestrial-aquatic microcosm experiment on the fate of 3.8 ppb DDE in water. The bioconcentration factors (BCFs) were calculated to be $3.6x10^{+4}$, $5.9x10^{+4}$, $1.2x10^{+4}$, and $1.1x10^{+4}$ for snail, mosquito larvae, fish, and algae in this experiment. NAWQA has measured DDE in whole fish at levels ranging up to 7300 µg/kg.

9.4 Risk Reduction

The third criterion asks if, in the sole judgment of the Administrator, regulation presents a meaningful opportunity for health risk reduction for persons served by public water systems. In evaluating this criterion, EPA looked at the total exposed population, as well as the population exposed to levels above the estimated HRL. Estimates of the populations exposed and the levels to which they are exposed were derived from the monitoring results. These estimates are included in Chapter 4 of this document and summarized in section 9.4.2 below.

In order to evaluate risk from exposure through drinking water, EPA considered the net environmental exposure in comparison to the exposure through drinking water. For example, if

exposure to a contaminant occurs primarily through ambient air, regulation of emissions to air provides a more meaningful opportunity for EPA to reduce risk than does regulation of the contaminant in drinking water. In making the regulatory determination, the available information on exposure through drinking water (Chapter 4) and information on exposure through other media (Chapter 5) were used to estimate the fraction that drinking water contributes to the total exposure. The EPA findings are discussed in Section 9.4.3 below.

In making its regulatory determination, EPA also evaluated effects on potentially sensitive populations, including the fetus, infants and children. Sensitive population considerations are included in section 9.4.4.

9.4.1 Risk Criterion Conclusion

There are about 18,000 people (0.01% of the population served by monitored PWSs) served by systems with DDE at the MRL ($\geq$0.8 µg/L). It is not possible to estimate the population exposed at either the HRL of ½ the HRL because both concentrations are less than the MRL. DDE concentration in the air is low as shown by limited data from North Dakota taken in 1993-94 in which air samples from two rural sites had DDE levels ranging from 6 to 200 pg/m^3. Therefore, exposure via inhalation is considered negligible. DDE also has been detected in food (at concentrations up to 0.1020 ppm) but levels in food materials have generally declined in the years since the use of DDT was banned in the United States. Due to its high K_{ow}, it is selectively partitioned into fatty tissue. Because of this, DDE is found in breast milk, milk, cheese, and fish. Estimated intakes of DDE in food during 1986 to 1991 were highest in infants (0.0441 µg/kg body weight/day). Intakes in adults were estimated to be between 0.0082 and 0.0119 µg/kg body weight/day.

Although the risk of exposure to DDE from drinking water cannot be determined due to the MRL exceeding the HRL, it would not exceed the estimated risk at the MRL, which is a risk of four excess cancer cases in a million exposed persons. Based on the levels found in ambient water it is unlikely that the levels of DDE in the public water system would exceed the HRL or ½HRL. On the basis of these observations, the impact of regulating DDE concentrations in drinking water on health risk reduction is likely to be small. Thus, the evaluation of third criterion is negative: regulation of DDE in public water systems would not reduce the risk to the population.

9.4.2 Exposed Population Estimates

There are no exposed population estimates at the HRL or ½ the HRL due to the fact that the MRL was greater than the HRL. There was only one large groundwater system where DDE was detected above the MRL, and the maximum concentrations of DDE in the ambient water were all below the HRL and ½HRL. Therefore, it is likely that only a small portion of the population is exposed to DDE in public water systems at either the HRL or ½HRL.

9.4.3 Relative Source Contribution

Relative source contribution analysis compares the magnitude of exposure expected via drinking water to the magnitude of exposure from intake of DDE in other media, such as food, air, and soil. Exposure via air is negligible. Due to DDE's low water solubility, persistence, and accumulation in lipids, food is likely to be the main source of exposure. DDT is still used in other countries and the U.S. imports food from these countries. Therefore, DDE may still be a concern in the food supply.

