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EPA Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories

Volume 2
Risk Assessment and Fish Consumption Limits
Third Edition

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Third Edition

Office of Science and Technology
Office of Water
U.S. Environmental Protection Agency
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LIST OF ACRONYMS

ACTH	adrenocortical trophic hormone
ARL	acceptable lifetime risk level
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BW	body weight
CAG	Carcinogenic Assessment Group
CCRIS	chemical carcinogenesis Research Information System
CDDs	chlorodibenzo-*p*-dioxins
CDF	chlorodibenzofurans
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CERCLIS	CERCLA List of Sites
CNS	central nervous system
COC	chain-of-custody
CR	consumption rate
CSF	cancer slope factor
DDD	p,p^1-dichlorodiphenyldichloroethane
DDE	p,p^1-dichlorodiphenyldichloroethylene
DDT	p,p^1-dichlorodiphenyltrichloroethane
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
FGDC	Federal Geographic Data Committee
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
γ-BHC	benzene hexachloride
γ-HCH	hexachlorocyclohexane
GC/ECD	gaschromatography/electron capture detection

GC/MS	gaschromatography/mass spectrometry
GI	gastrointestinal
GIS	geographic information system
GPS	Global Positioning System
HEAST	Health Effects Assessment Summary Tables
HRGC/HRMS	high-resolution gas chromatography/high-resolution mass spectrometry
HSDB	Hazardous Substances Data Bank
IRIS	Integrated Risk Information System
LD_{50}	lethal dose, 50% kill
LEL	lowest exposure limit
LIt	luteinizing hormone
LMS	linearized multistage (model)
LOAEL	lowest observed adverse effects level
LOD	limit of detection
MF	modifying factor
MFO	mixed function oxidase
MOE	margin of exposure
MS	meal size
NAS	National Academy of Sciences
NFTDR	National Fish Tissue Data Repository
NGO	nongovernmental organization
NHANES II	National Health and Nutrition Examination Survey
NIOSH	National Institute of Occupational Safety and Health
NLFWA	National Listing of Fish and Wildlife Advisories
NOAA	National Oceanic and Atmospheric Administration
NOAEL	no observable adverse effect level
NSCRF	National Study of Chemical Residues in Fish
NSDI	National Spatial Data Infrastructure
NTP	National Toxicology Program
OAPCA	Organotin Antifouling Paint Control Act
OPP	Office of Pesticide Programs

PAHs	polycyclic aromatic hydrocarbons
PCBs	polychlorinated biphenyls
PCDDs	polychlorinated dibenzo-*p*-dioxins
PCDFs	polychlorinated dibenzofurans
PCS	Permit Compliance System
PEC	potency equivalency concentration
PNAs	polynuclear aromatic hydrocarbons
POTW	publically owned treatment works
QA	quality assurance
QC	quality control
RAC	reference ambient concentrations
RBC	red blood cell
RCS	Relative Source Contribution
RDA	recommended dietary allowance
RfD	reference dose
RTECs	Registry of Toxic Effects of Chemical Substances
SAB	Science Advisory Board
SCE	sister chromatid exchange
SVs	screening values
2,4,5-T	2,4,5-trichlorophenoxyacetic acid
2,3,7,8-TCDD	2,3,7,8-tetrachlorodibenzo-*p*-dioxin
2,3,7,8-TCDF	2,3,7,8-tetrachlorodibenzofuran
2,4,5-TCP	2,4,5-trichlorophenol
TEC	toxicity equivalent concentrations
TRI	Toxic Release Inventory
UF	uncertainty factor
USDA	U.S. Department of Agriculture
USFWS	U.S. Fish and Wildlife Service
USGS	U.S. Geological Survey
WHO	World Health Organization
WOE	weight of evidence

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EXECUTIVE SUMMARY

State, local, tribal, and federal agencies currently use various methods to estimate risks to human health from the consumption of chemically contaminated, noncommercially caught fish and shellfish. A 1988 survey, funded by the U.S. Environmental Protection Agency (EPA) and conducted by the American Fisheries Society, identified the need for standardizing the approaches to evaluating risks and developing fish consumption advisories that are comparable across different jurisdictions. Four key components were identified as critical to the development of a consistent risk-based approach: standardized practices for sampling and analyzing fish, standardized risk assessment methods, standardized procedures for making risk management decisions, and standardized approaches to risk communication.

To address concerns raised by the survey respondents, EPA has developed a series of four documents designed to provide guidance to state, local, tribal, and regional environmental health officials responsible for issuing fish consumption advisories. The documents are meant to provide guidance only and do not constitute a regulatory requirement. The documents are:

Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories
Volume 1: Fish Sampling and Analysis
Volume 2: Risk Assessment and Fish Consumption Limits
Volume 3: Overview of Risk Management
Volume 4: Risk Communication.

Volume 1 was first released in September 1993, and a second edition followed in September 1995. Volume 2 was first released in June 1994 and was followed by a second edition in July 1997. Volume 3 was released in June 1996, and Volume 4 was released in March 1995. It is essential that all four documents be used together, since no single volume addresses all of the topics involved in the development of risk-based fish consumption advisories.

The objective of *Volume 2: Risk Assessment and Fish Consumption Limits* is to provide guidance on the development of risk-based meal consumption limits for 25 high-priority chemical contaminants (target analytes). The target analytes addressed in this guidance series were selected by EPA's Office of Water as particularly significant contaminants, based on their documented occurrence in fish and shellfish, their persistence in the environment, their potential for bioaccumulation, and their oral toxicity to humans. The criteria for their selection are discussed in Section 4 of Volume 1 of this series.

In addition to presenting monthly consumption limit tables, Volume 2 discusses risk assessment methods used to derive the limits and discusses procedures used to modify these limits to reflect local conditions. A toxicological profile summary for each of the target analytes presenting current toxicity data is also provided. Additional sources of information are listed for those seeking a more in-depth discussion of risk assessment methods.

The first edition of Volume 2 was reviewed by experts at the federal, state, tribal, and local levels who were members of the Fish Contaminant Workgroup. These individuals contributed significant technical information and guidance during the development of this document. Their input was used to revise the document to make it more useful and informative to public health professionals. The workgroup was not involved in reviewing this third edition because the basic risk assessment procedures had already been approved. This third edition was issued to update toxicological information for several of the target analytes; to incorporate the Agency's new health risk information, daily consumption rates, and body weight assumptions into the body of the document; and to reformat the monthly consumption limit tables.

This third edition provides risk assessors and managers with the most current toxicological information for each of the 25 target analytes and provides users with

- Detailed information on risk assessment methods, including information on population exposure, fish consumption patterns, consumption surveys, risk reduction through the use of various preparation and cooking procedures, and risk characterization (Section 2)

- Reformatted monthly consumption limits tables and instructions on how these tables can be modified to reflect local site-specific conditions for specific populations of concern (Section 3, Section 4)

- A toxicological profile summarizing current toxicity data for each target analyte (Section 5)

- A brief explanation of geographic information system (GIS) mapping tools for use in risk assessment and risk management (Section 6).

The information in this document may be used in conjunction with contaminant data from local fish and shellfish sampling programs and fish consumption surveys (or from fish consumption data provided in Appendix D), to select or calculate risk-based consumption limits for contaminated noncommercially caught fish and shellfish. The consumption limits may be used with other types of information (e.g., cultural and dietary characteristics of the populations of concern, social and economic impacts, and health issues, including benefits of fish consumption and accessibility of other food sources) to establish health advisories. The decision-making process for the development of fish advisories is discussed in the risk management document in this series (Volume 3).

EPA welcomes your suggestions and comments. A major goal of this guidance document series is to provide a clear and usable summary of critical information necessary to make informed decisions concerning fish consumption advisories. We encourage comments and hope this document will be a useful adjunct to the resources used by states, local governments, and tribal organizations in making decisions concerning fish advisories.

SECTION 1

INTRODUCTION

1.1 OVERVIEW

Toxic chemicals released to the environment from point sources such as industrial and municipal discharges and from nonpoint sources such as agricultural runoff and atmospheric deposition have contaminated surface waters and their sediments across the United States. In some areas, contamination arises from one or more related chemicals. For example, in the Hudson River in New York, attention has focused on high concentrations of a group of related chemicals called polychlorinated biphenyls, or PCBs. In other areas, a complex mixture of chemicals is present. For example, over 900 different synthetic organic compounds have been found in Puget Sound in Washington State, while nearly 1,000 chemical contaminants have reportedly been found in the Great Lakes.

Many chemical pollutants concentrate in fish and shellfish by accumulating in fatty tissues or selectively binding to fish muscle tissue (the fillet). Even extremely low concentrations of bioaccumulative pollutants detected in water or bottom sediments may result in fish or shellfish tissue concentrations high enough to pose health risks to fish consumers. Lipophilic contaminants, particularly certain organochlorine compounds, tend to accumulate in the fatty tissues of fish. Consequently, fish species with a higher fat content, such as carp, bluefish, some species of salmon, and catfish, may pose greater risks from some contaminants than leaner fish such as bass, sunfish, and yellow perch. Although exposure to some contaminants may be reduced by removing the fat, skin, and viscera before the fish is eaten, other contaminants, such as methylmercury, accumulate in the muscle tissue of the fillet and therefore cannot be removed by trimming. In addition, some fish are consumed whole or are used whole in the preparation of fish stock for soups and other foods. Under these conditions, the entire body burden of bioaccumulative contaminants contained in the fish would be ingested by the consumer (U.S. EPA, 1991b).

Results of a 1989 survey of methods to estimate risks to human health from consumption of chemically contaminated fish (Cunningham et al.,1990), funded by the U.S. Environmental Protection Agency (EPA) and conducted by the American Fisheries Society, identified the need for standardizing the approaches to assessing risks and for developing advisories for contaminated fish and shellfish. Four key components were identified as critical to the development of a consistent risk-based approach to developing consumption advisories: standard

practices for sampling and analyzing fish and shellfish, standardized risk assessment methods, standardized procedures for making risk management decisions, and standardized approaches to risk communication.

Note: Throughout this document series, the term "fish" refers to sport- and subsistence-caught freshwater, estuarine, and marine fish and shellfish, unless otherwise noted.

To address concerns raised by the survey, EPA developed a series of four documents designed to provide guidance to state, local, regional, and tribal environmental health officials who are responsible for issuing fish consumption advisories for noncommercially caught fish. The documents are meant to provide guidance only and do not constitute a regulatory requirement. The documents are: *Guidance for Assessing Chemical Contamination Data for Use in Fish Advisories, Volume 1: Fish Sampling and Analysis* (released 1993, revised in 1995 and 2000), *Volume 2: Risk Assessment and Fish Consumption Limits* (released in 1994 and revised in 1997 and 2000), *Volume 3: Risk Management* (released in 1996), and *Volume 4: Risk Communication* (released in 1995). EPA recommends that the four volumes of this guidance series be used together, since no one volume provides all the necessary information to make decisions regarding the issuance of fish consumption advisories.

This volume (Volume 2) provides guidance on risk assessment procedures to use in the development of risk-based consumption limits for the 25 high-priority chemical contaminants identified in Volume 1 (see Table 1-1).

The target analytes listed in Table 1-1 were selected by EPA's Office of Water as particularly significant fish contaminants, based on their occurrence in fish and shellfish (as evidenced by their detection in regional or national fish monitoring programs or by state issuance of a fish advisory), their persistence in the environment (half-life >30 days), their potential for bioaccumulation (BCF values >300), and their oral toxicity to humans.

1.2 OBJECTIVES

It should be noted that the EPA methodology described in both Volumes 1 and 2 of this guidance series offers great flexibility to the state users. These documents are designed to meet the objectives of state monitoring and risk assessment programs by providing options to meet specific state or study needs within state budgetary constraints. The users of this fish advisory guidance document should recognize that it is the consistent application of the EPA methodology and processes rather than individual elements of the program sampling design that are of major importance in improving consistency among state fish advisory

Table 1-1. Target Analytes Recommended for Fish Sampling Programs [a]

Metals
- Arsenic (inorganic)
- Cadmium
- Mercury (methylmercury)
- Selenium
- Tributyltin

Organochlorine Pesticides
- Chlordane, total (*cis*- and *trans*-chlordane, *cis*- and *trans*-nonachlor, oxychlordane)
- DDT, total (2,4'-DDD, 4,4'-DDD, 2,4'-DDE, 4,4'-DDE, 2,4'-DDT, 4,4'-DDT)
- Dicofol
- Dieldrin
- Endosulfan (I and II)
- Endrin
- Heptachlor epoxide[b]
- Hexachlorobenzene
- Lindane (γ-hexachlorocyclohexane; γ-HCH)[c]
- Mirex[d]
- Toxaphene

Organophosphate Pesticides
- Chlorpyrifos
- Diazinon
- Disulfoton
- Ethion
- Terbufos

Chlorophenoxy Herbicides
- Oxyfluorfen

PAHs[e]

PCBs
- Total PCBs (sum of PCB congeners or Aroclors)[f]

Dioxins/furans[g]

DDD = p,p' - dichlorodiphenyldichloroethane.
DDE = p,p' - dichlorodiphenyldichloroethylene.
DDT = p,p' - dichlorodiphenyltrichloroethane.
PAHs = Polycyclic aromatic hydrocarbons.
PCBs = Polychlorinated biphenyls.

[a] The reader should note that carbophenothion was included on the original list of target analytes. Because the registrant did not support reregistration of this chemical, all registered uses were canceled after December 1989. For this reason and because of its use profile, carbophenothion was removed from the recommended list of target analytes.

[b] Heptachlor epoxide is not a pesticide but is a metabolite of the pesticide heptachlor.

[c] Also known as γ-benzene hexachloride (γ-BHC).

[d] Mirex should be regarded primarily as a regional target analyte in the southeast and Great Lakes states, unless historic tissue, sediment, or discharge data indicate the likelihood of its presence in other areas.

[e] It is recommended that tissue samples be analyzed for benzo[*a*]pyrene and 14 other PAHs and that the order-of-magnitude relative potencies given for these PAHs be used to calculate a potency equivalency concentration (PEC) for each sample (see Section 5 of Volume 1).

[f] Analysis of total PCBs (as the sum of Aroclors or PCB congeners) is recommended for conducting human health risk assessments for total PCBs (see Sections 4.3.6 and 5.3.2.6 of Volume 1). A standard method for Aroclor analysis is available (EPA Method 608). A standard method for congener analyses is under development by EPA; however, it has not been finalized. States that currently do congener-specific PCB analyses should continue to do so and other states are encouraged to develop the capability to conduct PCB congener analyses. When standard methods for congener analysis have been verified and peer-reviewed, the Office of Water will evaluate the use of these methods.

[g] It is recommended that the 17 2,3,7,8-substituted tetra- through octa-chlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) and the 12 dioxin-like PCBs be determined and a toxicity-weighted total concentration calculated for each sample (Van den Berg et al., 1998) (see Sections 4.3.7 and 5.3.2.6 of Volume 1).

programs. For example, this document presents consumption limits that were calculated using a risk level of 1 in 100,000 (10^{-5}); however, states may choose to calculate consumption limits based on other risk levels.

One major factor currently affecting the comparability of fish advisory information nationwide is the fact that the states employ different methodologies to determine the necessity for issuing an advisory. For example, some states currently do not use the EPA methodology at all or use it only in their assessment of health risks for certain chemical contaminants. Often these states rely instead on exceedances of U.S. Food and Drug Administration (FDA) action levels or tolerances to determine the need to issue an advisory. FDA's mission is to protect the public health with respect to levels of chemical contaminants in all foods, including fish and shellfish.

FDA has developed both action levels and tolerances to address levels of contamination in foods. FDA may establish an action level when food contains a chemical from sources of contamination that cannot be avoided even by adherence to good agricultural or manufacturing practices, such as contamination by a pesticide that persists in the environment. An action level is an administrative guideline or instruction to the agency field unit that defines the extent of contamination at which FDA may regard food as adulterated. An action level represents the limit at or above which FDA may take legal action to remove products from the marketplace. Under the Food, Drug, and Cosmetic Act, FDA also may set tolerances for unavoidably added poisonous or deleterious substances, that is, substances that are either required in the production of food or are otherwise unavoidable by good manufacturing practices. A tolerance is a regulation that is established following formal, rulemaking procedures; an action level is a guideline or "instruction" and is not a formal regulation (Boyer et al., 1991).

FDA's jurisdiction in setting action levels or tolerances is limited to contaminants in food shipped and marketed in interstate commerce. Thus, the methodology used by FDA in establishing action levels or tolerances is to determine the health risks of chemical contaminants in fish and shellfish that are bought and sold in interstate commerce rather than in locally harvested fish and shellfish (Bolger et al., 1990). FDA action levels and tolerances are indicators of chemical residue levels in fish and shellfish that should not be exceeded for the general population who consume fish and shellfish typically purchased in supermarkets or fish markets that sell products that are harvested from a wide geographic area, including imported fish and shellfish products. However, the underlying assumptions used in the FDA methodology were never intended to be protective of recreational, tribal, ethnic, and subsistence fishers who typically consume larger quantities of fish than the general population and often harvest the fish and shellfish they consume from the same local waterbodies repeatedly over many years. If these local fishing and harvesting areas contain fish and shellfish with elevated tissue levels of chemical contaminants, these individuals potentially

could have increased health risks associated with their consumption of fish and shellfish.

The following chemical contaminants discussed in this volume have FDA action levels for their concentration in the edible portion of fish and shellfish: chlordane, DDT, DDE, DDD, dieldrin, heptachlor epoxide, mercury, and mirex. FDA has not set an action level for PCBs in fish, but has established a tolerance in fish for this chemical. FDA also has set action levels in fish for two chemical contaminants that are not discussed in this volume: chlordecone (Kepone) and ethylene dibromide. FDA had set an action level for toxaphene; however, this level was revoked in 1993 because FDA determined that toxaphene residues were no longer occurring as unavoidable contaminants in food (57 FR 60859). In addition, in 1981, FDA set an advisory level for dioxin in fish, in response to requests from the governors of the Great Lake states. This advisory level was nonenforceable federal advice and was provided with the intention that state and local authorities use it to develop their own control policies (Boyer et al., 1990).

Table 1-2 compares the FDA action levels and tolerances for these seven chemical contaminants with EPA's recommended screening values (SVs) for recreational and subsistence fishers calculated for these target analytes using the EPA methodology.

The EPA SV for each chemical contaminant is defined as the concentration of the chemical in fish tissue that is of potential public health concern and that is used as a threshold value against which tissue residue levels of the contaminant in fish and shellfish can be compared. The SV is calculated based on both the noncarcinogenic and carcinogenic effects of the chemical contaminant, which are discussed in detail in Volume 1 of this series (EPA, 2000a). EPA recommends that the more conservative of the calculated values derived from the noncarcinogenic rather than the carcinogenic effects be used because it is more protective of the consumer population (either recreational or subsistence fishers). As can be seen in Table 1-2, for the recreational fisher, the EPA-recommended values typically range from 2 to 120 times lower and thus are more protective than the corresponding FDA action or tolerance level. This difference is even more striking for subsistence fishers for whom the SVs are 20 to 977 times lower than the FDA values.

EPA and FDA have agreed that the use of FDA action levels for the purposes of making local advisory determinations is inappropriate. In letters to all states, guidance documents, and annual conferences, this practice has been discouraged by EPA and FDA in favor of EPA's risk-based approach to derive local fish consumption advisories.

Table 1-2. Comparison of FDA Action Levels and Tolerances with EPA Screening Values

Chemical Contaminant	FDA Action Level (ppm)	EPA SV for Recreational Fishers (ppm)	EPA SV for Subsistence Fishers (ppm)
Chlordane	0.3	0.114	0.014
Total DDT	5.0	0.117	0.014
Dieldrin	0.3	2.5×10^{-3}	3.07×10^{-4}
Heptachlor epoxide	0.3	4.39×10^{-3}	5.40×10^{-4}
Mercury	1.0	0.40	0.049
Mirex	0.1	0.80	0.098
	FDA Tolerance Level (ppm)		
PCBs	2.0	0.02	2.45×10^{-3}

Source: U.S. FDA, 1998.

1.3 SENSITIVE SUBPOPULATIONS

In addition to the risks borne by the general population as a result of consuming contaminated fish, various populations eating higher-than-average quantities of fish are at greater risk of having higher body burdens of bioaccumulative contaminants. Those at greatest risk include sport and subsistence fishers. In this document, subsistence fishers are defined as fishers who rely on noncommercially caught fish and shellfish as a major source of protein in their diets. In addition to these populations, pregnant women and children may be at greater risk of incurring adverse effects than other members of the populations because of their proportionally higher consumption rates and/or increased susceptibility to adverse toxicological effects.

EPA has provided this guidance to be especially protective of recreational fishers and subsistence fishers within the general U.S. population. EPA recognizes, however, that Native American subsistence fishers are a unique subsistence fisher population that needs to be considered separately. For Native American subsistence fishers, eating fish is not simply a dietary choice that can be completely eliminated if chemical contamination reaches unacceptable levels; rather eating fish is an integral part of their lifestyle and culture. This traditional lifestyle is a living religion that includes values about environmental responsibility and community health as taught by elders and tribal religious leaders (Harris and Harper, 1997). Therefore, methods for balancing benefits and risks from eating

contaminated fish must be evaluated differently than for the general fisher population.

For any given population, there can be a sensitive subpopulation comprising individuals who may be at higher than average risk due to their increased exposure or their increased sensitivity to a contaminant or both. For Native American subsistence fishers, exposure issues of concern that should be addressed as part of a comprehensive exposure assessment include the following:

- **Consumption rates and dietary preferences.** Harris and Harper (1997) surveyed traditional tribal members in Oregon with a subsistence lifestyle and determined a consumption rate of 540 g/d that included fresh, dried, and smoked fish. They also confirmed that the parts of the fish (heads, fins, skeleton, and eggs) that were eaten by this group were not typically eaten by other groups. Another study conducted of four tribes in the Northwest that also surveyed tribal members in Oregon, but did not target subsistence fishers, reported a 99th percentile ingestion rate of 390 g/d for tribal members (CRITFC, 1994). These consumption rates are much higher than the default consumption rates provided in this document for subsistence fishers, which emphasizes the need to identify the consumption rate of the Native American subsistence population of concern.

- **Community characteristics.** It is important to consider family-specific fishing patterns in any exposure scenario, and attention should be paid to the role of the fishing family with respect to the tribal distribution of fish, the sharing ethic, and providing fish for ceremonial/religious events. Entire communities are exposed if fish are contaminated, and the community contaminant burden as a whole must be considered, not just the maximally exposed individual.

- **Multiple contaminant exposures.** Multiple contaminant exposure is significant for Native American subsistence fishers. A large number of contaminants are often detected in fish tissues and their combined risk associated with the higher consumption rates and dietary preferences for certain fish parts could be very high even if individual contaminants do not exceed the EPA reference dose (Harper and Harris, 1999).

- **Other exposure pathways.** For Native American subsistence fishers, overall exposure to a contaminant may be underestimated if it fails to take into account nonfood uses of fish and other animal parts that may contribute to overall exposure, such as using teeth and bones for decorations and whistles, animal skins for clothing, and rendered fish belly fat for body paint (Harper and Harris, 1999). If other wildlife species (e.g., feral mammals, turtles, waterfowl) that also live in or drink from the contaminated waterbody are eaten, or if the contaminated water is used for irrigation of crops or for livestock watering or human drinking water, the relative source contribution

of these other pathways of exposure also must be considered. As with fish and wild game, plants are used by Native Americans for more than just nutrition. Daily cleaning, preparation, and consumption of plants and crafting of plant materials into household goods occurs throughout the year (Harris and Harper, 1997).

As in the general population, increased sensitivity to a chemical contaminant for Native Americans can result from factors such as an individual's underlying health status and medications, baseline dietary composition and quality, genetics, socioeconomic status, access to health care, quality of replacement protein, age, gender, pregnancy, and lactation. These factors are only partially considered in the uncertainty factor(s) used to develop an RfD (Harper and Harris, 1999).

Other important issues that need to be considered concern risk characterization and risk management. For Native American subsistence fishers, the use of an acceptable risk level of 1 in 100,000 (10^{-5}) may not be acceptable to all tribes. Each tribe has the right to decide for themselves what an acceptable level of risk is, and, in some cases, it may be zero risk to protect cultural resources. Ecological well-being or health is another key issue. Human health and ecological health are connected in many ways, and the ripple effects are often not recognized. For example, human health may be affected by injury to the environment, which affects the economy and the culture (Harper and Harris, 1999).

Native American subsistence fishers should be treated as a special high-risk group of fish consumers distinct from fishers in the general population and distinct even from other Native American fish consumers living in more suburbanized communities. Table 1-3 compares fish consumption rates for various fisher populations within the general population and specific Native American tribal populations. EPA currently recommends default fish consumption rates of 17.5 g/d for recreational fishers and 142.4 g/d for subsistence fishers. However, the tribal population fish consumption studies show that some Native American tribal members living in river-based communities (CRITFC, 1994) eat from 3 to 22 times more fish (from 59 g/d up to 390 g/d) than recreational fishers, and that traditional Native American subsistence fishing families may eat up to 30 times more fish, almost 1.2 1b/d (540 g/d) (Harris and Harper 1997). The fish consumption rate from Harris and Harper (1997) for Native American subsistence fishers (540 g/d) is also 3.8 times higher than the EPA default consumption rate for subsistence fishers (142.4 g/d) in the general population. The difference in fish consumption is due to the fact that the Native American subsistence fisher's lifestyle is not the same as a recreational fisher's lifestyle with additional fish consumption added, nor is it the same as the "average" Native American tribal member living in a fairly suburbanized tribal community. In addition to exposures from direct consumption of contaminated fish, Native American subsistence fishers also receive more exposure to the water and sediments associated with catching and preparing fish,

Table 1-3. Fish Consumption Rates for Various Fisher Populations

Source	Recreational fishers (g/d)	Subsistence Fishers (g/d)	Native American Subsistence fishers (g/d)	Native Americans (g/d)	Basis for Consumption Rate
U.S. EPA	17.5 [a]	142.4 [a]	70 (mean) [b] 170 (95th percentile)[b]	NA	Fish consumption rate from 1994 and 1996 Continuing Survey of Food Intake by Individuals (CSFII) (USDA/ARS, 1998)
Harris and Harper (1997)	NA	NA	540 (fresh, smoked, and dried)	NA	Surveyed members of the Confederated Tribes of the Umatilla Indian Reservation
CRITFC (1994)	NA	NA	NA	59 (mean) 170 (95th percentile) 390 (99th percentile)	Surveyed members of the Umatilla, Nez Perce, Yakama, and Warm Springs Tribes
Toy et al. (1996)	NA	NA	NA	53 (median, males) 34 (median, females) 66 (median, males) 25 (median, females)	Surveyed members of the Tulalip Tribe Surveyed members of the Squaxin Island Tribe

NA = Not available.
[a] These values were revised in the 3rd edition of Volume 1 of this series (U.S. EPA, 2000a)
[b] These values are from EPA's Exposure Factors Handbook (U.S. EPA, 1997f)

and possibly from drinking more unfiltered river water than more suburbanized tribal community members as well. The Native American subsistence fishing population should be treated as a separate group with a very unique lifestyle, distinct from recreational and subsistence fishers in the general U.S. population and even distinct from other Native American fisher populations.

1.4 CONTENTS OF VOLUME 2

Figure 1-1 shows how Volume 2 fits into the overall guidance series and lists the major categories of information provided. This volume covers topics necessary for conducting risk assessments related to consumption of chemically contaminated fish. The first four sections follow the anticipated sequence of activities to conduct a risk assessment, develop risk-based consumption limits, and prepare consumption limit tables for a range of fish contaminant levels, meal sizes, and consumer groups. The last two sections provide summary information on the toxicological properties of the 25 target analytes and geographic information system (GIS) mapping tools for risk assessment and risk management.

Section 1 of this document reviews the development of this guidance document series, lists the 25 target analytes of concern with respect to chemical contamination of fish and shellfish, summarizes additions and revisions to this third edition, and references information used in the development of this document.

Section 2 introduces the EPA four-step risk assessment process: hazard identification, dose-response assessment, exposure assessment, and risk characterization. Details on each of these steps are provided, along with a discussion of the major uncertainties and assumptions.

Section 3 of this document presents the information needed to calculate or modify the consumption limit tables provided for the 25 target analytes in Section 4. The reader is guided through calculations of risk-based consumption limits for carcinogenic and noncarcinogenic effects using the appropriate cancer slope factor (CSF) and reference dose (RfD). The reader is shown how selection of various input parameters such as the maximum acceptable risk level, consumer body weight, meal size, and time-averaging period influence fish consumption limits for single species diets. In addition, information is provided on methods for calculating consumption limits for single-species diets with multiple contaminants and multiple-species diets contaminated with a single or multiple contaminants.

The monthly consumption limits for each of the 25 target analytes are provided in Section 4.

Section 5 presents a toxicological profile summary for each of the 25 target analytes. Each profile summary contains a discussion of the pharmacokinetics, acute toxicity, chronic toxicity, reproductive and developmental toxicity,

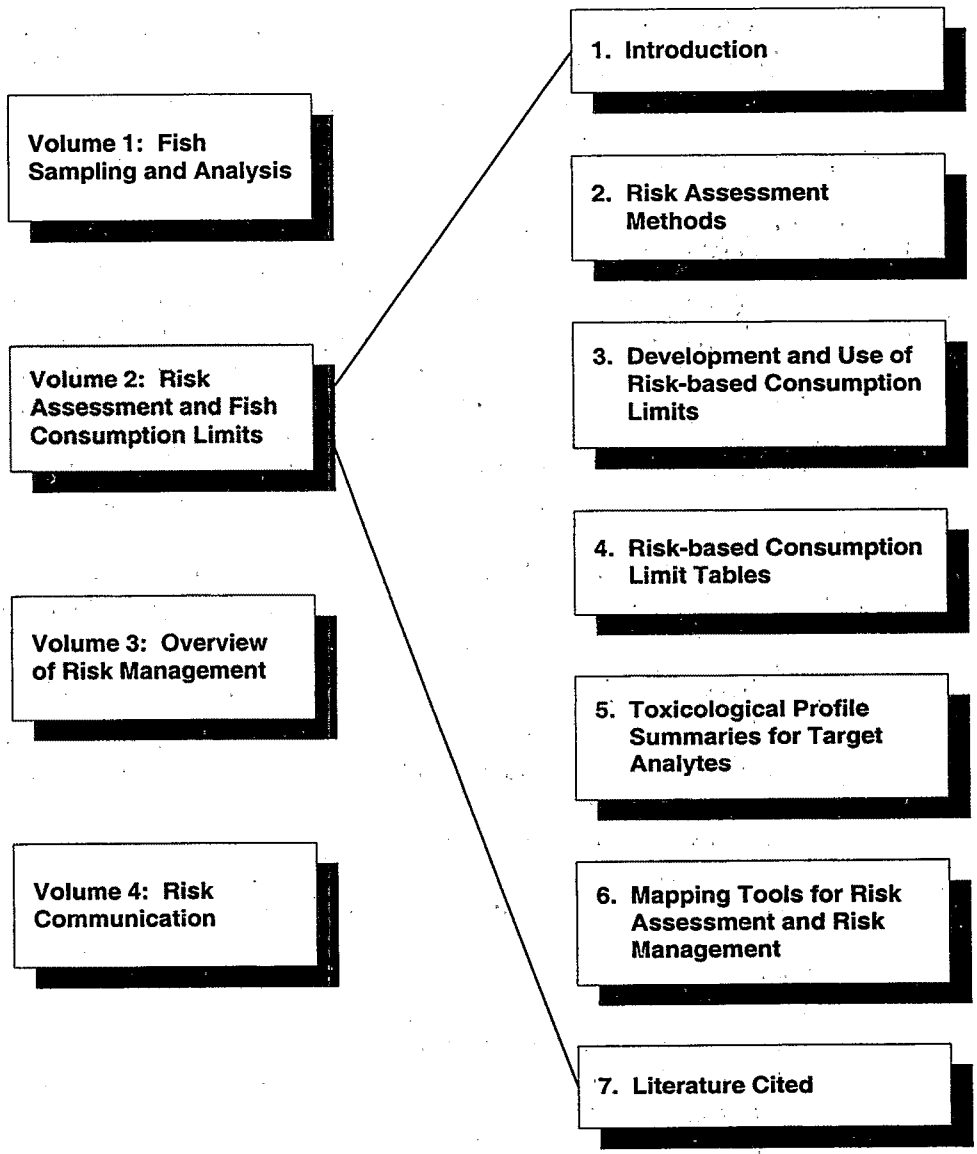

Figure 1-1. Series Summary: Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories.

mutagenicity, carcinogenicity, populations with special susceptibilities, interactive effects of the target analytes with other chemical contaminants, and critical data gaps with respect to toxicity. The most current EPA risk values (CSFs and RfDs) from sources such as EPA's Integrated Risk Information System (IRIS) and the Office of Pesticide Programs are provided, with a discussion of supporting dose-response data.

Section 6 has been added to provide readers with an overview of GIS mapping tools for use in risk assessment and risk management. Mapping can be used to display information germane to all aspects of fish advisory programs. Maps may focus on fish contaminant levels, waterbodies where fish advisories are in effect, sport and subsistence fishing locations, or consumption levels of target populations of fishers. The reader is provided with instructions to access EPA websites on the Internet to obtain additional GIS datasets and coverages.

In keeping with current EPA recommendations, discussions of uncertainty and assumptions are included in each section of the document. Although information was sought from a variety of sources to provide the best available data concerning the development of fish consumption advisories, limited data exist for some critical parameters (e.g., toxicological properties of certain chemicals and susceptibilities of specific populations such as the elderly, children, and pregnant or nursing women). Although substantial toxicological information is available for all target analytes discussed in this document, readers are cautioned to always consider the methods and values presented in the context of the uncertainty inherent in the application of science to policies for safeguarding the general public from environmental hazards.

The focus of this document is primarily on the risk due to consumption of non-commercially caught fish and shellfish from freshwater, estuarine, and marine waters. This document provides guidance on the evaluation of the overall risk associated with multimedia exposure to chemical contaminants found in fish (e.g., exposure resulting from other food sources, consumer products, air, water, and soil). EPA recommends that a comprehensive risk assessment be considered for all confirmed fish contaminants, including an evaluation of all significant exposure pathways (e.g., inhalation, dermal, and oral exposures).

Risk assessment and risk management of chemically contaminated fish are complex processes because of the many considerations involved in setting fish consumption advisories, including both the health risks and benefits of fish consumption, the roles of state and federal agencies, and the potential impact of advisories on economic and societal factors. These topics are discussed in Volume 3 of this guidance series (*Overview of Risk Management*). The final volume in the series deals with how risk managers can best communicate the health risks and benefits of fish consumption to the general public as well as recreational and subsistence fishers. These topics are detailed in Volume 4 (*Risk Communication).*

1.5 CHANGES TO VOLUME 2

The following changes were made to this edition:

Section 1:

- Included discussion of Native American subsistence fishers.
- Included new information on the development of FDA action levels and tolerances and provided rationale as to why states should adopt the EPA risk-based approach.

Section 2:

- Revised table on uncertainty factors to be consistent with new information.
- Revised developmental toxicity section: removed repetitive material and put detailed information from this section in Appendix E.
- Included information from recent EPA guidelines for the health risk assessment of chemical mixtures (1999).

Section 3:

- Revised consumption limit tables in Section 4 to be calculated as fish meals per month, at various fish tissue concentrations, for noncancer and cancer health endpoints.
- Assumed an acceptable risk of 1 in 100,000 in meal consumption limits; the second edition used an acceptable risk of 1 in 10,000, 1 in 100,000, and 1 in a million.
- Updated risk values used in consumption limit tables based on IRIS (1999) and new information from EPA's Office of Pesticide Programs.
- Assumed an 8-oz (0.227-kg) meal size for calculation consumption limits; the second edition assumed four meal sizes of 4, 8, 12, and 16 oz.
- Recommended a default value for meal size of shellfish.
- Assumed a monthly time-averaging period; the second edition assumed biweekly, 10-day, weekly, and monthly time-averaging periods.
- Updated discussion of multiple chemical interactions to be consistent with EPA's recent guidance on chemical mixtures.
- Revised examples using updated risk values from IRIS (1999).

Section 4:

- Prepared reformatted, streamlined consumption limit tables for each chemical, using assumptions outlined above (Section 3).
- The definition of "safe fish consumption" was changed from 30 fish meals per month to 16 fish meals per month.

Section 5:

- Updated chemical-specific information based on IRIS (1999) and other recent toxicological information on data sources.
- Included additional information on PCBs and dioxin analysis.

Section 6:

- Included new information on georeferencing of fish advisories in the new Internet version of the National Listing of Fish and Wildlife Advisories (NLFWA).

Section 7:

- Updated references.

1.6 SOURCES

Information from a wide range of government and academic sources was used in the development of this document. Current approaches developed by states, regional groups such as the Great Lakes Sport Fish Advisory Task Force, and federal agencies including EPA and FDA were reviewed. Section 7 contains a complete listing of literature sources cited in this document.

In addition, to review the first edition of this document, EPA assembled an Expert Review Group consisting of officials from several EPA offices, FDA, regional groups, and the following states: California, Florida, Michigan, Delaware, Illinois, Minnesota, Missouri, North Dakota, New Jersey, and Wisconsin. A list of the experts and their affiliations is provided in Appendix A. The Expert Review Group contributed significant technical information and guidance in the development of the first edition of this document. Written recommendations made by the experts were incorporated into the final document. Some members were also consulted further on specific issues related to their expertise. In a second round of reviews, this document was circulated to all states, several Native American tribes, and various federal agencies for comment, and additional modifications were made. Participation in the review process does not imply concurrence by these individuals with all concepts and methods described in this document. The Expert Review Group did not review the current edition of the document because the

basic risk assessment procedures had already been approved. This third edition was issued primarily to update new toxicological information for several analytes and to revise and streamline the consumption limit tables using updated exposure factors.

SECTION 2

RISK ASSESSMENT METHODS

2.1 INTRODUCTION

The presentation of risk assessment methods in this section follows the format of the risk assessment process recommended by EPA for cancer and noncancer toxicity:

- Hazard identification
- Dose-response assessment
- Exposure assessment
- Risk characterization (U.S. EPA, 1986a,b; IRIS, 1999).

EPA methods follow the outline developed in the National Academy of Sciences (NAS) report entitled *Risk Assessment in the Federal Government: Managing the Process* (NAS, 1983; see Figure 2-1). According to the NAS,

> . . . risk assessment can be divided into four major steps: hazard identification, dose-response assessment, exposure assessment, and risk characterization. A risk assessment might stop with the first step, hazard identification, if no adverse effect is found or if an agency elects to take regulatory action without further analysis, for reasons of policy or statutory mandate. (NAS, 1983)

Readers may wish to consult the NAS document, *Science and Judgement in Risk Assessment*, which updates and expands the 1983 work (NAS, 1994).

Hazard identification is the first step in the risk assessment process. It consists of a review of biological, chemical, and exposure information bearing on the potential for an agent to pose a specific hazard (Preuss and Erlich, 1986). Hazard identification involves gathering and evaluating data on the types of health effects associated with chemicals of concern under specific exposure conditions (e.g., chronic, acute, airborne, or food borne) (U.S. EPA, 1985).

Section 2.2 provides an overview and summary of the hazard identification process and specific information on hazard identification for chemical contaminants in noncommercially caught fish. It does not provide detailed guidance on hazard identification since EPA's Office of Water has already completed the hazard identification step with respect to fish contaminants. This work was undertaken to

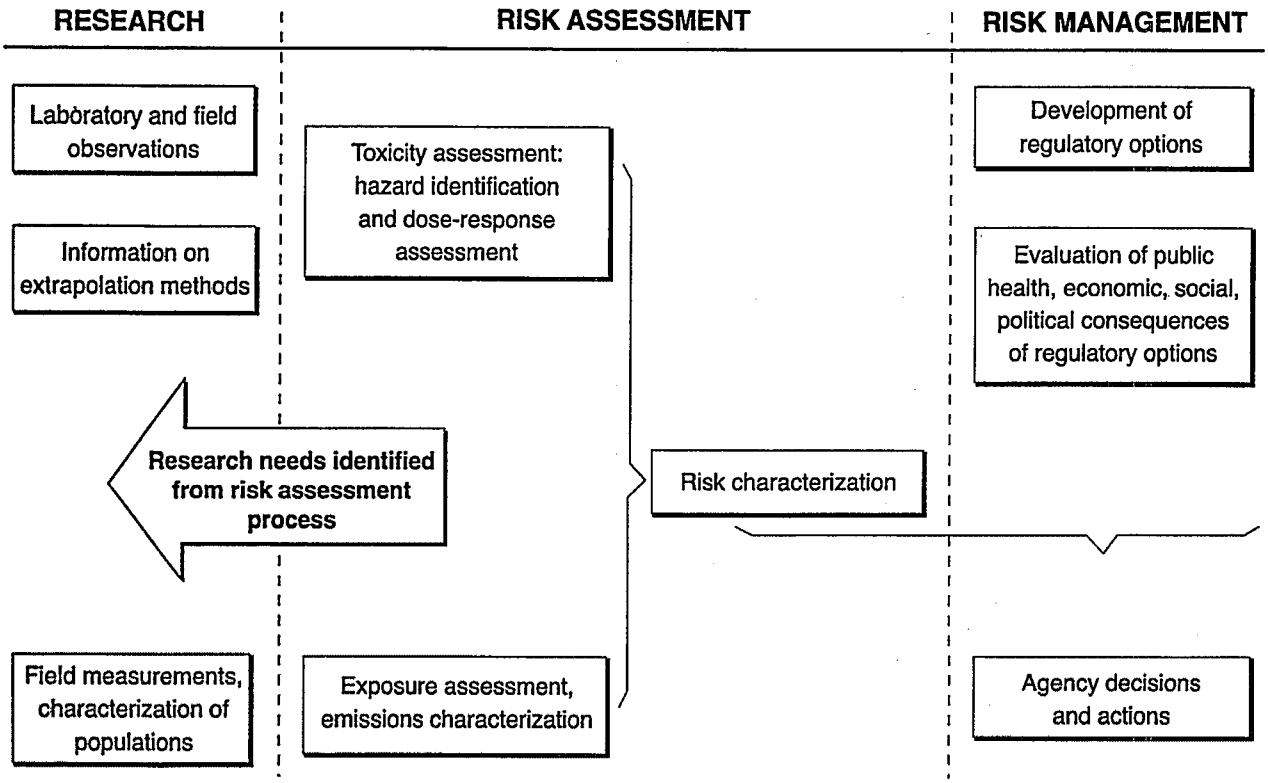

Figure 2-1. Elements or risk assessment and risk management (NAS, 1994).

identify the fish contamination target analytes of concern, as described in *Volume 1: Fish Sampling and Analysis* (U.S. EPA, 1993a, 1999a) in this guidance series. This process included an evaluation of information on toxicity, occurrence, persistence, and other factors. The methods for selecting the highest priority chemicals as target analytes are described in Volume 1 and summarized briefly in Section 2.2.1 of this document.

The second step in the risk assessment process is the evaluation of the dose-response dynamics for chemicals of concern (see Section 2.3). The dose-response dynamic expresses the relationship between exposure and health effects. To evaluate this relationship, the results of human and animal studies are reviewed; the dose-response evaluation may focus on specific types of effects (e.g., developmental, carcinogenic) or be designed to encompass all adverse effects that could occur under any plausible scenario.

The third step in the risk assessment process is exposure assessment (see Section 2.4). Individual exposure assessments use data on chemical residues in fish and human consumption patterns to estimate exposure for hypothetical

individuals. Population exposure assessments consider the distributions of exposure in a population. Exposure assessments are then combined with dose-response data to determine risk.

The final step in risk assessment is risk characterization (see Section 2.5), which provides an estimate of the overall individual or population risks. Risk characterization can be used by risk managers to prioritize resource allocation and identify specific at-risk populations; it is also used to establish regulations or guidelines and to estimate individual or population risk. In this document, risk characterization involves developing the risk-based consumption limits provided in Section 4. When risk characterization is used to estimate individual or population risk, it provides the risk manager with necessary information concerning the probable nature and distribution of health risks associated with various contaminants and contaminant levels.

The importance of describing and, when possible, quantifying the uncertainties and assumptions inherent in risk assessment has long been recognized, though not consistently practiced (Habicht, 1992). Uncertainty analysis is particularly critical in risk characterization and must be performed throughout the risk assessment process to adequately characterize assumptions in this last step of the process. Consequently, various sources of uncertainty are described and assumptions are discussed for each of the four activities that constitute risk assessment.

2.1.1 Other Information Sources

This document focuses on risk assessment as it applies primarily to fish advisories. EPA has issued several detailed guidelines for conducting specific portions of the risk assessment process that address the following areas:

- Exposure assessment (U.S. EPA, 1992a)
- Carcinogenicity risk assessment (U.S. EPA, 1986a, 1996b)
- Mutagenicity risk assessment (U.S. EPA, 1986b)
- Developmental toxicity risk assessment (U.S. EPA, 1991a)
- Assessment of female and male reproductive risk (U.S. EPA, 1996a)
- Health risk assessment of chemical mixtures (U.S. EPA, 1986c, 1999a)
- Exposure factors (U.S. EPA, 1990a).

These guidelines were developed by EPA to ensure consistency and quality among Agency risk assessments. EPA's Risk Assessment Forum is in the process of developing quantitative guidelines on dose-response assessment of systemic toxicants. One approach used to estimate reference doses for chronic exposure toxicity is presented in the Background Documents for IRIS. It is also found in many EPA publications and has been summarized in papers that discuss risk assessment within EPA (e.g., Abernathy and Roberts, 1994; Barnes and Dourson, 1988). Relevant sections of each of the above guidelines were consulted in developing this section, along with other resources cited throughout the section. Additional references are listed in Section 7.

2.2 HAZARD IDENTIFICATION

Hazard identification assesses the likelihood that exposure to specific chemicals under defined exposure conditions will pose a threat to human health. Hazard identification is often used effectively to determine whether a chemical or groups of chemicals occurring in a specific exposure situation require action. It has been narrowly defined for some applications to provide only chemical-specific hazard data (NAS, 1983). However, in the NAS document, *Science and Judgement in Risk Assessment*, the use of an iterative approach to evaluating risk is emphasized, which entails the use of relatively inexpensive screening techniques to determine when to proceed to more in-depth evaluations (NAS, 1994). This is analogous, in practice, to what is already frequently done at the state and local level. The early stages of risk assessment often include consideration of the existence or likelihood of exposure to determine the need for further work on a chemical. At the state, local, and tribal organization levels, administrators and risk managers concurrently evaluate both the hazard and the occurrence of chemicals to assess whether sufficient risk exists to justify an investment of time and resources in further action. Their needs for information to guide further action are, therefore, different from that of a federal agency, which may evaluate hazards independently of exposure considerations.

A preliminary risk evaluation typically precedes an in-depth risk assessment because most states, localities, and tribal organizations do not have the resources to conduct detailed risk analyses in the absence of information indicating that health risks may occur. Thus, this section discusses hazard identification as an approach to making preliminary decisions regarding further action on fish advisories. This approach is similar to the screening methodology used for the identification of the 25 target analytes addressed in this guidance series and is discussed in *Volume 1: Sampling and Analysis* in this series (U.S. EPA, 2000a).

Although hazard identification is essentially a screening process, it may entail a complex evaluation of the exposure scenarios and toxicological and biological properties of contaminants (e.g., bioavailability, degradation, existence of breakdown products and metabolites). Hazard identification ranges in scope from the use of existing summary data (e.g., IRIS or Agency for Toxic Substance and Disease Registry [ATSDR] Toxicological Profiles) to a detailed evaluation of each aspect of exposure and risk; the depth of analysis is usually determined by time and resource availability. For example, an evaluation of a contaminant's toxicological properties may include an analysis of all health endpoints likely to occur in the exposure scenarios of concern. EPA guidance (Habicht, 1992) describes hazard identification as:

> . . . a qualitative description based on factors such as the kind and quality of data on humans or laboratory animals, the availability of ancillary information (e.g., structure-activity analysis, genetic toxicity, pharmacokinetics) from other studies, and the weight-of-evidence from all of these data sources.

Under some circumstances, extensive data collection may be undertaken. For example, to evaluate carcinogenic risk, EPA has recommended the following information be reviewed in a hazard identification: physical-chemical properties, routes and patterns of exposure, structure-activity relationships, metabolic and pharmacokinetic properties, toxicological effects (including subchronic and chronic effects, interactions with other chemicals, pathophysiological reactions, and time-to-response analysis), short-term tests (including mutagenicity and DNA damage assessment), long-term animal studies, human studies, and weight-of-evidence (U.S. EPA, 1986a). At the state, local, and tribal organization level, this type of in-depth analysis is rarely carried out for each health endpoint of a chemical hazard, due to the time and resources required. Alternatively, databases such as IRIS and the Hazardous Substances Data Bank (HSDB), which summarize health endpoints and associated risk values, are inexpensive, readily available, and often consulted in the development of a hazard profile.

2.2.1 Approach for Fish Contaminants

The hazard identification step in risk assessment of chemically contaminated fish has been refined by EPA through careful review of the chemical characteristics considered to be critical in determining human health risk. These parameters are:

- High persistence in the aquatic environment
- High bioaccumulation potential
- Known sources of contaminant in areas of interest
- High potential toxicity to humans
- High concentrations of contaminants in previous samples of fish or shellfish from areas of interest (U.S. EPA, 1989a).

These characteristics are described in detail in *Volume 1: Fish Sampling and Analysis* in this series. Additional information on persistence and bioaccumulation potential may be obtained from EPA documents such as the *Technical Support Document for Water Quality-Based Toxics Control* from the Office of Water (U.S. EPA, 1991b), which contains a brief description of the bioaccumulation characteristics considered for the development of reference ambient concentrations (RAC). Readers may also wish to consult the open literature (e.g., Callahan et al., 1979; Lyman et al., 1982).

2.2.1.1 Toxicological Data—

The toxicity of a chemical to humans can be evaluated based on its acute (short-term) exposure toxicity and/or chronic (long-term) exposure toxicity. The chronic toxicity of a chemical is usually of primary concern for environmental toxicants; however, the varied consumption patterns of fish consumers complicate the analysis of fish contaminants. This issue is discussed in Section 2.4 in additional detail. There are a number of databases that contain risk values for various types of chronic toxicity (e.g., carcinogenicity, liver toxicity, and neurotoxicity). IRIS is a widely accepted data source because of the extensive review conducted on the

risk values contained in it. EPA's Health Effects Assessment Summary Tables (HEAST) are also frequently used (HEAST, 1997). Other relevant databases include HSDB, the National Cancer Institute's Chemical Carcinogenesis Research Information System (CCRIS), EPA's GENE-TOX, and the National Institute of Occupational Safety and Health's (NIOSH's) Registry of Toxic Effects of Chemical Substances (RTECS). All of the above databases except HEAST are available through TOXNET.*

2.2.1.2 Contaminant Data—

Information on the prevalence and measured concentrations of fish contamination has been generated through numerous sampling and analysis programs. EPA has provided a summary of preliminary screening results on the prevalence of selected bioaccumulative pollutants in fish and shellfish in Volume I of the *National Study of Chemical Residues in Fish* (U.S. EPA, 1992b). In addition, substantial guidance is provided in Volume 1 of this series on planning a sampling strategy and conducting fish contaminant analyses (U.S. EPA, 2000a).

Likely sources of contaminants are often known to state, regional, and tribal officials or can be identified through a review of data on manufacturing, toxic releases, or complaints regarding contamination of food, air, water, or soil. Recommended sources and lists for obtaining data on probable contaminants include

- EPA-recommended target analytes (see Table 1-1)
- Chemical releases reported in EPA's Toxics Release Inventory (TRI) database
- The Manufacturers' Index
- EPA priority pollutants
- State inventories of manufacturers and operations
- Chemicals identified in industrial and publicly owned treatment works (POTW) effluents as nonbiodegradable
- Known spills and contaminants (as reported under the Comprehensive Environmental Response, Compensation, and Liability Act [CERCLA] to the Office of Emergency and Remedial Response)
- EPA source inventory for contaminated sediments
- ATSDR's HAZDAT database
- Listing of Superfund (National Priority List) sites

* TOXNET is managed by the U.S. Department of Health and Human Services' National Library of Medicine (Bethesda, MD). For more information, call (800) 848-8990 (for Compuserve), (800) 336-0437 (for Telenet), (800) 336-0149 (for TYMNET), or (301) 496-6531 for technical assistance.

- Common-use chemicals based on practices in the state or region (e.g., agriculture or fuels).

This information can be used to describe local waterbodies, incorporating geographic and source-specific data. The geographic distribution of potential contaminants can be used to guide the selection of monitoring sites for sampling and analysis of potentially contaminated fish.

Volume II of the *National Study of Chemical Residues in Fish* (U.S. EPA, 1992b) provides an example of how information on the first three characteristics of chemical contaminants (high persistence in the aquatic environment, high bioaccumulation potential, and high concentrations of contaminants in previous samples of fish or shellfish from areas of interest) can be summarized to form the basis for a hazard evaluation. The document summarizes the results of the National Bioaccumulation Study, correlates contaminant prevalence with sources of pollutants, and briefly describes the chemical and toxicological properties of 37 chemicals and chemical groups (U.S. EPA, 1992b).

2.2.1.3 Sources of Exposure—

Hazard identification may also include a comprehensive evaluation of all sources of exposure, including those that augment the primary exposure of concern, to obtain an estimate of total exposure. For fish contaminants, a comprehensive exposure evaluation would involve an evaluation of exposures from other sources such as air, water, soil, the workplace, or other foods, including commercially caught fish. In some cases, in fact, other routes of exposure may contribute more to overall contaminant body burden than does contaminated noncommercially caught fish. It is beyond the scope of this guidance document to provide detailed direction on evaluating exposures occurring via other media; however, readers are encouraged to assess other sources of exposures in their hazard evaluations (see Section 2.4.5.6 for additional information).

If exposure from noncommercially caught fish consumption were added to already elevated exposure levels arising from other sources, it could produce an overall exposure associated with adverse health effects. Under such circumstances, a more stringent fish consumption limit (or some other risk management option) may be needed. Readers may wish to determine whether such an evaluation is warranted through consideration of the likelihood that exposures are occurring via nonfish routes and the availability of data and resources to carry out a comprehensive exposure evaluation.

EPA's Office of Water, in conjunction with the Interagency Relative Source Contribution Policy Workgroup, is currently developing guidance on the use of a Relative Source Contribution (RSC) approach. According to the preliminary information available on this approach:

The RSC concept could be used in fish advisory activities. The amount of exposure from fish consumed is determined along with the estimated exposure from all other relevant sources (e.g., drinking water, food, air, and soil) for the chemical of concern. By comparing the overall exposure with the Reference Dose, it can then be determined whether the amount of total exposure to the chemical may result in an adverse effect and warnings can be issued regarding the safety of consuming such fish (Borum, 1994).

The CERCLA office at EPA, which offers assistance on multimedia assessments of hazardous waste sites, may also be consulted for information on methods to estimate background levels of various contaminants. They have developed guidance documents that may be useful to those readers who plan to conduct comprehensive exposure assessments.

2.2.2 Assumptions and Uncertainty Analysis

Hazard identification, as described in this guidance, is a screening process used to select the chemicals and exposure scenarios of greatest concern. As a screening process, it uses simplifications and assumptions in each step of the process. Because each aspect of hazard is not examined in its entirety, the process generates some uncertainty.

Uncertainty is introduced by the variability in persistence and bioaccumulation potential of chemicals that may occur in untested media. The behavior of chemicals in all types of media cannot be anticipated. Interactions of the target analytes in sediments containing multiple chemical contaminants may cause chemicals to change their forms as well as their bioaccumulation and persistence characteristics. For example, binding of the target analyte to organic matter may cause it to become more or less persistent or available for bioaccumulation, or decomposition may occur, producing metabolites that have significantly different properties than those of the original target analyte. These chemical and biological interactions are more likely to occur in a complex system (e.g., a hazardous waste site), with relatively unstable chemicals, and with metals having multiple valence states.

The persistence of a chemical in the aquatic environment and its bioaccumulative potential are based on its physical and biochemical properties. Although the critical information is available for many chemicals of concern, it is not available for all chemicals. For example, chemicals that have been recently introduced into the environment may not be well characterized in terms of their persistence and bioaccumulation potential. Consequently, there is the potential for under- or overestimating the risk they pose to human health.

Estimation of chemical toxicity can be a source of significant uncertainty in the hazard identification process. A toxicity evaluation incorporates data on a variety of health endpoints and usually requires that human toxicity estimates be derived

from studies in experimental animals. There are often insufficient data in the toxicological literature to fully characterize the toxicity of a chemical. Some types of toxicity are well-described in the toxicological and risk literature. Others, such as developmental toxicity, neurotoxicity, and immunotoxicity, have only recently become subjects of intensive research. Although studies of developmental toxicity date from the 19th century, there has been a dramatic increase in both epidemiological and toxicological studies in recent years. Consequently, there are limited data for most chemicals on these types of effects. Uncertainties associated with toxicity and health risk values (e.g., cancer slope factor ([CSFs] and reference doses [RfDs]) are discussed in Section 2.3.

The two remaining characteristics of hazard identification (known sources of contaminants in areas of interest and high concentrations of contaminants in previous samples of fish or shellfish) are excellent indicators of potential hazard. A major uncertainty associated with these characteristics arises from the potential for omitting from sampling programs areas not known to be contaminated. During an era of limited resources, it is a common, but not necessarily valid, assumption that known contaminated areas should be the focus of evaluation and action. Given an array of known contaminated sites, attempts to identify additional contamination may appear unnecessary. However, it is recommended that readers conduct a detailed review of potential contamination sources for all waterbodies before determining whether or not adequate hazard identifications have been conducted.

Because the goal of the risk assessment process is protection of human health, it is typically designed to provide the maximum protection against underestimating risk. Therefore, the hazard identification step in the risk assessment process may result in the inclusion of chemicals or exposure situations that, later in the process, are found not to pose significant health risks. This type of approach is taken because the consequences of underestimating risk, or excluding a chemical that poses a public health hazard, are potentially more serious than the consequences of overestimating risk at this early stage of evaluation.

The hazard identification process forms the basis for decisions regarding those chemicals and exposure scenarios that warrant further analysis. It entails the collection and evaluation of information regarding toxicity, bioaccumulation potential, persistence, and prevalence. Although there is uncertainty associated with this aspect of the assessment, quantitative evaluation of the uncertainty can best be conducted in later steps in the risk assessment process. Because each aspect of hazard identification is carried out in more detail in the risk assessment steps that follow, the uncertainties and assumptions can be better refined and quantified during subsequent steps. The information generated on toxicity and exposure in this process also serves as the basis for the subsequent dose-response evaluation and exposure assessment steps in the risk assessment.

2.3 DOSE-RESPONSE ASSESSMENT

This section briefly outlines the current EPA methodology for carrying out a dose-response assessment. Additional information on dose-response evaluations is available in the references cited in Section 7.

A dose-response relationship expresses the correlation between exposure and health effects. To evaluate this relationship, the results of human and animal studies with controlled and quantified exposures are reviewed. This evaluation may focus on specific types of health effects or be designed to encompass all adverse effects that could occur under any plausible exposure scenario. Dose-response evaluations result in the derivation of toxicity values such as cancer potencies and reference doses.

Actual fish consumption patterns may not correspond well to the typical periods of exposure studied in toxicity tests (i.e., acute or chronic exposure). Many fish consumers ingest intermittent doses of varying sizes and may consume fish over a short period of time (e.g., a vacation) or on a regular basis over a lifetime. The potentially large, intermittent dose (bolus dose) has not been evaluated in most toxicity studies. Chronic exposure studies commonly use daily dosing and acute studies may use one or a few very large doses over a very short time period (e.g., 2 to 3 days). Short-term dosing is frequently used in developmental toxicity studies (discussed in Section 2.3.2.3); two of the 25 target analytes have RfDs based on developmental toxicity (methylmercury and PCBs).

Fish consumption patterns are discussed in more detail in Section 2.4.5.4 and Appendix B; however, when developing fish advisories, it is important to be aware that there is no information available on the impact of bolus dosing. The methods used to calculate fish consumption limits allow the daily RfD to be aggregated over a period of time (e.g., 1 month) into one or more meals. Thus the consumption **averaged** over 1 month corresponds to an **average** daily dose indicated by the RfD. However, the actual dose that may be consumed in 1 day can be approximately 30 times (in the case of a 30-day advisory) the daily RfD.

A bolus dose may not be a problem for many individuals; however, it is a concern for those who are particularly susceptible to toxicants. For example, a relatively large single dose may be problematic for those with decreased ability to detoxify chemicals (e.g., children and the elderly) and those with special susceptibilities (e.g., persons taking certain medications, children, and pregnant or lactating women). Potential adverse effects in some groups are noted for many of the target analytes in Section 5. For example, organochlorines may interact with some commonly prescribed pharmaceuticals; consequently, individuals using specific drugs may find the efficacy altered by large doses of contaminants that interact with their drug-metabolizing systems. Infants have an immature immune system and may be less able to detoxify certain chemicals. Children have rapidly developing organ systems that may be more susceptible to disruption. A NAS report, *Pesticides in the Diets of Infants and Children* (NAS, 1993), concluded that

children up to age 18 are substantially different from adults in the relative immaturity of their biochemical and physiological functions and structural features. These differences can alter responses to pesticides, especially during windows of vulnerability, leading to permanent alteration of the function of organ systems. The authors, who included pediatricians, toxicologists, epidemiologists, and other health specialists, concluded that:

> Infants and children may exhibit unique susceptibility to the toxic effects of pesticides because they are undergoing rapid tissue growth and development, but empirical evidence to support this is mixed
>
> and
>
> Traditional approaches to toxicological risk assessment may not always adequately protect infants and children (NAS, 1993).

Although the focus of the NAS report was on pesticides (many of the target analytes are currently or were formerly used as pesticides), much of the analysis is relevant to other chemical exposures as well. Readers may wish to refer to the NAS report for a more complete discussion of various related topics of interest including neurotoxicity in children, various dosimetry scaling methods, and consumption patterns.

A dose-response evaluation has already been carried out by EPA for the 25 target analytes addressed in this guidance series. These evaluations resulted in the calculation of risk values: either CSFs, RfDs, or both. The risk values used in this work and cited in the toxicological profiles in Section 5 were obtained primarily from EPA's IRIS database. All data searches were carried out in 1999. For chemicals lacking IRIS risk values, values were obtained from EPA's Office of Pesticide Programs (OPP) or EPA's Health Effects Assessment Summary Tables (HEAST, 1997).

A comprehensive dose-response evaluation requires an extensive review of both the primary literature, including journal articles and proceedings, and the secondary literature, such as books, government documents, and summary articles. It is typically very time consuming and requires data evaluation by toxicologists, epidemiologists, and other health professionals. Because risk values are available for the target analytes, it is not recommended that readers undertake further detailed dose-response evaluations for these chemicals. However, new data are continually being generated that may require evaluation. In addition, chemicals that are not included in the target analyte list may require analysis. It is strongly suggested that an evaluation begin with a review of current government documents on a chemical. In many cases, EPA, FDA, or ATSDR conducts detailed dose-response evaluations when a chemical is identified as an environmental pollutant or when new data become available. This may save readers hundreds of hours of research by providing data and risk values.

2.3.1 Carcinogenic Effects

EPA has proposed new guidelines for cancer risk assessment (U.S. EPA, 1996b). These guidelines have not been finalized yet but would supersede the existing cancer guidelines (U.S. EPA, 1986c). The following discussion presents information from the existing guidelines that has not changed in the proposed guidelines and highlights information that has changed. EPA (along with many other risk assessors) takes a probabilistic approach to estimating carcinogenic risks. Cancer risk is assumed to be proportional to cumulative exposure and, at low exposure levels, may be very small or even zero. EPA assumes that carcinogens do not have "safe" thresholds for exposure; that is, any exposure to a carcinogen may pose some cancer risk. Carcinogenic risk is usually expressed as a cancer potency (CSF) value with units of risk per milligram/kilogram/-day exposure. Risk may also be estimated for specific media. When risks in air and water are provided, these are referred to as unit risks because they are expressed as risk per one unit of concentration of the contaminant in air or water.

The cancer slope factor is derived from dose-response data obtained in an epidemiological study or a chronic animal bioassay. Because relatively high doses are used in most human epidemiological studies and animal toxicity studies, the data are usually extrapolated to the low doses expected to be encountered by the general population. The dose-response data from one or more studies are fit to standard cancer risk extrapolation models, which usually incorporate an upper-bound estimate of risk (often the 95 percent upper bound). This provides a margin of safety to account for uncertainty in extrapolating from high to low doses and variations in the animal bioassay data (IRIS, 1999). In the existing guidelines, the model used as a default to calculate the cancer potency is the linearized multistage (LMS) model. Cancer potency is estimated as the 95 percent upper confidence limit of the slope of the dose-response curve in the low-dose region. This method provides an upper estimate of risk; the actual risk may be significantly lower and may be as low as zero. In the proposed cancer guidelines, straight-line extrapolation for a linear default is proposed instead of the LMS model. The reason is that the LMS model gave an appearance of specific knowledge and sophistication unwarranted for a default model (U.S. EPA, 1996b).

Cancer potencies may be calculated for both oral and inhalation exposure. There are four major steps in calculating cancer potencies:

- Identify the most appropriate dose-response data
- Modify dose data for interspecies differences
- Develop an equation describing the dose-response relationship
- Calculate an upper confidence bound on the data.

These are described in more detail in the guidelines for cancer risk assessment (U.S. EPA, 1986a, 1996b) and in texts on risk assessment. Cancer slope factors are provided for those target analytes that EPA has determined have sufficient data to warrant development of a value. The values are listed in Table 3-1 and

discussed in Section 5; they were used to calculate the consumption limits in Section 4.

As discussed in Section 2.3.2.3, children may have special susceptibilities to some chemicals and some types of effects. Exposure to a carcinogen early in life may generate greater risk than exposure later in life. This is due to a variety of factors including the rapid growth and development ongoing in children and the proportionally greater consumption by children of some foods. The experimental literature on this subject is not conclusive and readers may wish to review the NAS report to obtain additional information (NAS, 1993).

2.3.2 Noncarcinogenic Effects

2.3.2.1 Acute Exposure—

Noncarcinogenic effects that occur over brief periods of time, e.g., a few hours or days, are considered to be acute exposure effects. They do not necessarily result in an acute (immediate) response, and so the exposure and response periods must be considered separately. The pesticide paraquat is an example of a chemical that usually causes no immediate response to acute exposure but often results in fatal outcomes after several days or weeks.

Acute exposures have traditionally been considered primarily in the realm of occupational health or poisoning incidents rather than environmental health because the brief, low-level exposures associated with most environmental exposures do not usually result in overt symptoms. The exceptions to this have been individuals with allergies or chemical sensitivities. However, there has been a very limited analysis of most environmental pollutants with regard to both the nature and the critical dose for acute nonlethal effects. Acute exposures are of concern for fish contaminants due to the ability of fish to bioaccumulate chemical contaminants to fairly high levels and the relatively large and frequent meals (i.e., bolus doses) that may be consumed by sport and subsistence fishers and their families.

The goal of an acute exposure dose-response evaluation is to identify a threshold exposure level below which it is safe to assume no adverse health effects will occur. There are no widely used methods within EPA for setting such exposure levels. EPA welcomes comments and recommendations on this and other methodologies.

Most toxicological information currently available on acute exposure is in the form of LD_{50}s from animal studies. These studies identify the (usually single) dose that was lethal to 50 percent of the study animals via a specific exposure route. The data are used primarily to give a qualitative sense of the acute toxicity of a chemical. The information is generally used for purposes of planning industrial and application processes, transportation, handling, disposal, and responses to accidental exposures. The data are also used for regulatory purposes and to select

the less-toxic alternatives among a group of chemical options. LD_{50}s may also be used to evaluate ecological toxicity.

LD_{50}s are not easily adaptable to an evaluation of the human response to acute exposures. Because they are focused on the level at which 50 percent of animals die, they do not provide information on other types of toxic responses, including those that led to death. Fatal toxic responses may be substantially different from the responses observed at lower, but still acutely toxic, doses. The LD_{50} also does not provide information on the exposure threshold for lethality, which is always lower (and may be much lower) than the exposure level required to kill 50 percent of the study subjects. For these reasons, the LD_{50}s have very limited utility in identifying a threshold for effects of acute exposure. LD_{50}s may, however, provide comparative information regarding differences in sensitivity between various age groups or sexes that can be used to evaluate toxicity qualitatively.

Human and veterinary poisoning centers (e.g., Poison Control Centers) are primary sources of data on acute exposure effects and thresholds. The poisoning data are limited, however, in many of the same ways in which LD_{50} data are limited. The severe responses that often lead to the reporting of an incident do not indicate the level at which more moderate responses may occur. In addition, the dose is often not known or is estimated imprecisely. The poisoned individual may have predisposing medical conditions or may have been exposed concurrently to other chemicals (including medicines) that affect the nature of the responses.

EPA's Health Advisories also provide some acute exposure information and guidance regarding 1- and 10-day exposure limits for children with an assumed 10-kg body weight (available from EPA's Office of Water). Additional information may be obtained from HSDB. A qualitative summary of acute effects and estimated human lethal doses is provided for most target analytes in Section 5.

2.3.2.2 Systemic Effects from Chronic Exposure—

Noncarcinogenic effects resulting from multiple exposures occurring over a significant period of time are also termed chronic exposure effects (IRIS, 1999). For humans, this usually means exposures over months or years. For animals in studies used to evaluate human chronic toxicity, the temporal definition of chronic exposure depends on the species but is usually defined as a significant portion of the animal's life. Chronic studies are reviewed to determine critical effects for specific chemicals. The critical effect is the first adverse effect, or its known precursor, that occurs as the dose rate increases (IRIS, 1999). Subchronic exposures in toxicity studies (usually 3 months to 1 year) may also be used to evaluate chronic toxicity.

To protect against chronic toxicity resulting from exposure to contaminants, EPA has developed RfDs. The RfD is defined as "an estimate (with uncertainty perhaps spanning an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of

deleterious effects during a lifetime" (U.S. EPA, 1987a). The use of IRIS RfDs is recommended for evaluation of chronic exposure toxicity of the target analytes. These are listed in Table 3-1 in Section 3 and again in Section 5. Additional chronic exposure toxicity data for the target analytes are presented in Section 5, with a brief description of how estimated exposure limits could be calculated based on chronic toxicity. Note that the RfDs listed in IRIS are subject to change as new methodologies and toxicological data become available. Readers are advised to consult the IRIS database to ensure that they are using the most up-to-date toxicity values.

RfDs calculated for chronic noncarcinogenic effects reflect the assumption that, for noncarcinogens and nonmutagens, a threshold exists below which exposure does not cause adverse health effects. This approach is taken for noncarcinogens because it is assumed that, for these types of effects, there are homeostatic, compensating, and adaptive mechanisms that must be overcome before a toxic endpoint is manifested (IRIS, 1999). (Some chemicals such as lead, however, appear to show nonthreshold noncarcinogenic effects.) It is recommended that concern be directed to the most sensitive individuals in a population, with the goal of keeping exposures below calculated RfDs for them (IRIS, 1999). RfDs are generally expressed in terms of milligrams of contaminant per kilogram consumer body weight per day (mg/kg-d).

There are two major steps to calculating RfDs: (1) identify the most appropriate no observed adverse effects level (NOAEL) or lowest observed adverse effects level (LOAEL) and (2) apply the relevant uncertainty and modifying factors.

1. Identify the Most Appropriate NOAEL or LOAEL

The following hierarchy may be useful in selecting a study from which to use a NOAEL or LOAEL:

- A human study is preferable to an animal study. When a human study is unavailable, an animal study is selected that uses a species most relevant to humans based on the most defensible biological rationale (e.g., pharmacokinetic data).
- In the absence of a clearly most relevant species, using the most sensitive species for the toxic effect of concern is preferable (e.g., exhibiting a toxic effect at the lowest dose).
- A study with the appropriate exposure route(s) is preferable; oral or gavage is appropriate for oral exposure.
- A study with sufficient subjects to obtain statistical significance at relatively low exposure levels is required.
- A recent study identifying adequately sensitive endpoints is preferred (e.g., not mortality).
- An adequate control population is required.

- In general, a NOAEL is preferable to a LOAEL. When a NOAEL is unavailable, the LOAEL that generates the lowest exposure threshold (after the application of uncertainty and modifying factors) is usually selected.

In addition to the criteria listed, a chronic (lifetime) study is preferable to a subchronic study (an acute study cannot be used to quantify risks associated with chronic exposure). It is important that exposure occurs over a significant portion of the experimental subject's life to parallel a lifetime exposure of the human population. Issues related to the quality of the study should also be considered in selecting the most appropriate studies. Additional information on selection criteria can be reviewed in the IRIS documentation file (U.S. EPA, 1987a).

2. Apply Relevant Uncertainty and Modifying Factors

The calculations for chronic systemic toxicity use the modifying and uncertainty factors as shown in Table 2-1. In addition, an uncertainty factor may be used when a chronic study is not available and a subchronic (e.g., 90-d) study is used. This is generally a tenfold factor (Abernathy and Roberts, 1994; IRIS, 1999). The product of all uncertainty/modifying factors may range widely depending on the toxicity database. If a chronic human epidemiologic study is available, the uncertainty factor may be as small as 1. However, uncertainty factors of 10,000 may be appropriate (Bolger et al., 1990; U.S. EPA, 1990b).

While uncertainty factors address specific concerns, the modifying factor covers a wider range of circumstances. A common modifying factor adjustment results from differences in absorption rates between the study species and humans, differences in tolerance to a chemical, or lack of sensitive endpoint. The default value for a modifying factor is 1, but may range up to 10 (see Table 2-1).

The uncertainty factor that deals with data gaps has been developed because the dose-response data often address a limited number of effects and may not adequately address effects of major concern. (Abernathy and Roberts, 1994). In some cases there are a number of studies, but the focus of analysis is narrow and not sufficiently sensitive. In other cases, there is not a sufficient number or breadth of studies. Other reasons for applying a modifying factor are discussed in the specific developmental toxicity guidance (U.S. EPA, 1991a); these include data on pharmacokinetics or other considerations that may alter the level of confidence in the data. EPA has used the criteria that the following studies be available for a high level of confidence in an RfD:

> . . . two adequate mammalian chronic toxicity studies in different species, one adequate mammalian 2-generation reproductive toxicity study, and two adequate mammalian developmental toxicity studies in different species (Dourson et al.,1992; U.S. EPA, 1989b).

The uncertainty and modifying factors are divided into the NOAEL or LOAEL to obtain an estimated dose using the following equation:

Table 2-1. Uncertainty Factors and Modifying Factors for Estimating Exposure Limits for Chronic Effects

Uncertainty or Modifying Factor	General Comments	Standard Value
Uncertainty factor: human (intraspecies)	Used to account for the variability of response in human populations. An intermediate factor of 3 (1/2 log unit of 10) may be used if the study examined effects in a sensitive subpopulation (e.g., asthmatics).	3 to 10
Uncertainty factor: animal to human (interspecies)	Used to account for differences in responses between animal study species and humans. An intermediate factor of 3 can be used if appropriate pharmacokinetic/ dynamic data are available to justify a reduction in the uncertainty factor.	3 to 10
Uncertainty factor: data gaps	Used to account for the inability of any study to consider all toxic endpoints. The intermediate factor of 3 (1/2 log unit) is often used when there is a single data gap exclusive of chronic data.	3 to 10
Uncertainty factor: LOAEL to NOAEL	Employed when a LOAEL instead of a NOAEL is used as the basis for calculating an exposure limit. For "minimal" LOAELs, an intermediate factor of 3 may be used.	3 to 10
Modifying factor	Has been used for differences in absorption rates, tolerance to a chemical, or lack of sensitive endpoint. The default value is 1.	1 to 10

LOAEL = Lowest observed adverse effects level.
NOAEL = No observed adverse effects level.
Source: Adapted from Abernathy and Roberts (1994). Their work also cites: Abernathy et al. (1993); Barnes and Dourson (1988); IRIS (1999); and Jarabek et al. (1990).

$$RfD = \frac{NOAEL \text{ or } LOAEL}{UF \bullet MF} \qquad (2\text{-}1)$$

where

RfD = RfD or exposure limit for the target analyte
NOAEL or LOAEL = NOAEL from the selected study
UF = multiplicative product of uncertainty factors
MF = modifying factor.

As a point of reference, EPA has estimated that the RfDs they develop have an uncertainty spanning approximately 1 order of magnitude (U.S. EPA, 1987a). As discussed previously, it is necessary to fully characterize the uncertainties and assumptions that are incorporated in fish consumption limits. A description of the variability in dose-response results and their impact on fish consumption limits, descriptions of the data gaps, study limitations, and assumptions are also important in providing a context for fish consumption limits based on developmental toxicity or other types of toxic effects. It may be useful to review the description of uncertainties and assumptions associated with dose-response evaluations provided in Sections 2.3.5 and 5.1.1.12. If this document is the only source consulted for dose-response data, note that the literature review conducted for the development of these values was limited to secondary sources such as ATSDR Toxicological Profiles, IRIS, HDSB, and standard toxicological texts (all are cited in the individual chemical discussions). The list of study characteristics provided in Section 2.3.2.2 may be useful for identifying data gaps and sources of uncertainty. The inclusion of this type of information in the risk management process that follows risk assessment will provide a better overall understanding of the limitations and uncertainties inherent in the fish consumption limits.

An alternative approach for developing RfDs involves the use of benchmark doses instead of a NOAEL or a LOAEL. The major limitation of NOAELs and LOAELs is their subjective reliance on experimental dose spacing and their inability to adequately account for variability in the dose-response slopes. EPA has developed guidelines for the use of the benchmark dose approach (U.S. EPA, 1995) and is in the process of drafting technical guidance for the application of the benchmark dose approach in cancer and noncancer dose-response assessment.

The benchmark dose approach involves fitting mathematical models to dose-response data and using the different results to select a benchmark dose that is associated with a benchmark response, such as a 10 percent decrease in body weight gain or a 10 percent increase in the incidence of a particular lesion.

2.3.2.3 Developmental Toxicity—

Developmental toxicity has been a recognized medical concern, research subject, and impetus for restricting exposures of pregnant women to developmental

contaminants for several decades. However, it is not as well studied as other health effects such as cancer, and significant gaps in our understanding of causality and appropriate protective measures remain. Developmental toxicity incorporates a wide range of effects involving all organ systems in the body. Prenatal and lactational exposure involves indirect exposure of the developing fetus; the effective dose may vary with the period of exposure and the specific chemical. In the past two decades, researchers have determined that the hypothetical maternal barrier, in the past thought to provide protection for the fetus during the prenatal period, does not effectively exist. In fact, prenatal exposure may be especially risky because of the rapid cell replication and differentiation that occurs in the fetus prior to birth. These same processes also occur at elevated rates in children and adolescents, causing them to be more susceptible to some chemical-induced toxicity than adults. Chemical exposures that cause alterations in the cell replication and developmental processes can lead to serious birth defects, miscarriages, stillbirths, developmental delays, and a variety of other adverse effects. A large number of toxic chemicals that have been tested in recent years have demonstrated developmental toxicity in animal test systems. Consequently, the exposure of pregnant women to toxic chemicals has become an area of considerable concern.

Many developmental effects may have environmental causes; however, it is difficult to establish a causal link in epidemiological studies due to confounders that arise from the variability in human exposure. It has been estimated that 70 percent of the developmental defects observed in children are a result of unknown factors (U.S. EPA, 1991a); some portion of the 70 percent may be attributable to environmental exposures.

EPA has studied issues in developmental toxicity and risk assessment for developmental toxicants over the past two decades and has developed guidance for evaluating developmental toxicants and establishing health-based exposure limits. The initial guidance for risk assessment of developmental toxicants was provided in 1986 (U.S. EPA, 1986b) and has been refined in the current *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991a). The recommended approach uses a NOAEL to calculate an RfD in a manner similar to that used for the calculation of an RfD based on chronic exposure toxicity. EPA is also considering use of a benchmark dose approach for developmental toxicants under some circumstances; consequently, the guidelines may be amended in the future (U.S. EPA, 1991a). The methodology described in this guidance document follows the current EPA recommendations. The reader is referred to this and other sources cited throughout this section and Appendix E for further information on developmental toxicity risk and risk assessment.

2.3.3 Mutagenicity/Genotoxicity

Mutagenicity and genotoxicity data are not generally used to develop risk estimates by themselves, although they are frequently used in conjunction with other information to evaluate other toxicity endpoints (e.g., cancer). There is a wide

variety of assays designed to assess the mutagenicity of chemicals; however, there is a limited amount of mutagenicity dose-response data that can be used in quantitative risk assessment. The majority of data involve in vitro test systems, which can provide only qualitative evidence of mutagenicity.

The evaluation of weight-of-evidence (WOE) for carcinogenicity, carried out by EPA for all chemicals having a cancer classification, includes an evaluation of mutagenicity data. Information on genetic toxicity also needs to be considered when developing risk values for developmental and reproductive system effects. Mutagenicity data are summarized in the toxicological profile summaries in Section 5. Readers are urged to consider this information in reviewing the toxicity of target analytes. Because information is less readily available on genetic toxicity and mutagenicity than on other types of risk assessment, and because this type of toxicity is relevant to evaluating developmental toxicity, a brief summary of the current EPA guidelines on these types of toxicity has been included in Appendix E.

2.3.4 Multiple Chemical Exposures: Interactive Effects

Most humans are simultaneously exposed to a number of environmental contaminants. Risk evaluations, however, typically proceed on a chemical-by-chemical basis. Similarly, the development of risk-based exposure guidelines typically focuses on the effects of exposure to chemicals individually rather than as a group. In many cases, the individual exposures and/or risks are then summed to estimate risks or safe exposure levels for a group of chemicals.

EPA provides guidance on chemical mixtures in risk assessments in *Guidelines for the Health Risk Assessment of Chemical Mixtures* (U.S. EPA, 1986c). EPA has recently published a supplement to the 1986 guidelines (U.S. EPA, 1999a). This document is intended to reflect the evolutionary scientific development in the area of chemical mixtures risk assessment. It proposes several different approaches depending on the nature and quality of the available data, the type of mixture, the type of assessment being made, the known toxic effects of the mixture or its components, the toxicologic or structural similarity of a class of mixture or of mixture components, and the nature of the environmental exposure.

The document proposes that the assessment begins with addressing whether the type of available data is whole mixture data or mixture component information.

Methods available for whole mixtures are then dependent on whether there is information directly available on the mixture of concern or only on similar mixtures. Methods available for component data are dependent on whether there are interactions data available, whether the components act with a similar mode of action, or whether the components can be thought of as belonging to a chemical class (U.S. EPA, 1999a).

A classification scheme is then used to assess the quality and nature of the available mixtures data. Exposure, health effects, and interactions information is

then assessed for quality. The results of this assessment determine the type of risk assessment approach to be used with the mixture. Examples of the approaches discussed include a mixture RfD or slope factor approach, a qualitative assessment, a hazard index approach, a weight-of-evidence approach, or response addition (U.S. EPA, 1999a).

The 1986 guidelines advise the use of the additive approach when data are available only on individual mixture components. The 1999 guidance also proposes an additive approach for low exposure levels when interactions information is not available. For the component chemicals in a mixture that show dissimilar toxicity, response addition is recommended. For the component chemicals in a mixture that show similar toxicity, dose addition is recommended. Under dose addition, the general procedure is to scale the doses of the components for potency and add the doses together; the mixtures response is then estimated for the combined mixtures dose. Under response addition, the general procedure is to first determine the risks per the exposure for the individual components; the mixtures risk is then estimated by adding the individual risks together (U.S. EPA, 1999a).

Section 3 provides a method for calculating exposure limits for multiple chemical occurrence in single or multiple fish species. The approach is recommended for use when chemicals have the same health endpoints and mechanisms of action.

The type of information that is often available (acute effects interactions and mechanisms of action) is not readily applicable to the quantitative assessment of chronic health risks of multiple chemical exposures (U.S. EPA, 1986c, 1999a). The guidelines recommend that this type of information be discussed in relation to its relevance to long-term health risks and interactive effects without making quantitative alterations in the risk assessment.

The information that may be implied from the toxicological nature of many of the target analytes is related to the chemical's interaction with basic processes, such as metabolism. When these functions are altered (e.g., by the induction of microsomal enzymes), the metabolism of other endogenous or exogenous chemicals may be altered. This is particularly problematic for individuals using pharmaceutical drugs to address medical conditions. As the PCB discussion in Section 5.7 notes, alteration in metabolism of medications may require adjustment of dosages. This is not a hypothetical problem; exposure to various chemicals has reportedly resulted in altered response to medications. Information regarding these types of effects are discussed in Section 5 for the target analytes.

EPA has developed a database to disseminate available information on interactive effects of chemical mixtures. This database, called MIXTOX, contains summaries of information from primary studies in the open literature on binary mixtures of environmental chemicals and pharmaceutical chemicals. Data provided include the duration of the study, animal species, dose ranges, site, effects, and interactions. Available MIXTOX information on the target analytes is presented in Section 5. The majority of data obtained through MIXTOX consisted of the results of acute

studies. Many studies indicated additive effects. Other types of interactions (e.g., inhibition, synergism) were usually not provided. The relevance of this information to specific waterbodies will depend on the chemical mixtures that are known to occur, based on fish sampling results. **In the absence of quantitative information on interactive effects, these guidelines suggest the use of an additive approach to evaluation of chemical mixtures for carcinogens and for noncarcinogens that are associated with the same adverse health endpoints.** The equation used in this approach is presented and discussed in Section 3.5.

2.3.5 Assumptions and Uncertainties

Numerous assumptions are required to develop risk values from dose-response data. Uncertainties arise from the assumptions, from the nature of the dose-response data, and from our imperfect understanding of human and animal physiology and toxicology. Depending on the quality of the studies, there may also be uncertainty regarding the nature and magnitude of the effects observed in toxicological and epidemiological studies. However, evaluation of study quality is a complex process and involves such diverse topics as animal housing conditions and pathological evaluations. Often there is not sufficient information provided in study summaries (either in a journal article or report) to evaluate fully the quality of the study and the assumption must be made that good laboratory practices and scientific methods were followed.

Major assumptions that are used in the evaluation of dose-response data are discussed at length in the EPA risk assessment guidance documents on specific toxicities (e.g., for carcinogenicity, numerous assumptions are discussed including the selection of the dose-response model, use of benign tumors in estimating response, use of the upper bound estimate of the slope, and use of surface area instead of body weight to adjust dose [U.S. EPA, 1986a,b,d; 1996b]).

A critical assumption underlying all animal-human extrapolations is that there is a relationship between toxicity in test animals and the toxicity anticipated in humans. There can be significant differences in metabolism and other physiological aspects of study animals and the human population (e.g., absorption, metabolism, and excretion). Although many of these aspects are well-characterized, the relationship between interspecies differences and the toxicity of specific chemicals is usually not known. There is also uncertainty regarding the appropriateness of the test species for evaluation of a chemical's effects on humans. Generally, the species of animal that most closely resembles humans in response to the toxicity of a particular chemical is used in the risk assessment. When such information is not available (as is often the case), the species of animal that is most sensitive to a particular effect is used in the evaluation of that effect for a chemical. Although the existence of a relationship between animal and human toxicity is acknowledged by most scientists, there is not universal consensus on the nature of the relationship for many chemicals and endpoints (e.g., male rat kidney toxicity associated with α-2-globulin may not be applicable to humans).

A second critical assumption is the existence of a threshold for most non-carcinogens and no threshold for carcinogens. The threshold issue is under evaluation for many chemicals and endpoints (e.g., epigenetic [nongenetic] carcinogens, developmental effects). Issues of this type will be resolved as more information becomes available on the basic mechanisms of toxicity and actions of specific chemicals. Future revisions of this document will provide additional guidance as it becomes available.

Additional uncertainty regarding dose rate and the duration of exposure is generated by the use of test animals. Many animal studies are conducted for the lifetime of the animals; however, the human lifetime is significantly longer than the 2-year study period of the usual experimental subjects (e.g., rats or mice), which may impact bioaccumulation and toxicity. When human studies are used as the basis for risk estimates, they are usually of occupationally exposed individuals, who were exposed intermittently during adulthood over two to three decades rather than continuously exposed over a lifetime. Often they are not followed into old age, when many effects become clinically detectable. In addition, human exposures are often confounded by concurrent exposure to other chemicals. Consequently, the use of human studies also introduces numerous uncertainties to the toxicity evaluation process.

Various assumptions are made in most risk assessments regarding the use of numeric adjustments for extrapolation of study results from animals or human studies to the general population. The extrapolation models used to estimate individual or population risks from animal or human studies introduce "margins of safety" to account for some aspects of uncertainty. These models are designed to provide an upper bound on cancer risk values and a conservative RfD for noncarcinogens. Uncertainties arise from the application of uncertainty and modifying factors in the calculation of RfDs. These factors are based on the best available scientific information and are designed to provide a safe margin between observed toxicity and potential toxicity in a sensitive human. The RfD is considered to be an estimate with uncertainty spanning approximately 1 order of magnitude. EPA considers the RfD to be a reference point to be used in estimating whether adverse effects will occur (IRIS, 1999). The IRIS Background Documentation has provided additional insight into the uncertainty inherent in RfDs:

> Usually doses less than the RfD are not likely to be associated with adverse health risks, and are, therefore, less likely to be of regulatory concern. As the frequency and/or magnitude of exposures exceeding the RfD increase, the probability of adverse effects in a human population increases. However, it should not be categorically concluded that all doses below the RfD are "acceptable" (or will be risk-free) and that all doses in excess of the RfD are "unacceptable" (or will result in adverse effects) (IRIS, 1999).

For carcinogens, the upper 95 percent confidence bound on the linear component of the linearized multistage model is currently used in estimating a cancer potency

to introduce a safety margin. It is assumed that this provides a plausible upper bound estimate of potency in the human population (U.S. EPA, 1986a). EPA's new cancer guidelines (which have not been finalized as of this writing) propose using straight-line extrapolation (U.S. EPA, 1996b).

Many numerical assumptions related to anatomy and physiology are used in calculating risk values (e.g., average adult body weight of 70 kg, animal dietary consumption estimates). The application of these assumptions depends on the type of data being used. These assumptions are typically based on a substantial amount of information on average or mean values. However, individual variations within the human population generate uncertainty related to the application of the assumptions.

Uncertainty is significantly related to the amount and quality of toxicological and epidemiological data available. There is a greater degree of certainty for chemicals having human epidemiological studies that encompass a variety of population subgroups over a dose range. However, this type of data is not usually available. Uncertainty related to the database is often endpoint-specific. For example, there may be a substantial amount of data regarding carcinogenic effects but little information on developmental toxicity. This is the case for many of the chemical contaminants discussed in Section 5.

Selection criteria for studies are listed for chronic and developmental toxicity in this section. Where the most appropriate types of data are not available (based on these selection criteria), there is usually greater uncertainty regarding the risk values and risk estimates that are calculated. Many of the criteria address the quality of the studies used to estimate dose-response parameters. Weight-of-evidence guidelines, also discussed in this section for specific toxicity types, provide useful insight into the adequacy of the data supporting a risk value.

Bioassays conducted on single cell lines generate greater uncertainty than animal studies due to their isolation from normal physiological processes. However, some types of effects can be studied most efficiently using these tests. Various types of mutagenicity and cellular level assays provide insight into the potential for genetic damage and damage to specific types of cell systems. These data are very difficult to interpret in the context of human risk because the relationship between study results and human effects has not been well-characterized. This type of study is most often used to support other study results (e.g., positive mutagenicity studies support animal studies indicating carcinogenicity).

Certain chemicals have such limited data for one or more toxic effects that toxicity reference values cannot be determined. Some of these chemicals are poorly characterized for all known/suspected toxicity endpoints. For other chemicals, data may be well-characterized for certain toxic effects, but inadequate for others. For instance, the carcinogenicity of organochlorines has been well-characterized in animals and humans, but other toxic endpoints, including systemic effects and

reproductive effects, have not been extensively investigated. Limitations for the 25 contaminants in this assessment are described in detail in Section 5.

EPA does not recommend specific factors for modifying toxicity data in cases where these data are so limited that a dose-response relationship cannot be determined. However, as the above examples show, lack of toxicity reference values for a given chemical does not necessarily mean that the chemical causes no effect. Therefore, readers will need to evaluate if the lack of specific kinds of toxicity data affect the adequacy of protection afforded by the consumption limit. For example, if the chemical is a suspected developmental toxicant, but quantitative developmental toxicity data are lacking, readers may determine that a consumption limit based on other health endpoints is not sufficiently protective of women of reproductive age and children.

In summary, uncertainty may be generated by many components of a dose-response evaluation. Some of these are dealt with quantitatively through the application of uncertainty factors, modifying factors, or the use of an upper bound estimate. Others may be referred to qualitatively, through a discussion of data gaps or inferential information (e.g., studies that appear to show greater susceptibility at certain ages). The goal of providing the qualitative information on uncertainty is to give the risk assessor and decision makers sufficient information on the context and support for risk values and estimates so that they can make well-informed decisions.

2.4 EXPOSURE ASSESSMENT

This section is meant to provide readers with a brief overview of EPA exposure assessment methodology. Readers wishing to conduct exposure assessments are advised to read the more detailed documents listed in Appendix B. Exposure assessment of contaminants in fish involves six components:

- Chemical occurrences in fish
- Geographic distribution of contaminated fish
- Individual exposure assessment
- Population exposure assessment
- Multiple species exposure
- Multiple chemical exposure.

Each of these components is discussed below.

2.4.1 Chemical Occurrences in Fish

Contaminant concentrations vary among different fish species, size classes within a fish species, fish tissues, and contaminants present in ecosystems. Chemical contaminants are not bioaccumulated to the same degree in all fish species. In addition, chemical contaminants are not distributed uniformly in fish tissues; some toxicants bind primarily to lipids and others to proteins. Fatty and/or larger fish

often contain higher organic contaminant concentrations than leaner, smaller fish. The correlation between increasing size (age) and contaminant tissue concentration observed for some freshwater fish species (Voiland et al., 1991) may be less evident in estuarine and marine species (U.S. EPA, 1995; Phillips and Spies, 1988). Knowing how contaminants differentially concentrate in fish enables risk managers to advise fish consumers on alternative fishing practices (consumption of smaller individuals in a contaminated species) and cooking practices (including skinning, trimming, and cooking procedure) to minimize exposure.

Volume 1 of this series, *Guidance for Assessing Chemical Contamination Data for Use in Fish Advisories, Volume 1: Fish Sampling and Analysis* (U.S. EPA, 2000a), provides comprehensive guidance on cost-effective, scientifically sound methods for use in fish contaminant monitoring programs designed to protect public health. It is designed to promote consistency in the data states use to determine the need for fish consumption advisories. By standardizing protocols across regions, risk managers can avoid significant differences in advisories when actual concentrations of chemical contaminants in fish are very similar.

Volume 1 suggests that screening values be compared to annual fish sampling and analysis data to determine where problems may exist. The document also discusses sampling design and field procedures for collecting and analyzing fish and shellfish tissue samples for pollutant contamination. It discusses specific cost-effective analytical methods, quality assurance/quality control (QA/QC) procedures, and identifies certified reference materials and federal agencies that conduct interlaboratory comparison programs. Procedures for data reporting and analysis that are consistent with the development of the National Fish Tissue Data Repository (NFTDR) are also included.