9.4.4 Sensitive Populations

The data from human studies are mostly epidemiological studies that compare the levels of DDE in serum or adipose tissues to a variety of health outcomes. In many cases there are conflicting study results even when there are strong similarities in methodologies. There is some evidence that elevated serum levels in pregnant women are correlated to premature delivery and lower infant birth weights. DDE may also have adverse effects on growth in children; these results, however, are not conclusive. Breast feeding of infants exposes them to DDE stored in their mothers adipose tissues as these stores are mobilized during lactation.

Animal studies suggest that males may be more susceptible than females to the endocrine disrupting effects of DDE. DDE is an antiandrogen and effects on the development of male sexual organs have been observed in a variety of rodent studies. The affinity of DDE for androgen receptors is stronger than its affinity for estrogen receptors.

9.5 Regulatory Determination Decision

As stated in Section 9.1.1, a positive finding for all three criteria is required in order to make a determination to regulate a contaminant. In the case of DDE, only the finding for the criterion on health effects is positive. DDE may have an adverse effect on human health. Based on the available drinking water monitoring data, DDE has been detected in one large groundwater PWS above the MRL of 0.8 μg/L, serving 17,670 people (0.01% of the population served by large PWSs). DDE was detected at very low concentrations in ambient water. The highest detection frequency was 7.46% in ambient ground water, and the highest maximum concentration detected was 0.062 μg/L (which was detected in ambient surface water). Commercial use of DDT, the parent compound of DDE, was phased out in the United States as of January 1, 1973. Accordingly, it appears that DDE does not occur in public water systems with a frequency and at levels of public health concern at the present time. DDE, however, is still present in the sediment and soils, thereby leading to its presence in fish and other food sources. Regulation of DDE in public water systems, however, does not appear to present a meaningful opportunity for health risk reduction.

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APPENDIX A: Abbreviations and Acronyms

ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BMDS	Benchmark Dose Software
BMI	body mass index
CCL	Contaminant Candidate List
DDA	2,2-bis(chlorophenyl)acetic acid
DDD	dichlorodiphenyldichloroethane
DDE	1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene
DDMU	1-chloro-2,2-bis[*p*-chlorophenyl]ethylene
DDNU	2,2-bis(chlorophenyl)acetonitrile
DDOH	2,2-bis(chlorophenyl)ethanol
EMAP	Environmental Monitoring and Trends Program
f.w.	fat weight basis
FR	Federal Register
gd	gestation days
HDL	high density lipoproteins
HED	human equivalent doses
Hg	mercury
HRL	Health Reference Level
IRIS	Integrated Risk Information System
K_{oc}	organic carbon/water partitioning coefficient
K_{ow}	octanol-water partitioning coefficient
LDL	low density lipoproteins
LOAEL	lowest observed adverse effect level
MCLG	Maximum Contaminant Level Goal
MDL	method detection limit
mg/kg-day	milligrams per kilogram per day
MRL	Minimum Reporting Level
mRNA	messenger ribonucleic acid
NAWQA	National Water Quality Assessment
NCOD	National Drinking Water Contaminant Occurrence Database
NDWAC	National Drinking Water Advisory Council
NOAEL	no observed adverse effect level
NOPES	non-occupational exposure to pesticides
NPDWR	National Primary Drinking Water Regulation
NPL	National Priorities List
NTP	National Toxicology Program
PCBs	polychlorinated biphenyls
p,*p*'-DDE	1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PWSs	Public Water Systems

RfD	reference dose
RLs	reporting levels
SDWA	Safe Drinking Water Act
SF	slope factor
SRBC	sheep red blood cells
SVOCs	semivolatile organic compounds
U.S. FDA	United States Food and Drug Administration
U.S. EPA	United States Environmental Protection Agency
UCMR 1	Unregulated Contaminant Monitoring Rule
VOCs	volatile organic compounds
w.w.	wet weight basis
WHO	World Health Organization