Information on contaminant distributions in different types of fish and fish tissues and across geographic areas is required for a number of reasons. Differential concentrations of contaminants in fish tissues and across fish species affect fish consumer exposures due to differences in individual consumption practices. The geographic origins and modes of transport of chemical contaminants determine the extent and location of these chemicals in fish. Identifying areas of high contamination enables readers to choose initial screening sites and focus limited resources on fisher populations most at risk from consuming contaminated fish.

Many readers will have information on the geographic distribution of contaminants in fish from their fish sampling and analysis programs. Others may need to identify areas of likely contamination. This topic is also discussed in Volume 1. This section briefly reviews likely patterns of chemical distribution based on chemical properties and other factors. Such geographic information is important in population exposure assessment and for risk communication; readers are encouraged to develop maps showing areas of fish contamination that, combined with demographic information, help target exposed fisher populations for additional risk communication and

outreach efforts. Mapping tools available for tracking locational data on fish contaminants, fish advisories, or other related data are discussed in Section 6.

2.4.2 Geographic Distribution of Contaminated Fish

The geographic extent of the fish contamination is an important element in determining the need for further action. These data are also useful in performing population exposure assessments and risk characterization. Two types of information are particularly useful: the locations where contaminated fish have been found and the sources of potential contamination. The first type of information is provided by fish sampling and analysis programs. When such data are absent, several available sources can help locate sites of possible contamination by the target analytes. Section 2.2.1.2 contains a list of sources of information on potential fish contaminants. Additional information on site selection for fish sampling and analysis programs is provided in Section 6 of Volume 1.

2.4.3 Individual Exposure Assessment

Individual exposure assessments provide descriptions of the overall, media-specific, or site-specific exposure of an individual. These may be normative or high (e.g., highly exposed individual) estimates or be based on actual measurement data.

Individual exposure assessments use essentially the same equation as that used with fish contaminants to calculate fish consumption limits, although they solve for different variables:

$$E_m = \frac{C_m \bullet CR}{BW} \qquad (2\text{-}2)$$

where

E_m = individual exposure to chemical contaminant *m* from ingesting fish (mg/kg-d)
C_m = concentration of chemical contaminant *m* in the edible portion of fish (mg/kg)
CR = mean daily consumption rate of fish (kg/d)
BW = body weight of an individual consumer (kg).

Individual exposure assessments use data on known chemical residues in fish (C_m) and on human consumption patterns (CR/BW) to estimate exposure (E_m) for hypothetical individuals within given populations (see Equation 2-2). Conversely, the consumption limits described in Section 3 and provided in Section 4 use the data on known chemical residues in fish (C_m) combined with dose-response data (CSFs and RfDs, which correspond to maximum "safe" exposure) to estimate maximum safe human consumption rates (CR_{lim}/BW; see Equations 3-1 and 3-3).

This document uses this equation only to calculate fish consumption limits. Volume 3 of this series provides additional information on estimating individual and population exposures for purposes of generating risk estimates used in risk management decisionmaking. Individual exposure assessment is discussed in this volume for informational purposes only; it is not used directly in developing the fish consumption limit tables. Increased detail is provided where information is shared between individual exposure assessments and consumption limit calculations.

Depending on the geographic region and/or contaminant involved, contaminant concentrations in fish (C_m) are determined by sampling and analysis programs conducted by public health departments, natural resource agencies, environmental protection agencies, FDA, EPA, and/or agricultural departments. The consumption rate (CR) represents the amount of fish an individual in a given population eats in a day and may be estimated through fish consumption surveys. Finally, the daily dose is divided by the consumer body weight (BW) to arrive at individual exposure.

By using information on the number of individuals in each exposure category, risk managers may aggregate exposures determined in individual assessments to derive population exposure assessments. Population exposure assessments can allow readers to focus limited resources on those contaminants or areas that may pose the highest risks to a large number of persons or to particular populations of interest (e.g., subsistence fishers).

Note: The consumption limits described in this document assume that no other exposure to any of the 25 target analytes occurs. However, a potentially significant source of contaminant exposure is the consumption of commercially caught freshwater, estuarine, and marine fish. Consumption limits for non-commercially caught fish may not be sufficiently protective of consumers of both commercially and noncommercially caught fish. It is recommended, therefore, that, whenever possible, readers take other significant sources of exposure into account when conducting exposure assessments and/or developing consumption limits.

2.4.3.1 Exposure Variables—

Equation 2-2 uses three parameters to calculate individual exposure (E_m) to fish contaminants from noncommercially caught fish: consumption rate (CR), consumer body weight (BW), and contaminant concentration (C_m). Equations 3-1, 3-2, and 3-3 in Section 3 also use body weight and contaminant concentration and meal size (MS) in developing consumption limits. With the exception of C_m, which is determined through sampling and analysis programs, these parameters are discussed below.

Body Weight

Both consumption limit and exposure assessment calculations require specific body weights (usually in kilograms) for individuals in order to derive the contaminant daily dose in milligrams contaminant per kilogram consumer body weight

per day (mg/kg-d). The *Exposure Factors Handbook* (U.S. EPA, 1990a) recommends values for average weights for children and adults, based on the second National Health and Nutrition Examination Survey (NHANES II). Conducted from February 1976 to February 1980, NHANES II surveyed approximately 28,000 noninstitutionalized U.S. civilians aged 6 months to 74 years. The survey oversampled population groups thought to be at risk from malnutrition (low-income individuals, preschool children, and the elderly). Adjusted sampling weights were then calculated for age, sex, and race categories to reflect body weight values for the estimated civilian, noninstitutionalized U.S. population. Although EPA recommends these values for typical Americans, they may not adequately represent some population groups (e.g., Asian-Americans, who are generally smaller in stature and have a lower body weight than the average U.S. citizen). If more accurate data on average body weights of local fisher populations are available, readers are encouraged to use them in place of the default values.

Table 2-2 lists recommended body weight values for adults, women of reproductive age (women from 18 to 45 years of age), and children. These values are derived from data in the *Exposure Factors Handbook* (U.S. EPA, 1990a); the values listed for adults are used directly, while the value for women of reproductive age represents an arithmetic average of three age groups (18-25, 26-35, and 36-45), and the value for children is an arithmetic average of two groups (children <3 and children from 3 to <6). A more protective body weight value for women of reproductive age would be to use the lower 95th percentile body weight of women ages 18 to 25 years (Blindauer, 1994). In this document, however, a body weight of 70 kg was used for all adults, including women of reproductive age, to calculate the consumption limits shown in Section 4.

Meal Size

Meal size is a critical parameter in expressing fish consumption limits, though it is not used directly in calculating exposure (which is expressed in mg/kg-d). Consumption limits expressed in terms of meals per given time period are more

Table 2-2. Mean Body Weights of Children and Adults

Age Group	Mean Body Weight (kg)		
	Males	Females	Males and Females (Averaged)
Adults	78	65	**70**
Women of reproductive age	-	64	-
Children <6	15	14	**14.5**

Source: Adapted from U.S. EPA (1990a).
Bolded values were used in the development of consumption limit tables in Section 4.

understandable than those expressed in kilograms per day. Meal size estimates can also be used to calculate peak acute exposures to fish contaminants (although that information is not used in this document).

Several values for average meal size have been determined through both non-commercial and commercial fish consumption surveys, although these values may not be comparable across studies. For instance, some surveys report meal sizes on the basis of whole, raw fish, while others refer to uncooked fillets. Still others do not specify whether the value is based on uncooked or raw fish. The average meal size most often cited is 227 g, or 8 oz (Anderson and Amrhein, 1993; Minnesota Department of Health, 1992; Missouri Department of Health, 1992; U.S. EPA, 1999a). This meal size corresponds to the value used in the Michigan Anglers Survey, in which individuals were asked to estimate their average meal size compared to a picture showing an 8-oz (227-g) fish meal (West et al., 1989). The same meal size also represents the high-end range used by Dourson and Clark (1990), which is based on the value used in the EPA *Region V Risk Assessment for Dioxin Contaminants* (U.S. EPA, 1988). A discussion of fish consumption surveys is provided in Appendix B.

EPA suggests using a default value of 8 oz (227 g) of cooked fish fillet per 72-kg consumer body weight as an average meal size for the general adult population for use in exposure assessments and fish advisories if population-specific data are not available. This meal size, however, is not likely to represent higher-end exposures, where persons consume more than the average amount in a given meal. These larger meal sizes are important to consider in cases where acute and/or developmental effects from consumption of contaminated fish are of concern.

Meal size can also differ for other population groups and must be scaled accordingly. Children and adolescents, for example, often consume more fish per kilogram body weight than adults. A national food consumption survey conducted by the U.S. Department of Agriculture (USDA) was used to scale the adult meal size value to child meal size values (USDA, 1983). The USDA survey evaluated consumption patterns of approximately 38,000 U.S. citizens over 3-day periods from 1977 to 1978 and is the largest consumption survey of its kind that includes fish. The survey results included meal size data for 10 age groups. Although respondents included both fishers and nonfishers, relative differences reported between the age groups were used to approximate differences in average meal size between different age categories within fisher populations in the current assessment. For children younger than 4 years old, EPA suggests using a default meal size of 3 oz (85 g) if population-specific data are not available. For older children, modifications in consumption limits can be made to tailor limits to their body weights and consumption patterns. The methodology to do so is discussed in Section 3.

Consumption Rate

Although it is necessary to estimate the overall average consumption rate in order to characterize risk, this information is not necessary to provide risk-based consumption limits as in Section 4. Consumption rate information is primarily used to make risk management decisions regarding the allocation of resources and implementation of various public health protection strategies related to consumption of contaminated fish. Fish consumption patterns and methods for evaluating the resulting risks are presented in Appendix B. However, due to the significant variability in fish consumption among individuals, readers are urged to conduct their own surveys to determine actual consumption levels when accurate risk estimates are required.

2.4.3.2 Averaging Periods Versus Exposure Durations—

The exposure duration is the time period over which an individual is exposed to one or more contaminants. In the case of an individual fisher, the exposure duration is equivalent to the time interval over which he or she catches and consumes fish. However, fish consumption is frequently not constant over the time period of interest for examining certain health endpoints (e.g., lifetime for chronic effects), particularly for short-term or seasonal recreational fishers. For short-term or seasonal fishers, periods of consumption must be averaged with periods during which no consumption occurs to correspond with the time periods over which chronic health effects are likely to develop. For example, the method usually employed to obtain a lifetime average daily dose is to divide the cumulative dose over an individual's lifetime by the number of days in an average lifetime. For developmental and subchronic effects, the time period over which dose is averaged is much shorter. Consequently, the time periods of concern chosen for use in exposure assessments are called averaging periods.

For pollutants with carcinogenic properties, EPA currently assumes that there is no threshold below which the risk is zero (i.e., for any nonzero exposure, there may be some increase in cancer risk). There is no current methodology for evaluating the difference in cancer risks between consuming a large amount of the carcinogenic contaminant over a short period of time and consuming the same amount over the course of one's lifetime. EPA's current cancer risk assessment guidelines recommend prorating exposure over the lifetime of the exposed individual (U.S. EPA, 1986c) and EPA's proposed cancer guidelines do not address this issue (U.S. EPA, 1996b). To provide usable and easily understood consumption guidance, the unit of 1 month was used as the basis for expressing meal consumption limits for all carcinogenic health endpoint tables shown in Section 4. The limits for carcinogens are based on the assumption that consumption over a lifetime, at the monthly rate provided, would yield a lifetime cancer risk no greater than an acceptable risk of 1 in 100,000.

The likelihood of occurrence of noncarcinogenic effects associated with chronic exposure is evaluated through the use of RfDs (as discussed in Section 2.3).

Exposure below the RfD is assumed by EPA to be without appreciable risk over a lifetime of exposure. Consequently, the relevant averaging time for both carcinogenic and noncarcinogenic chronic exposure is a lifetime.

As with the carcinogens, the unit of 1 month was used for all tables shown in Section 4 as the basis for expressing meal consumption limits based on chronic systemic health effects and developmental effects. The limits for noncarcinogens are based on the assumption that consumption over a lifetime, at the monthly rate provided, would not generate a health risk. Although consideration was given to inclusion of an acute exposure period (e.g., 1 day), insufficient information on 1-day consumption and acute effects is available to evaluate acute exposure for many of the fish contaminants at this time.

One or more large meals consumed in a short period (constituting an acute exposure or "bolus dose") may cause effects substantially different than those associated with long-term low-level exposures. EPA does not currently have a methodology that has Agency-wide approval for dealing with high-level short-term exposures. Consequently, no specific risk values have been provided in this series to evaluate such exposures (although in future revisions such data may be available). A qualitative summary of acute toxicity effects of the target analytes is provided in Section 5. In addition, there are numerous toxicity databases and books that describe the acute toxicity symptoms of the most common contaminants. State agencies may refer to these sources or their local poison control center for guidance on this topic.

Developmental toxicity is often evaluated in animal studies via bolus dose studies, with exposure over 1 to 3 days, because many adverse developmental effects are associated with exposures during critical developmental time periods. Severe developmental effects including stillbirths have been associated with exposures to high levels of pesticides in foods. Information is provided in a NAS report on developmental toxicity on special characteristics of infants and children that cause their exposures and risks to differ from those of adults (NAS, 1993). If very high exposures are likely to occur, state agency staff are encouraged to consider this exposure scenario in more detail.

2.4.3.3 Multiple Species Exposures—

Local information on the consumption of multiple fish species and fish contamination levels can be used to assess exposure and establish consumption limits for consumers with multiple species diets. Equation 2-2 can be modified, as follows, to consider consumption of multiple species:

$$E_{m,j} = \frac{\sum (C_{m,j} \bullet CR_j \bullet P_j)}{BW} \qquad (2\text{-}3)$$

where

$E_{m,j}$ = individual exposure to chemical contaminant *m* from ingesting fish species *j* (mg/kg-d)
$C_{m,j}$ = concentration of chemical contaminant *m* in the edible portion of fish species *j* (mg/kg)
CR_j = consumption rate of fish species *j* (kg/d)
P_j = proportion of a given fish species in an individual's diet (unitless)
BW = consumer body weight (kg).

Regional or local angler surveys that estimate catch data and measure fish consumption can provide data on the mix of species eaten by particular populations. One study, the Columbia River Survey (Honstead et al., 1971), is described in Rupp et al. (1979). This survey calculated the total number of each species of river fish eaten by residents in the area. Although the information is a composite of fishers and nonfishers, the data could be used to estimate the mix of species that an average individual in the area would eat. The Columbia River Survey also includes data on the mix of species consumed by each of 10 individuals who ate the most fish during the year, which might be used to estimate exposure for high-risk individuals. Readers may wish to incorporate similar information from local fish consumption surveys into multiple-species exposure assessments and/or consumption limits.

2.4.3.4 Multiple Chemical Exposures—

Fish can be contaminated with more than one chemical, and individuals can consume multiple species of fish that contain different contaminants. In these cases, exposure across species needs to be calculated separately for each chemical; these exposures can then be combined in a variety of ways to estimate risks of different health endpoints. Sections 3.4 and 3.5 provide methods for calculating consumption limits for individuals exposed to multiple contaminants in a single species and multiple species. Readers also may adapt these calculations (Equation 2-3) to estimate individual exposure to multiple fish contaminants.

2.4.4 Population Exposure Assessments—

Population exposure assessments are not directly used in developing risk-based consumption limits. Rather, they are primarily used in risk management (e.g., to prioritize resource allocation) and to identify particular subpopulations of interest (e.g., in areas where subsistence fishing is common).

2.4.4.1 Categories of Population Exposure Assessment Information—

Table 2-3 lists the categories of information necessary to evaluate population exposures. Categories 1 and 2 cover basic demographic data that are often available from the U.S. Census Bureau. Categories 3 and 4 relate directly to fish contamination and consumption patterns and should be collected at the local level

Table 2-3. Categories of Information Necessary for a Population Exposure Assessment

Category	Information
1	Age, sex, and body weight distribution of the population (demographic data)
2	Average and maximum residence time in an area where exposure is likely to occur
3	Consumption patterns over the population distribution
4	Levels of contaminants in fish tissue by species, age (size class), and waterbody
5	General nutritional status of various segments of the population
6	Food preparation and cooking methods
7	Concurrent exposures from other sources to fish contaminants (e.g., occupational, in drinking water or other foods, airborne, soil)

if possible. Consumption patterns are discussed in greater detail in Appendix B. Volume 1 of this series provides guidance on sampling and analysis for fish contaminants as specified in Category 4.

Categories 5, 6, and 7 deal with information, primarily available at the local level, that is important for overall risk assessment. If local information is absent, however, data from populations similar to those of concern may be used. If no local data are available, national data may be used. There are serious limitations to the use of national data, which are discussed in Appendix B. Using data from other populations introduces uncertainties. For example, assuming adequate nutritional status may not be appropriate in an area where nutrition may be impacted adversely by restrictive advisories. Many chemicals pose greater risks to people with poor nutritional status (see Section 5 for a chemical-specific discussion). Consequently, the use of simplifying assumptions may lead to an underestimate of risk (under other circumstances risks may be overestimated). If poor nutrition is suspected in populations with high consumption (e.g., sport or subsistence fishers), obtaining local information is particularly important.

Category 6 deals with information available primarily at the local level on fish preparation and cooking methods. For some chemical contaminants, skinning and trimming the fillet as well as cooking can reduce exposure intake. The effect that fish preparation and various cooking procedures has on reducing contaminant exposure is detailed in Appendix C.

Category 7, which deals with multimedia exposure assessment, may be significant in some areas. Concurrent exposures are important in estimating overall risk and in determining whether a critical threshold has been reached for threshold effects (i.e., noncarcinogenic effects). Information should be obtained through local sampling programs if possible. If local industries contribute to multimedia and occupational exposures, the overall assessment may be particularly important. More information on overall exposure assessment and sources of additional information are provided in Section 2.4.5.6.

This information allows the risk assessor to calculate exposure estimates for a population. The information may be collected on various groups within the population (subgroups) who have different consumption rates, culinary patterns, body weights, susceptibilities, etc.

Identification of susceptible subpopulations is necessary to protect these individuals adequately. For pregnant and nursing women, women planning to have children, small children, and people with preexisting health problems, the risk from consuming contaminated fish may be greater than for healthy men and healthy nonreproducing women. Some contaminants are particularly damaging during prenatal or postnatal development. Persons with preexisting health problems may be particularly susceptible to contaminants that interact with their medications or that are toxic to the organ systems affected by disease. For these people, low levels of contaminants may exacerbate their conditions, leading to health effects not generally experienced by healthy adults. (The special susceptibilities associated with the various target analytes are discussed in Section 5.) Due to the above factors, obtaining information on the exposure patterns of susceptible subgroups is important.

In assembling and reviewing this information, keep in mind the goals of the risk management activities for the population being evaluated. Decisionmakers should be aware of the information available and the type of information that will enable them to identify those at greatest risk. If resources are limited and only one population subgroup is to be evaluated, evaluating the most highly exposed subgroups rather than the "average" portion of a population may be advisable. The highly exposed groups will provide an estimate of the worst-case scenario. These groups are probably at the greatest health risk (if there is a risk) unless other groups have more susceptible members. Considering the population exposed at an "average" level is also important, but, under most circumstances, they will not be the highest risk group.

Uncertainties and assumptions made in assembling exposure data should be noted and conveyed to the decisionmakers. It is important to indicate whether the uncertainties and assumptions are expected to provide overestimates or underestimates of exposure and risk.

2.4.4.2 Categorizing Exposure Levels*—

Exposure assessments for a population describe a distribution of individual exposures. The distribution may be for a geographic area or a particular group of people (e.g., sport fishers at a particular lake, subsistence fishers in a specific tribe). It is usually advisable to obtain information on the range of average to high exposures. Gathering this information allows the decisionmakers to take actions appropriate for the majority of the population and protective of its most at-risk individuals. If sufficient resources to evaluate various aspects of exposure exist, it is recommended that exposure descriptions include the following (Habicht, 1992):

- Individuals at the central tendency and high-end portions of the exposure distribution
- Highly exposed population subgroups
- General population exposure.

This information can be used to estimate the range of risks from the average risk (central tendency) to the most at-risk individuals. The 1992 *Guidelines for Exposure Assessment* provide detailed and specific guidance regarding quantification and description for individuals and populations with higher than average exposure (U.S. EPA, 1992a). This guidance document was the source of information on the various exposure categories discussed below. As with all information provided in this document, these recommendations are provided for reference purposes; state, local, and tribal governments may elect to use any information they determine is appropriate in establishing fish advisory programs.

Central Tendency

The central tendency represents the "average" exposure in a population. This value can be derived from either the arithmetic mean or the median exposure level. Figure 2-2 shows the upper half of a normal population exposure distribution. When exposure is distributed normally as in the figure, the mean and median will coincide at the 50th percentile. When the exposure distribution is skewed, however, the mean and median may differ substantially.

Due to the skewed nature of many exposure distributions, the arithmetic mean may not be a good indicator of the midpoint of a distribution (e.g., the 50th percentile). Under these circumstances, a median value (e.g., the geometric mean) may provide more appropriate information (Habicht, 1992).

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* Populations who eat only commercial marine or freshwater fish are not addressed in this guidance because they are protected through regulation of commercial fish by the U.S. FDA. Exposure values designed to address consumers of commercially caught fish are not recommended for use in developing fish advisories.

Information on the central tendency of a population's exposure may be most useful in evaluating overall cancer risks and determining the average behavior within a group. It is not as useful in evaluating noncancer risks because such risks are based on a threshold for effects. People exposed at levels above the "average" level may have exposures exceeding the threshold for health effects. If only "average" levels are considered, the risks to these people will not be considered. In a normally distributed population, approximately 50 percent of the population will have exposures above the "average" level.

High-End Portions of the Risk Distribution

The high-end estimates of exposure are those between the 90th and 99.9th percentiles of the actual (either measured or estimated) distribution. They are plausible estimates of individual exposures at the upper end of the exposure distribution. Individuals at the high end of the exposure, dose, and risk distributions may differ, depending on factors such as bioavailability, absorption, intake rates, susceptibility, and other variables (U.S. EPA, 1992a). Risks may be reported at a distribution of high-end percentiles such as the 90th, 95th, and 98th.

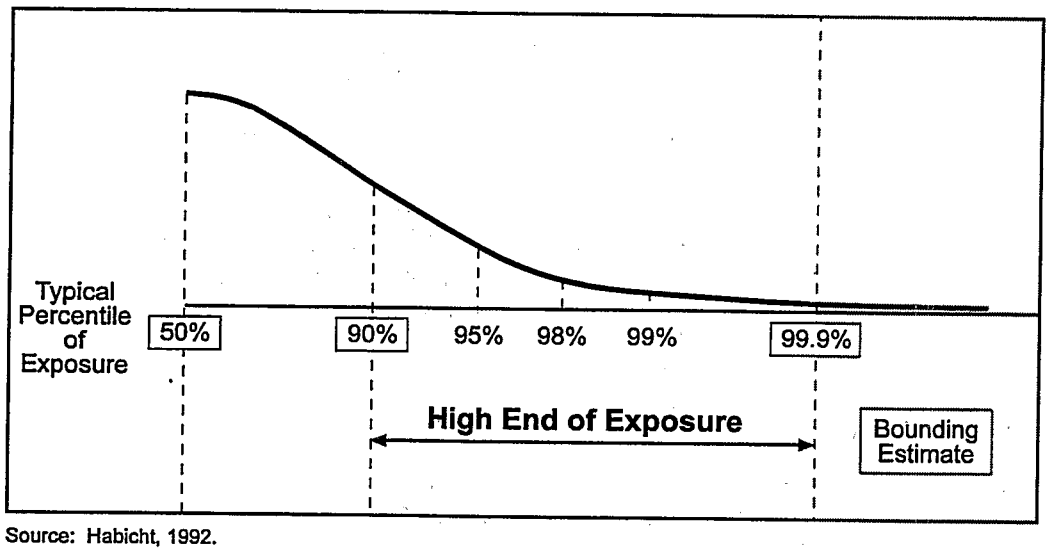
Figure 2-2 shows the location of the high-end exposure segment on a normal distribution. High-end exposure estimates include values falling within the actual exposure distribution rather than above it. If all factors (e.g., body weight, intake rates, absorption) are set to values maximizing exposure, an overestimate of exposure will likely result (U.S. EPA, 1992a). High-end exposure estimates are very useful in estimating population risks and establishing exposure limits because they provide a plausible worst-case scenario.

Highly Exposed Subgroups

When a subgroup is expected to have significantly different exposures or doses from that of the larger population, it is useful to evaluate their exposures.

Bounding Estimates

A bounding estimate of exposure is greater than the highest actual exposure, corresponding roughly to the upper 99.9th percentile of the population (see Figure 2-2). Bounding estimates are used primarily for screening purposes. Their utility is in providing the decision-maker with a maximum estimate encompassing the entire population (Habicht, 1992). They are most useful in eliminating pathways from further consideration (e.g., if the maximum shows no risk) rather than determining that a pathway is significant (U.S. EPA, 1992a). Although bounding estimates are not recommended for use in estimating risks associated with fish consumption, they may be useful in evaluating the upper bound of risk. Those with no risk at the upper bound can be eliminated from further concern.



Source: Habicht, 1992.

Figure 2-2. Schematic of exposure categories in upper half of a normal population distribution.

Data Gaps

The specific information collected for a population exposure assessment will depend on the goals and resources of the risk managers. Under ideal circumstances, detailed local information would be obtained on each category. When resources are limited, however, assumptions may be necessary for some categories of information. The EPA publication, *Guidelines for Exposure Assessment* (U.S. EPA, 1992a), provides the following options for addressing these data gaps:

- Narrow the scope of the assessment, particularly if the pathway or route with limited data makes a relatively small contribution to the overall exposure.
- Use conservative assumptions. Conservative assumptions, such as choosing a value near the high end of the concentration or intake range, tend to maximize estimates of exposure or dose. If an upper limit rather than a best estimate is used, express this clearly with the exposure estimate.
- Use models to estimate values and check the conservative nature of assumptions.
- Use surrogate data in cases where a clear relationship can be determined between an agent with usable data and the agent of concern.

- Use professional judgment, especially in cases where experts have years of observation of similar circumstances.

Data gaps can add significantly to the uncertainty associated with exposure and risk assessment. Assumptions may be made or data from nonlocal sources may be used to fill gaps. Selecting health-conservative data will yield health-conservative exposure and risk estimates; alternatively, selecting less conservative data will yield less conservative exposure and risk estimates. Decisions concerning data use will affect risk estimates and may determine where fish advisories are to be provided.

2.4.5 Uncertainty and Assumptions

Readers must evaluate if the exposure assumptions made in deriving risk-based consumption limits provide adequate protection to sensitive or highly exposed populations. Some of the assumptions associated with the exposure parameters can lead to underestimation of total risk (and therefore overestimation of allowable consumption). For example, the calculation of exposure to a given chemical may ignore background sources of that chemical. For chemicals that exhibit health effects based on a threshold level, the combination of background contaminant concentration and fish consumption exposure may exceed the threshold. The use of average fish contaminant concentrations to estimate exposure is another assumption that could underestimate risk if an individual regularly consumes fish from a contaminated waterbody.

Exposure assumptions may not always be sufficiently conservative. However, these assumptions may be balanced by overly conservative assumptions in other aspects of the assessment. Readers need to judge if the overall margin of safety afforded by the use of uncertainty factors and conservative assumptions provides satisfactory protection for fish consumers.

2.4.5.1 Chemical Contaminant Concentrations in Fish—

Exposure quantification requires information concerning fish contamination levels. Volume 1 contains a discussion of sampling and analysis that provides guidance on planning and carrying out a sampling program. The document recommends a two-tiered strategy for monitoring waterbodies for contaminated fish, including:

- Screening waterbodies routinely to identify locations where chemical contaminants in fish exceed levels of concern for human health

- Sampling waterbodies intensely where screening has identified elevated levels to determine the magnitude and geographic extent of the contamination.

Fish contamination varies considerably by waterbody and by fish species and size class. Therefore, even populations with similar consumption patterns may have differing exposures, depending on the contaminant levels in the waterbody used

for fishing. To capture these site-specific distinctions, population exposure analyses rely on the use of waterbody-specific data from local surveys on fish contamination. Relevant data from these surveys include levels of contaminants by fish species and size (length and/or weight).

Accurate determination of the chemical concentrations in fish is an important area of uncertainty that is discussed in detail in Section 8 of Volume 1 in this series. The limit of detection (LOD) for each of the 25 target analytes is given in the footnotes of the consumption limit tables in Section 4 and in Appendix F.

2.4.5.2 Dose Modifications Due to Food Preparation and Cooking—

EPA recommends the use of dose modification factors for setting health-based intake limits only when data on local methods of preparation and their impact on contaminant concentrations are available.

Several sources of uncertainty are associated with the dose modification factors presented in this guidance. Preparation methods are frequently unknown. The effectiveness of different preparation and cooking techniques in reducing contaminant concentrations varies greatly. In addition, information is limited regarding the toxicity of the degradation products generated during the heating of contaminated fish. Percentage reductions observed at one level of contamination may or may not be expected to hold true for different levels of contamination. These sources of uncertainty could lead to either under- or overestimates of exposure. Additional discussion on dose modification is provided in Appendix C.

2.4.5.3 Body Weight—

The estimates for body weight use several assumptions that affect the accuracy of the exposure assessment. First, the figures for body weight are taken from data collected in the late 1970s. Body weights can vary dramatically over time, and therefore the values may be an over- or underestimate of current body weights. In addition, average body weights were not distinguished for various ethnic populations. For example, Southeast Asian-American subsistence fishers may have slighter body frames and lower body weight than the general U.S. adult population. Compared to other assumptions, however, body weight values are associated with relatively low variability and uncertainty.

2.4.5.4 Consumption Rate and Averaging Period—

Fish consumption data are a necessary component of a population exposure assessment. Ideally, fish consumption information will include descriptive demographic information on the size and location of the fishing population using specific waterbodies; the age and sex of those consuming the fish; the size and frequency of the meals (over the short and long term); and the species of fish caught, portions of the fish consumed, and methods of fish preparation and

cooking. This section discusses the selection of fish consumption data and presents results obtained in numerous studies.

In general, fish consumption studies describe:

- Species of fish consumed by various subgroups within a population
- Temporal patterns of consumption
- Variety of preparation and cooking methods used by different populations.

Many studies provide some, but not all, of the above data.

Consumption patterns may differ significantly both within and between populations. Studies of fish consumption indicate that some groups within the general U.S. population may consume considerably greater quantities of fish than other members of the population.

This document focuses on noncommercial fishers (i.e., people who fish and consume their catch) and the people with whom they share their catch. This subpopulation may include sport fishers and subsistence fishers. Sport fishers include all noncommercial fishers who are not subsistence fishers. (They have also been referred to as recreational fishers.) Subsistence fishers, as previously defined, include people who rely on noncommercial fish as a major source of protein. Subsistence fishers may also catch fish for commercial sale; however, this activity comes under the jurisdiction of the FDA and is not considered in this document. There is often not a clear distinction between sport and subsistence fishers. Many individuals would not consider themselves subsistence fishers but do rely on noncommercially caught fish for a substantial portion of their diet. The mean or median estimates of consumption rates and patterns generally address the more casual sport fisher; the high-end estimates (upper percentiles) and patterns address the consumers at greater risk. In many of the older surveys, the high-end estimates were used as estimates of the consumption rates for all subsistence fishers. These estimates, however, may be inaccurate because some surveys excluded subpopulations that tended not to register for fishing licenses.

The two most sensitive variables involved in calculating individual exposure often are consumption rate and averaging period. Consumers of noncommercially caught fish differ immensely in their consumption habits. Some may consume fish for 1 week during a year or for several weekends each year (e.g., as recreational or sport fishers). Others may consume fish for much longer periods during a year (seasonal fishers) or may rely on fish year-round as a major part of their diet (subsistence fishers). Within these groups, some individuals are more susceptible to contaminants, including women of reproductive age, children, and persons with preexisting health problems.

Short-term recreational and seasonal fishers are assumed to be exposed to contaminated fish for only part of the year. Recreational vacation fishers are those who eat fish only a short time during the year. Seasonal fishers are often those

who live near a lake or river, who fish regularly throughout a season (e.g., summer fishing, winter ice fishing), and who eat their catch throughout the season but do not rely on fish as a major dietary staple during the rest of the year. Sport fishers have been shown to have higher fish consumption rates than the general U.S. population (U.S. EPA, 1989a); the potential for large exposures over short time periods makes them especially susceptible to acute, developmental, and subchronic health risks as compared to nonfishers.

Subsistence fishers eat fish as a major staple in their diets for a greater percentage of the year than do recreational fishers. In addition, subsistence fishers may prepare fish differently than do other groups; they may use the whole fish in soups or consume more highly contaminated tissues, such as the liver, brains, and subcutaneous fat. Both their longer exposure durations and consumption habits make many subsistence fishers more likely to be affected by cancer and adverse chronic systemic, developmental, and reproductive health effects resulting from fish contaminant exposure than those who do not fish or fish for shorter periods of time. Some populations that may subsist on noncommercially caught fish year-round, including certain Native American tribes, may be at higher risk (see Section 1.3). In addition, certain recent immigrants accustomed to self-sufficiency and fishing (particularly Asian-Americans) and economically disadvantaged populations may be at risk since much of their fishing might be expected to occur in more urbanized areas with higher levels of water pollution.

Any estimates of typical fish consumption patterns in a population include certain assumptions. West et al. (1989) described variations in fish consumption in communities in Michigan by ethnicity, income, and length of residence. In general, African Americans and Native Americans ate more fish than Caucasians; older individuals ate more fish than younger individuals; individuals with lower incomes tended to consume greater quantities of fish than individuals with higher incomes; and longer-term residents of the communities tended to consume more fish than other individuals. To the extent that members of the target population have characteristics associated with higher-than-average consumption, the recommended consumption values may underestimate their consumption. Unless surveyed specifically, subsistence fishers may be underrepresented by available surveys. Surveys associated with the issuance of fishing licenses are traditional mechanisms used in surveying fish consumption behavior; however, subsistence fishers may not apply for fishing permits or licenses. For example, Native Americans on reservations do not need fishing permits, and often times other groups (e.g., recent immigrants or the elderly) may not know that they need to have a license or find them too expensive to buy.

In addition, fish consumption limits that are based on single species for single chemicals do not account for exposures from multiple chemicals contaminating a single species or for multiple species diets. Consumption limits that focus on a single waterbody do not account for the possibility that consumption can occur from a variety of waterbodies. Single-species consumption limits also do not address related species that may be contaminated but were not sampled. Such

consumption limits could seriously underprotect persons who eat a variety of fish species from a number of waterbodies. Readers need to decide if consumption limits have a wide enough margin of safety to protect such consumers.

Other methodological assumptions may also lead to increased uncertainty. The calculation of consumption limits that express allowable dose as a number of meals over a given time period may neglect potential acute effects if consumption occurs over a very short time period. For example, a meal limit of two meals per month conceivably could be interpreted by consumers to mean that two meals on 1 day in a given month is allowable; this behavior could lead to short-term acute effects. This could be avoided by always expressing the consumption in terms of the time interval in which one meal may be consumed, (e.g., one meal per 2 weeks rather than two meals per month).

The use of averaging periods treats large, short-term doses as toxicologically equivalent to smaller, long-term exposures when comparing exposure to the toxicity reference value. This assumption may underestimate the potential toxicity to humans if the toxicity depends on a mechanism sensitive to large, intermittent doses. (This may occur more often with acute and developmental effects than with other effects.)

The averaging period of 1 month used in this document is based primarily on the types of health data currently available and the risk assessment methods recommended by EPA.

2.4.5.5 Multiple Species and Multiple Contaminants—

As discussed above, individuals often eat more than one species of noncommercially caught fish in their diet. If consumption limits or exposure assessments consider only a single-species diet, exposure from contaminated fish could be underestimated if other species have higher concentrations than the species under consideration. On the other hand, an exposure assessment may be overprotective if an individual's diet is a mix between contaminated and uncontaminated species. Use of local information to the extent possible to characterize mixed diets can prevent some of this uncertainty.

An individual may consume a given species that is contaminated with multiple chemicals, or may consume several species, each with different contaminants, or both. In these circumstances, exposure assessments that examine contaminants individually in individual species will underestimate exposure. This situation may be avoided by using Equation 2-3 in Section 2.4.3.3 for multiple species exposures and characterizing exposure to all known contaminants for a given individual. These exposure values can be used in methods described in Sections 3.4 and 3.5 to set consumption limits based on multiple species and multiple contaminants.

2.4.5.6 Other Sources of Exposure—

The methods described in this guidance consider exposure primarily from consumption of noncommercially caught fish. This approach may lead to an underestimation of exposure and, consequently, an underestimation of risk for some contaminants. Additional background exposure may cause individuals exposed to fish contaminants through other contaminant sources (e.g., other foods including commercially caught fish, drinking water, inhalation, or dermal contact) to experience adverse health effects and/or increased cancer incidence, even if they abide by the consumption rates recommended in fish consumption advisories. State agencies are encouraged to use available information on other sources of exposure whenever possible in setting consumption limits or to set the limits so that the allowable consumption accounts for only a fraction of the total allowable daily dose. These approaches would allow a margin of safety to guard against the potential for background exposure leading to exceeding the contaminant thresholds and/or maximum acceptable risk levels.

Nonfish Sources of Exposure

People may be exposed to one or more of the target analytes through sources or pathways other than noncommercially caught fish. These pathways include contaminants found in or on commercially caught fish, other food, drinking water, air, or other materials (e.g., soil or sediment).

Contact may often occur via more than one route of exposure (e.g., ingestion and dermal contact with contaminants in soil). The possibility of exposure via other pathways dictates that caution be used in setting health safety standards that do not take these other sources into account. The total exposures may cause the individual to exceed a safe exposure level, even though the exposure via fish consumption alone may be safe.

EPA is currently developing a relative source contribution method, which can be used to evaluate the amount of exposure contributed from various sources. The RSC method can be used to compare total contaminant exposure to that contributed by a specific source (e.g., fish); it is also useful in evaluating the total exposure from all sources. Information on the relative contribution of fish to overall exposure can be used to develop advisories that recommend sufficiently low exposure to ensure that total daily exposure is below an established targeted exposure level (e.g., an RfD). It is anticipated that information regarding the RSC method will be incorporated into future revisions of this document.

If state agencies have information about other pathways that may contribute significantly to exposure, then risk assessors are encouraged to use this information to calculate an appropriate total exposure limit. An alternative approach may be appropriate when nonfish exposures are suspected but have not been quantified. Depending on the magnitude of the suspected nonfish exposure, the fish advisory intake limits may be set at a level that accounts for some fraction of

the total allowable daily dose (e.g., 10, 20, or 30 percent). This allocates to the nonfish exposures the remaining percentage of the total exposure limit. The goal of both of these strategies is to ensure that the total pollutant exposure does not exceed the predetermined exposure limit.

One state program raised concerns that this series focuses on reductions in exposure via fish when exposures via multiple media may be occurring. However, it is important to note that, although exposure reductions can theoretically be made in any contaminated media, fish consumption may be the only source that can be readily reduced. It may not be possible to reduce air, drinking water, or other contaminant levels quickly, yet fish advisories have the potential for rapid exposure reduction in a population. Because fish consumption may contribute significantly to overall exposure for some population groups, modified consumption patterns may reduce overall exposure considerably. The relationship between fish and other contaminant source contributions to overall exposure should be communicated to risk managers so that both short- and long-range planning for exposure reduction can occur.

Estimating Total Exposure

The following discussion of exposure calculations is similar to that provided in Section 2.4.3 for individual exposure assessment. Exposure assessments provide descriptions of the overall, contaminant-specific, media-specific, or population-specific exposure of an individual or similarly exposed group. The following equation may be used to express exposure in a manner (mg/kg-d) that can be easily compared to an RfD or used to calculate cancer risks:

$$E_T = \frac{C_m \cdot CR}{BW} + E_A + E_W + E_F + E_O \qquad (2\text{-}4)$$

where

E_T = exposure from all sources (mg/kg-d) to contaminant (m)
C_m = concentration in the edible portion of fish (mg/g)
CR = mean daily consumption rate of fish (g/d)
BW = average body weight of the group (kg)
E_A = exposure from air sources (mg/kg-d)
E_W = exposure from water sources (mg/kg-d)
E_F = exposure from nonfish food sources (mg/kg-d)
E_O = exposure from other sources such as soil (mg/kg-d).

The equation expressing average daily consumption per kilogram in Appendix D can also be used to express fish-borne exposure (the C_m, CR, and BW portion of the equation). If the concentration in fish tissues is reduced due to preparation or cooking, the C_m value should be modified accordingly. Note that loss of

contaminants, with a proportional loss of fillet weight, will not change the concentration, which is expressed in milligrams of contaminant per kilogram of fish (mg/kg). Finally, the daily exposure (mg/d) is divided by consumer body weight (BW) to arrive at individual daily intake (mg/kg-d).

Body weights for various age groups of consumers are summarized in Table 3-5. If high estimates of body weight are used (e.g., adult male values), the risks and fish advisories will be less health conservative. If lower body weights are used (e.g., for small women), the risks and fish advisories will be more health conservative. When children's exposure is evaluated separately, their body weights should be used in conjunction with their estimated consumption rates. Risk managers may wish to consider the population they seek to protect with their fish advisories and whether they wish to protect the most at-risk groups in selecting a body weight. The selection of a body weight value will not have a substantial impact on the final values because the differences in body weight are relatively small (less than a factor of 2) compared to the uncertainties associated with most toxicological data.

Methods for estimating exposure to multiple contaminants and multiple fish species are discussed in Section 3 and equations are provided. These equations for individual exposure estimates can also be used for populations with similar exposure characteristics.

The type of exposure information collected and evaluated will depend on the resources and goals of the fish advisory program. Under ideal circumstances, pollutant levels would be evaluated in all media to which individuals may be exposed. For example, drinking water contaminant levels may be evaluated by the local water purveyor on a regular basis, and this information can be used to estimate waterborne exposure. When pesticides are the subject of concern, the evaluation may be more difficult because the levels present in food are not evaluated frequently at the local level. In addition to providing necessary information for the development of fish advisories, a total exposure assessment may highlight nonfish sources of exposure that merit attention.

Summarizing Exposure Information

Table 2-4 is a template for use in summarizing exposure information. It contains entry areas for fish exposure and exposure via other media. Risk assessors and managers may wish to use this template to organize their exposure data for various population groups or subgroups by chemical. The table is designed to organize data obtained from a specific location (e.g., an area adjacent to part of a waterbody or surrounding an entire waterbody). It is anticipated that the information entered in this table would be organized according to population subgroups with similar risk characteristics (i.e., a separate table should be pre-pared for children, women, etc).

As noted earlier, exposure levels may differ among subgroups within the fish-consuming population, depending on the species of fish that are caught, the

Table 2-4. Exposure Data Template

Location:

Population Subgroup (e.g., children, women 18-45 yr):

Population Size:

Body Weight:

Contaminant (level)	Fish Exposure Estimates (mg/kg-d)		Other Exposures								Subtotal of Other Exposures (mg/kg-d)		Total of All Exposures (mg/kg-d)	
			Air (mg/kg-d)		Water (mg/kg-d)		Food (mg/kg-d)		Other (e.g., soil) (mg/kg-d)					
	Central	High End[a]	Central	High End	Central	High End	Central	High End	Central	High End	Central	High End	Central	High End

[a]Risk assessors may wish to use a bounding estimate rather than a high end estimate (or both).

quantity of fish consumed, and the method of preparation and cooking used. In some cases, other factors will also affect exposure (e.g., seasonal changes in contaminant levels, the age of the fish). For purposes of risk assessment, specifically targeted risk information is obtained when the exposure of a population group is the same and their susceptibilities to the chemicals of interest are the same.

Estimates may be made for average, high-end, or upper-bound exposures within a population group. The use of average exposure values is not recommended because approximately one-half of the population will have exposures greater than the average (by definition). High-end estimates maximize the protection of public health. Upper-bound values may yield unrealistically high estimates of exposure and risk and are more appropriate for screening purposes than for risk assessment. Depending on the characteristics and needs of the fisher population, risk managers may elect to use the values they deem most appropriate.

The template provides entry areas for central tendency, high-end exposure, and bounding estimates. By including these categories of information, risk assessors can calculate a wider range of risk estimates and risk managers will have more complete information on which to base decisions concerning appropriate fish advisories. It may not be practical, however, to do three levels of calculations for each area, group, and contaminant. Table 2-4 does not contain a separate entry column for dose modifications due to cooking or cleaning. If these activities are known to reduce exposure, risk assessors may enter appropriately reduced exposure values to account for the dose reduction (see Appendix C for additional information).

The information entered in Table 2-4 will be used with risk values to calculate risks. For this reason, body weight, an essential component of risk calculations, is included. It is assumed that body weights corresponding to the population of interest will be used. For example, if specific calculations are to be carried out for women exposed to mercury, then a separate exposure table (or entry) for women, using appropriate consumption and body weight values, is advisable. Similarly, if risks are to be estimated for children or separate advisories developed for this group, information concerning children's exposure would be entered separately.

Exposures to contaminants from media other than fish may vary considerably for children in comparison to adults. Children have higher intakes of food, drinking water, soil, and air in relation to their body weight than do adults (NAS, 1993). In particular, infants consume significantly greater amounts of fluid than older children and adults. If contaminants are known or thought to occur in water supplies, infants may be a subpopulation for whom a separate analysis would be warranted, especially if water is used to mix formula. If the contaminant of concern is concentrated in human breast milk, breast-fed infants may be at greater risk.

Any exposure information that will modify the total exposure of the target population may be entered in the template to indicate differences from the larger

population. Situations such as workplace exposure, high periodic fish consumption, or other occurrences can be noted and evaluated for their impact on overall health and risk.

2.5 RISK CHARACTERIZATION

In general, the risk characterization step of the risk assessment process combines the information for hazard identification, dose-response assessment, and exposure assessment in a comprehensive way that allows the evaluation of the nature and extent of risk (Barnes and Dourson, 1988). Risk characterization can be used by risk managers to prioritize resource allocation and identify specific at-risk populations; it is also used to establish regulations or guidelines and to estimate individual or population risk. In this document, risk characterization has been used to develop the risk-based consumption limits provided in Section 4. The methods involved in developing consumption limits are described in detail in Section 3 and are not repeated here. When risk characterization is used to estimate individual or population risk, it serves to provide the risk manager with necessary information concerning the probable nature and distribution of health risks associated with various contaminants and contaminant levels.

Risk characterization in general has two components: presentation of numerical risk estimates, and presentation of the framework in which risk managers can judge estimates of risk (U.S. EPA, 1986a). A characterization of risk, therefore, needs to include not only numerical characterizations of risk, but also a discussion of strengths and weaknesses of hazard identification, dose-response assessment, and exposure and risk estimates; major assumptions and judgments should be made explicit and uncertainties elucidated (U.S. EPA, 1986a).

Numerical presentations of risk can include either estimates of individual risk or risks across a population. For example, for cancer risks, numerical estimates can be expressed as the additional lifetime risk of cancer for an individual or the additional number of cases that could occur over the exposed population during a given time period. Numerical risk estimates can also be expressed as the dose corresponding to a given level of concern (U.S. EPA, 1986a). These values can be used to estimate the environmental concentration or contact rate below which unacceptable health risks are not expected to occur. For the determination of fish advisories, the environmental concentration takes the form of screening values (i.e., contaminant concentrations in fish, as discussed in Volume 1) and the contact rate takes the form of risk-based consumption limits for specified populations.

Additional factors to be considered in risk characterization include:

- Possible exposure to the fish contaminant(s) from additional sources (e.g., air, water, soil, food other than fish, occupational activities)

- Characteristics of the population that may cause them to be more susceptible than the general population due to exposures to other toxicants, their general health and nutritional status, or their age

- An absence of sensitive study data for significant health endpoints such as developmental abnormalities, neurotoxicity, and immunotoxicity

- Recent toxicological study results indicating potential health risks not considered in the current risk values

- Information from local medical practitioners indicating likely risk-related health effects

- Economic, nutrition, or other hardships that may result from fishing restrictions.

Most of the factors listed above may lead a state agency to select more health-conservative risk values. For example, when information concerning a population (or subgroup) indicates that they have poor nutritional status that may increase their susceptibility to a local contaminant, state agencies may elect to modify the risk values they are using directly to provide an additional "margin of safety." Although the RfDs are designed to protect the most sensitive individuals, state agencies have discretion in determining the appropriate approach to protecting the public health of the people they serve.

The last factor listed above is an important risk management consideration. Use of health-conservative risk values will result in more restrictive fish advisories, which may have serious impacts on local populations.

In many cases the advantages and disadvantages of selecting specific risk values will affect members of communities in different ways. Groups at highest risk will be the most likely to gain from being alerted to health hazards (if they choose to take protective action). Alternatively, groups with relatively low risks may unnecessarily avoid consumption of food or participation in the sport of fishing, even though these may have overall benefits to them (i.e., the risks may be outweighed by the benefits).

There will invariably be tradeoffs between protection of public health and unwanted impacts of consumption restrictions. In some cases, the benefits of advisories may be a generally agreed-upon community value (e.g., preventing relatively high risks to pregnant women). Other cases may be less clear, especially when the scientific evidence on risks is limited. Decisionmakers are urged to consider the scientific information, fish consumption patterns, community characteristics, and other local factors carefully, along with potential positive and negative impacts of their decisions, when selecting risk values for screening or establishing advisory limits. Involving the affected communities in the decision-making process may be advisable under most circumstances.

See Appendix D for EPA's guidance for risk characterization, which discusses the basic principles of risk characterization.

2.5.1 Carcinogenic Toxicity

In this guidance series, screening values are defined as the concentrations of target analytes in fish tissue that are of potential public health concern and that are used as standards against which levels of contamination can be compared. For carcinogens, EPA recommends basing screening values on chemical-specific cancer slope factors. Screening values are used to establish the concentration in fish that can trigger further investigation and/or consideration of fish advisories for the waterbodies and species where such concentrations occur. The method for calculating screening values is given in Volume 1 of this series.

2.5.1.1 Individual Risk—

Using cancer slope factor and exposure data in mg/kg-d, cancer risks are calculated using the equation:

$$\text{Lifetime risk} = \text{exposure} \times \text{cancer potency} \qquad (2\text{-}5)$$

where

exposure = total exposure to a single contaminant from all sources (mg/kg-d)
cancer potency = upper bound of the lifetime cancer risk per mg/kg-d.

Note that cancer risk can be estimated for individual sources of exposure. Use of the total exposure value yields an estimate of lifetime cancer risk from all sources of a single contaminant. The resulting value is the upper bound of the estimated lifetime cancer risk for an individual or for a group with the same exposure level. Different exposure levels may be used in the above equation to calculate risks for different groups within a population having differing consumption rates, body weights, etc.

EPA cancer slope factors are based on an assumed exposure over a lifetime; consequently, adjustment for differences in consumption and body weight in childhood may not be necessary. Based on the occurrence of some childhood cancers, it is suspected that exposure to some chemicals may not require a lifetime to generate risk. However, carcinogenic toxicity tests in animals are usually conducted for the lifetime of the animal. Consequently, it is not possible to determine, for most contaminants, if there are risks that may be generated with a brief exposure duration. This remains an area of uncertainty. When human data are available, which is relatively rare, impacts on children are often better understood (e.g., risks are well known for ionizing γ radiation). In addition, it is worth noting that the lifetime cancer risk equation is the linear approximation that is reasonable for low doses/risks, but that cancer risk cannot exceed 1 and as it

approaches 10^{-2}, the exponential form of the equation is needed to make accurate estimates.

2.5.1.2 Population Risk—

The estimated population cancer risk is calculated by multiplying the number of people in an exposure group (with the same exposure) by the lifetime cancer risks calculated from the equation above. The population risk equation is:

(population cancer risk) = lifetime risk × (size of exposed population). (2-6)

For example, if 5,000 people are exposed at a risk level of one per thousand (1×10^{3}) (per lifetime), the overall risk to that population is five additional cancer cases ($5{,}000 \times 1 \times 10^{-3} = 5$) over the background level.

Because risks always vary across individuals, the population risk is calculated by either summing the risks for each individual or by multiplying the average risk across individuals by the population size. The total population risk may be expressed as

total population risk = average individual risk for group a × number of people in group a + average individual risk for group b × number of people in group b + average individual risk for group n × number of people in group n. (2-7)

Likewise, when multiple contaminant exposures occur, the total risk will equal the sum of the risks from individual contaminants at each exposure level.

2.5.2 Noncarcinogenic Toxicity

For chronic systemic toxicants, the RfD is used as a reference point in assessing risk. The RfD is an estimate, with an uncertainty of perhaps an order of magnitude, of a daily exposure that is likely to be without appreciable risk of deleterious health effects in the human population (including sensitive subgroups) over a lifetime.

2.5.2.1 Individual Risk—

The comparison of exposure to the RfD indicates the degree to which exposure is greater or less than the RfD. The following equation expresses this relationship:

$$\text{ratio} = \text{exposure}/\text{RfD} \qquad (2\text{-}8)$$

where

exposure = total exposure to a single contaminant from all sources (mg/kg-d)

RfD = reference dose or other noncarcinogenic exposure limit.

When the ratio obtained in the above equation is equal to or greater than 1 (i.e., when exposure exceeds the RfD), the exposed populations may be at risk. Although a margin of safety is incorporated into RfDs (see Section 2.3), actual thresholds are usually not known. Consequently, exposure above the RfD is not recommended. The likelihood of risk is related to the degree to which exposure exceeds the RfD. Risk also depends on individual characteristics; susceptibility to toxic exposures varies considerably in most populations. Consequently, the primary use of RfDs is to provide a protective exposure limit rather than to predict risks. In practice, however, they are often used to estimate risk.

2.5.2.2 Population Risk—

The population risk is expressed as the number of individuals with exposure levels greater than the RfD:

noncarcinogenic risk = population with exposure greater than the RfD. (2-9)

Reviewing the health basis for the risk estimate is useful when evaluating the risk estimates. A wide range of effects is used to establish RfDs. Some are very serious (e.g., retarded growth, liver damage, infertility, brain dysfunction) and others are of less concern (e.g., changes in enzyme levels indicative of preliminary stages of toxicity). In most cases the less serious effects will lead to serious effects as exposure levels increase above the RfD. This type of toxicity information should be considered when reviewing risk estimates.

Nonfish sources of exposure may be an important contributor to overall exposure. In some cases, exposure to a contaminant via fish consumption alone may not generate risk at the population's consumption level, but exposure to the contaminant in fish and other foods, water, soil, or air may exceed the RfD. Total exposure information can be used to obtain a much more accurate assessment of risk. When exposure occurs via other sources, the lack of total exposure assessment leads to an underestimate of exposure, and potentially of risk. Accurate risk information provides a more appropriate basis for decisions concerning the need for fish advisories.

An alternative approach is to express the dose as the magnitude by which the NOAEL exceeds the estimated dose (termed the margin of exposure, or the MOE). Where the MOE is greater than the product of the uncertainty and modifying factors (used in calculating an RfD from a NOAEL), then concern is considered to be low (Barnes and Dourson, 1988).

2.5.3 Subpopulation Considerations

A major goal in evaluating population risks is the identification of target populations. This document defines target populations as fish consumers determined by

decisionmakers to be in need of fish advisory programs. This section discusses the criteria for such a decision.

The identification of target populations involves both risk assessors and risk managers and requires both scientific and policy judgments.

A population would usually be targeted because they consume fish containing contaminants that may pose health hazards. In some cases, they may have known high exposures; in other cases, state agencies may have limited information suggesting they are at risk. Regardless of the supporting data available, determining who the target populations are is a critical step in establishing a fish advisory program.

A risk-based approach can be used to identify target populations. This approach requires decisions concerning the level of "acceptable" risk for carcinogenic and noncarcinogenic effects. For example, a health agency may determine that any population with cancer risk levels greater than 1 in 1 million requires a consumption advisory. For noncarcinogenic effects, exposures greater than the RfD by a factor of 1, 10, or some other value may be chosen to determine which groups require protection under a fish advisory program. Establishing an exposure limit for the purposes of identifying at-risk populations enables state agencies to equitably screen populations to determine where action is needed. Different subgroups within a population will often have differing consumption rates and may need to be considered individually to adequately address their levels of risk and need for program assistance. For example, children consuming contaminated fish at a rate that is safe for adults may be at risk due to their small body size and increased intake per unit of body weight (mg/kg-d). Choosing the levels at which populations are determined to need such advisories is a policy decision.

Defining acceptable risk has been a difficult problem at both the federal and local level. Federal programs have targeted various levels of cancer risk in developing regulations and guidance, and these levels often change over time and may be modified based on the needs of particular areas. "Acceptable" risk has also been defined and redefined in a number of legal cases.

Decisions concerning acceptable risk levels are often considered high-level policy decisions because they may affect the public's health directly. Many states have specific guidance written into their legislation concerning benchmark levels of risk (e.g., 1 in 1 million cancer risk is targeted in New Jersey for drinking water contaminants, modified by feasibility considerations).

Because of the importance of decisions concerning acceptable risk levels, state agencies are encouraged to seek input from a variety of sources, including target populations, when establishing these levels. The selection of specific groups as target populations is a critical decision because it affects who will be served, the levels of potential risk of those who will not be served, and the scope of the fish advisory program needed. EPA

encourages state, local, and tribal governments to consider the most sensitive populations when establishing programs. "Sensitive" in this context means those people who are at greatest risk due to their exposure, age, predisposing conditions, or other factors.

Some population groups may warrant more restrictive risk levels (e.g., children may be considered more susceptible than some other subgroups); however, levels of protection and provisions of services should be equitable across all persons served.

2.5.4 Multiple Species and Multiple Contaminant Considerations

Readers are encouraged to take multiple species consumption and/or multiple contaminant exposures into account when developing consumption limits and/or assessing risk. Methods for doing so are described in Sections 2.4.5.4, 3.4, and 3.5.

2.5.5 Incorporating Considerations of Uncertainty in Consumption Limits

Previous sections have discussed the many uncertainties associated with the estimates of exposure and toxicity data assessments that form the basis of the risk assessment and the derivation of risk-based consumption limits. Readers may wish to estimate the direction the uncertainties are likely to have on the risk estimates (i.e., do these uncertainties tend to exaggerate or diminish potential risk). The assumptions made in the risk assessments to account for uncertainties need to be clearly outlined (e.g., Section 2.3.5 contains a description of the nature of the uncertainties associated with each uncertainty factor applied in deriving an RfD). The use of the 95 percent upper confidence limit for the slope of the dose-response function at low doses for carcinogens is an example of a conservative assumption imbedded in most cancer slope factors. Likewise, exposure assessments frequently include conservative assumptions where data on actual exposure are absent, such as the assumption that no dose modification occurs when the cooking and preparation methods of target populations are unknown. Where possible, readers are encouraged to attempt to quantify the magnitude of the effect of such assumptions on the numerical risk estimates.

2.6 SUMMARIZING RISK DATA

This section describes methods for summarizing population exposure and risk. The risk assessment process can generate considerable data on various populations and geographic areas with details on numerous contaminants and levels of exposure. Organization of these data is useful so that the results can be reviewed in a meaningful way. Because different circumstances will require different data arrays, a number of templates are provided (Tables 2-5, 2-6, and 2-7) for organizing risk information for various purposes.

The presentation of the templates proceeds from the most specific (risk levels for a specific population at a specific waterbody) to more general risk summaries for a large geographic area. The templates are offered as a convenience and may contain entry areas that are not appropriate for all circumstances. State agency staff are encouraged to modify these or omit areas as needed.

Table 2-5 is a template that can be used to organize exposure data, risk values, and risk estimates. It is designed to be used for a specific population in a specific location with exposure to a contaminant at a known level. This table provides entry areas for the various factors that are used in calculating risk, as well as the actual risk estimates. Depending on the type of contaminants present and population characteristics, estimating risks for various subgroups may be advisable. This data display will allow agencies to highlight which groups within a population are at highest risk and to summarize the risks to a particular population. This table can also be used to evaluate the varied impacts on risk that may occur as a result of changing assumptions concerning consumption patterns, contaminant concentrations, and risk values.

Fish contaminants and contaminant concentrations are listed in the left column. If different concentrations are expected in different size fish, different tables can be developed for the various concentrations. Table 2-5 includes entries for central tendencies, high-end, and bounding exposure and risk estimates. It is not expected that all these variables will be calculated for all groups and conditions. This information, however, provides a range of estimates that can be used in prioritizing activities and designing appropriate programs. The template has entry areas for both fish and nonfish exposures.

Some agencies may not have information on nonfish exposures or may choose not to evaluate other sources of exposure in determining appropriate fish advisories. Risk assessors may modify the categories of information listed in this table to suit the specific characteristics of their local populations and fish advisory programs.

Table 2-5 also provides information lines for risks to women 18 to 45 years of age, the reproductive age for many women. This separate entry area was provided because many health officials are particularly concerned about developmental effects that may arise from exposure to long-term or bolus doses of fish contaminants, especially mercury. Separate entry areas for children were also provided because their consumption in relation to their body weight is often greater than that of adults. Consequently, their risks may be higher for noncarcinogens (carcinogenic risk estimates are based on a lifetime exposure, including childhood).

Evaluation of the risks to multiple groups may be warranted when more than one population uses a particular waterbody. Under those circumstances, various data summaries may be needed to provide data for differing fish advisories. For example, sport fishers and subsistence fishers may use the same waterbody but have different risks based on their varied consumption habits.

Table 2-5. Risk Estimates

Location:
Population:
Population Size:
Contaminant:
Contaminant Concentration:

Specific Subgroups	Fish Exposure Estimates		Other Exposures	Subtotal of Other Exposures		Total All Exposures		Risk Values			Other Factors (e.g., special susceptibilities due to nutritional status, disease, etc.)
	Central Tendency	High-End Estimate[a]		Central Tendency	High-End Estimate	Central Tendency	High-End Estimate	Non-carcinogen	Carcinogen	Alternatives	
Total Population											
<18 yr											
>18 yr											
Women, 18-45											

Risk Estimate

Central Tendency						High-End Estimate					
Noncarcinogen (% of RfD)		Carcinogen (Lifetime Risk)		Alternatives (% of Alternatives)		Noncarcinogen (% of RfD)		Carcinogen (Lifetime Risk)		Alternatives (% of Alternatives)	
Fish Only	All Exposures	Fish Only	All Exposures	Fish Only	All Exposures	Fish Only	All Exposures	Fish Only	All Exposures	Fish Only	All Exposures

Table 2-6. Risk Characterization

Location:

Population:

Population Size:

Contaminant Level (mg/kg)	Total					
	Central Tendency			High-End Estimate or Bounding Estimate		
	Carcinogen (Lifetime Risk)	Noncarcinogen (% of RfD)	Alternatives (% of Altern.)	Carcinogen (Lifetime Risk)	Noncarcinogen (% of RfD)	Alternatives (% of Altern.)

Table 2-7. Risk Summaries for a Waterbody

Population Group	Risk Estimates Based on High-End Exposures		
	Cancer Risks	Noncancer Risks	Other Risks
Total Population A			
<18 yr			
>18 yr			
Women 18-45 yr			
Total Population B			
<18 yr			
>18 yr			
Women 18-45 yr			
Total Population C			
<18 yr			
>18 yr			
Women 18-45 yr			
Aggregate of A,B,C			
<18 yr			
>18 yr			
Women 18-45 yr			

Table 2-5 provides entry areas for the various factors used to calculate risk. State agencies may wish to use this format to evaluate the sensitivity of the final risk estimates to variations in input factors such as fish exposure, other exposures, risk values, contaminant concentrations, and body weight. This type of sensitivity analysis will provide information on the importance of the various factors. When uncertainty exists about one of the inputs, such as a risk value or contaminant level, its relative importance in the overall estimates of risk can be evaluated.

Table 2-6 provides a template to be used to summarize risk data for a specific population using information presented in Table 2-5. This table focuses on health risk assessment and does not include information on the variables used to calculate risk, such as exposures and risk values. Table 2-6 is particularly useful when the same populations are exposed to more than one contaminant or multiple

concentrations of the same contaminant. The risk results for different contaminants may be entered by listing different chemicals down the left column and their corresponding risks across the same row. Alternatively, risks resulting from different contaminant levels can be entered in the left column when exposures to varied species are occurring with differing concentrations of contaminants.

If an additive effect is suspected, the total carcinogenic or noncarcinogenic risks could then be summed for the population or subgroup. Risk estimates may be modified if either a synergistic or antagonistic effect is expected.

Table 2-7 is a template designed to summarize risks for more than one population using a particular waterbody. This approach allows state agencies to obtain an overall estimate of the risks associated with fishing in a specific waterbody. This type of information may be particularly useful in evaluating the need for an advisory over a large geographic area and for a number of waterbodies.

Geographically based fish advisory efforts may target particular regions or areas based on overall risks for the waterbodies in an area. Waterbody-specific risk data can be used to prioritize efforts and may show concentrations of risk that would not be obvious using small population units as groups for comparison. They may also be used to determine that no action is necessary if the sum of all population risks is negligible. If a geographic approach is used in the development of fish advisories, Section 6, which gives an overview of mapping techniques, should be consulted.

Table 2-7 uses summary information from Tables 2-5 or 2-6 and assumes that state agencies will have focused their attention on a particular aspect of the risk distribution (i.e., central tendency, high-end, or bounding estimates). High-end values are listed in the table because it is recommended that fish advisories be based on highly, but realistically, exposed individuals and risks. State agencies may elect, however, to choose some other portion of the risk distribution.

Table 2-7 also provides data entry areas for three populations surrounding a waterbody (A, B, and C) and for various subgroups within those areas. Data entry areas are provided for cancer, noncancer, and "other" risks. The third variable is provided because some decisionmakers may wish to evaluate more than one type of risk in a particular category or use more than one risk value (e.g., liver damage and developmental toxicity). Data entry areas are also provided at the bottom of the table to summarize the risks across populations for the total population and for various subgroups. As with all the tables in this document, state agencies may wish to modify this table to address their specific needs.

State agencies may wish to compare risks at different waterbodies over large geographic areas. Table 2-8 provides a template designed to summarize risk data collected for specific waterbodies and populations. The table may be used to summarize risks to the overall populations or to specific subpopulations using a

waterbody. If subpopulation risks are of interest, the format provided in Table 2-8 can be followed with four rows used for each waterbody.

Table 2-8. Risk Summaries for a Geographic Area

Waterbody Location	Risk Estimates Based on High-End Exposures	
	Carcinogenic Effects	Noncarcinogenic Effects
Total Risk:		

SECTION 3

DEVELOPMENT AND USE OF RISK-BASED CONSUMPTION LIMITS

3.1 OVERVIEW AND SECTION ORGANIZATION

This section describes the derivation and use of the risk-based consumption limit tables provided in Section 4. Consumption limit tables were developed for each of the 25 target analytes listed in Table 1-1 and described in further detail in Volume 1 of this series. This section discusses

- Equations used to calculate the consumption limit tables
- Default values used in developing the consumption limit tables
- Modifications to the consumption limit calculations to allow for different input values and for multiple species consumption and/or multiple contaminant exposure.

Methods for deriving consumption limits for chemical contaminants with carcinogenic and/or noncarcinogenic effects are described. When available data indicate that a target analyte is associated with both carcinogenic and noncarcinogenic health effects, consumption limits based on both types of effects are calculated. In these cases, it is recommended that the toxicological effect resulting in the more conservative consumption limits be used to issue an advisory since resulting limits would be protective of both types of health effects. Methods for calculating consumption limits for a single contaminant in a multiple species diet or for multiple contaminants causing the same chronic health effects endpoints are also discussed. Species-specific consumption limits are calculated as fish meals per month, at various fish tissue concentrations, for noncancer and cancer health endpoints.

Developing fish consumption limits also requires making assumptions about the edible portions of fish because most chemical contaminants are not evenly distributed throughout the fish. The portion of the fish typically eaten may vary by fish species and/or the dietary habits of the fisher population of concern. Most fishers in the United States consume fish fillets. Therefore, it is recommended that contaminant concentrations be measured using skin-on fillets for scaled fish species and skinless fillets for scaleless fish species (e.g., catfish) (see Section 6.1.1.6 in Volume 1 of this series for further discussion of edible fish and shellfish sample types). However, for populations that ingest whole fish, consumption

values corresponding to whole fish contaminant concentrations are more appropriate. Fish consumption patterns are discussed in more detail in Appendix B.

People may be exposed to one or more fish contaminants through sources or pathways other than through consumption of recreationally or subsistence caught fish. These sources include ingestion of contaminated commercially caught fish, other contaminated foods, or contaminated drinking water; inhalation of the contaminant; or dermal contact with contaminated materials including soil and sediment. Caution should be used in setting health safety standards that do not take these other sources into account (see Section 2 for further discussion). Methods for quantifying exposure via sources other than consumption of recreationally or subsistence caught fish are not discussed in detail in this series.

3.2 EQUATIONS USED TO DEVELOP RISK-BASED CONSUMPTION LIMITS

Two equations are required to derive meal consumption limits for either carcinogenic or noncarcinogenic health effects. The first equation (3-1 for carcinogenic effects or Equation 3-3 for noncarcinogenic effects) is used to calculate daily consumption limits in units of milligrams of edible fish per kilogram of consumer body weight per day (mg/kg-d); the second equation (3-2) is used to convert daily consumption limits to meal consumption limits over a specified period of time (e.g., 1 month). Toxicological benchmark values for carcinogenic and noncarcinogenic health effects used in the calculation of risk-based consumption limits are summarized in Table 3-1.

3.2.1 Calculation of Consumption Limits for Carcinogenic Effects

To calculate consumption limits for carcinogenic effects, it is necessary to specify an "acceptable" lifetime risk level (ARL). The appropriate risk level for a given population is determined by risk managers; see Volume 3 for further discussion of selection of appropriate risk level. This document presents consumption limits that were calculated using a risk level of 1 in 100,000 (10^{-5}). Equations 3-1 and 3-2 were used to calculate risk-based consumption limits for the 12 target analytes with cancer slope factors (see Table 3-1), based on an assumed 70-yr exposure. A 70-yr lifetime is used in keeping with the default value provided in EPA's *Exposure Factors Handbook* (U.S. EPA, 1990a). This is a normative value; individuals may actually be exposed for greater or lesser periods of time, depending on their lifespan, consumption habits, and residence location. It should be noted that no populations were identified as being particularly susceptible to the carcinogenic effects of the target analytes.

3.2.1.1 Calculation of Daily Consumption Limits—

Equation 3-1 calculates an allowable daily consumption of contaminated fish based on a contaminant's carcinogenicity, expressed in kilograms of fish consumed per day:

Table 3-1. Risk Values Used in Risk-Based Consumption Limit Tables

Target Analyte	Noncarcinogens: Chronic RfD[a] (mg/kg-d)	Carcinogens: CSF[a] $(mg/kg\text{-}d)^{-1}$
Metals		
Arsenic (inorganic)[c]	3×10^{-4}	1.5
Cadmium	1×10^{-3}	NA
Mercury (methylmercury)[d]	1×10^{-4}	NA
Selenium	5×10^{-3}	NA
Tributyltin[b]	3×10^{-4}	NA
Organochlorine Pesticides		
Total chlordane (sum of *cis*- and *trans*-chlordane, *cis*- and *trans*-nonachlor, and oxychlordane)[e]	5×10^{-4}	0.35
Total DDT (sum of 4,4'- and 2,4'- isomers of DDT, DDE, and DDD)[f]	5×10^{-4}	0.34
Dicofol[g]	4×10^{-4}	withdrawn
Dieldrin	5×10^{-5}	16
Endosulfan (I and II)	6×10^{-3}	NA
Endrin	3×10^{-4}	NA
Heptachlor epoxide	1.3×10^{-5}	9.1
Hexachlorobenzene	8×10^{-4}	1.6
Lindane (γ-hexachlorocyclohexane; γ-HCH)[i]	3×10^{-4}	1.3
Mirex	2×10^{-4}	NA
Toxaphene[h,j]	2.5×10^{-4}	1.1
Organophosphate Pesticides		
Chlorpyrifos[k]	3×10^{-4}	NA
Diazinon[l]	7×10^{-4}	NA
Disulfoton	4×10^{-5}	NA
Ethion	5×10^{-4}	NA
Terbufos[m]	2×10^{-5}	NA
Chlorophenoxy Herbicides		
Oxyfluorfen[n]	3×10^{-3}	7.32×10^{-2}
PAHs[o]	NA	7.3
PCBs		
Total PCBs	2×10^{-5}	2.0[p]
Dioxins/furans[q]	NA	1.56×10^{5}

CSF = Cancer slope factor $(mg/kg\text{-}d)^{-1}$.
DDD = p,p' -dichlorodiphenyldichloroethane.
DDE = p,p' -dichlorodiphenyldichloroethylene
DDT = p,p' -dichlorodiphenyltrichloroethane.
NA = Not available in EPA's Integrated Risk Information System (IRIS, 1999).
PAH = Polycyclic aromatic hydrocarbon.
PCB = Polychlorinated biphenyl.
RfD = Oral reference dose (mg/kg-d).

(continued)

Table 3-1 (continued)

[a] Unless otherwise noted, values listed are the most current oral RfDs and CSFs in EPA's IRIS database (IRIS, 1999).
[b] The RfD value listed is for the IRIS (1999) value for tributyltin oxide.
[c] Total inorganic arsenic should be determined.
[d] Because most mercury in fish and shellfish tissue is present primarily as methylmercury (NAS, 1991; Tollefson, 1989) and because of the relatively high cost of analyzing for methylmercury, it is recommended that total mercury be analyzed and the conservative assumption be made that all mercury is present as methylmercury. This approach is deemed to be most protective of human health and most cost-effective. The National Academy of Sciences (NAS) conducted an independent assessment of the RfD and concluded, "On the basis of its evaluation, the committee consensus is that the value of EPA's current RfD for methylmercury, 0.1 µg/kg per day, is a scientifically justifiable level for the protection of human health."
[e] The RfD and CSF values listed are derived from studies using technical-grade chlordane (IRIS, 1999). No RfD or CSF values are given in IRIS (1999) for the *cis*- and *trans*-chlordane isomers or the major chlordane metabolite, oxychlordane, or for the chlordane impurities *cis*- and *trans*-nonachlor. It is recommended that the total concentration of *cis*- and *trans*-chlordane, *cis*- and *trans*-nonachlor, and oxychlordane be determined.
[f] The RfD value listed is for DDT. The CSF value is 0.34 for total DDT (sum of DDT, DDE, and DDD). The CSF value for DDD is 0.24. It is recommended that the total concentration of the 2,4′- and 4,4′-isomers of DDT and its metabolites, DDE and DDD, be determined.
[g] The RfD value is from the Registration Eligibility Decision (RED). Dicofol (U.S. EPA, 1998a).
[h] The RfD value listed is from the Office of Pesticide Program's Reference Dose Tracking Report (U.S. EPA, 1997c).
[i] IRIS (1999) has not provided a CSF for lindane. The CSF value listed for lindane is from HEAST, 1997.
[j] The RfD value has been agreed upon by the Office of Pesticide Programs and the Office of Water.
[k] Because of the potential for adverse neurological developmental effects, EPA recommends the use of a Population Adjusted Dose (PAD) of $3x10^{-5}$ mg/k-d for infants, children to the age of six, and women ages 13-50 (U.S. EPA, 2000b).
[l] The RfD value is from a memo data April 1, 1998, Diazinon: Report of the Hazard Identification Assessment Review Committee. HED DOC. NO. 012558 (U.S. EPA, 1998c).
[m] The RfD value listed is from a memorandum dated September 25, 1997; Terbufos-FQPA Requirement Report of the Hazard Identification Review (U.S. EPA, 1997h).
[n] The CSF value is from a memo dated 9/24/98; REVISED Oxyfluorfen (GOAL) Quantitative Risk Assessment (Q1*) Based on CD-1 Male Mouse Dietary Study With 3/4's Interspecies Scaling Factor. HED Document No. 012879 (U.S. EPA, 1998c).
[o] The CSF value listed is for benzo[*a*]pyrene. Values for other PAHs are not currently available in IRIS (1999). It is recommended that tissue samples be analyzed for benzo[*a*]pyrene and 14 other PAHs and that the order-of-magnitude relative potencies given for these PAHs (Nisbet and LaGoy, 1992; U.S. EPA, 1993b) be used to calculate a potency equivalency concentration (PEC) for each sample (see Section 5.3.2.4 of Volume 1).
[p] The CSF is based on a carcinogenicity assessment of Aroclors 1260, 1254, 1242, and 1016. The CSF presented is the upper-bound slope factor for food chain exposure. The central estimate is 1.0 (IRIS, 1999).
[q] The CSF value listed is for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) (HEAST, 1997). It is recommended that the 17 2,3,7,8-substituted tetra- through octa-chlorinated dibenzo-*p*-dioxins and dibenzofurans and the 12 dioxin-like PCBs be determined and a toxicity-weighted total concentration be calculated for each sample, using the method for estimating Toxicity Equivalency Concentrations (TEQs) (Van den Berg et al., 1998).

$$CR_{lim} = \frac{ARL \bullet BW}{CSF \bullet C_m} \quad (3\text{-}1)$$

where

CR_{lim} = maximum allowable fish consumption rate (kg/d)
ARL = maximum acceptable individual lifetime risk level (unitless)
BW = consumer body weight (kg)
CSF = cancer slope factor, usually the upper 95 percent confidence limit on the linear term in the multistage model used by EPA [(mg/kg-d)$^{-1}$], (see Section 2 for a discussion of this value)
C_m = measured concentration of chemical contaminant *m* in a given species of fish (mg/kg).

The calculated daily consumption limit (CR_{lim}) represents the amount of fish (in kilograms) expected to generate a risk no greater than the maximum ARL used, based on a lifetime of daily consumption at that consumption limit.

3.2.1.2 Calculation of Meal Consumption Limits—

Daily consumption limits may be more conveniently expressed as the allowable number of fish meals of a specified meal size that may be consumed over a given time period. The consumption limit is determined in part by the size of the meal consumed. An 8-oz (0.227-kg) meal size was assumed. Equations 3-1 and 3-2 can be used to convert daily consumption limits, the number of allowable kilograms per day (calculated using Equation 3-1), to the number of allowable meals per month:

$$CR_{mm} = \frac{CR_{lim} \bullet T_{ap}}{MS} \quad (3\text{-}2)$$

where

Cr_{mm} = maximum allowable fish consumption rate (meals/mo)
Cr_{lim} = maximum allowable fish consumption rate (kg/d)
MS = meal size (0.227 kg fish/meal)
T_{ap} = time averaging period (365.25 d/12 mo = 30.44 d/mo).

Equation 3-2 was used to convert daily consumption limits, in kilograms, to meal consumption limits over a given time period (month) as a function of meal size. Monthly consumption limits for carcinogenic effects in adults in the general population were derived for 13 of the 25 target analytes in Section 4.

Other consumption rates, such as meals per week, could also be calculated using this equation by substituting, for example, 7 d/wk for 30.44 d/mo. In using

Equation 3-2 in the table calculations in Section 4, the reader should note that 1 month was expressed as 365.25 d/12 mo or 30.44 d/mo.

3.2.1.3 Input Parameters—

Calculating risk-based consumption limits for carcinogenic effects requires developing appropriate values for the parameters in the equations. The default values used to calculate the consumption limits listed in Section 4 are shown in Table 3-2; a range of values is provided for the measured contaminant concentration in fish tissue (C_m) to represent a broad spectrum of contaminant concentrations. See consumption limit tables in Section 4. Development and modification of these values are discussed in Section 3.3.

EXAMPLE 1: Calculating Monthly Consumption Limits for Carcinogenic Health Endpoints in the General Population for Chlordane

Table 3-2. Input Parameters for Use in Risk Equations

Equation Parameter[a]	Values
Maximum acceptable risk level (ARL)	10^{-5} (unitless)
Cancer slope factor (CSF)[b] Reference dose (RfD)	$(mg/kg\text{-}d)^{-1}$ mg/kg-d
Consumer body weight (BW)	70 kg (general adult population)
Average fish meal size (MS)	8 oz (0.227 kg)
Measured contaminant concentration in edible fish and shellfish tissue (C_m)[c]	mg/kg (ppm) varies with local conditions for each chemical contaminant, for each species, and for each size (age) class within a species
Time-averaging period (T_{ap})	30.44 d/mo (monthly limit)

[a] Selection of the appropriate maximum acceptable risk level, consumer body weight, and average fish meal size are considered risk management decisions. For information regarding these values, see Sections 2 and 5 of this document and Volume 3.

[b] Most of the CSFs and RfDs were obtained from EPA's Integrated Risk Information System (IRIS, 1999). The RfDs not listed in IRIS were obtained from EPA's Office of Pesticide Programs. The CSFs and RfDs used in the risk equations are listed in Table 3-1 and are discussed in Section 5.

[c] Values for contaminant concentrations should be determined from local fish sampling and analysis programs conducted in the waterbody of concern as described in Volume 1.

Using Equations 3-1 and 3-2, the monthly meal consumption limits were calculated for the carcinogenic effects of chlordane for adults in the general population as shown in Table 3-3. **Note**: In this section, the monthly consumption limits for chlordane for both carcinogenic and chronic (noncarcinogenic) health effects are used to illustrate various modifications to the monthly consumption limit tables.

3.2.2 Calculation of Consumption Limits for Noncarcinogenic Effects

Noncarcinogenic health effects caused by consumption of contaminated fish include systemic effects such as liver, kidney, neurological, muscular, ocular, reproductive, respiratory, circulatory, or other organ toxicities and adverse developmental/reproductive effects from acute and chronic exposure. Risk-based consumption limit tables for chronic exposure health effects were developed for adults and young children for 23 of the 25 target analytes using RfDs for chronic systemic health effects.

3.2.2.1 Calculation of Daily Consumption Limits—

Equation 3-3 calculates an allowable daily consumption (CR_{lim}) of contaminated fish, based on a contaminant's noncarcinogenic health effects, and is expressed in kilograms of fish per day:

$$CR_{lim} = \frac{RfD \bullet BW}{C_m} \qquad (3\text{-}3)$$

where

CR_{lim} = maximum allowable fish consumption rate (kg/d)
RfD = reference dose (mg/kg-d)
BW = consumer body weight (kg)
C_m = measured concentration of chemical contaminant *m* in a given species of fish (mg/kg).

CR_{lim} represents the maximum lifetime daily consumption rate (in kilograms of fish) that would not be expected to cause adverse noncarcinogenic health effects. Most RfDs are based on chronic exposure studies (or subchronic studies used with an additional uncertainty factor). Because the contaminant concentrations required to produce chronic health effects are generally lower than those causing acute health effects, the use of chronic RfDs in developing consumption limits is expected to also protect consumers against acute health effects. They are designed to protect the most sensitive individuals.

To calculate weekly fish meal consumption limits, Equation 3-3 was modified as follows:

$$C_m = \frac{RfD \times BW}{CR_{lim}} \quad (3\text{-}4)$$

Using this equation, one can calculate the level of chemical contamination (C_m) in a given species of fish assuming that a 70-kg adult consumes a maximum of one 8-oz (0.227-kg) meal/wk.

3.2.2.2 Calculation of Meal Consumption Limits—

Equation 3-2 is used to convert daily consumption limits, in kilograms, to meal consumption limits over given time periods as a function of meal size. An 8-oz meal size was assumed in the calculations. Monthly consumption limits were derived for all target analytes in Section 4 except PAHs and dioxins, for which RfD values are not available. Monthly consumption limits pertain to recreational fishers (see Section 2.4.5.4). Where appropriate, risk assessors may choose to derive consumption limits based on a shorter time-averaging period such as a 14-d period (see Section 3.3.6). Note that, irrespective of the time-averaging period selected (e.g., 7-d, 10-d, 14-d, monthly), the same chronic systemic RfDs are applicable; the difference is in the averaging periods used in Equation 3-2.

Note: This approach does not expressly limit the amount of fish that may be consumed in a given day during the specified time period, so care must be taken to inform consumers of the dangers of eating large amounts of contaminated fish in one meal when certain acute or developmental toxicants are of concern.

3.2.2.3 Input Parameters—

For noncarcinogenic effects, calculating risk-based consumption limits requires developing appropriate values for similar parameters to those required for carcinogenic effects (see Table 3-2).

3.2.3 Developmental Effects

This guidance document does not calculate consumption limits specifically for developmental effects. For the majority of target analytes, sufficiently detailed developmental toxicity data are not available. For two analytes, methylmercury and PCBs, sufficient data are available demonstrating that women exposed to these chemicals may transfer sufficient amounts in utero or through breast feeding to induce pre- or postnatal developmental damage in their offspring. The interim RfD for methylmercury (1×10^{-4} mg/kg-d) is based on developmental effects in humans (i.e., neurologic changes in Iraqi children who had been exposed in utero).

EXAMPLE 2: Calculating Monthly Consumption Limits for Chronic Systemic Health Endpoints for Recreational Fishers for Chlordane

Using Equations 3-3 and 3-2, the monthly meal consumption limits were calculated for the noncarcinogenic and carcinogenic health effects of chlordane for recreational fishers as shown in Table 3-3. Note: In comparing the consumption limit tables for chlordane based on carcinogenic and noncarcinogenic effects for the general population, it is apparent that the carcinogenic endpoint results in a more conservative consumption limit assuming an ARL of 10^{-5} and equivalent meal sizes and contaminant concentrations in fish tissues. For example, based on a chemical contaminant level in fish tissue of 0.1 ppm, an adult could eat seven 8-oz fish meals assuming an ARL of 10^{-5}. Given the same level of tissue contamination, an adult could eat >30 8-oz meals per month based on noncarcinogenic effects of chlordane. To protect consumers from both the carcinogenic and noncarcinogenic effects of chlordane, a risk assessor may choose to base consumption limits on the more conservative meal sizes derived for carcinogenic effects. In this situation, a risk assessor or risk manager may wish to issue the consumption advisory based on the carcinogenic effects of chlordane, which would be protective of chronic health effects given the above-stated assumptions.

Thus, the consumption limits would be protective against developmental effects for methylmercury.

3.3 DEFAULT AND ALTERNATIVE VALUES FOR CALCULATING CONSUMPTION LIMITS

The consumption limit tables provided in Section 4 are based on default values for consumer body weights and average meal sizes. This section describes the default values shown in Tables 3-1 and 3-2 and provides alternative input values and multipliers for use in modifying and/or recalculating the consumption limit tables.

Seven variables are involved in calculating the values in the consumption limit tables (see Equations 3-1 through 3-3):

- Maximum acceptable risk level (ARL)
- Cancer slope factor (CSF)
- Chronic reference dose (RfD)
- Consumer body weight (BW)
- Fish meal size (MS)
- Contaminant concentration in edible fish tissue (C_m)
- Time-averaging period (30-d period).

Monthly meal consumption limit tables for both the carcinogenic and noncarcinogenic health effects of chlordane are used as examples to illustrate the effects of modifying one or more of the variables listed above.

Table 3-3. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - Chlordane

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.15	0 - 0.0084
16	>0.15 - 0.29	>0.0084 - 0.017
12	>0.29 - 0.39	>0.017 - 0.022
8	>0.39 - 0.59	>0.022 - 0.034
4	>0.59 - 1.2	>0.034 - 0.067
3	>1.2 - 1.6	>0.067 - 0.089
2	>1.6 - 2.3	>0.089 - 0.13
1	>2.3 - 4.7	>0.13 - 0.27
0.5	>4.7 - 9.4	>0.27 - 0.54
None (<0.5)	>9.4	>0.54

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg, an RfD of $5x10^{4}$ mg/kg-d, and a cancer slope factor (CSF) of 0.35 $(mg/kg\text{-}d)^{-1}$
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for chlordane is 5×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

3.3.1 Maximum Acceptable Risk Level

The consumption limit tables shown in Section 4 for target analytes with carcinogenic effects were calculated for maximum individual ARL of 10^{-5}. Note that the variable ARL appears in the numerator of Equation 3-1, the equation for calculating the daily consumption limit for carcinogens. Because ARL appears in multiples of 10, one may derive new meal consumption limits from the existing tables by multiplying or dividing the existing meal consumption limits by factors of 10, as appropriate. In the same way, changing the ARL by a factor of 10 would cause the same meal consumption limits to be valid for chemical concentrations 10 times higher or 10 times lower than those associated with the original ARL (see Table 3-4).

Table 3-4. Monthly Fish Consumption Limits for Carcinogenic Health Endpoints - Chlordane

Risk Based Consumption Limit[a]	Recommended Risk-Based Consumption Limit (meals per month, 8-oz meal size) Fish tissue Concentrations (*ppm, wet weight*)			
Fish Meals/Month	**ARL 10^{-4}**	**ARL 10^{-5}**	**ARL 10^{-6}**	**ARL 10^{-7}**
Unrestricted (>16)	0 - 0.084	0 - 0.0084	0 - 0.00084	0 - 0.000084
16	>0.084 - 0.17	>0.0084 - 0.017	>0.00084 - 0.0017	>0.000084 - 0.00017
12	>0.17 - 0.22	>0.017 - 0.022	>0.0017 - 0.0022	>0.00017 - 0.00022
8	>0.22 - 0.34	>0.022 - 0.034	>0.0022 - 0.0034	>0.00022 - 0.00034
4	>0.34 - 0.67	>0.034 - 0.067	>0.0034 - 0.0067	>0.00034 - 0.00067
3	>0.67 - 0.89	>0.067 - 0.089	>0.0067 - 0.0089	>0.00067 - 0.00089
2	>0.89 - 1.3	>0.089 - 0.13	>0.0089 - 0.013	>0.00089 - 0.0013
1	>1.3 - 2.7	>0.13 - 0.27	>0.013 - 0.027	>0.0013 - 0.0027
0.5	>2.7 - 5.4	>0.27 - 0.54	>0.027 - 0.054	>0.0027 - 0.0054
None (<0.5)	>5.4	>0.54	>0.054	>0.0054

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.

Notes:
1. Consumption limits are based on adult body weight of 70 kg and a cancer slope factor of 0.35 (mg/kg-d^{-1}).
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for chlordane is 1 x 10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. ARL = Acceptable risk level.

3.3.2 Cancer Potencies and Chronic Reference Doses (q_1*s and RfDs)

Table 3-1 contains the risk values used in the development of the consumption limit tables shown in Section 4. All of the CSFs and RfDs were obtained from EPA databases, primarily from IRIS (1999). Preference was given to IRIS values because these values represent consensus within EPA. When IRIS values were not available, RfDs from other EPA sources were used (see Section 5).

3.3.3 Consumer Body Weight (BW)

The consumption limit tables in Section 4 are based on fish consumer body weight of 70 kg (156 lb), the average body weight of male and female adults in the U.S. population (U.S. EPA, 1990a).

As Equation 3-3 shows, consumption limits are linearly related to body weight. That is, the higher the body weight assumed for the population of concern, the higher the consumption limits. EPA's *Exposure Factors Handbook* (U.S. EPA, 1990a) provides additional specific body weight information that can be used to adjust the body weight component of Equation 3-3. The values can also be used to develop a set of multipliers to directly adjust consumption limits for body weight variations.

Table 3-5 provides a range of average body weights (based on age and sex) for the U.S. population and their associated multipliers. Values in bold are those values used in the calculation of the consumption limit tables in Section 4. A **multiplier** is provided for each age group, which represents the number by which the meal consumption limits in the **general adult population** tables may be multiplied to calculate new meal consumption limits using an alternative body weight.

3.3.3.1 Derivation of Multipliers for Body Weight Adjustment—

Body weight multipliers represent the ratio of the alternative body weight to the standard 70-kg adult body weight. Body weight multipliers were calculated as follows:

$$\text{Multiplier}_{BW} = \frac{\text{Alternative Consumer Body Weight}}{\text{General Adult Body Weight}} \quad (3\text{-}5)$$

To derive modified consumption limits using alternative values for body weight, multiply the existing consumption limits (in meals per month) found in the tables for the **70-kg adult fisher consumer** by the multiplier associated with the new body weight:

$$\text{New } CR_{mm} = CR_{mm_{70\text{-kg BW}}} \bullet \text{Multiplier}_{BW} \quad (3\text{-}6)$$

where

Cr_{mm} = maximum allowable fish consumption rate (meals/mo)
$CR_{mm_{70\text{-kg BW}}}$ = maximum allowable fish consumption rate of a 70-kg fish consumer (meals/mo)
BW = consumer body weight (kg)
Multiplier_{BW} = body weight multiplier (unitless).

3.3.4 Meal Size

Meal size is defined as the amount of fish (in kilograms) consumed at one meal. EPA has identified a value of 8 oz (227 g) of uncooked fish fillet per 70-kg consumer body weight as an average meal size for adults in the general population assuming consumption of noncommercially caught fish only. At this

Table 3-5. Average Body Weights and Associated Multipliers

Age Group (yr)[a]	Average Male Body Weight (kg)	Average Female Body Weight (kg)	Average Body Weight for Males and Females Combined (kg)	Multiplier[b]
<3	11.9	11.2	11.6	0.17
3 to 6	17.6	17.1	17.4	0.25
0 to 6	14.8	14.2	14.5	0.21
6 to 9	25.3	24.6	25.0	0.36
9 to 12	35.7	36.2	36.0	0.51
12 to 15	50.5	50.7	50.6	0.72
15 to 18	64.9	57.4	61.2	0.87
18 to 25	73.8	60.6	67.2	0.96
25 to 35	78.7	64.2	71.5	1.0
35 to 45	80.9	67.1	74.0	1.1
45 to 55	80.9	68.0	74.5	1.1
55 to 65	78.8	67.9	73.4	1.0
65 to 75	74.8	66.6	70.7	1.0
18 to 45	—	64	—	0.91
18 to 75	**78.1**	**65.4**	**71.8[c] (70)[c]**	**1.0**

[a] Numbers in bold represent the default values used to calculate the consumption limit tables.

[b] The body weight multiplier is multiplied by the consumption limits associated with 72-kg adult fish consumers to obtain new consumption limits using the alternative body weight (see Section 3.3.3). The body weight multiplier represents the alternative body weight divided by the adult body weight.

[c] Per recommendations in the Exposure Factors Handbook, the body weight value of 71.8 kg was rounded to 70 kg (U.S. EPA, 1990a).

EPA recommends that the same default value be used for shellfish. However, EPA is currently investigating this issue and a different default value may be recommended in the future. Readers may wish to develop fish consumption limits using other meal sizes obtained from data on local fish consumption patterns and/or other fish consumption surveys as appropriate (see Appendix B). Table 3-6 provides alternative meal sizes and their associated multipliers. To obtain modified consumption limits using alternative values for meal size, multiply the existing consumption limits found in the tables for the **8-oz meal size** by the multiplier associated with the new meal size:

$$\text{New } CR_{mm} = CR_{mm_{8\text{-oz MS}}} \bullet \text{Multiplier}_{MS} \qquad (3\text{-}7)$$

where variables are as previously defined.

In addition, if specific meal consumption limits are desired for consumers ages 4 to adult, modifications can be made for both body weight and meal size using the following equation:

$$\text{New } CR_{mm} = CR_{mm_{70 \text{ kg BW,8-oz MS}}} \bullet \text{Multiplier}_{BW} \bullet \text{Multiplier}_{MS} \qquad (3\text{-}8)$$

where the parameters are as previously defined.