APPENDIX B: BMD Modeling Output

female mice

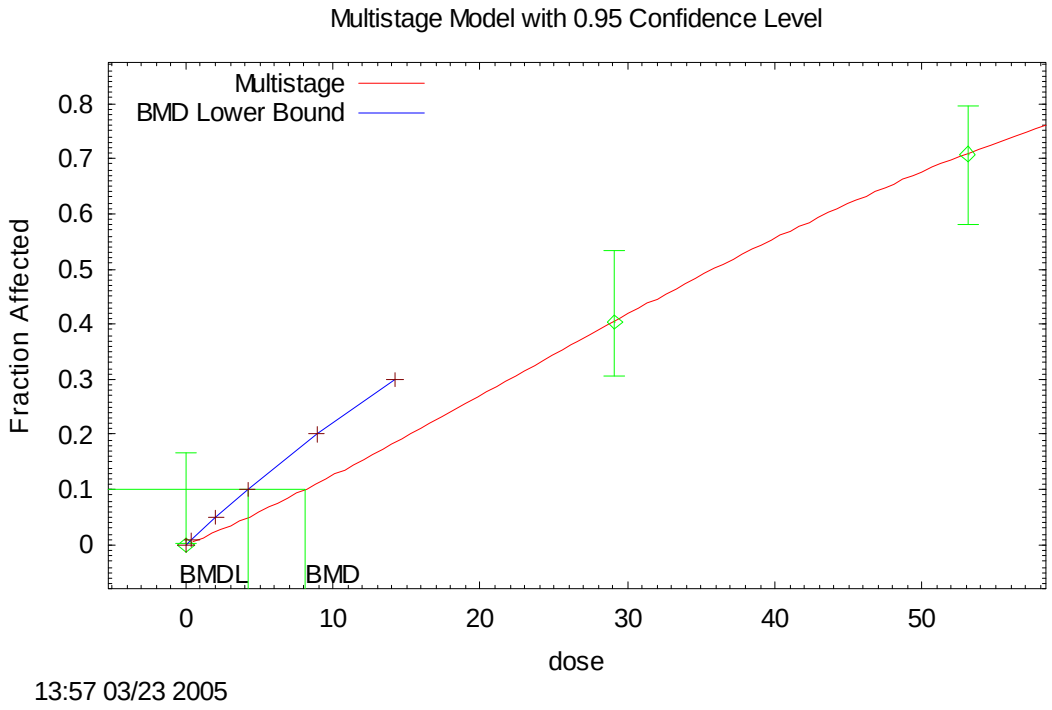
NCI dose	NCI food consumption (kg/day)	NCI terminal BW (kg)	NCI dose (mg/kg-day)	NCI fem	NCI fem n	HED
0	0.0061	0.037	0	0	19	0
148	0.0061	0.031	29.12258	19	47	4.160369
261	0.0061	0.03	53.07	34	48	7.581429

Model	ED10	LED	AIC	p-value
Log-logistic	**12.42**	**3.13**	**125**	**1.00**
Quantal linear	5.06	4.03	124	0.66
Gamma	10.69	4.19	125	1.00
Multistage (2)	**8.09**	**4.19**	**125**	**1.00**
Weibull	10.69	4.19	125	1.00
Log-probit	13.23	7.72	125	1.00
Probit	13.72	10.34	128	0.17
Logistic	14.30	10.79	129	0.13
Quantal quadratic	14.64	13.05	125	0.53

male mice

NCI dose	NCI food consumption (kg/day)	NCI terminal BW (kg)	NCI dose (mg/kg-day)	NCI male	NCI male n	HED
0	0.0064	0.037	0	0	19	0
148	0.0064	0.0345	27.45507	7	41	3.922153
261	0.0064	0.033	50.61818	17	47	7.231169

Model	ED10	LED	AIC	p-value
Log-probit	**19.90**	**15.71**	**101**	**1.00**
Quantal linear	**12.93**	**9.39**	**101**	**0.84**
Quantal quadratic	23.43	19.96	102	0.74
Log-logistic	18.91	8.20	103	1.00
Gamma	18.64	9.58	103	1.00
Multistage (2)	17.69	9.58	103	----------
Weibull	18.64	9.58	103	1.00
Probit	24.72	19.35	104	0.36
Logistic	26.06	20.55	105	0.31
mean	**16.42**	**12.55**		


Multistage Model with 0.95 Confidence Level
Multistage
BMD Lower Bound
Fraction Affected
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
BMDL
BMD
0
10
20
30
40
50
dose
13:57 03/23 2005