3.3.5 Contaminant Concentration in Fish Tissue

Chemical contaminant concentrations in fish tissue are influenced by the specific species and age (size) class of the fish sampled, the chemical properties of the chemical contaminant (e.g., degradation rate, solubility, bioconcentration potential), and the contaminant level in the waterbody. A detailed discussion of selection of target species for use in fish sampling and analysis programs is presented in Section 3 of Volume 1 of this guidance series. In addition, the reader may obtain some indication of the range of contaminant concentrations possible for a specific target analyte in a specific species by reviewing results of regional and national fish sampling programs such as the EPA *National Study of Chemical Residues in Fish* (U.S. EPA, 1991b), The National Contaminant Biomonitoring Program (Kidwell et al., 1995), the U.S. Fish and Wildlife Service National Contaminant Biomonitoring Program (Lowe et al., 1985; Schmitt et al., 1990), and the National Oceanic and Atmospheric Association (NOAA) Status and Trends Program (NOAA, 1989).

Note: The chemical contaminant concentration in fish tissue values used in calculating the risk-based consumption limits should be derived from monitoring data obtained from fish sampling and analysis programs and be specific to the waterbody, fish species, and fish size (age) class that were sampled.

3.3.6 Modifying Time-Averaging Period (T_{ap})

Calculated daily consumption limits represent the maximum amount of fish (in kilograms) expected to generate a risk no greater than the maximum ARL used for carcinogens or the maximum amount of fish (in kilograms) that would be expected not to cause adverse noncarcinogenic health effects based on a lifetime of daily consumption at that consumption rate. Most fish consumers, however, do not think about consumption in kilograms per day. Therefore, consumption limits may be more conveniently communicated to the fish-consuming public expressed as the allowable number of fish meals of a specified meal size that may be consumed over a given time period.

Monthly consumption limits were derived for all target analytes as shown in Section 4. For chemical contaminants with carcinogenic properties, there is no current methodology for evaluating the difference in cancer risks between consuming a large amount of the carcinogenic contaminant over a short period of time and consuming the same amount over the course of a lifetime. Therefore, EPA's current cancer risk assessment guidelines recommend prorating exposure

over the lifetime of the exposed individual (U.S. EPA, 1986a). To provide usable and easily understood consumption guidance, the time-averaging period of 1 month was used as the basis for expressing meal consumption limits in Section 4. In certain situations, risk managers may wish to calculate alternate consumption limits for different time intervals. For example, the state of Minnesota calculates consumption limits for mercury for 3-week (vacation), 3-month (seasonal), and annual time periods. This is done for mercury because it is eliminated from the body in a relatively short time period (half-life of approximately 50 days) and also because of seasonal fish consumption patterns in the state.

3.4 MODIFICATION OF CONSUMPTION LIMITS FOR A SINGLE CONTAMINANT IN A MULTISPECIES DIET

Equations 3-1 and 3-3 may be modified to calculate consumption limits for exposure to a single contaminant through consumption of several different fish species. This section describes the modifications required to do this.

Individuals often eat several species of fish in their diets. Equations 3-1 and 3-3, however, are based on contaminant concentrations in a single species of fish. Where multiple species of contaminated fish are consumed by a single individual, such limits may not be sufficiently protective. If several fish species are contaminated with the same chemical, then doses from each of these species must first be summed across all species eaten in proportion to the amount of each fish species eaten. This is described by Equation 3-9:

$$C_{tm} = \sum_{j=1}^{n} C_{mj} \bullet P_j \qquad (3\text{-}9)$$

where

C_{tm} = total concentration of chemical contaminant *m* in an individual's fish diet (mg/kg)
C_{mj} = concentration of chemical contaminant *m* in species *j* (mg/kg)
P_j = proportion of species *j* in the diet (unitless).

Note: This equation requires that the risk assessor know or be able to estimate the proportion of each fish species in the exposed individual's diet. Equation 3-9 yields the weighted average contaminant concentration across all fish species consumed (C_{tm}), which then may be used in modified versions of Equations 3-1 to 3-3 to calculate overall and species-specific risk-based consumption limits for carcinogenic and noncarcinogenic effects as shown in Sections 3.4.1 and 3.4.2.

3.4.1 Carcinogenic Effects

The equation to calculate an overall daily consumption limit based on exposure to a single carcinogen in a multiple species diet is very similar to Equation 3-1. However, in place of C_m, which indicates the average chemical contaminant concentration in one species, Equation 3-10 uses the equation for C_{tm}, the

weighted average chemical contaminant concentration across all of the species consumed:

$$CR_{lim} = \frac{ARL \bullet BW}{\sum_{j=1}^{n} (C_{mj} \bullet P_j) \bullet CSF} \quad (3\text{-}10)$$

where

CR_{lim} = maximum allowable fish consumption rate (kg/d)
ARL = maximum acceptable lifetime risk level (unitless)
BW = consumer body weight (kg)
C_{mj} = concentration of chemical contaminant *m* in fish species *j* (mg/kg)
P_j = proportion of a given species in the diet (unitless)
CSF = cancer slope factor, usually the upper 95 percent confidence limit on the linear term in the multistage model used by EPA ([mg/kg-d])$^{-1}$).

The daily consumption limit for each species is then calculated as:

$$CR_j = CR_{lim} \bullet P_j \quad (3\text{-}11)$$

where

Cr_j = consumption rate of fish species *j* (kg/d)
CR_{lim} = maximum allowable fish consumption rate (kg/d)
P_j = proportion of a given species in the diet (unitless).

Meal consumption limits may then be calculated for each species as before using Equation 3-2 (see Section 3.2), with CR_j substituted for CR_{lim} in the equation. Note that Equation 3-11 may be used before or after Equation 3-2, with the same results.

3.4.2 Noncarcinogenic Effects

For noncarcinogenic effects, the equation to calculate an overall daily consumption limit based on exposure to a single noncarcinogenic chemical in a multiple species diet is similar to Equation 3-3 for a single species. However, in place of C_m, which indicates the chemical contaminant concentration in one species, Equation 3-12 uses the equation for C_{tm}, the weighted average chemical contaminant concentration across all of the species consumed:

$$CR_{lim} = \frac{RfD \bullet BW}{\sum_{j=1}^{n} (C_{mj} \bullet P_j)} \quad (3\text{-}12)$$

where the parameters are as defined above. The consumption rate for each species is then calculated using Equation 3-11. Meal consumption limits for each species may then be calculated as before using Equation 3-2.

3.5 MODIFICATION OF CONSUMPTION LIMITS FOR MULTIPLE CONTAMINANT EXPOSURES

Equations 3-10 and 3-12 discussed in Section 3.4 can be further modified to develop consumption limits for multiple chemical exposures across single or multiple fish species. Section 2.3.4 provides additional information on exposure to multiple chemical contaminants.

Individuals who ingest chemically contaminated fish may be exposed to a number of different chemicals simultaneously. This could occur when: (1) a single fish species is contaminated with several different chemical contaminants; (2) an individual consumes a mixture of species in his or her diet, each contaminated with a different chemical; or (3) some combination of the above circumstances occurs.

EXAMPLE 10: Calculating Consumption Limits for a Single Contaminant in a Multispecies Diet

The combined results from a fish sampling and analysis program and a local fish consumption survey determine that local fishers eat a diet of 30 percent catfish contaminated with 0.006 mg/kg chlordane and 70 percent trout contaminated with 0.008 mg/kg chlordane. The RfD for chlordane reported in IRIS is 0.00005 mg/kg/d (IRIS, 1999). Because chlordane causes both chronic health and carcinogenic effects, consumption limits must be calculated for both health endpoints. The CSF for chlordane reported in IRIS is 0.35 per (mg/kg-d)$^{-1}$ (IRIS, 1999). The average body weight of an adult is estimated to be 70 kg.

Carcinogenic Effects: Using a risk level of 10^{-5} and the values specified above, Equation 3-5 yields a daily consumption rate of 0.028 kg/d, based on carcinogenic endpoints:

$$CR_{lim} = \frac{10^{-5} \bullet 70 \text{ kg}}{(0.006 \text{ mg/kg} \bullet 0.3 + 0.008 \text{ mg/kg} \bullet 0.7) \bullet 0.35 \text{ per mg/kg-d}}$$

$$= 0.029 \text{ kg/d} .$$

Equation 3-2 is then used as before to calculate a monthly meal consumption limit, based on a meal size of 8 oz (0.227 kg):

$$CR_{mm} = \frac{0.029 \text{ kg-d} \bullet 30.44 \text{ d/mo}}{0.227 \text{ kg/meal}} = 38.8 \approx 39 \text{ meals/mo} .$$

(continued)

EXAMPLE 10 (continued)

Equation 3-2 yields a meal consumption limit of 39 8-oz meals per month based on chlordane's carcinogenicity.

Based on a diet of 70 percent trout and 30 percent catfish:

$$CR_{trout} = 39 \text{ 8-oz meals/mo} \bullet 0.7 = 27 \text{ 8-oz meals/mo} .$$

An adult may safely consume 27 8-oz meals of trout and 12 8-oz meals of catfish per month.

Note: In both cases the meal consumption limits were rounded down. This is a conservative approach. One might also **round up** the number of meals of the species with the **lower** contaminant concentration, and **round down** the number of meals of the species with the **higher** contaminant concentration, so that the total number of fish meals per month equals that found by using Equations 3-6 and 3-2.

Noncarcinogenic Effects: Equation 3-8 is used to calculate the daily consumption limit based on chlordane's noncarcinogenic health effects using the RfD rather than the CSF

$$CR_{lim} = \frac{5 \times 10^{-4} \text{ mg/kg-d} \bullet 70 \text{ kg}}{0.006 \text{ mg/kg} \bullet 0.3 + 0.008 \text{ mg/kg} \bullet 0.7} = 4.73 \text{ kg/d} .$$

As with carcinogenic effects, Equation 3-2 is used to convert the daily consumption limit of 0.570 kg fish to a meal consumption limit:

$$CR_{mm} = \frac{4.73 \text{ kg/d} \bullet 30.44 \text{ d/mo}}{0.227 \text{ kg/meal}} = 634.3 \approx 634 \text{ meals/mo} .$$

This analysis indicates that 4.73 kg/d is equivalent to 634 8-oz fish meals per month or over two 8-oz fish meals per day under this mixed-species diet. This is categorized as safe fish consumption (represented by ">16" meals/ month) and has been defined as an intake limit of 16 meals per month for the monthly consumption limit tables in Section 4. Thus, based on the above results, risk managers might choose to issue a consumption advisory for adults based on chlordane's carcinogenic effects, the more sensitive of the two health endpoints.

Possible toxic interactions in mixtures of chemicals are usually placed in one of three categories:

- **Antagonistic**—the chemical mixture exhibits less toxicity than the chemicals considered individually
- **Synergistic**—the chemical mixture is more toxic than the sum of the individual toxicities of the chemicals in the mixture
- **Additive**—the toxicity of the chemical mixture is equal to the sum of the toxicities of the individual chemicals in the mixture.

Using available data is especially important in cases where mixtures exhibit synergistic interactions, thereby increasing toxicity. Very little data are available on the toxic interactions between multiple chemicals, however, and no quantitative data on interactions between any of the target analytes considered in this document were located. Some qualitative information is provided in Section 2.3.4.

If all of the chemicals in a mixture induce the same health effect by similar modes of action (e.g., cholinesterase inhibition), contaminants may be assumed to contribute additively to risk (U.S. EPA, 1986c), unless specific data indicate otherwise. Chemicals in a particular class (e.g., organochlorine or organophosphate pesticides) usually have similar mechanisms of toxicity and produce similar effects. Effects of chemicals and chemical groups are discussed in more detail in Section 5. For mixtures of chemicals that produce similar toxicological endpoints, EPA recommends dose addition. This procedure involves scaling the doses of the components for potency and adding the doses together; the mixtures response is then estimated for the combined dose (U.S. EPA, 1999a).

Some chemical mixtures may contain chemicals that produce dissimilar health effects. For these chemicals, EPA recommends response addition. This procedure involves first determining the risks for the exposure for the individual components; the mixture risk is then estimated by adding the individual risks together (U.S. EPA, 1999a).

3.5.1 Carcinogenic Effects

Few empirical studies have considered response addition in any depth, and few studies have modeled cancer risk from joint exposure. If interactions data are available on the components of the chemical mixture, EPA recommends that they be incorporated into the risk assessment by using the interactions-based hazard index or by including a qualitative assessment of the direction and magnitude of the impact of the interaction data (U.S. EPA, 1999a).

A detailed discussion of the interactions-based hazard index approach is available in EPA's proposed guidance for conducting health risk assessment of chemical mixtures (U.S. EPA, 1999a). For calculating consumption limits, additivity will be assumed for both carcinogenic and noncarcinogenic effects of components of chemical mixtures.

Equation 3-13 can be used to calculate a daily consumption rate for chemical mixtures of carcinogens in single or multiple fish species. It is similar to

Equation 3-1, with the summation of all species and all chemicals substituted for C_m in the denominator:

$$CR_{lim} = \frac{ARL \bullet BW}{\sum_{m=1}^{x}\left(\sum_{j=1}^{n} C_{mj} \bullet P_j\right) \bullet CSF} \quad (3\text{-}13)$$

where

CR_{lim} = maximum allowable fish consumption rate (kg/d)
ARL = maximum acceptable lifetime risk level (unitless)
BW = consumer body weight (kg)
C_{mj} = concentration of chemical contaminant *m* in species *j* (mg/kg)
P_j = proportion of a given species in the diet (unitless)
CSF = cancer slope factor, usually the upper 95 percent confidence limit on the linear term in the multistage model used by EPA ([mg/kg-d]$^{-1}$).

Meal consumption limits for mixtures of carcinogens are then calculated using Equation 3-2. When only one fish species is involved, Equation 3-13 may be simplified to Equation 3-14:

$$CR_{lim} = \frac{ARL \bullet BW}{\sum_{m=1}^{x} C_m \bullet CSF} \quad (3\text{-}14)$$

where the variables are as previously defined.

3.5.2 Noncarcinogenic Effects

Equation 3-15 can be used to calculate a daily consumption rate for noncarcinogenic chemical mixtures in single or multiple fish species. It is similar to Equation 3-3, with the summation of all species and all chemicals assumed to act additively. Equation 3-3 has been modified with the respective summation of concentrations (C_{mj}) substituted in the denominator and their respective RfDs in the numerator.

$$CR_{lim} = \sum_{\substack{m=1 \\ j=1}}^{x}\left(\frac{RfD_m \bullet P_m}{(C_{mj} \bullet P_j)}\right) \bullet BW \quad (3\text{-}15)$$

where the parameters are as previously defined and P_m = proportion by weight of chemical in diet. Meal consumption limits are then calculated using Equation 3-2, as above. Again, when only one fish species is involved, Equation 3-15 can be simplified to Equation 3-16:

$$CR_{lim} = \sum_{m=1}^{x} \left(\frac{RfD_m \bullet P_m}{C_m} \right) \bullet BW \qquad (3\text{-}16)$$

where the variables are as previously defined. Note that Equations 3-15 and 3-16 may **not** be used for contaminants causing dissimilar noncarcinogenic health effects.

EXAMPLE 11: Calculating Consumption Limits for Multiple Contaminants in a Single Species Diet

A single fish species is contaminated with 0.04 mg/kg chlordane and 0.01 mg/kg heptachlor epoxide. A maximum acceptable risk level of 10^{-5} and an adult body weight of 72 kg are used. Because chlordane and heptachlor epoxide cause both carcinogenic and chronic systemic health effects, both health endpoints must be considered in establishing consumption limits for these chemicals.

Carcinogenic Effects: The CSF for chlordane reported in IRIS is 0.35 per (mg/kg-d) (IRIS, 1999). The CSF for heptachlor epoxide reported in IRIS is 9.1 per (mg/kg-d) (IRIS, 1999). Equation 3-10 is used to calculate daily consumption rate based on the combined carcinogenic effects of both contaminants:

$$CR_{lim} = \frac{10^{-5} \bullet 70}{(0.04 \bullet 0.35) + (0.01 \bullet 9.1)} = 0.007 \text{ kg/d} .$$

A daily consumption rate of 0.007 kg fish per day is calculated. Using Equation 3-2, this daily consumption rate is converted to a meal consumption limit of one 4-oz meal per month (or six 8-oz meals per year).

Noncarcinogenic Effects: Chlordane and heptachlor are both organochlorine pesticides and cause many similar noncarcinogenic effects. Heptachlor epoxide is a metabolite of the organochlorine pesticide, heptachlor. When heptachlor is released into the environment, it quickly breaks down into heptachlor epoxide. Therefore, the toxicity values used in this document are for heptachlor epoxide, not heptachlor (see Section 5.3.7). Adverse liver effects formed the basis of the RfDs for both chemicals (IRIS, 1999). A combined daily consumption limit based on an RfD of 5×10^{-4} mg/kg-d for chlordane and 1.3×10^{-5} mg/kg-d for heptachlor was calculated using Equation 3-12:

(Continued)

EXAMPLE 11 (continued)

$$CR_{lim} = \left(\frac{5 \times 10^{-4} \text{ mg/kg-d}}{0.04 \text{ mg/kg}} + \frac{1.3 \times 10^{-5} \text{ mg/kg-d}}{0.01 \text{ mg/kg}} \right) \cdot 70 \text{ kg} = 0.97 \text{ kg/d} .$$

Equation 3-12 yields a daily consumption rate of 0.97 kg fish/d at the contaminant concentrations described above. Using Equation 3-2, a meal consumption limit of 130 4-oz meals per month is calculated. Therefore, based on the carcinogenic and chronic systemic consumption limits calculated for combined heptachlor epoxide and chlordane contamination, a risk manager may choose to advise (1) limiting fish consumption to six 8-oz meals per year, based on the combined carcinogenic effects; or (2) limiting fish consumption to 133 4-oz-meals/month, based on noncarcinogenic effects. **In general, EPA advises that the more protective meal consumption limit (in this case, the limit for the carcinogenic effect) serve as the basis for a fish consumption advisory to be protective of both health effects endpoints.**

3.5.3 Species-Specific Consumption Limits in a Multiple Species Diet

Equation 3-11 is used to calculate the risk-based consumption limits for each species in a multiple species diet, for both carcinogenic and noncarcinogenic toxicity where the variables are as defined above. CR_{lim} is calculated using Equations 3-13 or 3-15, for carcinogenic and noncarcinogenic toxicity, respectively. As with the consumption limits for single chemicals, these consumption limits are valid only if the assumed mix of species in the diet is known and if the contaminant concentrations in each species are accurate.

EXAMPLE 12: Calculating Consumption Limits for Multiple Contaminants in a Multispecies Diet

Chlorpyrifos and diazinon both cause cholinesterase inhibition, so are considered together when developing meal consumption limits. The RfD for chlorpyrifos is 0.0003 mg/kg-d, (EPA, 2000b), and the RfD for diazinon is 0.0007 mg/kg/d (U.S. EPA, 1998b).

A local fish consumption survey reveals that adult fishers consume trout and catfish at a ratio of 70:30, respectively. A fish sampling and analysis program reports chlorpyrifos and diazinon contamination in both species. Trout fillets are contaminated with 4.0 mg/kg chlorpyrifos and 0.3 mg/kg diazinon. Catfish fillets are contaminated with 6.0 mg/kg chlorpyrifos and 0.8 mg/kg diazinon. Given an adult body weight of 70 kg, a risk-based consumption rate of 0.15 kg fish per day is calculated using Equation 3-11:

(Continued)

EXAMPLE 12 (continued)

$$CR_{lim} = \left(\frac{0.0003}{(4.0 \bullet 0.7) + (6.0 \bullet 0.3)} + \frac{0.0007}{(0.3 \bullet 0.7) + (0.8 \bullet 0.3)} \right) \bullet 70$$

$$= 0.11 \text{ kg/d} .$$

Using Equation 3-2, a meal consumption limit of 15 8-oz meals per month is derived. **Note:** If chlorpyrifos and diazinon did not cause the same health endpoint, then separate meal consumption limits would have to be calculated for each as described in Section 3.4.2, with the more protective meal consumption limit usually serving as the basis for a fish consumption advisory (see Section 3.5.2).

Based on a diet of 70 percent trout and 30 percent catfish:

$$CR_{trout} = 15 \text{ 8-oz meals/mo} \bullet 0.7 = 10 \text{ 8-oz meals/mo} .$$

An adult may safely consume 10 8-oz meals of trout and 5 8-oz meals of catfish per month. Again, as mentioned in Section 3.4.2, rounding down both species-specific consumption limits is a conservative approach.

SECTION 4

RISK-BASED CONSUMPTION LIMIT TABLES

4.1 OVERVIEW AND SECTION ORGANIZATION

This section provides consumption limit tables for carcinogenic and chronic health endpoints for the general adult population for all of the target analytes listed in Table 1-1.

Variables used to calculate the consumption limits include fish meal size, consumer body weight, contaminant concentration in the fish tissue, the time-averaging period selected (monthly), the reference dose for noncarcinogenic health endpoints, and the cancer potency factor and the maximum acceptable risk level for carcinogenic health endpoints. Default values for the variables are presented in Section 3 and described in greater detail in Section 2.

Each consumption table lists, by chemical, the maximum number of fish meals per unit time (monthly) that may be safely eaten. Readers may use these tables by: determining the chemical contaminant concentration in fish surveyed in local fish sampling and analysis programs and reading the value for the maximum number of meals per month that may be safely eaten for each contaminant for noncancer and cancer endpoints. For those contaminants with monthly fish consumption limits calculated for both the noncancer and cancer endpoints, EPA recommends using the more conservative of the two values. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.

Some of the contaminant concentrations shown in the consumption limit tables are below current laboratory detection limits. Because of improvements in chemical analysis procedures and associated technologies, however, chemical detection limits regularly decrease. The fish tissue concentrations that are currently below the limit of detection are provided so that risk managers may use them once lower detection limits are achievable through improvements in analytical procedures. **Note:** The reader should be aware that detection limits presented here are derived from state-of-the-art state, regional, and national fish monitoring programs and may not be representative of detection limits achievable in all laboratories. Readers should consult with the analytical chemists in their state responsible for analyzing fish tissue samples to ensure that their detection limits are comparable to those presented. If the detection limits presented are lower than those achieved in the state's program, the reader should make

necessary adjustments to the tables. The detection limits presented here are to provide general guidance on detection limits typically achievable using current analytical procedures. The reader should review Section 6 of Volume 1 for further information on chemical analysis procedures and associated detection and quantitation limits for the target analytes.

4.2 CONSUMPTION LIMIT TABLES

Tables 4-1 through 4-25 are consumption limit tables for carcinogenic and chronic systemic health endpoints for each of the target analytes. Readers using the tables as a basis for fish consumption advisories should note that the values given in the tables are valid **only** for single contaminants in single-species diets. Sections 3.4 and 3.5 describe methods for calculating consumption limits for multiple contaminant situations and for multiple fish species diets.

Table 4-1. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - Arsenic (inorganic)

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations, *(ppm, wet weight)*	Fish Tissue Concentrations *(ppm, wet weight)*
Unrestricted (>16)	0 - 0.088	0 - 0.002
16	>0.088 - 0.18	>0.002 - 0.0039
12	>0.18 - 0.23	>0.0039 - 0.0052
8	>0.23 - 0.35	>0.0052 - 0.0078
4	>0.35 - 0.7	>0.0078 - 0.016
3	>0.7 - 0.94	>0.016 - 0.021
2	>0.94 - 1.4	>0.021 - 0.031
1	>1.4 - 2.8	>0.031 - 0.063
0.5	>2.8 - 5.6	>0.063 - 0.13
None (<0.5)	>5.6	>0.13

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg, an RfD of $3x10^{4}$ mg/kg-d, and a cancer slope factor (CSF) of 1.5 $(mg/kg-d)^{-1}$
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for arsenic is 5×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-2. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Cadmium

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.088
16	>0.088 - 0.18
12	>0.18 - 0.23
8	>0.23 - 0.35
4	>0.35 - 0.7
3	>0.7 - 0.94
2	>0.94 - 1.4
1	>1.4 - 2.8
0.5	>2.8 - 5.6
None (<0.5)	>5.6

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $1x10^{-3}$ mg/kg-d.
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for cadmium is 5×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-3. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Methylmercury

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.029
16	>0.029 - 0.059
12	>0.059 - 0.078
8	>0.078 - 0.12
4	>0.12 - 0.23
3	>0.23 - 0.31
2	>0.31 - 0.47
1	>0.47 - 0.94
0.5	>0.94 - 1.9
None (<0.5)	>1.9

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.

[b] Chronic, systemic effects.

Notes:

1. Consumption limits are based on an adult body weight of 70 kg and an interim RfD of $1x10^{-4}$ mg/kg-d.
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for methylmercury is 1×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-4. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Selenium

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 1.5
16	>1.5 - 2.9
12	>2.9 - 3.9
8	>3.9 - 5.9
4	>5.9 - 12
3	>12 - 16
2	>16 - 23
1	>23 - 47
0.5	>47 - 94
None (<0.5)	>94

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $5x10^{3}$ mg/kg-d.
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for selenium is $17x10^{-3}$ mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-5. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Tributyltin

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.088
16	>0.088 - 0.18
12	>0.18 - 0.23
8	>0.23 - 0.35
4	>0.35 - 0.7
3	>0.7 - 0.94
2	>0.94 - 1.4
1	>1.4 - 2.8
0.5	>2.8 - 5.6
None (<0.5)	>5.6

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $3x10^{-4}$ mg/kg-d.
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for tributyltin is $2x10^{-3}$ mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-6. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - Chlordane

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.15	0 - 0.0084
16	>0.15 - 0.29	>0.0084 - 0.017
12	>0.29 - 0.39	>0.017 - 0.022
8	>0.39 - 0.59	>0.022 - 0.034
4	>0.59 - 1.2	>0.034 - 0.067
3	>1.2 - 1.6	>0.067 - 0.089
2	>1.6 - 2.3	>0.089 - 0.13
1	>2.3 - 4.7	>0.13 - 0.27
0.5	>4.7 - 9.4	>0.27 - 0.54
None (<0.5)	>9.4	>0.54

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg, an RfD of $5x10^{-4}$ mg/kg-d, and a cancer slope factor (CSF) of 0.35 $(mg/kg\text{-}d)^{-1}$
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for chlordane is 1×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-7. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - DDT

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.015	0 - 0.0086
16	>0.015 - 0.029	>0.0086 - 0.017
12	>0.029 - 0.039	>0.017 - 0.023
8	>0.039 - 0.059	>0.023 - 0.035
4	>0.059 - 0.12	>0.035 - 0.069
3	>0.12 - 0.16	>0.069 - 0.092
2	>0.16 - 0.23	>0.092 - 0.14
1	>0.23 - 0.47	>0.14 - 0.28
0.5	>0.47 - 0.94	>0.28 - 0.55
None (<0.5)	>0.94	>0.55

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg, an RfD of $5x10^{-4}$ mg/kg-d, and a cancer slope factor (CSF) of 0.34 $(mg/kg\text{-}d)^{-1}$
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for DDT is 1×10^{-4} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-8. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Dicofol

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.088
16	>0.088 - 0.18
12	>0.18 - 0.23
8	>0.23 - 0.35
4	>0.35 - 0.7
3	>0.7 - 0.94
2	>0.94 - 1.4
1	>1.4 - 2.8
0.5	>2.8 - 5.6
None (<0.5)	>5.6

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $4x10^{-4}$ mg/kg-d.
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for dicofol is $1x10^{-3}$ mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-9. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - Dieldrin

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentration (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.015	0 - 0.00018
16	>0.015 - 0.029	>0.00018 - 0.00037
12	>0.029 - 0.039	>0.00037 - 0.00049
8	>0.039 - 0.059	>0.00049 - 0.00073
4	>0.059 - 0.12	>0.00073 - 0.0015
3	>0.12 - 0.16	>0.0015 - 0.002
2	>0.16 - 0.23	>0.002 - 0.0029
1	>0.23 - 0.47	>0.0029 - 0.0059
0.5	>0.47 - 0.94	>0.0059 - 0.012
None (<0.5)	>0.94	>0.012

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg, an RfD of $5x10^{5}$ mg/kg-d, and a cancer slope factor (CSF) of 16 $(mg/kg\text{-}d)^{-1}$
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for dieldrin is $1x10^{-4}$ mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-10. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Endosulfan

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 1.8
16	>1.8 - 3.5
12	>3.5 - 4.7
8	>4.7 - 7
4	>7 - 14
3	>14 - 19
2	>19 - 28
1	>28 - 56
0.5	>56 - 110
None (<0.5)	>110

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $6x10^{3}$ mg/kg-d..
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for endosulfan is 5×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-11. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Endrin

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.088
16	>0.088 - 0.18
12	>0.18 - 0.23
8	>0.23 - 0.35
4	>0.35 - 0.7
3	>0.7 - 0.94
2	>0.94 - 1.4
1	>1.4 - 2.8
0.5	>2.8 - 5.6
None (<0.5)	>5.6

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $3x10^{4}$ mg/kg-d.
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for endrin is 1×10^{-4} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-12. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - Heptachlor Epoxide

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations *(ppm, wet weight)*	Fish Tissue Concentrations *(ppm, wet weight)*
Unrestricted (>16)	0 - 0.0038	0 - 0.00032
16	>0.0038 - 0.0076	>0.00032 - 0.00064
12	>0.0076 - 0.01	>0.00064 - 0.00086
8	>0.01 - 0.015	>0.00086 - 0.0013
4	>0.015 - 0.031	>0.0013 - 0.0026
3	>0.031 - 0.041	>0.0026 - 0.0034
2	>0.041 - 0.061	>0.0034 - 0.0052
1	>0.061 - 0.12	>0.0052 - 0.01
0.5	>0.12 - 0.24	>0.01 - 0.021
None (<0.5)	>0.24	>0.021

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg, an RfD of 1.3×10^{-5} mg/kg-d, and a cancer slope factor (CSF) of 9.1 $(mg/kg\text{-}d)^{-1}$
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for heptachlor epoxide is 1×10^{-4} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-13. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - Hexachlorobenzene

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.23	0 - 0.0018
16	>0.23 - 0.47	>0.0018 - 0.0037
12	>0.47 - 0.63	>0.0037 - 0.0049
8	>0.63 - 0.94	>0.0049 - 0.0073
4	>0.94 - 1.9	>0.0073 - 0.015
3	>1.9 - 2.5	>0.015 - 0.02
2	>2.5 - 3.8	>0.02 - 0.029
1	>3.8 - 7.5	>0.029 - 0.059
0.5	>7.5 - 15	>0.059 - 0.12
None (<0.5)	>15	>0.12

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Note:
1. Consumption limits are based on an adult body weight of 70 kg, an RfD of $8x10^{-4}$ mg/kg-d, and a cancer slope factor (CSF) of 1.6 $(mg/kg\text{-}d)^{-1}$
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for hexachlorobenzene is 1×10^{-4} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-14. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - Lindane

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.088	0 - 0.0023
16	>0.088 - 0.18	>0.0023 - 0.0045
12	>0.18 - 0.23	>0.0045 - 0.006
8	>0.23 - 0.35	>0.006 - 0.009
4	>0.35 - 0.7	>0.009 - 0.018
3	>0.7 - 0.94	>0.018 - 0.024
2	>0.94 - 1.4	>0.024 - 0.036
1	>1.4 - 2.8	>0.036 - 0.072
0.5	>2.8 - 5.6	>0.072 - 0.14
None (<0.5)	>5.6	>0.14

[a] The assumed meal size is 8 oz (0.227 kg). A range of chemical concentrations are presented that are conservative, e.g. the 12 meal per month levels represent the concentrations associated with 12 meals up to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg, an RfD of $3x10^{-4}$ mg/kg-d, and a cancer slope factor (CSF) of 1.3 $(mg/kg-d)^{-1}$
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for lindane is 1×10^{-4} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-15. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Mirex

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.059
16	>0.059 - 0.12
12	>0.12 - 0.16
8	>0.16 - 0.23
4	>0.23 - 0.47
3	>0.47 - 0.63
2	>0.63 - 0.94
1	>0.94 - 1.9
0.5	>1.9 - 3.8
None (<0.5)	>3.8

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and RfD of 2×10^{-4} mg/kg-d
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for mirex is 1×10^{-4} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-16. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - Toxaphene

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.073	0 - 0.0027
16	>0.073 - 0.15	>0.0027 - 0.0053
12	>0.15 - 0.2	>0.0053 - 0.0071
8	>0.2 - 0.29	>0.0071 - 0.011
4	>0.29 - 0.59	>0.011 - 0.021
3	>0.59 - 0.78	>0.021 - 0.028
2	>0.78 - 1.2	>0.028 - 0.043
1	>1.2 - 2.3	>0.043 - 0.085
0.5	>2.3 - 4.7	>0.085 - 0.17
None (<0.5)	>4.7	>0.17

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg, an RfD of 2.5×10^{-4} mg/kg-d, and a cancer slope factor (CSF) of 1.1 $(mg/kg\text{-}d)^{-1}$
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for toxaphene is 3×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-17. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Chlorpyrifos

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.088
16	>0.088 - 0.18
12	>0.18 - 0.23
8	>0.23 - 0.35
4	>0.35 - 0.7
3	>0.7 - 0.94
2	>0.94 - 1.4
1	>1.4 - 2.8
0.5	>2.8 - 5.6
None (<0.5)	>5.6

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $3x10^{-4}$ mg/kg-d.*
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for chlorpyrifos is 2×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

* Because of the potential for adverse neurological development effects, EPA recommends the use of a Population Adjusted Dose (PAD) of $3x10^{-5}$ mg/kg-d for infants, children to age six, and women aged 13-50.

Table 4-18. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Diazinon

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.21
16	>0.21 - 0.41
12	>0.41 - 0.55
8	>0.55 - 0.82
4	>0.82 - 1.6
3	>1.6 - 2.2
2	>2.2 - 3.3
1	>3.3 - 6.6
0.5	>6.6 - 13
None (<0.5)	>13

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $7x10^{4}$ mg/kg-d.
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for diazinon is 2×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-19. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Disulfoton

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.012
16	>0.012 - 0.023
12	>0.023 - 0.031
8	>0.031 - 0.047
4	>0.047 - 0.094
3	>0.094 - 0.13
2	>0.13 - 0.19
1	>0.19 - 0.38
0.5	>0.38 - 0.75
None (<0.5)	>0.75

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.

[b] Chronic, systemic effects.

Notes:

1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $4x10^{5}$ mg/kg-d.
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for disulfoton is 2×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-20. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Ethion

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.15
16	>0.15 - 0.29
12	>0.29 - 0.39
8	>0.39 - 0.59
4	>0.59 - 1.2
3	>1.2 - 1.6
2	>1.6 - 2.3
1	>2.3 - 4.7
0.5	>4.7 - 9.4
None (<0.5)	>9.4

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $5x10^{-4}$ mg/kg-d.
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for ethion is 2×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-21. Monthly Fish Consumption Limits for Noncarcinogenic Health Endpoint - Terbufos

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.0059
16	>0.0059 - 0.012
12	>0.012 - 0.016
8	>0.016 - 0.023
4	>0.023 - 0.047
3	>0.047 - 0.063
2	>0.063 - 0.094
1	>0.094 - 0.19
0.5	>0.19 - 0.38
None (<0.5)	>0.38

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and an RfD of $2x10^{5}$ mg/kg-d.
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for terbufos is 2×10^{-3} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-22. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - Oxyfluorfen

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.88	0 - 0.04
16	>0.88 - 1.8	>0.04 - 0.08
12	>1.8 - 2.3	>0.08 - 0.11
8	>2.3 - 3.5	>0.11 - 0.16
4	>3.5 - 7	>0.16 - 0.32
3	>7 - 9.4	>0.32 - 0.43
2	>9.4 - 14	>0.43 - 0.64
1	>14 - 28	>0.64 - 1.3
0.5	>28 - 56	>1.3 - 2.6
None (<0.5)	>56	>2.6

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Noted:
1. Consumption limits are based on an adult body weight of 70 kg, an RfD of $3x10^{3}$ mg/kg-d, and a cancer slope factor (CSF) of 0.0732 $(mg/kg\text{-}d)^{-1}$
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for oxyfluorfen is 1×10^{-2} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-23. Monthly Fish Consumption Limits for Carcinogenic Health Endpoint - PAHs

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	NA	0 - 0.0004
16	NA	>0.0004 - 0.0008
12	NA	>0.0008 - 0.0011
8	NA	>0.0011 - 0.0016
4	NA	>0.0016 - 0.0032
3	NA	>0.0032 - 0.0043
2	NA	>0.0043 - 0.0064
1	NA	>0.0064 - 0.013
0.5	NA	>0.013 - 0.026
None (<0.5)	NA	>0.026

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects. An RfD is not available (NA) for this compound.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and a cancer slope factor (CSF) of 7.3 $(mg/kg\text{-}d)^{-1}$. No RfD was available (June 1999).
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for PAHs is 1×10^{-6} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-24. Monthly Fish Consumption Limits for Carcinogenic and Noncarcinogenic Health Endpoints - PCBs

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppm, wet weight*)
Unrestricted (>16)	0 - 0.0059	0 - 0.0015
16	>0.0059 - 0.012	>0.0015 - 0.0029
12	>0.012 - 0.016	>0.0029 - 0.0039
8	>0.016 - 0.023	>0.0039 - 0.0059
4	>0.023 - 0.047	>0.0059 - 0.012
3	>0.047 - 0.063	>0.012 - 0.016
2	>0.063 - 0.094	>0.016 - 0.023
1	>0.094 - 0.19	>0.023 - 0.047
0.5	>0.19 - 0.38	>0.047 - 0.094
None (<0.5)	>0.38	>0.094

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.
* Concentration reported in parts per quadrillion (nanogram per kg or 10-9 g/kg.

Notes:
1. Consumption limits are based on an adult body weight of 70 kg, and RfD of $2x10^{5}$, and a cancer slope factor (CSF) of 2 $(mg/kg\text{-}d)^{-1}$.
2. NONE = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for PCBs (sum of Aroclors) is 2×10^{-2} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

Table 4-25. Monthly Fish Consumption Limits for Carcinogenic Health Endpoint - Dioxins/Furans

Risk Based Consumption Limit[a]	Noncancer Health Endpoints[b]	Cancer Health Endpoints[c]
Fish Meals/Month	Fish Tissue Concentrations (*ppm, wet weight*)	Fish Tissue Concentrations (*ppt*-TEQ, wet weight*)
Unrestricted (>16)	NA	0 - 0.019
16	NA	>0.019 - 0.038
12	NA	>0.038 - 0.05
8	NA	>0.05 - 0.075
4	NA	>0.075 - 0.15
3	NA	>0.15 - 0.2
2	NA	>0.2 - 0.3
1	NA	>0.3 - 0.6
0.5	NA	>0.6 - 1.2
None (<0.5)	NA	>1.2

[a] The assumed meal size is 8 oz (0.227 kg). The ranges of chemical concentrations presented are conservative, e.g., the 12-meal-per-month levels represent the concentrations associated with 12 to 15.9 meals.
[b] Chronic, systemic effects. An RfD is not available (NA) for this compound.
[c] Cancer values represent tissue concentrations at a 1 in 100,000 risk level.
* Concentration reported in parts per trillion (nanogram per kg or 10^{-9} g/kg

Notes:
1. Consumption limits are based on an adult body weight of 70 kg and a cancer slope factor (CSF) of 1.56×10^{5} $(mg/kg\text{-}d)^{-1}$. No RfD available (June 1999).
2. None = No consumption recommended.
3. In cases where >16 meals per month are consumed, refer to Equations 3-1 and 3-2, Section 3.2.1.2, for methods to determine safe consumption limits.
4. The detection limit for dioxins/furans is 1×10^{-6} mg/kg.
5. Instructions for modifying the variables in this table are found in Section 3.3.
6. Monthly limits are based on the total dose allowable over a 1-month period (based on the RfD). When the monthly limit is consumed in less than 1 month (e.g., in a few large meals), the daily dose may exceed the RfD (see Section 2.3).

SECTION 5

TOXICOLOGICAL PROFILE SUMMARIES FOR TARGET ANALYTES

5.1 INTRODUCTION

This section presents toxicological profile summaries for the target analytes in the same order in which they are listed in Table 1-1. Toxicity data were collected for the target analytes from a variety of sources. Major sources used were IRIS, HSDB, ATSDR Toxicological Profiles, the Office of Pesticide Programs toxicological database, and recent toxicological reviews. The EPA risk values discussed in this section were used along with exposure data (e.g., meal size and fish contaminant concentration) to calculate the fish consumption limits provided in Section 4. Primary literature searches and reviews were not conducted for the development of this section due to time and resource constraints.

EPA evaluates dose-response data for chemicals of environmental concern on an ongoing basis. However, new toxicological data are continually being generated. Consequently, there may be recent information that is not yet incorporated into the EPA risk values. This may be particularly relevant for developmental toxicity, which is the subject of much current research. The toxicological summaries provide the reader with information that can be used to calculate alternative health-based risk values and fish consumption limits. The methods for carrying this out are described in Sections 2 and 3.

Risk values are also provided in the individual profiles, accompanied by a discussion of a number of toxicity studies for each target analyte, which yield various dose-response results. These give some indication of the variability in the types of effects and doses at which various effects were observed.

5.1.1 Categories of Information Provided for Target Analytes

Specific types of information were sought for all target analytes to address health and risk concerns for carcinogenic, developmental, and chronic exposure (noncarcinogenic) effects. These include pharmacokinetics, acute and chronic toxicity, reproductive and developmental toxicity, mutagenicity, carcinogenicity, special susceptibilities, interactive effects, and critical data gaps. The categories of information provided for each target analyte are listed in Table 5-1. Although the same types of information were sought for all analytes, the information presented for the contaminants

Table 5-1. Health and Toxicological Data Reviewed for Target Analytes

Category	Specific Information
Background	Chemical structure/group Use and occurrence
Pharmacokinetics	Target tissues Absorption Deposition-bioaccumulation potential/half-life/body burden Metabolism Excretion Susceptible subgroups
Acute toxicity	Quantitation Susceptible subgroups
Chronic toxicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Database quality Susceptible subgroups Current risk values
Reproductive and developmental toxicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Database quality Susceptible subgroups Current risk values
Mutagenicity	Type Quantitation Source Database quality
Carcinogenicity	Organ systems Animal studies-quantitation Human studies-quantitation Other studies-quantitation Database quality Outstanding issues
Special susceptibilities	Subgroups of concern
Interactive effects	Qualitative Quantitative MIXTOX results
Critical data gaps	Description
Summary of EPA risk values	Cancer slope factor and reference dose

varies, depending on the types of data available. Many of the analytes listed have been recognized as environmental contaminants for a number of years and have a fairly comprehensive toxicological database. Others have been introduced into the environment relatively recently; consequently, only limited information is available on these chemicals.

When a substantial amount of information was available on a contaminant, the information included in the discussions focused on areas relevant to the toxicities under evaluation. For example, a significant amount of pharmacokinetic data is available for some chemicals in the ATSDR Toxicological Profiles. In this document, most information was briefly synopsized; however, detailed information on human milk bioconcentration was included for developmental toxicants if lactational exposure was of concern. In addition, when the toxicological data indicated that a particular type of information, not reported, was required for full exploration of relevant toxic effects, additional information was identified in the Data Gaps Section (e.g., the interaction of DDT with pharmaceutical efficacy arising from DDT-induced increases in levels of microsomal enzymes).

The information collected is categorized by the temporal nature of the exposure (e.g., acute, chronic). These groupings are most applicable to the standard risk assessment methods that were employed to calculate risk values. The temporal groupings and methods of evaluating dose-response data are briefly discussed in Section 2, with a description of uncertainties and assumptions associated with dose-response evaluation.

5.1.1.1 Pharmacokinetics—

A brief summary of the pharmacokinetic data is presented for many chemicals. The information was included if it had a bearing on the development of fish consumption limits or would be useful to the reader in evaluating the toxicological characteristics of a chemical. For more detailed information on pharmacokinetics, the reader is referred to the ATSDR profiles and the primary literature.

For most chemicals there was not sufficient quantitative information, such as absorption, uptake, distribution, metabolism, excretion, and metabolite toxicity, in the data reviewed to recommend modifications in exposure to yield an altered internal dose. Some chemicals contained in the IRIS database have risk values that have incorporated pharmacokinetic considerations. If additional information relevant to quantitative risk assessment becomes available, it will be included in future versions of this guidance document.

5.1.1.2 Acute Toxicity—

Very little acute exposure toxicity data were located that could have a quantitative bearing on the development of fish consumption limits. A qualitative description of acute effects is included. The minimum estimated lethal dose to humans and a brief discussion of the acute effects are included if the data were available.

5.1.1.3 Chronic Toxicity—

Under the chronic exposure heading, significant effects associated with long-term exposure are listed. These include effects on the major organs and systems: the liver, kidney, gastrointestinal, cardiovascular, and reproductive systems. The chronic exposure data for each analyte include a description of an RfD listed in IRIS or obtained from other sources and the critical study serving as the basis for that RfD, including the species tested, duration of the study, and critical effect noted. Information is provided on any special issues concerning the critical study or RfD (e.g., if the study is old or has very few subjects or if the confidence in the RfD is listed as "low").

Data are also provided on effects observed in recent dose-response studies or effects that were not the subject of the IRIS RfD critical study. This was done to provide a more comprehensive picture of the overall toxicological nature of the chemicals than could be obtained from reviewing the RfD critical study alone. For most analytes, the information is primarily a qualitative description of effects. For chemicals that have significant new toxicological data available, details are provided on NOAELs, LOAELs, some study characteristics, and the usual categories of uncertainty and modifying factors that should be considered for significant studies. These are provided to give readers the option of developing exposure limits as they deem necessary.

5.1.1.4 Redproductive and Developmental Toxicity—

Reproductive and developmental toxicity data were obtained for each target analyte. Section 2.3.2.3 contains general information on developmental toxicity, including definitions and special issues related to developmental toxicity.

For many chemicals, information is provided on the tendency of the chemical to accumulate in body tissue. Many of the target analytes bioaccumulate and/or preferentially seek fatty tissues. When such accumulation occurs, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing fetus. Any body burden may result in exposure, but lipid-seeking chemicals, such as organochlorines, are often rapidly mobilized at the onset of pregnancy and may result in elevated contaminant exposure to the developing fetus. As a result, it may be necessary to reduce the exposure of females of reproductive age in order to reduce their overall body burden. For example, if a female has been exposed to methylmercury, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected depending on the timing and extent of prior exposure. This is noted for bioaccumulative analytes in the individual toxicological profiles.

5.1.1.5 Mutagenicity—

Although there were many reported mutagenicity bioassays for target analytes, little in vivo mutagenicity dose-response data were located. In vivo studies are recommended by EPA for risk assessments of suspected mutagens. A brief summary of the results of the mutagenicity assays for the analytes is provided. There are numerous studies available for some of the contaminants; consequently, it was not feasible to list all results. To provide a more concise overview of the results of greatest concern, the nature of the positive studies is given. The direction of the majority of results is also given (e.g., primarily positive, negative, or mixed).

5.1.1.6 Carcinogenicity—

Cancer slope factors and descriptive data were obtained primarily from IRIS, HEAST, and OPP. Preference was given to IRIS values; however, when IRIS values were not available, values developed by Agency program offices (e.g., OPP) are provided. The program office values have not necessarily undergone the extensive interagency review required for inclusion in the IRIS database, although many have been reviewed by scientists within and outside of EPA.

There are often insufficient studies to evaluate the carcinogenicity of a chemical. EPA has recognized this and formalized the lack of data as classification D: "not classifiable as to human carcinogenicity" in EPA's cancer weight of evidence scheme (U.S. EPA, 1986a). Many target analytes fall into this category; for others, no data were found in the sources consulted regarding their carcinogenicity. For chemicals with insufficient or no data on carcinogenicity in the databases consulted, the text under the "Carcinogenicity" heading states that: "insufficient information is available to determine the carcinogenic status of the chemical." This statement is used for chemicals lacking a cancer slope factor unless an Agency-wide review has determined that there is evidence that the chemical is **not** carcinogenic (i.e., an E classification as provided in IRIS, 1999). For a complete description of EPA's weight-of-evidence classification scheme, see EPA's *Guidelines for Carcinogenic Risk Assessment* (U.S. EPA, 1986a). EPA's proposed cancer guidelines have replaced this weight-of-evidence classification scheme with a narrative with descriptors in three categories: "known/likely," "cannot be determined," or "not likely" (U.S. EPA, 1996b).

5.1.1.7 Special Susceptibilities—

Toxicity data often indicate that some groups of individuals may be at greater risk from exposure to chemicals or chemical groups. For example, a chemical that causes a specific type of organ toxicity will usually pose a greater risk to individuals who have diseases of that organ system (e.g., immunotoxicity poses a greater risk to those with immunosuppression or with immature immune systems). Persons with some genetic diseases (e.g., enzyme disorders), nutritional deficiencies, and metabolic disorders may also be at greater risk due

to exposure to some chemicals. Qualitative data on special susceptibilities are provided for many of the target analytes. However, there are no quantitative data on subgroup susceptibilities for most chemicals that would enable the risk assessor to modify risk values.

The RfDs are designed to take into account the most susceptible individuals, and RfDs often incorporate an uncertainty factor to account for variability within the human species. Susceptible subgroups are those that exhibit a different or more enhanced response than most persons exposed to the same level of the chemical in the environment. Reasons include genetic makeup, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking).

5.1.1.8 Interactive Effects—

Data on interactive effects were located for many, but not all, of the target analytes. Most data on interactive effects were obtained from ATSDR Toxicological Profiles. Often the data indicate that certain classes of chemicals may be of concern. For example, most organochlorines induce the mixed function oxidase system. These chemicals may lead to unanticipated and exaggerated or diminished effects arising from simultaneous exposure to other chemicals that rely on the same metabolic system. In some cases this leads to potentiation (increased toxicity) and in others it hastens the process of detoxification.

The MIXTOX database, developed by EPA, was also used to obtain information on interactive effects (MIXTOX, 1992). The database provides a very brief summary of results of studies on combinations of chemicals. Most interactions are reported as "potentiation," "inhibition" or "antagonism" (decreased toxicity), "no apparent influence," or "additive." The interactions that differ from additive or no apparent influence are reported because it is assumed, in the absence of contrary information, that the toxicity of mixtures of chemicals will be additive for the same target tissue (see Section 2.3). The interactive terminology used in MIXTOX is used in this document.

5.1.1.9 Critical Data Gaps—

Data gaps noted in IRIS files, the OPP toxicological database, RfD summaries, and the ATSDR Toxicological Profiles are listed. In addition, data gaps that have been identified from a review of the studies are listed, along with the reasons that additional data are considered necessary.

5.1.1.10 Summary of EPA Levels of Concern—

The EPA risk values (RfDs and cancer slope factors) discussed in each section and used in the development of fish consumption limits are summarized in Table 3-1.

5.1.1.11 Major Sources—

At the end of each target analyte file is a list of the major sources of information consulted. Major sources are those that have been cited more than once. Within the text of each target analyte file, all information is provided with citations.

The IRIS files were consulted in early 1999 for cancer slope factors, chronic exposure RfDs, and additional study data. ATSDR Toxicological Profiles were also consulted when available. The profiles have extensive toxicity, pharmacokinetic, and epidemiological data reviews.

5.1.1.12 Statement Regarding Uncertainty—

There are always significant uncertainties associated with estimating health risks and safe exposure levels for human populations. Although these are discussed in Section 2, their importance warrants their mention in this section also. The risk values provided for each chemical in this section are based on human or animal studies that evaluated either a small subset of the human population or an entirely different species. In either case, we can only **estimate** the relevance of the study results to humans. Although a quantitative methodology is used to extrapolate from various types of studies to the general human population, there is considerable uncertainty in the estimated relationship between study populations and the human population.

The use of uncertainty factors and upper bound cancer risk estimates provides a margin of safety to account for some aspects of uncertainty in the extrapolation. However, our knowledge of response variability in the human population is very limited. The variations in response, which are engendered by age, sex, genetic heterogeneity, and preexisting disease states, may be considerable. Consequently, although current approaches to assessing risk involve estimating the upper bound values for deriving exposure or risk and are intended to be protective rather than predictive, the reader is urged to carefully review the information provided in this section on data gaps and uncertainties.

It is important to describe the uncertainties and assumptions when recommending fish consumption limits. With respect to toxicity, these include both uncertainties associated with specific chemicals and uncertainties and assumptions associated with the dose-response evaluation process (described in Section 2). In some cases, a variety of dose-response data will enable the reader to provide a quantitative estimation of the range of potential risk values that could be used to calculate exposure and fish consumption limits. A description of data gaps may also be useful to the risk manager in determining the best course of action. For chemicals having limited data, only a qualitative description may be possible.

5.1.2 Abbreviations Used and Scientific Notation

The glossary contains a description of additional terms and abbreviations used in this section.

Scientific notation is used where the values are less than 0.001 unless it would introduce confusion to the text (e.g., when presenting a range, the same format is used for both values in the range). In the summaries of risk values, all noncancer risk values are presented in scientific notation to facilitate comparison across health endpoints.

5.2 METALS

5.2.1 Arsenic

5.2.1.1 Background—

Arsenic is a naturally occurring element in the earth's crust that is usually found combined with other elements. Arsenic combined with elements such as oxygen, chlorine, and sulfur is referred to as inorganic arsenic; arsenic combined with carbon and hydrogen is referred to as organic arsenic. In this toxicological profile, arsenic refers to inorganic arsenic and its associated compounds. Organic arsenic compounds, such as arsenobetaine (an organic arsenic compound found in the edible parts of fish and shellfish) are not discussed, since these compounds are considered to be relatively nontoxic and not a threat to human health (ATSDR, 1999c).

5.2.1.2 Pharmacokinetics—

Pharmacokinetic studies show that water-soluble arsenic compounds are well-absorbed across the gastrointestinal tract. They appear to be transported throughout the body. Analysis of tissues taken at autopsy from people who were exposed to arsenic found arsenic present in all tissues of the body. The arsenic levels in hair and nails were the highest, with somewhat lower levels in internal organs (ATSDR, 1999c).

The metabolism of arsenic consists mainly of a reduction reaction, which converts pentavalent arsenic to trivalent arsenic, and methylation reactions, which convert arsenite to monomethylarsonic acid and dimethylarsenic acid. The primary excretion route for arsenic and metabolites is in the urine, with human studies showing that 45 to 85 percent is excreted in the urine within 1 to 3 days of ingestion. Very little is excreted in the feces (ATSDR, 1999c).

5.2.1.3 Acute Toxicity—

Arsenic is a recognized human poison. Single large doses, approximately 600 µg/kg-d or higher, taken orally have resulted in death. Acute oral exposure to lower levels of arsenic has resulted in effects on the gastrointestinal system (nausea, vomiting, diarrhea); central nervous system (headaches, weakness, lethargy, delirium); cardiovascular system (sinus tachycardia, hypotension, shock); and the liver, kidney, and blood (anemia, leukopenia). The limited available data have shown arsenic to have low to moderate acute toxicity to animals. Lethal oral doses to animals are higher than those in humans based on data showing that the oral LD_{50} values for arsenic range between 15 and 112 mg/kg (ATSDR, 1999c).

5.2.1.4 Chronic Toxicity—

The primary effects noted in humans from chronic exposure to arsenic are effects on the skin. Oral exposure has resulted in a pattern of skin changes that include the formation of warts or corns on the palms and soles along with areas of darkened skin on the face, neck, and back. Blackfoot disease, a disease characterized by a progressive loss of circulation in the hands and feet, leading ultimately to necrosis and gangrene, is associated with arsenic exposure (ATSDR, 1999c). Other effects noted from chronic oral exposure include peripheral neuropathy, cardiovascular disorders, gastrointestinal disorders, hematological disorders, and liver and kidney disorders.

IRIS provides an RfD for inorganic arsenic of 3.0×10^{-4} mg/kg-d, based on a NOAEL (adjusted to include arsenic exposure from food) of 0.0008 mg/kg-d and an uncertainty factor of 3. This was based on two studies that showed that the prevalence of hyperpigmentation and skin lesions increased with both age and dose for individuals exposed to high levels of arsenic in drinking water. There were also some cardiovascular effects noted. Other human studies support these findings, with several studies noting an increase in skin lesions from chronic exposure to arsenic through the drinking water. An uncertainty factor of 3 was used to account for both the lack of data to preclude reproductive toxicity as a critical effect and for uncertainty as to whether the NOAEL of the critical studies accounts for all sensitive individuals (IRIS, 1999).

EPA has medium confidence in the studies on which the RfD was based and in the RfD. The key studies were extensive epidemiologic reports that examined the effects of arsenic in a large number of people. However, doses were not well-characterized, other contaminants were present, and potential exposure from food or other sources was not examined. The supporting studies suffer from other limitations, primarily the small populations studied. However, the general database on arsenic does support the findings in the key studies; this was the basis for EPA's "medium confidence" ranking of the RfD (IRIS, 1999).

5.2.1.5 Reproductive and Developmental Toxicity—

Limited information is available on the developmental effects of arsenic in humans. No overall association between arsenic in drinking water and congenital heart defects was detected in an epidemiological study, although an association with one specific lesion (coarctation of the aorta) was noted. In another study, a marginal association (not statistically significant) was found between detectable levels of arsenic in drinking water and spontaneous abortions. The odds ratio for the group with the highest arsenic concentration was statistically significant. However, a similar association was found for a number of compounds, which indicates that the association could be random or due to other risk factors (ATSDR, 1999c). A study of babies born to women exposed to arsenic dusts in a copper smelter in Sweden showed a higher-than-expected incidence of congenital malformations.

Minimal or no effects on fetal development have been observed in chronic oral exposure studies of pregnant rats or mice to low levels of arsenic in drinking water. Malformations were produced in 15-d hamster fetuses via intravenous injections of arsenic into pregnant dams on day 8 of gestation, while another study reported that very high single oral doses of arsenic were necessary to cause prenatal fetal toxicity (IRIS, 1999).

5.2.1.6 Mutagenicity—

Arsenic has not been reported to directly react with DNA in many studies. Studies have shown that arsenic chromosomal aberrations and sister chromatid exchange in human lymphocytes reported positive results, while others were negative. One study in mouse bone marrow cells reported an increase in micronuclei, while another did not report an increase in chromosomal breaks and exchanges (ATSDR, 1999c). In vitro studies have also reported both positive and negative results. Arsenic was negative in the bacterial colorimetric assay: SAS Chromotest (HSDB, 1999), and positive for reverse mutations in bacteria, morphological transformations, sister chromatid exchange, and chromosomal aberrations in Syrian hamster embryo cells. Arsenic was also positive for chromosomal aberrations in human leukocytes and lymphocytes, sister chromatid exchange, enhancement or inhibition of DNA synthesis, and hyperdiploidy and chromosomal breakage in human lymphocytes (ATSDR, 1999c).

5.2.1.7 Carcinogenicity—

EPA has classified inorganic arsenic in Group A—Known Human Carcinogen. This is based on the increased incidence in humans of lung cancer through inhalation exposure and the increased risk of nonmelanoma skin, bladder, liver, kidney, and lung cancer through drinking water exposure (IRIS, 1999).

Animal studies have not associated arsenic exposure, via ingestion, with cancer. All cancer studies in rodents with arsenic have reported negative results. However, the meaning of this nonpositive data is uncertain because the mechanism of action in causing human cancer is not known, and rodents may not be good models for arsenic-induced carcinogenicity (IRIS, 1999).

To estimate the risks posed by ingestion of arsenic, EPA uses data from Taiwan concerning skin cancer incidence, age, and level of exposure via drinking water. In 37 villages that had obtained drinking water for 45 years from artesian wells with various elevated levels of arsenic, more than 40,000 individuals were examined for hyperpigmentation, keratosis, skin cancer, and blackfoot disease. The local well waters were analyzed for arsenic, and the age-specific cancer prevalence rates were found to be correlated with both local arsenic concentrations and age (duration of exposure). The oral cancer potency is 1.5 per mg/kg-d (IRIS, 1999).

EPA's current regulation for arsenic in drinking water (50 μg/L) has recently been called into question. The conclusions of a recent National Research Council/National Academy of Sciences report on arsenic in drinking water suggest that the current drinking water regulation needs to be lowered based on risks of skin, lung, and bladder cancer (NRC, 1999).

5.2.1.8 Special Susceptibilities—

No studies regarding unusual susceptibility of any human subpopulation to arsenic are available. However, it is possible that some members of the population might be especially susceptible because of lower than normal methylating capacity. This could result from a dietary deficiency of methyl donors such as choline or methionine or a deficiency of the vitamin coenzymes (folacin, Vitamin B_{12}) involved in transmethylation reactions (ATSDR, 1999c; Rogers, 1995).

5.2.1.9 Interactive Effects—

Arsenic tends to reduce the effects of selenium, and selenium can decrease the effects of arsenic. No clear evidence exists for significant interactions between arsenic and other metals; the existing data do not suggest that arsenic toxicity is likely to be significantly influenced by concomitant exposure to other metals. Some evidence suggests that a positive interaction between arsenic and benzo(*a*)pyrene can occur for lung adenocarcinomas in animals. Other studies suggest that chemicals that interfere with the methylation process could increase the toxicity of arsenic (ATSDR, 1999c)

5.2.1.10 Critical Data Gaps—

There is a substantial database on the toxicity of arsenic, both in humans and in animals. However, there are some areas where studies are lacking. Further epidemiological studies on the health effects of arsenic at low doses would be valuable. Additional studies on developmental and reproductive effects of arsenic would also be useful (ATSDR, 1999c).

5.2.1.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	3.0×10^{-4} mg/kg-d
Carcinogenicity	1.5 per mg/kg-d.

5.2.1.12 Major Sources—

ATSDR (1999c), HSDB (1999), IRIS (1999), Rogers (1995).

5.2.2 Cadmium

5.2.2.1 Background–

Cadmium is a heavy metal that occurs naturally in the earth's crust. It can be released into the environment through a wide variety of industrial and agricultural activities. It accumulates in human and other biological tissue and has been evaluated in both epidemiological and toxicological studies. ATSDR has determined that exposure conditions of most concern are long-term exposures to elevated levels in the diet (ATSDR, 1997).

The FDA has estimated that cadmium exposure among smokers is approximately 10 µg/d (0.01 mg/d). Passive exposure of nonsmokers may also be a source of exposure (U.S. FDA, 1993). This should be considered in evaluating the total exposure and risks associated with cadmium.

5.2.2.2 Pharmacokinetics–

Cadmium is not readily absorbed when exposure occurs via ingestion. Most ingested cadmium passes through the gastrointestinal (GI) tract without being absorbed. Studies in humans indicate that approximately 25 percent of cadmium consumed with food was retained in healthy adults after 3 to 5 days; this value fell to 6 percent after 20 days. Absorption may be much higher in iron-deficient individuals. Evaluations of the impact of cadmium complexation indicate that cadmium absorption from food is not dependent upon chemical complexation. However, some populations with high dietary cadmium intakes have elevated blood cadmium levels, which may be due to the particular forms of cadmium in their food (ATSDR, 1997).

Cadmium absorption studies in animals indicate that the proportion of an oral dose that is absorbed is lower in animals than in humans. Absorption is elevated during pregnancy, with whole-body retention in mice of 0.2 percent in those that had undergone pregnancy and lactation and 0.08 percent in those that had not. In rats, absorption decreased dramatically over the early lifetime, ranging from 12 percent at 2 hours to 0.5 percent at 6 weeks after birth. The placenta may act as a partial barrier to fetal exposure, with cord blood concentrations being approximately half those of maternal blood. The human data on placental concentrations are conflicting. Cadmium levels in human milk are approximately 5 to 10 percent of those found in blood (ATSDR, 1997).

Much of the cadmium absorbed into the blood is sequestered by metallothionein, and plasma cadmium is found primarily bound to this protein. This binding appears to protect the kidney from the otherwise toxic effects of cadmium. It has been suggested that kidney damage by cadmium occurs primarily due to unbound cadmium (ATSDR, 1997). Once cadmium is absorbed, it is eliminated slowly; the biological half-life has been estimated at 10 to 30 years (U.S. FDA, 1993).

Body stores of iron, zinc, and calcium may affect absorption and retention, although the retention may not be in readily available tissues (e.g., intestinal wall versus blood). The greatest concentrations of cadmium are typically found in the liver and kidney. Cadmium is not directly metabolized, although the cadmium ion binds to anionic groups in proteins, especially albumin and metallothionein (ATSDR, 1997).

5.2.2.3 Acute Toxicity—

Effects of acute oral exposure to cadmium include GI irritation, nausea, vomiting, abdominal pain, cramps, salivation, and diarrhea. In two human cases, lethal doses caused massive fluid loss, edema, and widespread organ destruction. The ingested doses that caused death were 25 mg cadmium/kg and 1,840 mg cadmium/kg (ATSDR, 1997).

5.2.2.4 Chronic Toxicity—

Kidney toxicity is a significant concern with cadmium exposure. Increased death rates from renal disease have been observed in exposed human populations in Belgium, England, and Japan (ATSDR, 1997). There are also extensive animal data indicating that the kidney is a target organ. IRIS contains an RfD of 0.001 mg/kg-d in food based upon a NOAEL of 0.01 mg/kg-d in multiple human studies. The critical effect was significant proteinuria (an indicator of kidney toxicity). To calculate the RfD, it was assumed that 2.5 percent of cadmium in food was absorbed and approximately 5 percent in water was absorbed. Using an uncertainty factor of 10 to account for intrahuman variability in cadmium sensitivity, the RfD for cadmium in food was calculated to be 0.001 mg/kg-d. The RfD was calculated using a toxicokinetic model to determine the highest level of cadmium in the human renal cortex not associated with significant proteinuria and therefore was not based on a single study. EPA's confidence in the database and the RfD is high (IRIS, 1999).

The FDA has calculated a tolerable daily intake of 55 µg/person-d, which is approximately equal to 0.78 µg/kg-d (7.8×10^{-4} mg/kg-d) in a 70-kg person and 5.5 µg/kg-d (0.005 mg/kg-d) in a 10-kg child (their example uses 2+ years of age). The FDA value is based upon a pharmacokinetic approach that utilized the critical body burden associated with kidney toxicity. See U.S. FDA (1993) for more details.

Cadmium causes many other types of toxic effects in addition to nephrotoxicity. In humans, some studies have suggested an association between neurotoxicity and cadmium exposure at levels below those that cause kidney toxicity (no additional details available). Cadmium exposure reduces the GI uptake of iron, which may cause anemia if iron intakes are low. Bone disorders including osteomalacia, osteoporosis, and spontaneous bone fracture have been observed in some chronically exposed individuals. Increased calcium excretion associated

with cadmium-induced renal damage may lead to increased risk of osteoporosis, especially in postmenopausal women, many of whom are already at risk of osteoporosis. Cardiovascular toxicity and elevated blood pressure have been suggested in some human studies; however, the results are conflicting (ATSDR, 1997).

Animal studies indicate that cadmium ingestion causes a wide variety of alterations in the function of the immune system. Some aspects of the system were enhanced and others were impaired (e.g., susceptibility to virally induced leukemia). In short-term studies, serious effects occurred at levels as low as 1.9 mg/kg-d and less serious effects (induction of antinuclear antibodies) at 0.75 mg/kg-d in a 10-wk study in mice (ATSDR, 1997). No longer-term studies were located.

5.2.2.5 Reproductive and Developmental Toxicity—

Reproductive and developmental toxicity has been associated with oral cadmium exposure both in short- and long-term studies. In 10-d prenatal dosing studies in rats at 18.4 mg/kg, malformations, including split palate and dysplasia of the facial bones and rear limb, were observed with a NOAEL of 6.1 mg/kg-d. A similar study in rats found delayed ossification at 2 mg/kg-d. Other studies have found gross abnormalities and reduced fetal weight at doses ranging from 1.5 to 19.7 mg/kg-d (ATSDR, 1997). Oral cadmium exposure of young mice depresses their humoral immune responses; the study did not find the same effect in adult mice (ATSDR, 1997).

More sensitive measures of effects for cadmium have identified effects at much lower doses. ATSDR has determined that:

> . . . the most sensitive indicator of development toxicity of cadmium in animals appears to be neurobehavioral development. Offspring of female rats orally exposed to cadmium at a dose of 0.04 mg/kg-day prior to and during gestation had reduced exploratory locomotor activity and rotorod performance at age 2 months. . . (ATSDR, 1997).

Reduced locomotor activity and impaired balance were noted at a LOAEL of 0.04 mg/kg-d with 11 weeks of exposure occurring prior to and during gestation. The effects were also observed at 0.7 mg/kg-d with exposure occurring only during gestation. Neurobehavioral effects were observed in other developmental studies and in chronic studies of effects in adult animals. Two longer-term studies yielding similar neurobehavioral results were conducted with maternal exposures of 7.0 and 14.0 mg/kg-d (see numerous citations in Baranski et al., 1983; ATSDR 1997).

Studies of developmental toxicity in human populations have been conducted on women exposed via inhalation in the workplace. Decreased birth weight has been reported in two studies, one with statistically significant results and the other

lacking statistical significance. Inhalation studies in animals have found structural and neurobehavioral abnormalities similar to those found in the oral dosing studies (ATSDR, 1997).

Based on the mutagenicity data results (discussed below), heritable defects may result from exposure to cadmium. However, mutagenicity assays do not provide dose-response data suitable for use for the calculation of a risk value. Calcium deficiency has been shown to increase the fetotoxicity of cadmium, and lindane exposure increased developmental toxicity in animal studies (ATSDR, 1997).

5.2.2.6 Mutagenicity—

Results of bacteria and yeast assays have been mixed. Results were conflicting in chromosomal aberration studies on human lymphocytes treated both in vitro and obtained from exposed workers. Mouse and hamster germ cell studies indicate that cadmium may interfere with spindle formation resulting in aneuploidy. Positive results have also been obtained in Chinese hamster ovary and mouse lymphoma cell assays (IRIS, 1999).

5.2.2.7 Carcinogenicity—

Epidemiological studies have been conducted on population groups in high cadmium exposure areas via food and water, and organ-specific cancer rates have been examined (kidney, prostate, and urinary tract). Most studies yielded negative results. A study in Canada found that elevated rates of prostate cancer paralleled the elevated cadmium exposure of the populations studied. In animals, oral studies conducted at relatively low exposure levels (up to 4.4 mg/kg-d) have yielded negative results. One study in rats showed an increase in prostatic proliferative lesions, leukemia, and testicular tumors in rats fed cadmium in a zinc-controlled diet. Rats fed zinc-deficient diets had decreased overall incidence for tumors of the prostate, testes, and hematopoietic system thus indicating that zinc deficiency in the diet may inhibit the carcinogenic effects of cadmium ingestion. EPA has determined that data are insufficient to determine the carcinogenic status of cadmium by the oral route.

An increased risk for respiratory tract cancers has been observed in several epidemiological studies of workers exposed to cadmium-containing fumes and dusts. For this reason, cadmium is classified as a probable human carcinogen (B1) by EPA based on **inhalation** studies in humans. The airborne cancer potency is 1.8×10^{-3} per $\mu g/m^3$ (IRIS, 1999).

5.2.2.8 Special Susceptibilities—

Populations with genetically determined lower ability to induce metallothionein are less able to sequester cadmium. Populations with depleted stores of dietary components such as calcium and iron due to multiple pregnancies and/or dietary deficiencies may have increased cadmium absorption from the GI tract.

Increased calcium excretion associated with cadmium-induced renal damage may lead to increased risk of osteoporosis, especially in postmenopausal women. The relationship between cadmium toxicity and iron levels is not well established; however, in some studies it appears that iron-deficient individuals may be at greater risk. Individuals with kidney disease, diabetes, and age-related decreased kidney function may be at greater risk of cadmium-induced kidney toxicity (ATSDR, 1997).

Immunological effects may be of concern for children because it appears, based upon animal studies, that young individuals may be at greater risk than adults. In addition, the immune system is not fully developed in humans until approximately 12 years of age. Immunological effects have also been observed in multiple animal studies of adults. These pose special risks for individuals with compromised immune systems (e.g., those with AIDS).

A variety of types of developmental effects have been associated with cadmium exposure (see discussion above). These all pose special risks for infants and children, as well as women of reproductive age.

5.2.2.9 Interactive Effects—

Dietary deficiencies of calcium, protein, zinc, copper, iron, and vitamin D may cause increased susceptibility to adverse skeletal effects from cadmium exposure. Lead increased neurotoxicity and selenium decreased the clastogenic effect of cadmium on bone marrow. Exposure to chemicals that induce metallothionein (e.g., metals) reduced toxicity with parenteral cadmium exposure (ATSDR, 1997).

MIXTOX reports a number of interactive studies on cadmium and selenium compounds. The studies have yielded mixed results with reports of inhibition, potentiation, additive effects, and no effects (MIXTOX, 1992).

5.2.2.10 Critical Data Gaps—

A joint team of scientists from ATSDR, National Toxicology Program (NTP), and EPA have identified the following data gaps: immunotoxicity, neurotoxicity, and developmental toxicity in human populations, quantitative data on acute and intermediate toxicity in humans, and chronic exposure studies in humans using sensitive indicators of kidney toxicity, animal and human studies of carcinogenic effects, human genotoxicity, animal reproductive, immunotoxicity, and pharmacokinetic studies (ATSDR, 1997).

5.2.2.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	1×10^{-3} mg/kg-d
Carcinogenicity	Group B1 (probable human carcinogen).

5.2.2.12 Major Sources—

ATSDR (1997), HSDB (1993), IRIS (1999), U.S. FDA (1993).

5.2.3 Mercury

5.2.3.1 Background—

Mercury is widely distributed in the environment due to both natural and anthropogenic processes. It is released generally as elemental mercury (Hg^0) or divalent mercury (Hg^{2+}). It can be converted between these forms and may form mercury compounds by chemical processes in air, water, and soil. Biological processes in other media, primarily soil and sediment, can convert inorganic mercury into organic, mostly methylmercury.

In fish tissue, the majority of mercury is methylmercury. Generally, the amount of mercury in fish tissue increases with the age and the size of the fish. The accumulation of mercury in fish varies among species; for the most part, the fish-eating species of fish accumulate higher concentrations of mercury than do non-piscivorous fish. Mercury is found in highest concentrations in organs and muscle.

Data on mercury toxicity have been reviewed for inclusion in IRIS. Currently there are both RfDs and cancer assessments in IRIS for elemental mercury, inorganic mercury (mercuric chloride), and methylmercury (interim RfD). EPA, in response to a mandate of the Clean Air Act Amendments of 1990, has prepared a multivolume *Mercury Study Report to Congress*. This has been peer reviewed extensively including a recent review by the Science Advisory Board (SAB). (U.S. EPA, 1997d). Methylmercury has also been the subject of evaluation by numerous states. Detailed analyses have been conducted in some specific areas, including evaluation of data regarding blood and hair mercury levels, toxic effects, and biological half-life values to estimate safe consumption levels of contaminated fish (Shubat, 1991, 1993; Stern, 1993).

As discussed in previous sections, a total exposure assessment is beyond the scope of this document. Readers may wish to consult other sources to obtain information on background levels of methylmercury in the environment. Additional information on dietary sources of mercury is available in the FDA *Adult Total Diet Study*, conducted from October 1977 through September 1978, which contains information on total mercury content (not restricted to methylmercury) in a number of foods (Podrebarac, 1984). Readers are also referred to Volume III, *An Assessment of Exposure from Anthropogenic Mercury Emissions in the United States* of the *Mercury Study Report to Congress* (U.S. EPA, 1997d).

5.2.3.2 Pharmacokinetics—

Methylmercury is rapidly and nearly completely absorbed from the gastrointestinal tract; 90 to 100 percent absorption is estimated (WHO, 1990).

Methylmercury is somewhat lipophilic, allowing it to pass through lipid membranes of cells and facilitating its distribution to all tissues, and it binds readily to proteins. Methylmercury in fish binds to amino acids in fish muscle tissue.

The highest methylmercury levels in humans are generally found in the kidneys. Methylmercury in the body is considered to be relatively stable and is only slowly transformed to form other forms of mercury. Methylmercury readily crosses the placental and blood/ brain barriers. Estimates for its half-life in the human body range from 44 to 80 days (U.S. EPA, 1997d). Excretion of methylmercury is via the feces, urine, and breast milk. Methylmercury is also distributed to human hair and to the fur and feathers of wildlife; measurement of mercury in these materials has served as a useful biomonitor of contamination levels.

5.2.3.3 Acute Toxicity—

Acute high-level exposures to methylmercury may result in impaired central nervous system function, kidney damage and failure, gastrointestinal damage, cardiovascular collapse, shock, and death. The estimated lethal dose is 10 to 60 mg/kg (ATSDR, 1999).

5.2.3.4 Chronic Toxicity—

Although both elemental and methylmercury produce a variety of health effects at relatively high exposures, neurotoxicity is the effect of greatest concern. This is true whether exposure occurs to the developing embryo or fetus during pregnancy or to adults and children.

Human exposure to methylmercury has generally been through consumption of contaminated food. Two major episodes of methylmercury poisoning through fish consumption have occurred. The first occurred in the early 1950s among people, fish-consuming domestic animals such as cats, and wildlife living near Minamata City on the shores of Minamata Bay, Kyushu, Japan. The source of the methylmercury contamination was effluent from a chemical factory that used mercury as a catalyst and discharged wastes into the bay where it accumulated in the tissues of fish and shellfish that were dietary staples of this population. Average fish consumption was reported to be in excess of 300 g/d (reviewed by Harada et al., 1995); 20 times greater than is typical for recreational fishers in the United States. By comparison, about 3 to 5 percent of U.S. consumers routinely eat 100 grams of fish per day. Among women of childbearing age, 3 percent routinely eat 100 grams of fish per day.

Symptoms of Minamata disease in children and adults included: impairment of peripheral vision, disturbances in sensations ("pins and needles" feelings, numbness) usually in the hands and feet and sometimes around the mouth, incoordination of movements as in writing, impairment of speech, hearing, and walking, and mental disturbances. It sometimes took several years before individuals were aware that they were developing the signs and symptoms of methylmercury poisoning. Over the years, it became clear that nervous system damage could occur to the fetus if the mother ate fish contaminated with methylmercury during pregnancy.

In 1965, another methylmercury poisoning incident occurred in the area of Niigata, Japan. The signs and symptoms of disease in Niigata were similar to those of methylmercury poisoning in Minamata.

Methylmercury poisoning also occurred in Iraq following consumption of seed grain that had been treated with a fungicide containing methylmercury. The first outbreak occurred prior to 1960; the second occurred in the early 1970s. Imported mercury-treated seed grains that arrived after the planting season were ground into flour and baked into bread. Unlike the long-term exposures in Japan, the epidemic of methylmercury poisoning in Iraq was short in duration lasting approximately 6 months.

The signs and symptoms of disease in Iraq were predominantly in the nervous system: difficulty with peripheral vision or blindness, sensory disturbances, incoordination, impairment of walking, and slurred speech. Both children and adults were affected. Infants born to mothers who had consumed methylmercury-contaminated grain (particularly during the second trimester of pregnancy) showed nervous system damage even though the mother was only slightly affected.

Recent studies have examined populations that are exposed to lower levels of methylmercury as a consequence of routine consumption of fish and marine mammals, including studies of populations around the Great Lakes and in New Zealand (Kjellstrom et al., 1986a, 1986b), the Amazon basin (e.g., Lebel et al., 1996; Marsh et al., 1995b), the Seychelles Islands (Marsh et al., 1995a), and the Faroe Islands (Dahl et al., 1996). The last two studies are of large populations of children presumably exposed to methylmercury in utero. Very sensitive measures of developmental neurotoxicity in these populations are still being analyzed and published. A 1998 workshop discussed these studies and concluded that they have provided valuable new information on the potential health effects of methylmercury. Significant uncertainties remain, however, because of issues related to exposure, neurobehavioral end points, confounders and statistics, and study design.

The EPA interim RfD for methylmercury is based on data on neurologic changes in 81 Iraqi children who had been exposed in utero; that is, their mothers had eaten methylmercury-contaminated bread during pregnancy. The data were

collected by interviewing the mothers of the children and by clinical examination by pediatric neurologists conducted approximately 30 months after the poisoning episode. The incidence of several endpoints (including late walking, late talking, seizures, or delayed mental development and scores on clinical tests of nervous system function) were mathematically modeled to determine a mercury level in hair (measured in all the mothers in the study) that was associated with no adverse effects. Delays in motor and language development were defined by the following criteria:

- Inability to walk two steps without support by 2 years of age
- Inability to respond to simple verbal communication by age 2 years among children with good hearing
- Scores on physical examination by a neurologist who assessed cranial nerve signs, speech, involuntary movements, limb tone, strength, deep tendon reflexes, plantar responses, coordination, dexterity, primitive reflexes, sensation, posture, and ability to sit, stand, walk, and run
- Assessment of mental development or the presence of seizures based on interviews with the child's mother.

In calculating the mercury level in hair that was associated with no adverse effects in children exposed in utero, EPA used a benchmark dose (in this instance the lower bound for 10 percent risk of neurological changes) based on modeling of all effects in children. This lower bound was 11 ppm methylmercury in maternal hair. A dose-conversion equation was used to estimate a daily intake of 1.1 µg methylmercury/kg body weight-day that, when ingested by a 60-kg individual, will maintain a concentration of approximately 44 µg/L of blood or a hair concentration of 11 µg mercury/g hair (11 ppm).

A composite uncertainty factor of 10 was used to account for the following: variability in the human population (particularly the variation in biological half-life and variability in the hair-to-blood ratio for mercury), lack of data on long-term sequelae of exposure, and the lack of a two-generation reproductive study. The resulting interim RfD for methylmercury is 1×10^{-4} mg/kg-d or 0.1 µg/kg-d (IRIS, 1999).

The range of uncertainty in the interim methylmercury RfD and the factors contributing to this range were evaluated in qualitative and quantitative uncertainty analyses. The uncertainty analyses indicated that paresthesia (numbness or tingling) in the hands and feet and occasionally around the mouth in adults is not the most reliable endpoint for dose-response assessment because it is subject to the patient's recognition of the effect. Paresthesia in adults is not the basis for EPA's interim methylmercury RfD.

There are, however, uncertainties associated with the interim RfD based on developmental effects from methylmercury in children exposed in utero. There are difficulties with reliability in recording and classifying events such as late walking in children because the data were collected approximately 30 months after the child's birth. In addition, the data were collected on a population that did not necessarily follow Western cultural practices or use Western calendars in the recording of events such as first steps or first words. It should be noted, however, that the endpoints used represented substantial developmental delays; for example, a child's inability to walk two steps without support at 2 years of age, inability to talk based on use of two or three meaningful words by 2 years, or presence of generalized convulsive seizures. There is both variability and uncertainty in the pharmacologic parameters that were used in estimating the ingested mercury dose. There is also a degree of uncertainty introduced by the size of the study population (81 mother-child pairs).

The interim RfD is supported by additional studies in children exposed in utero. These include investigations among Cree Indians in Canada and New Zealanders who consume large amounts of fish. In these studies, the hair concentration of mercury was used to monitor mercury exposure over time. Conclusions by the investigators in their official reports cite developmental delays among the children born of mothers whose hair mercury concentrations during pregnancy were 6 to 18 ppm, consistent with the benchmark dose of 11 ppm. The published data on the pilot study portion of the ongoing work in the Seychelles Islands (data on children of about 5 years of age) are also consistent with EPA's benchmark dose.

A 1997 review by the Science Advisory Board determined that the RfD is scientifically sound as supported by data in published human and animal studies. The RfD is a risk assessment tool, not a risk management decision. Judgments as to a "safe" dose and exposure are decisions that involve risk management components.

Two new major prospective longitudinal studies, one in the Seychelles Islands and the other in the Faroe Islands, have recently begun to publish their findings in the literature. In November 1998, a federally sponsored workshop, Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury, concluded that the results from the Faroe and Seychelles Islands studies are credible and provide valuable new information on the potential health effects of methylmercury. Significant uncertainties remain, however, because of issues related to exposure, neurobehavorial endpoints, confounders and statistics, and design (NIEHS, 1999).

The Science Advisory Board stated that the Seychelles and Faroe Island studies have advantages over the studies in Iraq and New Zealand; they have much larger sample sizes, a larger number of developmental endpoints, potentially more sensitive developmental endpoints, and control a more extensive set of potentially confounding factors. However, the studies also have some limitations in terms of low exposures and ethnically homogeneous societies. The SAB

concluded that the interim RfD may need to be reassessed in terms of the most sensitive endpoints from these new studies. The National Academy of Sciences (NAS) conducted an independent assessment of the interim RfD. They concluded "On the basis of its evaluation, the committees' consensus is that the value of EPA's current RfD for methylmercury, 0.1 µg/kg per day, is a scientifically justifiable level for the protection of public health." However, the NAS recommended that the Iraqi study no longer be used as the scientific basis for the RfD. They recommended that the developmental neurotoxic effects of methylmercury reported in the Faroe Islands study be used for the derivation of the RfD (NAS, 2000a).

5.2.3.5 Reproductive and Developmental Toxicity—

Data are available on reproductive and developmental effects in rats, mice, guinea pigs, hamsters, and monkeys. Convincing data from a number of human studies i.e., Minamata Japan) also indicate that methylmercury causes subtle to severe neurologic effects depending on dose and individual susceptibility. EPA considers methylmercury to have sufficient human and animal data to be classified as a developmental toxicant.

Methylmercury accumulates in body tissue; consequently, maternal exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing fetus. In addition, infants may be exposed to methlymercury through breast milk. Therefore, it is advisable to reduce methylmercury exposure to women with childbearing potential to reduce overall body burden.

5.2.3.6 Mutagenicity—

Methylmercury appears to be clastogenic but not to be a point mutagen; that is, mercury causes chromosome damage but not small heritable changes in DNA.

EPA has classified methylmercury as being of high concern for potential human germ cell mutagenicity. The absence of positive results in a heritable mutagenicity assay keeps methylmercury from being included under the highest level of concern. The data on mutagenicity were not sufficient, however, to permit estimation of the amount of methylmercury that would cause a measurable mutagenic effect in a human population.

5.2.3.7 Carcinogenicity—

Experimental animal data suggest that methylmercury may be tumorigenic in animals. Chronic dietary exposures of mice to methylmercury resulted in significant increases in the incidences of kidney tumors in males but not in females. The tumors were seen only at toxic doses of methylmercury. Three human studies have been identified that examined the relationship between methylmercury exposure and cancer. There was persuasive evidence of

increased carcinogenicity attributable to methylmercury exposure in any of these studies. Interpretation of these studies was limited by poor study design and incomplete descriptions of methodology and/or results. EPA has not calculated quantitative carcinogenic risk values for methylmercury (IRIS, 1999). EPA has found methylmercury to have inadequate data in humans and limited evidence in animals and has classified it as a possible human carcinogen, Group C.

All of the carcinogenic effects were observed in the presence of profound damage to the kidneys. Tumors may be formed as a consequence of repair in the damaged organs. Evidence points to a mode of action for methylmercury carcinogenicity that operates at high doses certain to produce other types of toxicity in humans. Given the levels of exposure most likely to occur in the U.S. population, even among consumers of large amounts of fish, methylmercury is not likely to present a carcinogenic risk.

5.2.3.8 Special Susceptibilities—

The developing fetus is at greater risk from methylmercury exposure than are adults. Data on children exposed only after birth are insufficient to determine if this group has increased susceptibility to central nervous system effects of methlymercury. In addition, children are considered to be at increased risk of methylmercury exposure by virtue of their greater food consumption (mg food/kg body weight) by comparison to adult exposures. Additional risk from higher mercury ingestion rates may also result from the apparently decreased ability of children's bodies to eliminate mercury.

5.2.3.9 Interactive Effects—

Potassium dichromate andatrazine may increase the toxicity of mercury, although these effects have been noted only with metallic and inorganic mercury. Ethanol increases the toxicity of methylmercury in experimental animals. Vitamins D and E, thiol compounds, selenium, copper, and possibly zinc are antagonistic to the toxic effects of mercury (ATSDR, 1999).

5.2.3.10 Critical Data Gaps—

Additional data are needed on the exposure levels at which humans experience subtle, but persistent, adverse neurological effects. Data on immunologic effects and reproductive effects are not sufficient for evaluation of low-dose methyl-mercury toxicity for these endpoints.

5.2.3.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	1×10^{-4} mg/kg-d
Carcinogenicity	Group C (possible human carcinogen).

5.2.3.12 Major Sources—

ATSDR (1999), IRIS (1999), Shubat (1993a), Stern (1993), U.S. EPA (1997d).

5.2.4 Selenium

5.2.4.1 Background—

Selenium is an element that occurs naturally in many areas and is produced through industrial processes. It is an essential nutrient with a recommended dietary allowance (RDA) of 55 µg/d (0.055 mg) for adult men and women. The Tolerable Upper Intake Level for adults is set at 400 µg/d (0.4 mg/d) based on selenosis as the adverse effect (NAS, 2000b). ATSDR has identified daily intake at nontoxic levels of approximately 0.05 to 0.15 mg/d (ATSDR, 1996a; HSDB, 1993). This is approximately equivalent to 7×10^{-4} to 2×10^{-3} mg/kg-d in a 70-kg individual.

Selenium plays a critical role in the antioxidant enzyme glutathione peroxidase. Selenium deficiency has been associated with muscle degeneration in humans. A serious form of this, congestive cardiomyopathy (Keshan disease), has been studied in areas of China with low naturally occurring levels of selenium. Selenium has also been shown to have a protective effect against chemically induced cancers in laboratory animals (Robbins et al., 1989). Although selenium is an essential nutrient, it is toxic at high exposure levels and is mutagenic in some test systems (ATSDR, 1996a).

Definitive information concerning the chemical forms of selenium found in fish is not available (U.S. EPA, 1993a). Due to the lack of information on chemical forms, the toxicities of a variety of selenium forms are included in the discussion below. In some parts of the United States, particularly in western states, soil concentrations lead to selenium levels in plants that can cause human exposure at potentially toxic levels (ATSDR, 1996a). This exposure should be considered in evaluating the overall exposure to selenium and in developing fish consumption advisories.

5.2.4.2 Pharmacokinetics—

Selenium contained in food is generally associated with proteins as organic selenium compounds. It is easily absorbed by the body and accumulates primarily in the liver and kidneys. It accumulates to a lesser extent in the blood, lungs, heart, testes, and hair. Most of the selenium that enters the body is quicky excreted in the urine, feces, and breath (ATSDR, 1996a).

5.2.4.3 Acute Toxicity—

Signs of acute selenium poisoning include difficulty in walking; labored breathing; cyanosis of the mucous membranes; congestion of the liver; endocarditis and myocarditis; degeneration of the smooth musculature of the GI tract, gall bladder and bladder; and erosion of the long bones. Subacute selenosis (prolonged exposure at relatively high doses) causes impaired vision, ataxia, disorientation, and respiratory distress (IRIS, 1999). "Blind staggers" disease is a disease in livestock that results from acute consumption of plants high in selenium. It is characterized by impaired vision, aimless wandering behavior, reduced consumption of food and water, and paralysis (ATSDR, 1996a).

5.2.4.4 Chronic Toxicity—

IRIS provides an RfD of 0.005 mg/kg-d for selenium and selenium compounds based on a NOAEL of 0.015 mg/kg-d from a 1989 human epidemiological study that found clinical selenosis at the LOAEL of 0.023 mg/kg-d. The NOAEL was calculated from regression analysis of blood selenium levels and selenium intake. An uncertainty factor of 3 rather than 10 was used for intraspecies variability. EPA has medium confidence in the study on which the RfD was based due to some possible interactions that were not fully explored. But because there are many animal and epidemiologic studies that support the principal study, EPA has high confidence in the database and, consequently, in the RfD (IRIS, 1999).

In epidemiological studies of populations exposed to high levels of selenium in food and water, discoloration of the skin, loss of nails and hair, excessive tooth decay and discoloration, garlic odor in the breath and urine, lack of mental alertness, and listlessness were reported (IRIS, 1999). In high-selenium areas of China, peripheral anesthesia and pain in the limbs have been reported. Exaggerated tendon reflexes, convulsions, paralysis, and hemiplegia were estimated to occur at a minimum chronic exposure of 0.053 mg/kg-d. A NOAEL of 0.027 mg/kg-d was estimated (ATSDR, 1996a).

In animals, neurological dysfunction, respiratory distress, skin lesions with alopecia, necrosis and loss of hooves, emaciation, and liver toxicity as indicated by increases in serum transaminases and alkaline phosphatase have been seen (IRIS, 1999). Cows with high, naturally occurring dietary exposures were found to have irritation in the upper GI tract (ATSDR, 1996a; IRIS,1999).

Lifetime exposure of mice to sodium selenate or sodium selenite at 0.57 mg/kg-d caused amyloidosis of the lung, liver, kidney, adrenal gland, and heart. Mice appear to be more sensitive to selenium with regard to lung toxicity than rats. (ATSDR, 1996a).

Hematological effects have been observed in multiple acute and chronic animal studies. Rats subchronically exposed to wheat containing selenium at a dose of

0.56 mg/kg-d for 6 weeks had a 79 percent reduction of blood hemoglobin (ATSDR, 1996a).

Bone softening in rats has been noted with an LOAEL of 0.2 mg/kg-d with exposure over several months (less than 100 days). Other musculoskeletal effects have also been observed in livestock. Adverse effects on the liver and kidneys have been observed in multiple animal studies with LOAELs of 0.1 mg/kg-d and above. Endocrine effects have been observed in animals fed seleniferous wheat at doses of 0.4 mg/kg-d for 6 weeks. Dermal effects have been observed at doses as low as 0.016 mg/kg-d in humans with dietary exposure (ATSDR, 1996a). Depression of the immune system was observed in rats exposed subchronically to sodium selenite at 0.7 mg/kg-d. At lower doses (0.07 mg/kg-d and 0.28 mg/kg-d), mixed results were obtained, with a stimulation of some components of the immune system and depression of others (ATSDR, 1996a).

5.2.4.5 Reproductive and Developmental Toxicity—

Limited information is available on the reproductive and developmental toxicity of selenium in humans. In animals, selenium has caused growth retardation, decreased fertility, embryotoxicity, fetotoxicity, and teratogenic effects.

A multigenerational study in mice dosed with selenate at 0.39 mg/kg-d identified a significant increase in young deaths in the F1 generation and increased runts in the F1 through F3 generations. Because only one dose was used, only a LOAEL can be obtained from this study. A one-generation mouse study found a NOAEL of 0.39 mg/kg-d. An early five-generation study identified a NOAEL of 0.075 mg/kg-d and a LOAEL of 0.125 mg/kg-d with a 50 percent reduction in the number of young reared at that dose (IRIS, 1999).

Multiple studies have determined that exposure of livestock (e.g., sheep, pigs, cattle) to naturally seleniferous diets resulted in fetal malformations and interference with normal fetal development. Malformations were associated with other manifestations of toxicity. The specific selenium compounds associated with these effects have not been identified (ATSDR, 1996a). At 0.4 mg, pigs exposed from 8 weeks of age had offspring with significantly reduced birth weight and weaning weights (ATSDR, 1996a).

Chronic exposure studies in animals have identified multiple adverse effects on the reproductive ability of animals and on offspring viability. Effects include: altered menstrual cycles in monkeys exposed to 0.08 mg/kg-d for 30 days, reduced rates of conception at 0.4 mg/kg-d in pigs exposed from 8 weeks of age (other offspring effects are listed under developmental effects), abnormal length estrus cycles in rats exposed subchronically to 0.31 mg/kg-d, increased fetal resorption and decreased conception rate in livestock exposed at a LOAEL of approximately 0.5 mg/kg-d, failure to breed in a three-generation study of mice exposed at 0.57 mg/kg-d, no effects in a two-generation study of rats at 0.21

mg/kg-d, and a 50 percent reduction in the number of young successfully reared with maternal exposure to 0.35 mg/kg-d for 1 year. Male fertility also appears to be affected by selenium exposure. Decreased sperm counts have been observed in male rats exposed subchronically to 0.1 mg/kg-d and higher while abnormal sperm and decreased testicular weights were observed at 0.2 mg/kg-d (ATSDR, 1996a).

5.2.4.6 Mutagenicity—

Data on the mutagenicity of selenium and its compounds are mixed. There are many positive mutagenicity assays on selenium compounds including unscheduled DNA synthesis, increased chromosomal aberrations in human lymphocytes and in the bone marrow of rats, and an increase in sister chromatid exchanges in human whole-blood cultures. There are also assays with negative results (IRIS, 1999).

Inorganic selenium compounds appear to have genotoxic effects at relatively high doses and antigenotoxic effects at lower doses. For example, a study of mice exposed to mutagens and given doses of 0.05 to 0.125 mg/kg-d of selenium indicates that selenium may inhibit the mutagenic effects of chemical agents (ATSDR, 1996a).

5.2.4.7 Carcinogenicity—

Epidemiological studies that used the selenium concentration in crops as an indicator of dietary selenium have generally reported an inverse association between selenium levels and cancer occurrence. Animal studies have reported that selenium supplementation results in a reduced incidence of several tumor types (ATSDR, 1996; IRIS, 1999). EPA has determined that selenium is not classifiable as to its carcinogenicity in humans (Group D) because of insufficient data. EPA has classified selenium sulfide, an insoluble salt, as a probable human carcinogen (B2) based on liver and lung tumors in oral exposure studies in multiple species (IRIS, 1999).

5.2.4.8 Special Susceptibilities—

ATSDR has listed the following groups as potentially having greater susceptibility: pregnant women and their fetuses, persons exposed to high fluoride levels in drinking water (evidence equivocal), those with vitamin E deficiencies, and insulin-dependent diabetics (ATSDR, 1996a).

5.2.4.9 Interactive Effects—

Selenium alters the toxicity of many chemicals. It reduces the toxicity of mercury, cadmium, lead, silver, and copper. Most forms of selenium interact with arsenic to reduce the toxicity of both elements. Selenium also interacts with vitamins,

sulfur-containing amino acids, xenobiotics, and essential and nonessential elements (ATSDR, 1996a).

5.2.4.10 Critical Data Gaps—

ATSDR has reported the following data gaps: human epidemiological data for all relevant effects, relationship between selenium dietary exposure levels and cancer; mechanisms of genotoxicity, reproductive, immunotoxicity, neurotoxicity, especially behavioral and histopathological CNS effects, pharmacokinetic, and bioaccumulation; and bioavailability from environmental media (ATSDR, 1996a).

5.2.4.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	5×10^{-3} mg/kg-d
Carcinogenicity	Group D (not classifiable).

5.2.4.12 Major Sources—

ATSDR (1996a), HSDB (1993), IRIS (1999).

5.2.5 Tributyltin Oxide

5.2.5.1 Background—

Tributyltin oxide belongs to the organometallic family of tin compounds that have been used as biocides, disinfectants, and antifoulants. This compound and other tributyltin compounds have high bioconcentration factors in aquatic organisms and are acutely and chronically toxic to these organisms at low concentrations. Because of concerns over these compounds' effects on nontarget aquatic species, in 1986 EPA initiated a special review of tributyltin compounds used as antifoulants (U.S. EPA, 1986e). In 1988, the Organotin Antifouling Paint Control Act (OAPCA) was enacted, which contained interim and permanent tributyltin restrictions as well as environmental monitoring, research, and reporting requirements.

The tributyltin compounds registered for use as antifoulants are: tributyltin oxide, tributyltin adipate, tributyltin dodecenyl succinate, tributyltin sulfide, tributyltin acetate, tributyltin acrylate, tributyltin fluoride, tributyltin methacrylate, and tributyltin resinate (U.S. EPA, 1986e). This toxicological profile discusses only tributyltin oxide, since this is the only tributyltin compound with risk assessment information (an RfD) and there is more toxicological information on this compound than any other.

5.2.5.2 Pharmacokinetics—

The pharmacokinetic information available consists of data on organotin compounds as a group; there are few data specific to tributyltin oxide. Organotin

compounds appear to be absorbed in mammals, with studies in rats showing detection of tin compounds in the gastrointestinal tract, kidney, and liver, with little retention observed in the brain and blood. One study specific to tributyltin oxide found the highest levels of tin in the liver and kidneys, with levels in the brain and adipose tissue at 10 to 20 percent of the liver and kidney levels. The metabolism of organotin compounds appears to involve dealkylation, with the liver as the active site. There are no data regarding the excretion of organotin compounds (ATSDR, 1992).

5.2.5.3 Acute Toxicity—

The limited available data show tributyltin oxide to be quite toxic to animals, with oral LD_{50}s ranging between 122 and 194 mg/kg in rats (ATSDR, 1992; HSDB, 1999) and 52 to 130 mg/kg in mice (WHO, 1999).

5.2.5.4 Chronic Toxicity—

There are no studies on the effects of tributyltin oxide in humans. Animal studies have shown effects on the blood (lowered corpuscular volume and hemoglobin mass and decreased leukocytes) and liver, and immunological effects including thymus atrophy and depletion of T-lymphocytes in the spleen and lymph nodes from tributyltin exposure (ATSDR, 1992; HSDB, 1999).

IRIS provides an RfD for tributyltin oxide of 3.0×10^{-4} mg/kg-d, based on a benchmark dose (10 percent relative change as the benchmark response) of 0.03 mg/kg-d and an uncertainty factor of 100. This was based on a chronic rat feeding study in which immunotoxicity was observed. The uncertainty factor of 100 reflects the uncertainty in extrapolating from laboratory animals to humans and the uncertainty in the range of human sensitivity (IRIS, 1999; U.S. EPA, 1997g).

EPA has high confidence in the studies on which the RfD was based, medium to high confidence in the overall database, and medium to high confidence in the RfD. This is based on the fact that the principal study was a well-designed and well-conducted chronic toxicity assay.(IRIS, 1999; U.S. EPA, 1997g).

5.2.5.5 Reproductive and Developmental Toxicity—

No studies are available on the reproductive and developmental effects of tributyltin oxide in humans. In a two-generation reproductive study in rats, there were no effects on mating, pregnancy, fertility, litter size, or pup survival in either generation. Compound-related developmental effects were limited to decreased pup body weight during lactation in both generations at the high dose. The NOAEL for reproductive toxicity in this study was 4.4 mg/kg-d, the highest dose tested. The NOAEL for developmental toxicity was 0.34 mg/kg-d (U.S. EPA, 1997g). When pregnant rats were exposed to high doses of tributyltin oxide (>10 mg/kg-d), decreased numbers of live births and decreased growth and viability of

the offspring were reported. While these findings demonstrate the fetotoxic potential of tributyltin oxide, a nonspecific effect of tributyltin oxide cannot be ruled out because of overt maternal toxicity seen at the doses used (HSDB, 1993). A developmental study in mice reported dose-related decreases in fetal weights, some skeletal abnormalities, such as fused ribs and cleft palates, at all dose levels and also in the controls. Weaknesses of this study include the occurrence of developmental effects in both treated and control animals, maternal toxicity, and lack of information on the statistical evaluation of the data (ATSDR, 1992; U.S. EPA, 1997g).

5.2.5.6 Mutagenicity—

Results from in vitro studies on tributyltin oxide have been primarily negative. Tributyltin oxide was negative in a variety of studies with *Salmonella typhimurium* and Chinese hamster cells; the only positive results were with metabolic activation. In vivo studies were also mainly negative; the compound was negative in *Drosophila melanogaster* and in the micronucleus test (at cytotoxic doses) in mice. One positive result was obtained in the micronucleus test where increased micronuclei in erythrocytes were noted (ATSDR, 1992; HSDB, 1999).

5.2.5.7 Carcinogenicity—

No human studies are available. Cancer bioassays following oral exposure have been conducted in rats and mice. The study in rats noted an increased incidence of some benign tumors at the highest dose level. However, this study is inconclusive because of increased mortality at the high dose and variable background rates for the tumors observed. In the mouse study, no increase in tumor incidence was observed. EPA has classified tributyltin oxide as Group D for carcinogenicity - not classifiable as to human carcinogenicity (U.S. EPA, 1997g).

5.2.5.8 Special Susceptibilities—

There is some evidence that a child might be more sensitive to the toxic effects of tributyltin oxide. For example, preweanling rats were shown to be more sensitive than adult rats to the immunotoxic effects of tributyltin oxide. Because the RfD is based on the effects observed when weanlings were dosed for the remainder of their lives, any potential childhood sensitivity is already accounted for. Animal toxicity studies showed no evidence of gender differences in the toxic responses to tributyltin oxide (U.S. EPA, 1997g).

5.2.5.9 Interactive Effects—

Limited information is available on the interactive effects of tributyltin oxide. Sulfur-containing compounds have been shown, in vitro, to interact with tributyltin compounds to produce other compounds with lower hemolytic activity (ATSDR, 1992).

5.2.5.10 Critical Data Gaps—

No human data are available to characterize the toxicity of tributyltin oxide. A wealth of data from laboratory animals, however, is available. These data adequately characterize the noncancer toxicity from oral exposure to tributyltin oxide. EPA has high confidence in this assessment. The species studied include monkey, dog, rat, and mouse. In addition, there is a two-generation reproduction study and several developmental studies in rats and mice. The principal study and a variety of supporting studies convincingly demonstrate that the critical effect for tributyltin oxide is immunotoxicity. The potential for neurotoxicity has not been completely studied (U.S. EPA, 1997g).

5.2.5.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	3.0×10^{-4} mg/kg-d
Carcinogenicity	Group D (not classifiable).

5.2.5.12 Major Sources—

ATSDR (1992a), HSDB (1999), IRIS (1999), U.S. EPA (1997g).

5.3 ORGANOCHLORINE PESTICIDES

5.3.1 Chlordane

5.3.1.1 Background–

Chlordane is an organochlorine insecticide comprised of the sum of *cis*- and *trans*-chlordane and *trans*-nonachlor and oxychlordane for purposes of health advisory development (U.S. EPA, 1997e). First introduced in 1947, it was used extensively on agricultural crops, livestock, lawns, and for termite control. Because of concern over cancer risk, human exposure, and effects on wildlife, most uses were banned in 1978, and all uses were banned by 1988. Due to its long half-life and ability to concentrate in biological materials, it is still widely distributed in fish in the United States.

5.3.1.2 Pharmacokinetics–

Chlordane is extremely lipid soluble, and lipid partitioning of chlordane and its metabolites has been documented in both humans and animals. Concen trations of chlordanes (cis- and trans-isomers and metabolites) detected in human liver samples were 17-fold higher when expressed on a fat rather than a wet weight basis. Chlordane is metabolized via oxidation, which results in a number of metabolites, including oxychlordane, that are very persistent in body fat. Reductive dehalogenation of chlordane forms free radicals, which are hypothesized to be significant in chlordane toxicity (ATSDR, 1994a).

Human studies have found chlordane in pesticide applicators, residents of homes treated for termites, and those with no known exposures other than background (e.g., food or airborne). Human milk fat contained a mean chlordane residue of approximately 188 ppm. Oxychlordane residues were detected in 68 percent of human milk samples in a low-pesticide-usage area and in 100 percent of the 50 samples tested in Hawaii. It is anticipated that all routes of exposure were involved in maternal exposure to chlordane. Fat accumulation of chlordane appears to depend on the exposure duration (ATSDR, 1994a).

Mechanisms of toxicity include: the binding of chlordane and its metabolites irreversibly to cellular macromolecules, causing cell death or disrupting normal cellular function; increasing tissue production of superoxide radicals, which accelerates lipid peroxidation and disrupts the function of membranes; possible suppression of hepatic mitochondrial energy metabolism; and alteration of neurotransmitter levels in various regions of the brain; a reduction in bone marrow stem cells prenatally; and suppression of gap junction intercellular communication (ATSDR, 1994a).

5.3.1.3 Acute Toxicity—

Chlordane is moderately to highly toxic with an estimated lethal dose to humans of 6 to 60 g (IRIS, 1999). Effects reported in humans after acute exposure include headaches, irritability, excitability, confusion, incoordination, seizures, and convulsions. There is also some evidence that acute exposures to chlordane may be associated with immunologic dysregulation, aplastic anemia in humans (U.S. EPA, 1997e).

5.3.1.4 Chronic Toxicity—

IRIS provides an RfD of 5.0×10^{-4} mg/kg-d based on a NOAEL of 0.15 mg/kg-d for hepatic necrosis in a 2-yr feeding study in mice (IRIS, 1999). The LOAEL in the principal study was 0.75 mg/kg-d. An uncertainty factor of 300 was applied to the NOAEL, 10 each for inter- and intraspecies variability and 3 for lack of any reproductive studies. The confidence in the principal study is rated medium, as is the confidence in the database.

Multiple neurological effects have been reported in humans exposed both acutely and chronically to chlordane. When adults (109 women and 97 men) who had been exposed to uncertain levels of chlordane via both air and oral routes were examined, significant ($p < 0.05$) differences were observed with a battery of neurophysiological and neuropsychological function tests (U.S. EPA, 1997e). Also, profiles of mood states (including tension, depression, anger, vigor, fatigue, and confusion) all were affected significantly ($p < 0.0005$) as compared to a referent population.

5.3.1.5 Reproductive and Developmental Toxicity—

According to the IRIS file, "there have been 11 case reports of CNS effects, blood dyscrasias and neuroblastomas in children with pre/postnatal exposure to chlordane and heptachlor" (IRIS,1999).

ATSDR reports a number of developmental effects. Prenatal and early postnatal exposure in mice may have permanent effects on the immune system, including a reduction in the number of stem cells required to form the mature immune system. Effects were observed at 4 mg/kg-d. Neurological effects include abnormal behavior and increased seizure thresholds in mice at 1 mg/kg-d prenatal and postnatal (via lactation) exposure (no NOEL was identified). Alterations in plasma corticosterone levels were observed, which may result from a change in the neuroendocrinological feedback mechanisms (ATSDR, 1994a).

Concerning cancer in children, see the discussion in Section 5.3.1.7.

5.3.1.6 Mutagenicity—

Mutagenicity assays of chlordane have yielded mixed results, with positive results generally obtained in higher organism cell assays and negative results in bacterial assays (IRIS, 1999).

5.3.1.7 Carcinogenicity—

Chlordane is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. An increased incidence of hepatocellular carcinoma was observed in both sexes in mice in two separate studies using different strains. Hepatocellular carcinomas were also observed in another study in male mice using a third strain. The oral cancer slope factor of 0.35 per mg/(kg-d) is the geometric mean of the cancer potencies calculated from five data sets (IRIS, 1999).

Five compounds structurally related to chlordane (aldrin, dieldrin, heptachlor, heptachlor epoxide, and chlorendic acid) have produced liver tumors in mice. Chlorendic acid also has produced liver tumors in rats.

Neuroblastoma and acute leukemia have also been associated with prenatal and early childhood exposure to chlordane (ATSDR, 1994a).

5.3.1.8 Special Susceptibilities—

Based on the results of animal studies showing prenatal exposure causes damage to the developing nervous and immune systems, fetuses and children may be at greater risk than adults from chlordane exposure. According to ATSDR:

> Given the generally greater sensitivity to toxicants of incompletely developed tissues, it seems possible that prenatal exposure of humans to chlordane could result in compromised immunocompetence and subtle neurological effects (ATSDR, 1994a).

Due to the interactive effects of chlordane with other chemicals via microsomal enzymes (see Section 5.3.1.9), ATSDR has cautioned that: "doses of therapeutic drugs and hormones may require adjustment in patients exposed to chlordane." The results of an acute animal study suggest that protein-deficient diets may also increase the toxic effects of chlordane (ATSDR, 1994a).

ATSDR has listed the following populations as unusually susceptible: those with liver disease or impaired liver function; infants, especially those with a hereditary predisposition to seizures; and the fetus (ATSDR, 1994a).

5.3.1.9 Interactive Effects—

Chlordane is a potent inducer of hepatic microsomal enzymes. Chlordane exposure has been associated with an increased rate of metabolism of therapeutic drugs, hormones, and many other endogenous and xenobiotic compounds. Exposure to other chemicals that induce the same enzymes may increase the toxicity of chlordane by enhancing its metabolism to its toxic intermediate. The acute toxic effects of aldrin, endrin, and methoxychlor with chlordane were greater than the additive sum of the individual toxicities (ATSDR, 1994a).

It has been suggested that increased dietary vitamins C or E or selenium may be protective against free-radical-induced toxicity (ATSDR, 1994a).

MIXTOX reported synergistic effects between chlordane and endrin in mice exposed via gavage and both potentiation and inhibition with γ-hexachlorocyclohexane in rodents exposed via gavage. Synergism is reported with toxaphene and malathion together with chlordane in mice exposed via gavage (MIXTOX, 1992).

5.3.1.10 Critical Data Gaps—

IRIS lists the following data gaps for chlordane: chronic dog feeding study, rat reproduction study, rat teratology study, and rabbit teratology study (IRIS, 1999). Other studies that are needed include a multigeneration study, which includes a measurement of reproductive system toxicity, immunological effects—particularly with developmental exposures, pharmacokinetic studies, and studies to determine methods for reducing body burden (ATSDR, 1994a).

5.3.1.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	5×10^{-4} mg/kg-d
Carcinogenicity	0.35 per mg/kg-d.

5.3.1.12 Major Sources—

ATSDR (1994a), HSDB (1993), IRIS (1999), EPA (1997e).

5.3.2 DDT, DDE, DDD

5.3.2.1 Background—

DDT is an organochlorine pesticide that has not been marketed in the United States since 1972 but is ubiquitous due to its widespread use in previous decades and its relatively long half-life. DDT's close structural analogs, DDE and DDD, are metabolites of DDT and have also been formulated as pesticides in the past (Hayes, 1982). DDT is very widely distributed; it has been found in seals in

Finland and reptiles in the Everglades (HSDB, 1993). The NHANES II study (National Human Monitoring Program of the EPA) detected DDE, a metabolite of DDT, in 99 percent of the 12- to 74-yr-old study subjects (living in the Northeast, Midwest, and South). The median level was 11.8 ppb in blood serum (HSDB, 1993).

Although some use of DDT continues throughout the tropics, it remains of human health concern in the United States primarily due to its presence in water, soil, and food (Hayes, 1982). Because individuals are typically exposed to a mixture of DDE, DDT, and DDD and their degradation and metabolic products (ATSDR, 1994b), the sum of the 4,4'- and 2,4'- isomers of DDT, DDE, and DDD should be considered in the development of fish consumption limits for this group of chemicals (U.S. EPA, 1993a).

5.3.2.2 Pharmacokinetics—

DDT and its analogs are stored in fat, liver, kidney, and brain tissue; trace amounts can be found in all tissues (Hayes, 1982). DDE is stored more readily than DDT (Hayes, 1982). DDT is eliminated through first-order reduction to DDD and, to a lesser extent, to DDE. The DDD is converted to more water-soluble *bis* (p-chlorophenyl)-acetic acid, with a biological half-life of 1 year. DDE is eliminated much more slowly, with a biological half-life of 8 years. Because elimination occurs slowly, ongoing exposure may lead to an increase in the body burden over time.

5.3.2.3 Acute Toxicity—

The low effect dose for severe effects (acute pulmonary edema) in infants has been reported to be 150 mg/kg. In adults, behavioral effects were noted at 5 to 6 mg/kg and seizures at 16 mg/kg (HSDB, 1993).

Evidence from acute exposure studies of dogs indicates that DDT may sensitize the myocardium to epinephrine. This was observed for both injected epinephrine and epinephrine released by the adrenal glands during a seizure and resulted in ventricular fibrillation (Hayes, 1982). DDT may concurrently act on the CNS, in a manner similar to that of other halogenated hydrocarbons, to increase the likelihood of fibrillation (Hayes, 1982). Chronic exposure to 10 mg/kg-d did not produce increased incidence of arrhythmias in rats or rabbits (Hayes, 1982).

DDD is considered less toxic than DDT in animals. Symptoms develop more slowly and have a longer duration with DDD than with DDT exposure. Lethargy is more significant and convulsions are less common than with DDT exposure (HSDB, 1993).

5.3.2.4 Chronic Toxicity—

Extensive research has been conducted on chronic and subchronic exposure effects of DDT in animals and in humans working with DDT. These studies have primarily focused on carcinogenic effects, which are discussed in Section 5.3.2.7. Studies have also identified liver damage, and there is limited evidence that DDT may cause leukocytosis and decreased hemoglobin level (Hayes, 1982).

Immunological effects have been associated with exposure to DDT. Exposure to DDT at 2.63 mg/kg-d for 10 days resulted in immunological effects in rabbits. With 31 days of exposure at 1 mg/kg-d in rats, a decrease in the number of mast cells was observed. A relatively recent 8-week study in rabbits found decreases in germinal centers of the spleen and atrophy of the thymus at 0.18 mg/kg-d. Other effects were observed at higher doses. No studies were provided on immunological effects following chronic exposure (ATSDR, 1994b).

IRIS lists an oral RfD of 5×10^{-4} mg/kg-d for DDT based on liver effects with a NOAEL of 0.05 mg/kg-d from a 27-wk rat feeding study conducted in 1950. Uncertainty factors of 10 each for inter- and intraspecies variability were used; however, the usual factor of 10 for a less-than-lifetime study was not applied "because of the corroborating chronic study in the data base" (IRIS, 1999). The corroborating study was conducted in 1948.

5.3.2.5 Reproductive and Developmental Toxicity—

DDT causes embryotoxicity and fetotoxicity but not teratogenicity in experimental animals (ATSDR, 1994b). Studies indicate that estrogen-like effects on the developing reproductive system occur (ATSDR, 1994b). This also occurs with chronic exposure as discussed in Section 5.3.2.4. Rabbits exposed to 1 mg/kg-d early in gestation had decreased fetal brain, kidney, and body weights (ATSDR, 1994b). Prenatal exposure in mice at 1 mg/kg on 3 intermittent days resulted in abnormal gonad development and decreased fertility in offspring, which was especially evident in females (Hayes, 1982).

A three-generation rat reproduction study found increased offspring mortality at all dose levels with a LOAEL of 0.2 mg/kg-d. Three other reproduction studies found no effects at much higher dose levels (IRIS, 1999). Effects on the urogenital system were found with 8 days' prenatal exposure in mice. Behavioral effects in mice exposed prenatally for 7 days were noted at 17.5 mg/kg-d (HSDB, 1993).

Prenatal 1-day exposure of rabbits to DDT resulted in an abnormal persistence of preimplantation proteins in the yolk sac fluid. The results suggest that DDT caused a cessation of growth and development before implantation or during later uterine development. The authors suggest that damage can be repaired but may result in offspring with prenatal growth retardation in the absence of gross abnormalities (HSDB, 1993). Most dosages tested for these effects have been

relatively high. Postnatal exposure of rats for 21 days to 21 mg/kg (the only dose tested) resulted in adverse effects on lactation and growth.

In dogs, placental passage of DDT to the fetus has been demonstrated. This was confirmed in mice. Primary targets include the liver, adipose tissue, and intestine. Rabbit blastocysts (a very early stage of development) contained a significant amount of DDT shortly after administration to the mother (HSDB, 1993).

Biomagnification in human milk has been observed. In lactating women with an intake of 5×10^{-4} mg/kg-d of DDT, the milk contained 0.08 ppm. This was calculated to result in infant doses of 0.0112 mg/kg-d, which is approximately 20 times the dosage to the mothers (HSDB, 1993).

DDT is suspected of causing spontaneous abortion in humans and cattle (Hayes, 1982). The average concentration of DDE in the blood of premature babies (weighing <2,500 g) was significantly greater than those of higher birth weight infants (HSDB, 1993). The relationship between spontaneous abortion, premature delivery, and maternal exposure and body burden requires clarification.

DDT accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If a female has been exposed to DDT, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

DDT may have reproductive system toxicity. It appears to bind to uterine tissue and have estrogenic activity (Hayes, 1982). Metabolites of DDT bind to the cytoplasmic receptor for estrogen, which may result in inadvertent hormonal response (agonist) or depress normal hormonal balance (antagonist). Either may result in reproductive abnormalities (HSDB, 1993). The animal studies of the reproductive system have yielded mixed results. Chronic animal studies have identified LOELs that range over orders of magnitude. Serious adverse effects (decreased fertility and decreased litter size) have been observed at 0.35 and 0.91 mg/kg-d, respectively, in subchronic animal studies. Edema of the testes occurred at 2 mg/kg-d in a rat study. NOAELs are not available for these studies. Other studies have identified NOAELs ranging from 2.4 to 10 mg/kg-d with severe effects at 12 mg/kg-d (increased maternal and offspring death) (ATSDR, 1994b). Significant reproductive (function and lactation) abnormalities have also been observed at higher doses (83 mg/kg-d in rats and at 33.2 mg/kg-d in mice). Function abnormalities have also been observed in dogs (Hayes, 1982).

5.3.2.6 Mutagenicity--

Genotoxicity studies in human systems strongly suggest that DDT may cause chromosomal damage (ATSDR, 1994b). This is supported by in vitro and in vivo

studies in animals (ATSDR, 1994b) and in some bacterial assays (HSDB, 1993). There are multiple positive assays including human lymphocytes, human leukocytes, human fibroblasts, an oncogenic transformation, and unscheduled DNA synthesis in rats in multiple studies (ATSDR 1994b; HSDB, 1993).

5.3.2.7 Carcinogenicity—

DDE, DDT, and DDD are all considered probable human carcinogens (B2) based on animal studies, with cancer potencies of 0.24, 0.34, and 0.34 per mg/kg-d, respectively (IRIS, 1999). Liver tumors were associated with each chemical. It is noted in the IRIS file that 24 of the 25 carcinogenicity assays of DDT have yielded positive results. The occupational studies of workers exposed to DDT are of insufficient duration to assess carcinogenicity (IRIS, 1999). Elevated leukemia incidence, particularly chronic lymphocytic leukemia, was noted in two studies of workers. Lung cancer has also been implicated in one study. Bone marrow cells in experimental animals have also been affected by exposure, including an increase in chromosomal fragments in the cells (HSDB, 1993).

It is recommended that the total concentration of the 2,4'- and 4,4'-isomer of DDT and its metabolites, DDE and DDD, be evaluated as a group using the cancer potency of 0.34 per mg/kg-d (U.S. EPA, 1993a). In addition, the EPA Carcinogenicity Assessment Group has recommended that this value be used for combinations of dicofol with the above three compounds (U.S. EPA, 1993a).

5.3.2.8 Special Susceptibilities—

Based on the information obtained from a recent developmental study that found neurotoxicity and structural brain alterations at relatively low exposures (approximately 50-fold less than in adults), children may be at greater risk from DDT exposure than adults.

The results of the cardiac toxicity studies are not consistent; however, it is safest to assume that exposure to DDT or its analogs **may** pose a risk for individuals with cardiac disease at exposure levels estimated to be safe for the general population (Hayes, 1982).

Individuals exposed to DDT may metabolize some drugs more rapidly than the general population (HSDB, 1993). For example, increased phenobarbital metabolism resulting from an increased body burden of DDT (10 µg) led to a 25 percent decrease in effectiveness of the drug in experimental animals. The toxicity of chloroform was enhanced by the addition of DDT to the diet due to its capacity as a microsomal stimulator (HSDB, 1993). Alterations in the metabolism of drugs, xenobiotics, and steroid hormones may result from DDT exposure due to DDT's induction of the hepatic mixed-function oxidase system at relatively low doses (HSDB, 1993). Individuals who use medications that involve the mixed function oxidase system directly (MFO inhibitors) or through metabolic processes may be at risk for alteration of the drug's efficacy and/or timing if they are exposed

to DDT. Information is not available for this document on the specific relationships between various pharmaceuticals and DDT/DDE/DDD body burdens or intakes. This type of information merits further investigation.

ATSDR notes that persons with diseases of the nervous system or liver may be particularly susceptible to the effects of DDT (ATSDR, 1994b). Based on information discussed above concerning biomagnification in milk, nursing infants may also be at greater risk due to their increased exposure.

5.3.2.9 Interactive Effects—

As discussed in Section 5.3.2.8, DDT exposure may alter the response to drugs, xenobiotics, and endogenous steroid hormones. DDT is reported to promote some tumorigenic agents and antagonize others. The actions may be related to the induction of microsomal enzymes (ATSDR, 1994b).

5.3.2.10 Critical Data Gaps—

IRIS notes the lack of a NOAEL for reproductive effects and a relatively short duration for the critical study on which the RfD is based.

Information was not located for this document on the specific relationships between various pharmaceuticals and DDT/DDE/DDD body burdens or intakes. Information on the relationship between pre- and postnatal exposure and behavioral effects and maternal exposure and milk concentrations is also needed.

An interagency group of researchers from NTP, ATSDR, and EPA have identified the following data gaps: pharmacokinetic data; animal studies on respiratory, cardiovascular, GI, hematological, musculoskeletal, and dermal/ocular effects; the significance of subtle biochemical changes such as the induction of microsomal enzymes in the liver and the decreases in biogenic amines in the nervous system in humans; an epidemiological study in humans of estrogen-sensitive cancers including endometrial, ovarian, uterine, and breast cancer; reproductive system toxicity; developmental toxicity; a multiple assay battery for immunotoxicity; subtle neurological effects in humans; and mechanisms of neurotoxicity in the neonate (ATSDR, 1994b).

5.3.2.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	5×10^{-4} mg/kg-d (DDT only)
Carcinogenicity	0.34 per mg/kg-d. (sum of the 4,4' and 2,4'-isomers of DDT DDE, and DDD)

5.3.2.12 Major Sources—

ATSDR (1994b), Hayes (1982), HSDB (1993), IRIS (1999).

5.3.3 Dicofol (Kelthane)

5.3.3.1 Background—

Dicofol is an organochlorine miticide/pesticide first registered for use in 1957. Dicofol is used mainly on cotton, apples, and citrus crops; most of the use is in California and Florida (U.S. EPA, 1998a). Dicofol is considered a DDT analog based on its structure and activity (Hayes and Laws, 1991). In the past, dicofol often contained 9 to 15 percent DDT and its analogs. In 1989, EPA required that these contaminants constitute less than 0.1 percent of dicofol (HSDB, 1993).

5.3.3.2 Pharmacokinetics—

Studies with radiolabeled dicofol in rats indicated that most of the label was eliminated in the feces after oral dosing (U.S. EPA, 1998a). Intact dicofol was preferentially stored in adipose tissue. The major metabolic pathway was reductive halogenation to dichlorodicofol and subsequent oxidation to more water-soluble compounds.

5.3.3.3 Acute Toxicity—

The acute oral LD_{50} for dicofol in rats was 587 mg/kg (U.S. EPA, 1998a). A single large oral dose of dicofol to rats caused ataxia at 350 mg/kg and weight loss at 75 mg/kg. The NOAEL for neurotoxicity in this study was 15 mg/kg. An acute dietary RfD of 0.05 mg/kg-d was calculated based on this NOAEL and using an uncertainty factor of 300 (U.S. EPA, 1998a).

5.3.3.4 Chronic Toxicity—

No RfD is currently listed in the IRIS file for this chemical (IRIS, 1999). The OPP has recently derived an RfD of 0.0004 mg/kg-d for chronic dietary exposure (U.S. EPA, 1998a). The critical effect was hormonal toxicity, based on inhibition of adrenocortical trophic hormone (ACTH)-stimulated release of cortisol in dogs. The NOAEL of 0.12 mg/kg-d was divided by an uncertainty factor of 300 (10X for interspecies variation, 10X for intraspecies extrapolation, and 3X for the protection of infants and children.

5.3.3.5 Reproductive and Developmental Toxicity—

In a two-generation reproduction study in rats, the NOAEL for reproductive toxicity was 0.4 mg/kg-d based on the ovarian vacuolation in the F1 females, an effect on reproductive physiology. For offspring toxicity, the NOAEL was 2 mg/kg-d based on decreased F2 pup viability (U.S. EPA, 1998a).

In a special one-generation postnatal toxicity study in rats, the NOAEL for both offspring and parental toxicity was 1.7 mg/kg-d, based on histopathologic findings in the liver. No treatment-related effects were observed on parameters of

reproductive function or performance. The NOAEL for reproductive toxicity was >9.8 mg/kg-d (U.S. EPA, 1998a).

No developmental toxicity was seen in a study in rats. The NOAEL was 25 mg/kg-d, the highest dose tested. In a developmental toxicity study in rabbits, the NOAEL was 4 mg/kg-d, based on an increased incidence of abortions in the does at 40 mg/kg-d (U.S. EPA, 1998a).

5.3.3.6 Mutagenicity—

Dicofol was negative for mutagenicity in the Ames test and for structural chromosomal aberrations in Chinese hamster ovary cells. Dicofol did not induce a clastogenic response in the chromosomes of rat bone marrow cells after oral dosing (U.S. EPA, 1998a). Studies of dicofol in human lymphoid cells in vitro were positive with an incidence of events 13 times that of controls. It induced sister chromatid exchange with activation. Other mutagenicity studies in bacteria have yielded negative results (HSDB, 1993).

5.3.3.7 Carcinogenicity—

In 2-yr carcinogenicity studies in mice and rats, dicofol administration resulted in an increase in liver adenomas and combined liver adenomas and carcinomas in male mice (U.S. EPA, 1998a). No increase in tumor incidence was observed in female mice or in rats or in another 2-yr feeding study in either sex of rats. Dicofol has been classified as a group C carcinogen (possible human carcinogen) based on the increase in liver adenomas and combined liver adenomas and carcinomas in male mice (U.S. EPA, 1998a).

5.3.3.8 Special Susceptibilities—

Toxicity data for dicofol provide no indication of increased susceptibility of rats or rabbit fetuses following in utero exposures in the prenatal developmental toxicity studies or following postnatal exposure in the two-generation reproduction study. For this reason, the additional 10X Safety Factor for the protection of infants and children was reduced to 3X (U.S. EPA, 1998a).

5.3.3.9 Interactive Effects—

As with other organochlorine pesticides, microsomal enzyme induction occurs and may cause interactions with other chemicals. No additional data were located (U.S. EPA, 1998a).

5.3.3.10 Critical Data Gaps—

EPA is requiring a developmental neurotoxicity study in rats for dicofol (U.S. EPA, 1998a). No other data gaps were identified (U.S. EPA, 1998a).

5.3.3.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	4.0×10^{-4} mg/kg-d
Carcinogenicity	Group C (possible human carcinogen).

5.3.3.12 Major Sources—

HSDB (1993), U.S. EPA (1993e), U.S. EPA (1998a).

5.3.4 Dieldrin

5.3.4.1 Background—

Dieldrin is an organochlorine pesticide that was phased out between 1974 and 1987. Dieldrin was mainly used on soil-dwelling pests and for termite control. It continues to be detected nationwide due to its relatively long half-life. Dieldrin is also a product of aldrin metabolism, a structurally similar organochlorine pesticide which is also no longer in use (ATSDR, 1991).

5.3.4.2 Pharmacokinetics—

Dieldrin is absorbed from the GI tract and transported via the hepatic portal vein and the lymphatic system. It is found shortly after exposure in the liver, blood, stomach, and duodenum. Dieldrin is lipophilic and is ultimately stored primarily in fat and tissues with lipid components (e.g., brain) (ATSDR, 1991).

In dosing studies with volunteers at 0.0001 to 0.003 mg/kg-d over 2 years, the time to achieve equilibrium was approximately 15 months. A dynamic equilibrium was theorized with the average ratio of the concentration in adipose tissue to blood of 156. Cessation of dosing led to decreases in blood levels following first-order kinetics with a half-life ranging from 141 to 592 days and an average of 369 days (ATSDR, 1991).

The metabolism of dieldrin is described in detail in ATSDR (1991). Sex and species differences have been reported in the metabolism and tissue distribution of dieldrin based on chronic exposure studies and toxicokinetic studies in animals. Males appear to metabolize and excrete dieldrin more rapidly than females (ATSDR, 1991).

A correlation between exposure and dieldrin levels in human breast milk has been established. Placental transfer of dieldrin has been observed in women, with higher concentrations measured in fetal blood than in maternal blood (ATSDR, 1991).

5.3.4.3 Acute Toxicity—

Acute effects include possible hematological effects in humans (pancytopenia and thrombocytopenia, immunohemolytic anemia) (ATSDR, 1991). An estimated human lethal dose is 65 mg/kg (HSDB, 1993).

5.3.4.4 Chronic Toxicity—

IRIS provides an RfD of 5×10^{-5} mg/kg-d based on a NOAEL of 0.005 mg/kg-d from a 1969 2-year rat feeding study that found liver lesions (focal proliferation and hyperplasia). Uncertainty factors of 10 each for inter- and intraspecies variability were applied (IRIS, 1999). Liver toxicity has been observed in multiple animal studies and in human acute exposure episodes. Adaptive changes (e.g., liver enlargement) have been observed at 0.00035 mg/kg-d in a subchronic rat study.

Although the critical effect in the IRIS study was liver lesions, it was noted that, at the next highest dose (0.05 mg/kg-d), "all animals became irritable and exhibited tremors and occasional convulsions" (IRIS, 1999). There was no listing of additional neurobehavioral studies in the IRIS file. As an organochlorine pesticide, it is expected that dieldrin is a CNS toxicant. This is supported by acute toxicity effects of dieldrin and the neurotoxicity studies listed below.

Other effects associated with dieldrin exposure include: arterial degeneration in rats with a chronic exposure to 0.016 mg/kg-d, hematological disorders in experimental animals at 0.25 and 1 mg/kg-d, musculoskeletal pathology at 0.015 mg/kg-d in a chronic rat study, kidney degeneration and other changes at 0.125 mg/kg-d in chronic animal studies in multiple species, hypertension in humans (exposure level unknown), and multiple deficits in immune system function in multiple studies (ATSDR, 1991). Increased susceptibility to tumor cells was observed in a subchronic mouse study (dose not specified in material reviewed) (HSDB, 1993).

Neurological effects of dieldrin have been observed in experimental animals and in humans exposed acutely and chronically. Wheat mixed with aldrin and lindane was consumed for 6 to 12 months by a small human population. Effects were attributed to aldrin (converted to dieldrin via metabolism) because the wheat had been mixed with lindane in previous years without adverse effect. A variety of CNS disorders were observed, and abnormal EEGs were noted. Some symptoms (myoclonic jerks, memory loss, irritability) continued for at least 1 year after cessation of exposure. A child is believed to have developed mild mental retardation as a result of exposure. Quantitative exposure information was not available in the data reviewed (ATSDR, 1991).

Neurotoxicity has been observed in humans with chronic inhalation and dermal exposures (ATSDR, 1991). Chronic exposure of pesticide applicators to dieldrin led to idiopathic epilepsy, which ceased when exposure was terminated (HSDB,

1993). Dermal and inhalation exposure were the likely routes of exposure. No exposure quantitation was available.

A 1967 study of human exposure effects over 18 months at levels up to 0.003 mg/kg-d identified no effects on the CNS (as measured by EEG), peripheral nerve activity, or muscle activity (ATSDR, 1991).

Animal studies have identified neurological effects including behavioral disorders and learning deficits at doses of 0.1 to 0.25 mg/kg-d in subchronic and chronic studies. Higher doses produced more dramatic effects (e.g., convulsions, tremors). Cerebral edema and degeneration were found with chronic exposure of rats to 0.016 mg/kg-d (ATSDR, 1991). Neural lesions (cerebral, cerebellar, brainstem, and vascular) were observed in chronically exposed rats at 0.004 mg/kg-d (HSDB, 1993).

5.3.4.5 Reproductive and Developmental Toxicity—

IRIS provides limited information regarding the developmental toxicity of dieldrin. A NOAEL of 6 mg/kg-d was obtained from a mouse teratology study with exposure occurring from the 7th to 16th day of gestation. Fetotoxicity (decreased numbers of caudal ossification centers and an increased incidence of extra ribs) was observed with an LOAEL of 6 mg/kg-d. This study was not considered in development of the IRIS file because 41 percent of the maternal fatalities occurred at the LOAEL dose (IRIS, 1999).

A variety of effects in multiple organ systems have been observed in experimental animals exposed prenatally to dieldrin. Skeletal anomalies and malformations (e.g., cleft palate, webbed foot, open eyes, extra ribs) were identified at relatively large doses (LEL of 3 mg/kg-d) (ATSDR, 1991).

Abnormalities of the CNS, eye, and ear were noted with a TD L_o (similar to a LOAEL) of 30.6 mg/kg prenatal exposure, and craniofacial abnormalities were observed at a single prenatal dose of 15 mg/kg-d (HSDB, 1993). Liver damage has been observed in experimental animals at dosages as low as 0.016 mg/kg-d (ATSDR, 1991). Note that liver lesions are the basis for the chronic toxicity RfD derived from a study of adult animals, as reported in IRIS (IRIS, 1999). A multigeneration study in mice found histological changes in liver, kidney, lungs, and brain tissues in the first and second generation offspring at an LOAEL of 3 ppm (0.075 mg/kg-d) (HSDB, 1993).

Multiple studies have reported increased postnatal mortality following prenatal exposure to dieldrin. Studies in dogs, rats, and mice have found LELs of 0.125 to 0.65 mg/kg-d associated with high mortality in offspring in the absence of increased maternal mortality. Studies designed to evaluate the underlying causes of mortality suggest that cardiac glycogen depletion, leading to cardiac failure, may be causal (ATSDR, 1991).

Neural lesions in prenatally exposed rats were found at an LOAEL of 0.004 mg/kg-d. Effects included cerebral edema, internal and external hydrocephalus, and focal neuronal degeneration. Postnatal exposure of rats from day 5 of gestation to 70 days of age resulted in increased learning ability at 3.5×10^{-4} mg/kg-d (the only dose tested). ATSDR has cautioned that "interpretation of the results is difficult because the significance of improved performance in behavioral paradigms is unknown, and the study is limited because only one dose of dieldrin was tested" (ATSDR, 1991). In a rat multigeneration study, a TD L_o of 0.014 mg/kg-d with behavioral effects was observed (HSDB, 1993).

Dieldrin is known to accumulate in human milk. In one study of 102 samples in the United States, 91.2 percent of the samples contained measurable levels of dieldrin, with a mean concentration of 0.062 ppm lipid basis. Another U.S. study found 80 percent of the 1,436 samples were positive with a range of 0.16 to 0.44 ppm milk fat (HSDB, 1993). This indicates that lactation may provide a significant dietary source in infants with mothers who have been exposed to dieldrin. As discussed above, studies in humans also determined that dieldrin can pass through the placenta and is found in fetal blood.

Neurotoxicity appears to be a relatively sensitive endpoint for developmental toxicity. The association of neurotoxic effects with dieldrin exposure is supported by the observation of neurological effects in human populations exposed to dieldrin. The study noted in the paragraph above that identified neural lesions associated with prenatal exposure provided an LOAEL of 0.004 mg/kg-d provides the most sensitive developmental toxicity measure of those reviewed. If the LOAEL from this study were used to calculate an estimated exposure limit for developmental effects, the standard uncertainty factors would typically take into consideration inter- and intraspecies variability and the use of an LOAEL rather than a NOAEL.

As with the other organochlorines, it is anticipated that dieldrin can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If a female has been exposed to dieldrin, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

Dieldrin causes reproductive system disorders in animals and one study suggests that it may cause adverse effects in humans. In a study evaluating the blood and placental levels of organochlorines associated with premature labor or spontaneous abortions in women, positive results were obtained for aldrin. Most exposed subjects had multiple chemical exposures; consequently, interpretation of study results is difficult (ATSDR, 1991). See also notes regarding estrogenic activity in Section 5.3.4.7.

Studies of reproductive effects in animals indicate that exposure to dieldrin may cause a number of adverse effects. Dieldrin exposure causes changes in the levels of serum luteinizing hormone (LH) in females and gonadotropin in males. Dieldrin interferes with the binding of dihydrotestosterone to male sex hormone receptors (HSDB, 1993). These three hormones are critical to normal reproductive function. A mouse study found decreased fertility with exposure to 1.3 mg/kg-d in females and 0.5 mg/kg-d in males. Another study found no effects at much higher exposure levels. Adverse reproductive effects in dogs exposed at LOAEL of 0.15 mg/kg-d for 14 months prior to mating included increased stillbirth rates, delayed estrus, reduced libido, and a lack of mammary function and development. Maternal behavior was studied in mice exposed for 4 weeks prior to delivery until weaning at 1.95 mg/kg-d. Exposed maternal animals violently shook the pups, ultimately killing them; others neglected their litters (ATSDR, 1991).

5.3.4.6 Mutagenicity—

There is limited information on the mutagenicity of dieldrin. Positive in vivo studies have found an increased incidence in the number of abnormal metaphases in dividing spermatocytes and in univalents. Dominant lethal assays (in vivo) have yielded mixed results. In vitro assays have also yielded mixed results. Positive results have been obtained in cultured human lung cells and mouse bone marrow cells (both found increases in chromosome aberrations) and sister chromatid exchange (SCE) assays.

Dieldrin may not act directly on DNA; however, it may act by depressing transfer RNA activity, increasing unscheduled DNA synthesis, and inhibiting metabolic cooperation and gap junctional intercellular communication, according to mechanistic studies. The inhibition of gap junctional communication may be responsible for carcinogenic activity through depressing the cells' ability to control excess proliferation. This inhibition has been correlated with strains and species in which dieldrin has been shown to be carcinogenic. This type of activity is considered promotion rather than initiation of tumors (ATSDR, 1991).

5.3.4.7 Carcinogenicity—

Dieldrin is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The oral cancer slope factor is 16 per mg/kg-d. Liver carcinoma was identified in the animal studies. The geometric mean of 13 data sets (with a range of a factor of 8) was used to develop the cancer potency (IRIS, 1999).

A variety of tumor types have been observed in animal studies including pulmonary, lymphoid, thyroid, and adrenal (ATSDR, 1991). ATSDR has concluded that dieldrin is probably a tumor promotor, based on genotoxicity and mechanistic studies reviewed (ATSDR, 1991). Dieldrin has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive

cells (Soto et al., 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer (Davis et al., 1993). In addition to potential carcinogenic effects, dieldrin may also cause disruption of the endocrine system due to its estrogenic activity (Soto et al., 1994).

5.3.4.8 Special Susceptibilities—

ATSDR has identified the following populations as unusually susceptible: very young children with immature hepatic detoxification systems, persons with impaired liver function, and persons with impaired immune function (ATSDR, 1991). Based on the toxicity data reviewed above, individuals with the following diseases or disorders may also be at increased risk: hypertension, hematological disorders, musculoskeletal diseases, neurological diseases, and kidney disease.

The data also indicate that prenatal exposure may generate risks to children at relatively low levels of exposure. Postnatal exposure, especially via lactation, may also be a significant concern.

5.3.4.9 Interactive Effects—

In cows, dieldrin exposure increased the toxicity of diazinon; greater depression in blood cholinesterase activity occurred, leading to severe clinical signs (HSDB, 1993).

MIXTOX has reported inhibition between dieldrin and hexachlorobenzene in rats exposed orally via food. Studies have also reported additive effects (MIXTOX, 1992).

5.3.4.10 Critical Data Gaps—

A joint team of scientists from EPA, NTP, and ATSDR have identified the following study data gaps: mechanism of animal carcinogenicity, genotoxicity in vivo and in vitro, reproductive system toxicity, developmental toxicity, especially mechanisms of postnatal mortality and teratogenesis, immunotoxicity, neurotoxicity focusing on sensitive endpoints, and pharmacokinetics (ATSDR, 1991).

5.3.4.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	5×10^{-5} mg/kg-d
Carcinogenicity	16 per mg/kg-d.

5.3.4.12 Major Sources—

ATSDR (1991), HSDB (1993), IRIS (1999).

5.3.5 Endosulfan I, II

5.3.5.1 Background—

Endosulfan is an organochlorine pesticide comprised of stereoisomers designated I and II, which have similar toxicities (U.S. EPA, 1993a). Endosulfan I and II are referred to collectively as endosulfan; discussions refer to both isomers unless otherwise noted. Endosulfan has been in use since 1954.

5.3.5.2 Pharmacokinetics—

Endosulfan is absorbed through the GI tract and is distributed throughout the body. Endosulfan is metabolized to lipophilic compounds and both the parent and metabolites are found initially primarily in the kidney and liver and fatty tissue, with distribution to other organs occurring over time. Endosulfan can induce microsomal enzyme activity and is a nonspecific inducer of drug metabolism. In sheep, approximately 1 percent of a single dose was recovered in milk. Females may accumulate endosulfan more readily than males according to animal studies. This may be causal in the higher toxicity seen in females (see Acute Toxicity below) (ATSDR, 1993a).

5.3.5.3 Acute Toxicity—

Acute accidental or intentional ingestion of large amounts of endosulfan has resulted in death in humans. However, available data are insufficient to estimate a lethal dose of endosulfan in humans. Mice appear to be quite sensitive to endosulfan's lethal effects with an LD_{50} of 7 mg/kg. In rats, exposed males and females appear to have different sensitivities to the lethal effects of endosulfan (e.g. oral LD_{50} values were 10-23 mg/kg in females and 40-125 mg/kg in males). Insufficient data were available to determine whether differences in sensitivity to lethal effects exist between males and females of species other than the rat. Acute toxicity in humans and animals involve a large number of organ systems (respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal). The most prominent sign of acute overexposure to endosulfan in both humans and animals is central nervous system stimulation (hyperactivity, tremors, decreased respiration, convulsions) (ATSDR, 1993a)."

5.3.5.4 Chronic Toxicity—

IRIS provides an RfD of 6×10^{-3} mg/kg-d (IRIS 1999). The principal study on which this RfD is based was a 2-yr feeding study in rats. Reduced body weight gain in males and females, increased incidence of marked progressive glomerulonephrosis, and blood vessel aneurysms in males were observed. The LOAEL for systemic toxicity was 2.9 mg/kg-day in males and 3.8 mg/kg-d in females. The NOAEL for systemic toxicity was 0.6 mg/kg-d in males and 0.7 mg/kg-d in females. The NOAEL of 0.6 mg/kg-d was divided by an uncertainty factor of 100; 10 for intraspecies variability and 10 for interspecies extrapolation.

5.3.5.5 Reproductive and Developmental Toxicity—

In a two-generation reproduction study in rats, no evidence of reproductive toxicity was found at the highest dose tested of 6 mg/kg-d. The NOAEL for offspring toxicity was 1 mg/kg-d based on increased pituitary and uterine weights at the next higher dose of 6 mg/kg-d. A number of adverse effects were noted in a developmental study in rats (increased incidence of misaligned sternebrae, extra ribs, poor ossification). However, the study had a number of deficiencies and the US EPA recommended that it be repeated. In a study in rabbits, no developmental effects were noted at the highest dose tested of 1.8 mg/kg-d (IRIS, 1994).

5.3.5.6 Mutagenicity—

Results of mutagenicity assays of endosulfan are mixed, with multiple positive and negative studies (ATSDR, 1993a; HSDB, 1993; IRIS, 1999). Endosulfan has resulted in an increase in the percentage of aberrant colonies and the frequency of gene convertants and revertants in yeast and was genetically effective without activation. Longer duration of exposure increased effects (HSDB, 1993). In vivo assays have found chromosomal aberrations and gene mutations in mice (ATSDR, 1993a). However, some of these data may be suspect because some formulations contained epichlorohydrin, a known genotoxic chemical, as a stabilizer (ATSDR, 1993).

5.3.5.7 Carcinogenicity—

ATSDR has concluded that the available animal study data were negative or inconclusive (ATSDR, 1993b). EPA has classified endosulfan in Group E (evidence of noncarcinogenicity for humans) (U.S. EPA, 1999c).

5.3.5.8 Special Susceptibilities—

The limited toxicity data available for endosulfan suggest that several subgroups of the population may be more susceptible to endosulfan exposure than the general population. These subgroups include those with liver, kidney, immunological, or blood diseases; compromised immune systems such as AIDS patients, infants, and elderly people; hematologic disorders; seizure disorders; and low protein diets (see below) (ATSDR, 1993a).

> There is evidence from animal studies indicating that unborn and neonates may be more susceptible to the toxic effects of endosulfan because hepatic detoxification systems are immature and therefore unable to metabolize xenobiotic substances efficiently (ATSDR, 1993a).

5.3.5.9 Interactive Effects—

Human anecdotal information suggests that endosulfan may act synergistically with alcohol (ATSDR, 1993a). In rats, moderate protein deprivation doubled the toxicity of endosulfan (ATSDR, 1993a).

Pentobarbital and endosulfan have demonstrated an interactive effect that is probably related to microsomal enzyme activity. Endosulfan induces the mixed function oxidase system (ATSDR, 1993a). Vitamin A inhibited the endosulfan-induced activity of the mixed function oxidase system (ATSDR, 1993a).

5.3.5.10 Critical Data Gaps—

The increased susceptibility of female rats to endosulfan should be studied to determine the underlying cause and to evaluate whether the effect occurs with chronic species other than the rat.

Additional data are needed on the teratogenic and neurobehavioral effects during development resulting from endosulfan exposure. Current data do not provide a consistent picture nor do they explain underlying mechanisms of toxicity.

A joint team of scientists from ATSDR, NTP, and EPA have identified the following data gaps: acute oral exposure studies, mechanisms of anemia-inducing effects, reproductive system toxicity and related performance, developmental toxicity studies, mechanisms of immunotoxicity, sensitive neurological function and histological studies for long-term exposures, epidemiological studies, pharmacokinetics of intermediate and chronic duration exposures, and studies evaluating mechanisms underlying the differences in male and female toxicity. No ongoing studies were identified for endosulfan (ATSDR, 1993a).

5.3.5.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	6×10^{-3} mg/kg-d
Carcinogenicity	Group E (no evidence of carcinogenicity).

5.3.5.12 Major Sources—

ATSDR (1993a), HSDB (1993), IRIS (1999), U.S. EPA (1993g).

5.3.6 Endrin

5.3.6.1 Background—

Endrin is an organochlorine pesticide whose registration was canceled in 1984 (U.S. EPA, 1993a).

5.3.6.2 Pharmacokinetics—

Endrin, like the other organochlorine pesticides, is lipophilic. It bioaccumulates and is distributed in fat, the liver, the brain, and kidneys and is rapidly metabolized in mammals via oxidation of the methylene bridge. Metabolic products are probably more toxic than endrin and the toxic entity has been hypothesized to be 12-ketoendrin. In humans, this compound is excreted directly in urine and feces (ATSDR, 1990).

5.3.6.3 Acute Toxicity—

The primary target of endrin is the central nervous system (ATSDR, 1990).

5.3.6.4 Chronic Toxicity—

IRIS provides an RfD of 3×10^{-4} mg/kg-d based on a NOAEL of 0.025 mg/kg-d from a 1969 chronic exposure dog study that identified mild histological effects in the liver and occasional convulsions in study subjects exposed at the LOAEL of 0.05 mg/kg-d. Uncertainty factors of 10 each for inter- and intraspecies variability were applied (IRIS, 1999).

OPP tox one-liners list a 1959 2-year dog feeding study with a LOAEL of 0.015 mg/kg-d based on hypersensitivity in the neck and shoulder area. Increased erythropoiesis was noted at 0.125 mg/kg-d (U.S. EPA, 1993k). The LOAEL of 0.015 is within 1 order of magnitude of the LOAEL identified in the critical IRIS study.

5.3.6.5 Reproductive and Developmental Toxicity—

No developmental effects were listed in the IRIS file for endrin (IRIS, 1999). ATSDR listed a number of prenatal exposure studies that identified structural abnormalities and neurotoxicity associated with endrin exposure. Structural abnormalities have been observed in mice and hamsters exposed to endrin. These include fused ribs and cleft palate at 5 mg/kg-d for 3 prenatal days and webbed foot and open eye effects in hamster fetuses prenatally exposed for 1 day. Meningeocephaloceles in hamsters were caused by a single prenatal exposure "above" 1.5 mg/kg and fused ribs "above" 5 mg/kg in hamsters. In mice, a single prenatal exposure to 2.5 mg/kg caused an increase in open eyes. Exencephaly and fused ribs were seen with one exposure at 9 mg/kg endrin. A rat study reported no developmental effects with exposure to 0.45 mg/kg-d (it was not clear if behavioral effects were evaluated) (ATSDR, 1990). The variation in effects is probably due in part to the different prenatal periods during which exposure occurred (see ATSDR, 1990). Reproductive outcome was adversely affected in hamsters exposed to 1.5 mg/kg-d with decreased survival of pups (16 percent mortality) (ATSDR, 1990).

Nervous system effects are a significant concern with organochlorine exposure.

In hamsters, abnormally increased pup activity in hamsters was observed with 1.5 mg/kg prenatal exposures for 9 days. The NOAEL for these behavioral effects was 0.075 mg/kg-d (ATSDR, 1990). In rats, increased activity was seen with prenatal exposure to 0.3 mg/kg-d (ATSDR, 1990). Abnormally increased activity has been observed for other organochlorine pesticides (see DDT) and has been associated with probable altered learning ability and permanent structural changes to the brain.

As noted in the pharmacokinetics section above, endrin can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

5.3.6.6 Mutagenicity—

In vitro assays of endrin suggest that it is not genotoxic. There were no in vivo assay results located (ATSDR, 1990).

5.3.6.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of endrin. EPA has classified endrin as a Group D carcinogen (not classifiable as to human carcinogenicity). Some studies have yielded positive results and some studies that reported negative results were considered to be inadequate (IRIS, 1999). Tumors have been noted in the adrenal glands, pituitary glands, liver, mammary gland, uterus, and thyroid in various studies and multiple species (IRIS, 1999). Endrin is structurally related to a number of chemicals that are carcinogenic in test animals, including chlordane, aldrin, dieldrin, heptachlor, and chlorendic acid (IRIS, 1999). Because endrin has been classified as a Group D carcinogen, no cancer potency has been listed by EPA.

5.3.6.8 Special Susceptibilities—

ATSDR has reported that children may be more sensitive to acute endrin exposure than adults, based on effects observed in children during a poisoning incident. Children appeared more susceptible to neurotoxic effects and have exhibited convulsions. This is supported by results observed in experimental animals where young rats were more susceptible than adults (ATSDR, 1990).

In addition, the skeletal and behavioral abnormalities associated with endrin exposure in experimental animals indicate that prenatal exposure may generate special risks.

Based on animal studies, females may be more susceptible than males to endrin-induced toxicity (ATSDR, 1990).

5.3.6.9 Interactive Effects—

Dietary pretreatment with endrin potentiates the hepatotoxicity of carbon tetrachloride. MIXTOX has reported synergism between endrin and chlordane in mice with gavage exposure (MIXTOX, 1992).

5.3.6.10 Critical Data Gaps—

A joint team of researchers from ATSDR, NTP, and EPA have identified the following data gaps: human responses to acute, intermediate (14 to 365 days), and chronic exposures; subchronic reproductive tests in various species; immunotoxicity studies of animals and humans; human dosimetry studies; pharmacokinetic studies; and studies of interspecies differences in metabolism and toxicity (ATSDR, 1990).

5.3.6.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	3×10^{-4} mg/kg-d
Carcinogenicity	Group D (not classifiable).

5.3.6.12 Major Sources—

ATSDR (1990), IRIS (1999), U.S. EPA (1993k).

5.3.7 Heptachlor Epoxide

5.3.7.1 Background—

Heptachlor epoxide is a breakdown product of the organochlorine pesticides heptachlor and chlordane and is a contaminant of both products. It is more toxic than either parent compound (ATSDR, 1993b). Although most uses of heptachlor were suspended in 1978 and chlordane was removed from the market in 1988 (U.S. EPA, 1993h), heptachlor epoxide continues to be a widespread contaminant due to its relatively long half-life.

5.3.7.2 Pharmacokinetics—

Based upon animal and limited human data, heptachlor epoxide is absorbed through the GI tract and is found primarily in the liver, bone marrow, brain, and fat, although it is distributed widely to other tissues as well. It is stored primarily in fat. Fetal blood levels were approximately four times those measured in women. Levels in human milk range from zero to 0.46 ppm (ATSDR, 1993b).

Heptachlor epoxide has a very long half-life, particularly in adipose tissue. Human tissue levels have correlated well to age, with 97 percent of North Texas residents tested (ages 41 to 60) having measurable levels. Based on the Texas study, heptachlor epoxide tissue levels have not decreased appreciably since the 1960s (ATSDR, 1993b).

5.3.7.3 Acute Toxicity—

The LD_{50}s for heptachlor range from 40 to 162 mg/kg in rodents (ATSDR, 1993b).

5.3.7.4 Chronic Toxicity—

IRIS provides an RfD of 1.3×10^{-5} mg/kg-d based on an LOAEL of 0.0125 mg/kg-d from a 60-week dog feeding study reported in 1958. The critical effect was increased liver-to-body-weight ratios in both males and females at the lowest dose tested. Uncertainty factors of 10 each were applied for inter- and intraspecies variability and the use of an LOAEL rather than a NOAEL (IRIS, 1999). No additional uncertainty factors were applied for the use of a less-than-lifetime study. The principal study is of low quality and there is low confidence in the RfD (IRIS, 1999).

Animal studies have identified the following effects associated with heptachlor (and subsequently heptachlor epoxide via metabolism) or heptachlor epoxide directly: elevated bilirubin and white blood cell count, increased serum creatinine phosphokinase levels suggestive of muscle damage, muscle spasms secondary to CNS stimulation, adrenal gland pathology, and neurological disorders (ATSDR, 1993b). Significant changes in EEG patterns were found in female adult rats exposed to 1 and 5 mg/kg-d for three generations (ATSDR, 1993b).

5.3.7.5 Reproductive and Developmental Toxicity—

A human study conducted in Hawaii was not considered adequate due to many study design deficiencies (ATSDR, 1993b). In another epidemiological study of women who had premature deliveries, significantly higher levels of heptachlor epoxide and other organochlorine pesticides were detected in sera (ATSDR, 1993b).

A 1973 two-generation dog reproductive study identified a NOAEL of 0.025 mg/kg-d with an LOAEL of 0.075 mg/kg-d with liver lesions in pups. Other studies with higher LELs based on a lethality endpoint are listed in the IRIS file. They were not used in this evaluation due to insufficient information. The IRIS file notes data gaps as rat and rabbit teratology studies (IRIS, 1999).

Exposure of adult rats to 6 mg/kg-d caused lens cataracts in 22 percent of the adults, 6 to 8 percent of the F1 generation offspring, and 6 percent of the F2 generation offspring. A rat study with exposure to 0.25 mg/kg-d occurring 60 days

prior to mating and during gestation resulted in severely reduced pup survival (15 percent) at 21 days postpartum (ATSDR, 1993b).

As noted in Section 5.3.7.2, heptachlor can accumulate in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and females with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

A study of reproductive system toxicity with males and females dosed at 0.25 mg/kg-d prior to and during gestation found a significantly decreased pregnancy rate among exposed animals. Based on specific fertility tests, it was determined that males were most likely affected and that sperm were probably killed (ATSDR, 1993b). Another reproductive system toxicity study with doses at and above 0.075 mg/kg-d resulted in the failure of animals to reproduce. There were serious deficiencies in this study (ATSDR, 1993b).

5.3.7.6 Mutagenicity—

Mixed results have been obtained in mutagenicity assays of heptachlor epoxide.

5.3.7.7 Carcinogenicity—

Heptachlor epoxide is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals. The oral cancer slope factor is 9.1 per mg/kg-d. This value is based on the geometric mean of several studies that identified liver carcinomas (IRIS, 1999). Five structurally related compounds have produced tumors in mice and rats: chlordane, aldrin, dieldrin, heptachlor, and chlorendic acid (IRIS, 1999).

Statistically significant increases in adenomas and carcinomas of the thyroid were found in female rats. Some researchers discounted the results due to the low incidence and known variability in the control population (ATSDR, 1993b).

Heptachlor (and consequently heptachlor epoxide) exposures have been associated with cerebral gliosarcoma in children exposed prenatally. Multiple chromosomal abnormalities were also identified in the tumor cells. It was not determined whether the effects were caused by environmental or familial factors (ATSDR, 1993b).

5.3.7.8 Special Susceptibilities—

Based on the toxicity data reviewed above, individuals with diseases or disorders of the following systems may be at greater risk than the general population: liver, hematopoietic, musculoskeletal, neurological, and adrenal gland. ATSDR has

noted that preadolescent children may be more susceptible due to their greater rate of glutathionine turnover (ATSDR, 1993b). In addition, children exposed prenatally may be at higher risk, based on the results of developmental toxicity studies.

5.3.7.9 Interactive Effects—

Heptachlor induces the mixed function oxidase system. No specific interactive effects have been noted.

5.3.7.10 Critical Data Gaps—

The IRIS file notes data gaps as rat and rabbit teratology studies (IRIS, 1999). A joint team of scientists from EPA, NTP, and ATSDR have identified the following data gaps: a model to describe the relationship between tissue and blood levels and exposure in humans, chronic oral exposure effects in humans, epidemiological and in vivo animal genotoxicity studies, developmental and reproductive toxicity studies and neurotoxicity and immunotoxicity studies in animals, and pharmacokinetic studies (ATSDR, 1993b).

5.3.7.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	1.3×10^{-5} mg/kg-d
Carcinogenicity	9.1 per mg/kg-d.

5.3.7.12 Major Sources—

ATSDR (1993b), IRIS (1999).

5.3.8 Hexachlorobenzene

5.3.8.1 Background—

Hexachlorobenzene was used as a fungicide on seeds of onions, sorghum, wheat, and other grains until 1984. It was also used in pyrotechnics and as a chemical intermediate but is no longer used commercially in the United States (ATSDR, 1996b).

5.3.8.2 Pharmacokinetics—

Hexachlorobenzene is persistent in the body, accumulating preferentially in fat and tissues with a high lipid content, because of its lipophilic nature. It is found in human breast milk (ATSDR, 1996b), which may be a significant route of exposure for young children. Hexachlorobenzene is also readily transferred through the placenta from the mother to the fetus in animal experiments. Hexachlorobenzene is very slowly converted by microsomal enzymes in the liver

to its major metabolites, pentachlorophenol, pentachlorothiphenol, and pentachlorobenzene, which are mainly excreted in the urine.

5.3.8.3 Acute Exposure—

Acute exposure studies in animals indicate a relatively low acute toxicity with LD_{50}s between 1,700 and 4,000 mg/kg (ATSDR, 1996b). Exposure to hexachlorobenzene does not appear to cause the acute neurological effects observed with the organochlorines that have been used as insecticides (e.g., DDT). Based on animal studies, the following systems are adversely affected following acute exposure: liver, kidney, hematological, endocrine, and dermal (ATSDR, 1996b).

5.3.8.4 Chronic Toxicity—

Hexachlorobenzene exposure of a large number of people in Turkey occurred between 1955 and 1959 due to consumption of contaminated grain. No precise exposure estimates are available for children or adults in this episode; it is likely that exposures occurred over a continuum, with some individuals consuming much higher levels than others. Researchers have estimated relatively low exposure levels occurred over several years as a result of consumption (50 to 200 mg/d). These exposure levels are approximately 0.7 to 2.9 mg/kg-d for a 70-kg individual. It should be emphasized that the exposure estimates are unverified (ATSDR, 1996b).

The following effects have been associated with hexachlorobenzene exposure in individuals exposed chronically via contaminated bread (Turkey): shortening of the digits due to osteoporosis, painless arthritis, decreased uroporphyrin synthase levels, muscle weakness, rigidity and sensory shading, thyroid enlargement, and histopathological changes in the liver often accompanied by skin lesions (ATSDR, 1996b). These effects were also observed in numerous animal studies (See discussion under Section 5.3.8.5 also.)

The hepatic system appears to be the most sensitive systemic endpoint for hexachlorobenzene exposure, IRIS provides an RfD value of 8×10^{-4} mg/kg-d based on a NOAEL of 0.08 mg/kg-d in a lifetime rat study. An uncertainty factor of 100 was applied; 10 for interspecies and 10 for intraspecies variability. Numerous other studies identified NOAELs in the same numerical range, so the confidence in the database is rated as high. The IRIS file notes that the sensitive endpoint of porphyria, which is an effect noted in exposed human populations, was not evaluated in the critical animal study, so the confidence in the RfD is rated as medium (IRIS, 1999).

5.3.8.5 Reproductive and Developmental Toxicity—

Lactational exposure to hexachlorobenzene is of significant concern, based on the rapid transfer of the chemical through breast milk and effects observed in children of exposed mothers in a contamination incident in Turkey. In a study of nursing infants, blood levels of hexachlorobenzene were two to five times that of their mothers; tissue levels were higher as well. A study of monkeys found that the concentration in milk was 17 times higher than that in maternal serum (ATSDR, 1996b). Young children (under 1 year) of lactating mothers who were exposed via contaminated bread had an extremely high mortality rate. Skin lesions, weakness, and convulsions were reported in these infants. Although adults were also adversely affected, children appeared to be at higher risk. The maternal exposure was roughly estimated to be 0.7 to 2.9 mg/kg-d (ATSDR, 1996b).

Among slightly older children (average age of 7), exposure via food resulted in the development of small or atrophied hands and fingers, short stature, pinched faces, osteoporosis in the hands, and other arthritic changes. Exposure was estimated to be approximately 0.7 to 2.9 mg/kg-d (ATSDR, 1996b).

It is known that hexachlorobenzene can cross the human placenta; however, no data were available on effects resulting from prenatal exposure in humans. Very limited information is available on experimental animals. Cleft palate and kidney abnormalities were observed in one study in a single litter and fetus at 100 mg/kg-d (ATSDR, 1996b). In another study, the survivability of prenatally exposed rats was significantly reduced at 2 mg/kg-d (estimated from ppm with conversion factor of 0.05 mg/kg per 1 ppm diet for rats). Death was attributed to maternal body burden and cumulative lactational exposure (ATSDR, 1996b). Alterations in immune function levels were reported in pre- and postnatally exposed rats at 4 mg/kg (ATSDR, 1996b).

As noted above, hexachlorobenzene accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If a female has been exposed to hexachlorobenzene, even if exposure is reduced during pregnancy, the outcome of that pregnancy may be affected, depending on the timing and extent of prior exposure.

5.3.8.6 Mutagenicity—

The results of mutagenicity studies on hexachlorobenzene are mixed (IRIS, 1999). Hexachlorobenzene was negative in dominant lethal studies (in vivo) at doses from 60 to 221 mg/kg (ATSDR, 1996b).

5.3.8.7 Carcinogenicity—

Carcinogenic assays of hexachlorobenzene in animals have identified an increased incidence of multiple tumor types including hepatomas, hemangioendotheliomas, liver, and thyroid tumors in multiple species. EPA developed a cancer potency of 1.6 mg/kg-d based on liver carcinoma in female rats exposed via diet. In support of this value, cancer potencies were calculated for 14 different data sets; the results were within 1 order of magnitude. Hexachlorobenzene is classified as a probable human carcinogen (B2) based on the results of animal studies (IRIS, 1999).

Follow-up studies of exposure victims in Turkey have not identified cancers in the 25- and 20- to 30-year exposure cohorts; however, ATSDR suggests that the enlarged thyroids noted in members of these groups have not been sufficiently investigated (ATSDR, 1996b). It should also be noted that most cancers have multiple-decade latency periods and often occur in the later part of life. Consequently, it will not be possible to assess the carcinogenic impact of exposures in Turkey for some time.

5.3.8.8 Special Susceptibilities—

ATSDR has concluded that young children are susceptible to hexachlorobenzene exposure based on human poisoning episodes. Exposure led to permanent debilitating effects. Both human and animal data suggest that the risk of exposure to nursing infants may be greater than the risk to their mothers (ATSDR, 1996b).

Based on the toxicity data reviewed above, individuals with liver disease may be at greater risk than the general population.

5.3.8.9 Interactive Effects—

Hexachlorobenzene induces microsomal enzymes. Pentachlorophenol increases the porphyrinogenic effects of hexachlorobenzene. Hexachlorobenzene potentiated the thymic atrophy and body weight loss caused by 2,3,7,8-TCDD. A 50 percent food deprivation increased liver hypertrophy and microsomal enzyme induction by hexachlorobenzene (ATSDR, 1996b).

5.3.8.10 Critical Data Gaps—

A joint team of scientists from EPA, NTP, and ATSDR have identified the study following data gaps: human carcinogenicity, in vivo and in vitro genotoxicity, animal reproductive toxicity, animal developmental toxicity, immunotoxicity studies in humans, and pharmacokinetics (ATSDR, 1996b). Information is needed to develop a model that can be used to estimate the relationship between maternal intake, human milk concentration, and adverse effects in infants.

5.3.8.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	8×10^{-4} mg/kg-d
Carcinogenicity	1.6 per mg/kg-d.

5.3.8.12 Major Sources—

ATSDR (1996b), IRIS (1999).

5.3.9 Lindane (γ-hexachlorocyclohexane)

5.3.9.1 Background—

Lindane is an organochlorine pesticide that is comprised of isomers of hexachlorocyclohexane, with the γ isomer constituting the major (>99 percent) component. There appears to be some difference in toxicity of the various hexachlorocyclohexane isomers (U.S. EPA, 1993a). The following data assume that lindane can be defined as the γ isomer. Lindane is used primarily for controlling wood-inhabiting beetles and as a seed treatment. Lindane is also used as a prescription pharmaceutical to control head lice and mites (scabies) in humans.

5.3.9.2 Pharmacokinetics—

Lindane is readily absorbed by the GI tract following oral exposure. Distribution is primarily to the adipose tissue but also to the brain, kidney, muscle, spleen, adrenal glands, heart, lungs, blood, and other organs. It is excreted primarily through urine as chlorophenols. The epoxide metabolite may be responsible for carcinogenic and mutagenic effects (ATSDR, 1994c).

Male exposure to lindane through the environment results in accumulation in testes and semen in addition to the tissues listed above (ATSDR, 1994c). See also a discussion in Section 5.3.9.5 of the accumulation of lindane by pregnant women.

5.3.9.3 Acute Toxicity—

The estimated human lethal dose is 125 mg/kg (HSDB, 1993). Occupational and accidental exposures in humans have resulted in headaches, vertigo, abnormal EEG patterns, seizures, and convulsions. Death has occurred primarily in children.

5.3.9.4 Chronic Toxicity—

IRIS provides an RfD of 3×10^{-4} mg/kg-d based on a NOAEL of 0.33 mg/kg-d from a subchronic rat study that found liver and kidney toxicity at higher doses. Uncertainty factors of 10 each for inter- and intraspecies variability and the use

of a less-than-lifetime study were applied (IRIS, 1999). The confidence in the principal study, database, and RfD are rated as medium. A recently completed 2-year study is under evaluation and may provide additional information regarding toxicity (U.S. EPA, 1993i). Liver damage has been observed in many animal studies and appears to be the most sensitive effect (U.S. EPA, 1993i). Immune system effects have been observed in humans exposed via inhalation and in orally dosed animals. A 5-week study in rabbits found immunosuppression at 1 mg/kg-d (ATSDR, 1994c).

Most observed effects in humans exposed accidentally to lindane are neurological. Behavioral effects have also been noted in many studies on experimental animals, and at relatively high levels seizures were reported. More subtle behavioral effects were noted at an LOAEL of 2.5 mg/kg-d with 40 days of exposure in rats. No NOAEL was reported (ATSDR, 1994c).

5.3.9.5 Reproductive and Developmental Toxicity—

Two developmental toxicity studies in rats and rabbits both identified a NOAEL of 10 mg/kg (no effects were described for higher doses). A three-generation rat study found no adverse reproductive effects at 5 mg/kg-d, the highest dose tested (U.S. EPA, 1993i). A recent mouse study found increased resorptions at 5 mg/kg-d. Studies in rats and mice have found increased incidence of extra ribs at 5 to 20 mg/kg-d (ATSDR, 1994c). There are multiple studies showing pre- and postimplantation fetotoxicity and skeletal abnormalities resulting from prenatal exposure at higher doses (HSDB, 1993).

Lindane accumulates in the fatty tissue of pregnant (and nonpregnant) women where it can be transferred to the fetus through the placenta and to infants through breast milk. Human milk concentrations are approximately five to seven times greater than maternal blood levels. Concentrations in maternal blood are proportional to the length of time over which exposure occurred, with older women having higher blood levels. During pregnancy, the lindane concentration in blood from fetal tissue, uterine muscle, placenta, and amniotic fluid was higher than levels in maternal adipose tissue, and blood serum levels increased during delivery (ATSDR, 1994c). There is little information on the effects of exposure during lactation. One study (dose unspecified) in rats indicated that exposure during gestation and lactation did not cause developmental effects; however, this is not consistent with other studies that found effects associated with gestational exposure.

Based on what is known regarding the transfer of lindane into human milk, nursing infants must be considered at some risk if their mothers have been exposed to significant amounts of lindane (lindane is a lipid-seeking chemical). Additional information is needed to characterize the relationship between maternal intake, body burden (blood or adipose levels), milk concentrations, and adverse effects.

Multiple studies have reported that lindane exposure (as measured by body tissue level of lindane) is associated with premature labor and spontaneous abortions. The causal relationship has not been established for this action (ATSDR, 1994c); however, the reproductive system effects discussed in Section 5.3.9.4 (biochemical changes in uterine, cervical, and vaginal tissues and antiestrogenic effects) may be involved.

As noted above, lindane accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. As a result, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden. If exposure is reduced during pregnancy but has occurred prior to pregnancy, the pregnancy outcome may be affected, depending on the timing and extent of prior exposure.

Two recent reproductive studies in rats found adverse effects on the male reproductive system. In a 7-wk study, decreased sperm counts were noted at 50 mg/kg-d and, in a 180-d study, seminiferous tubular degeneration was noted at 6 mg/kg-d with a NOAEL of 3 mg/kg-d. An older study had identified the same effects at 64.6 mg/kg-d in a 3-mo study. Experimental data indicate that the female reproductive system may also be altered by lindane exposure. A study of rats found uterine, cervical, and vaginal biochemical changes at 20 mg/kg-d in a 30-d study. Antiestrogenic effects were found at 20 mg/kg-d in female rats in a 15-wk study with a NOAEL of 5 mg/kg-d. This action was also found in two other recent studies (ATSDR, 1994c).

5.3.9.6 Mutagenicity—

In animals, ingestion of technical-grade hexachlorocyclohexane-induced dominant lethal mutations in mice. Studies found that lindane binds to mouse liver DNA at a low rate. Based on a review of genotoxicity studies, ATSDR concluded that lindane "has some genotoxic potential, but the evidence for this is not conclusive" (ATSDR, 1994c).

5.3.9.7 Carcinogenicity—

Lindane has been classified as Group B2/C (probable/possible human carcinogen) (U.S. EPA, 1999c) and a cancer potency of 1.3 per mg/kg-d has been listed (HEAST, 1997). Lindane's related isomers, alpha and beta hexachlorocyclohexane, are classified as probable human carcinogens and have cancer potencies similar to that of lindane. In addition to tumors identified in experimental animals, human study data indicate that this chemical may cause aplastic anemia (U.S. EPA, 1993a).

5.3.9.8 Special Susceptibilities—

ATSDR has recommended that pregnant and/or lactating women should not be exposed to lindane. The potential for premature labor and spontaneous abortion is noted (ATSDR, 1994c). People with epilepsy, cerebrovascular accidents, or head injuries who have lower thresholds for convulsions may be at greater risk of lindane-induced CNS toxicity and seizures. Also, individuals with protein-deficient diets, liver or kidney disease, or immunodeficiencies may be at greater risk from lindane exposure than the general population (ATSDR, 1994c).

Children may also be at greater risk from lindane exposure because of the immaturity of their immune and nervous systems. ATSDR has cautioned that:

> Infants and children are especially susceptible to immuno-suppression because their immune systems do not reach maturity until 10 to 12 years of age (ATSDR, 1994c).

5.3.9.9 Interactive Effects—

High- and low-protein diets and vitamin A and C deficiencies increased the toxicity of lindane in experimental animals. Vitamin A supplements decreased toxicity. Cadmium inhibited the metabolism of lindane. Combined cadmium and lindane exposure caused significant embryotoxic and teratogenic effects in rats at dosages that caused no effects when administered alone. Exposure to the α, β, and δ hexachlorocyclohexane isomers may reduce the neurotoxic effects of lindane (ATSDR, 1994c).

MIXTOX has reported mixed results for studies of lindane and chlordane, lindane and hexachlorobenzene, lindane and toxaphene, and lindane and mirex interactions, including inhibition, no effect, and potentiation for these combinations in rodents exposed via gavage (MIXTOX, 1992).

5.3.9.10 Critical Data Gaps—

As discussed above, effects on both the male and female reproductive systems have been evaluated in short-term studies. Evaluation of these effects in a longer-term study and identification of the underlying mechanisms of toxicity would provide information needed for a more complete evaluation of toxicity and dose-response dynamics. Additional information is also needed, as noted in Section 5.3.9.5, on the potential for exposure via lactation and on mechanisms and dose-response for premature labor and spontaneous abortion.

ATSDR has identified data gaps that include chronic duration oral studies; in vivo genotoxicity tests; reproductive, developmental immunotoxicity, and neurotoxicity studies; human studies correlating exposure levels with body burdens of lindane and with specific effects; and pharmacokinetic studies (ATSDR, 1994c).

5.3.9.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	3×10^{-4} mg/kg-d
Carcinogenicity	1.3 per mg/kg-d.

5.3.9.12 Major Sources—

ATSDR (1994c), HSDB (1993), IRIS (1999).

5.3.10 Mirex

5.3.10.1 Background—

Mirex was used as both an organochlorine pesticide and fire retardant from the late 1950s until 1975 (U.S. EPA, 1993a). A major use of mirex was for the control of ants, particularly fire ants in the southern United States. Mirex has the potential to concentrate many thousandfold in food chains (Hayes and Laws, 1991).

5.3.10.2 Pharmacokinetics—

Mirex is a lipophilic compound and is readily taken up in fat tissue. The highest residues were found in fat and the liver. Based on a study in cows, it is also found in milk. At 0.01- and 1-ppm dietary exposure for 32 weeks, cows' milk levels were 0.01 to 0.08 ppm (U.S. EPA, 1993m).

No clear data on half-life in humans were found; however, studies in primates found that 90 percent of the original dose was retained in fat after 106 days. The researchers predicted that mirex had an extremely long half-life in monkeys. Based on this, mirex would be expected to have a very long half-life in humans.

5.3.10.3 Acute Toxicity—

Acute hepatic effects have been observed in experimental animals. These may result from the following cytological effects: disaggregated ribosomes, glycogen depletion, formation of liposomes, and proliferation of smooth endoplasmic reticulum (U.S. EPA, 1993m).

5.3.10.4 Chronic Toxicity—

IRIS lists a chronic exposure RfD of 2×10^{-4} mg/kg-d for mirex based on a NOAEL of 0.07 mg/kg-d from a chronic (2-year) dietary rat study. Effects noted in the study at higher doses were: splenic fibrosis, nephropathy, renal medullary hyperplasia, multiple types of liver damage, and cystic follicles of the thyroid. The RfD is based on the latter two critical effects. Uncertainty factors of 10 each were applied for inter- and intraspecies variability and a factor of 3 was applied for lack of a complete database (multigenerational data on reproductive effects and cardiovascular toxicity data). The IRIS file also indicates that effects on the testes

(testicular degeneration, hypocellularity, and depressed spermatogenesis), which were noted in other studies, may not have been detected in the critical study because of age-related degenerative changes in the study animals (IRIS, 1999).

5.3.10.5 Reproductive and Developmental Toxicity—

Studies in animals suggest that both male and female reproductive systems are adversely affected by mirex. Acute exposure of male rats to 6 mg/kg-d mirex daily for 10 days decreased their fertility significantly. Although residues of mirex were found in the testes of the 6-mg/kg-d dose-group males, this did not affect reproduction parameters in subsequent mating trials. The authors attributed the observed decrease in the incidence of pregnancy in females mated with males in this dose group to a subclinical toxic effect as suggested by reduction in body weight gain in the dosed males (ATSDR, 1995a).

In a 28-day dietary study, decreased sperm count was noted in male rats at dosages as low as 0.025 mg/kg-d; testicular degeneration was observed at dosage levels of 2.5 and 3.7 mg/kg-d. However, mirex fed to rats at 1.3 to 3.1 mg/kg-d for two generations resulted in no decrease in fertility. In contrast, females given 1.8 to 2.8 mg/kg-d for two generations produced a decreased number of litters. Administration of 0.25 mg/kg-d to male and female rats for 91 days prior to mating and then through lactation resulted in decreased mating and litter size (ATSDR, 1995a).

Exposure of maternal rats and mice during gestation resulted in increases in resorptions and stillbirths and decreases in postnatal viability at doses as low as 1.25 mg/kg-d when administered from gestation days 4 through 22. Examination of fetuses at the end of gestation showed increases in the incidence of edematous fetuses and fetuses with cardiac arrhythmia; the incidence was slightly increased at doses as low as 0.1 mg/kg-d. Additional effects were reported in a few studies and included enlarged cerebral ventricles; undescended testes; cleft palate; short tail; decreased skeletal ossification, fetal weight, and liver and kidney weights; and liver and thyroid lesions. Cataracts were also observed in offspring in several studies from pre- and postnatal exposures (ATSDR, 1995a).

5.3.10.6 Mutagenicity—

Most genotoxicity tests reported in the tox one-liners are bacterial assays and are negative (U.S. EPA, 1993m). A dominant lethal mutagenicity test in rats (in vivo) found a decreased incidence of pregnancy at 6 mg/kg-d with a NOEL of 3 mg/kg-d. Exposure took place over 10 days prior to mating. However, parameters indicative of dominant lethality were unaffected by treatment (ATSDR, 1995a)

5.3.10.7 Carcinogenicity—

A marked increased incidence in neoplastic nodules in the liver of both male and female rats was observed in a 2-year feeding study with mirex (NTP, 1990). This effect was noted at doses of 0.7 mg/kg-d and above in males and at 3.8 mg/kg-d and above in females. In addition, increased tumors of the adrenal gland in male rats and mononuclear cell leukemias in female rats were observed. EPA's Office of Pesticide Programs has classified mirex as Group B2 (probable human carcinogen) (HEAST, 1997). In addition, NTP considers mirex as "reasonably anticipated to be a human carcinogen" based on sufficient evidence of carcinogenicity in experimental animals (NTP, 2000).

5.3.10.8 Special Susceptibilities—

Juveniles may be more susceptible than adults based on the results of animal studies. At 60 ppm (approximately 3 mg/kg-d), adult mice exposed for 15 days experienced only weight loss; this level was lethal for young mice (Hayes and Laws, 1991).

Based on a review of the toxicity data above, individuals with diseases or disorders of the following organ systems may be at higher risk than the general population: kidney, liver, spleen, thyroid, parathyroid, cardiovascular, and male reproductive. Due to the developmental toxicity observed in experimental animals, prenatal exposure and lactation exposure may pose a risk to children. The possibility exists that newborn children may also develop cataracts if exposed to mirex shortly after birth (ATSDR, 1995a).

5.3.10.9 Interactive Effects—

Mirex induces the mixed function oxidase system. No specific interactive effects have been noted.

MIXTOX reports mixed results for interactions between lindane and mirex and for Aroclor 1254 and mirex. Other studies of Aroclor and mirex have not found interactive results (MIXTOX, 1992).

5.3.10.10 Critical Data Gaps—

Additional information is needed on the developmental effects of mirex to identify a NOAEL for sensitive developmental toxicity endpoints so that a well-founded exposure limit for developmental effects can be determined. In a related area, the mutagenicity data indicate a potential mutagenic effect based on in vivo studies. A better understanding of the relationship between the results of these types of studies and mutagenic effects in the human population is needed. The chronic exposure toxicity studies do not provide consistent results. Additional clarification of the NOAELs for sensitive endpoints in this area is needed.

5.3.10.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	2×10^{-4} mg/kg-d
Carcinogenicity	Group B2 (probable human carcinogen).

5.3.10.12 Major Sources—

ATSDR (1995a), Hayes and Laws (1991), IRIS (1999), U.S. EPA (1993m).

5.3.11 Toxaphene

5.3.11.1 Background—

Toxaphene is an organochlorine pesticide that is comprised of a mixture of at least 670 chlorinated camphenes. Toxaphene was probably the most heavily used pesticide in the United States during the 1970s after DDT was banned. It was banned for most uses in 1982; all uses were banned in 1990. However, due to its relatively long half-life, it persists in the environment. The soil half-life is approximately 1 to 14 years (HSDB, 1993).

5.3.11.2 Pharmacokinetics—

The components of toxaphene are metabolized in mammals via dechlorination, dehydrodechlorination, and oxidation, primarily through the action of the mixed function oxidase system and other hepatic microsomal enzymes. Conjugation may occur but is not a major route of metabolism. Each component of toxaphene has its own rate of biotransformation, making the characterization of toxaphene pharmacokinetics complex. Some components of toxaphene are highly lipophilic and poorly metabolized; these components may accumulate in body fat (ATSDR, 1996c).

5.3.11.3 Acute Toxicity—

Acute high-level exposures to toxaphene and toxaphene-contaminated food have resulted in death in adults and children with an estimated minimum lethal dose of 2 to 7 g, which is equivalent to 29 to 100 mg/kg for an adult male. LD_{50} values in rats were 80 mg/kg for females and 90 mg/kg for males. Transient liver and kidney effects, and periods of memory loss have been observed in humans after single large oral exposures. In animals, the most sensitive organ is the liver. Toxicity to the central nervous system, kidney, and adrenal glands have also been observed (ATSDR, 1996c).

5.3.11.4 Chronic Toxicity—

IRIS does not provide a discussion of chronic effects of exposure to toxaphene or an RfD (IRIS, 1999). An RfD of 2.5×10^{-4} mg/kg-d is listed in the Office of

Pesticide Program's Reference Dose Tracking Report (U.S. EPA, 1997c) and has been agreed upon by the Office of Pesticide Programs and the Office of Water.

Chronic exposure to toxaphene may result in damage to the following organ systems: liver, kidney, adrenal, immunological, and neurological. Chronic exposure to toxaphene may cause hormonal alterations. A study on chronic exposures found increased levels of hepatic metabolism of the hormones estradiol and estrone and a decrease in their uterotropic action. Some adverse effects of toxaphene that do not occur with a single exposure may result from repeated exposures. Exposures at 0.06 mg/kg-d over 5 weeks caused adrenal hormone reductions, whereas a single dose of 16 mg/kg did not cause effects.

5.3.11.5 Reproductive and Developmental Toxicity—

Women exposed to toxaphene by entering a field that had recently been sprayed with the chemical exhibited a higher incidence of chromosomal aberrations in cultured lymphocytes than did unexposed women. Dermal and inhalation were the probable routes of exposure; however, the exposure was not quantified (ATSDR, 1996c). Animal study results suggest that toxaphene does not interfere with fertility in experimental animals at the doses tested (up to 25 mg/kg-d) (ATSDR, 1996c).

Adverse developmental effects, including immunosuppressive and behavioral effects, were noted in experimental animals at levels below those required to induce maternal toxicity. Immunosuppression (reduction in macrophage levels, cell-mediated immunity, and humoral immunity) was observed in test animals exposed during gestation and nursing as were alterations in kidney and liver enzymes and delayed bone development. Other adverse effects noted in offspring of maternally exposed individuals included histological changes in the liver, thyroid, and kidney (ATSDR, 1996c).

Toxaphene is known to be rapidly conveyed into breast milk after maternal exposure to the chemical. The half-life of toxaphene in milk has been estimated at 9 days.

As noted above, toxaphene accumulates in body tissue; consequently, exposure occurring prior to pregnancy can contribute to the overall maternal body burden and result in exposure to the developing individual. Therefore, it is necessary to reduce exposure to children and women with childbearing potential to reduce overall body burden.

Depending on the timing and extent of an individual's prior exposure to toxaphene, the outcome of pregnancy may be affected even if exposure during pregnancy is reduced.

5.3.11.6 Mutagenicity—

Changes in human genetic material have been noted in workers exposed to toxaphene (HSDB, 1993). There are also numerous positive mutagenicity assays of toxaphene: the Ames test, sister chromatid exchange, chromosomal aberrations in toxaphene-exposed humans, and forward mutation assays. The implications of this for human germ cells are not known. One assay designed to assess the effects of dominant lethal effects on implantations in mice yielded negative results. Some data suggest that the polar fraction of toxaphene may be more mutagenic than the nonpolar fraction (ATSDR, 1996c; HSDB, 1993).

5.3.11.7 Carcinogenicity—

Toxaphene is classified as a probable human carcinogen (B2) by EPA based on oral studies in animals (IRIS, 1999). No conclusive human epidemiological studies are available for toxaphene (ATSDR, 1996c). Oral administration of toxaphene resulted in an increased incidence of hepatocellular carcinomas and neoplastic nodules in mice, and thyroid tumors in rats (IRIS, 1999). The cancer potency is 1.1 per mg/kg-d, based on liver tumors in experimental animals (IRIS, 1999).

Toxaphene has recently been observed to have estrogenic effects on human breast cancer estrogen-sensitive cells (Soto et al., 1994). Xenoestrogens have been hypothesized to have a role in human breast cancer (Davis et al., 1993). In addition to potential carcinogenic effects, toxaphene may also cause disruption of the endocrine system due to its estrogenic activity (Soto et al., 1994).

5.3.11.8 Special Susceptibilities—

A protein-deficient diet may increase the toxicity of toxaphene approximately threefold based on an LD_{50} study in rats (ATSDR, 1996c). Individuals with latent or clinical neurological diseases, such as epilepsy or behavioral disorders, may be at higher risk for toxaphene toxicity. In addition, children may be especially susceptible to toxaphene-induced neurotoxicity based on early reports of acute ingestion toxicity (ATSDR, 1996c).

Other individuals who may be at higher risk are those with diseases of the renal, nervous, cardiac, adrenal, and respiratory systems. Individuals using certain medications are also at potential risk due to the induction of hepatic microsomal enzymes by toxaphene (discussed further in the following section).

5.3.11.9 Interactive Effects—

Metabolism of some drugs and alcohol may be affected by toxaphene's induction of hepatic microsomal enzymes. This was observed in a man using warfarin as an anticoagulant while he used toxaphene as an insecticide. The effectiveness of the drug was reduced because toxaphene's induction of microsomal enzymes increased the drug's metabolism (ATSDR, 1996c).

Based on acute studies in animals and anecdotal reports of acute exposure in humans, exposure to chemicals that increase microsomal mixed-function oxidase systems (e.g., lindane) are likely to reduce the acute toxicity of other chemicals detoxified by the same system (e.g., toxaphene) because the system is functioning at a higher than normal level. Toxaphene, in turn, may reduce the acute toxicity of chemicals that require this system for detoxification (ATSDR, 1996c).

5.3.11.10 Critical Data Gaps—

The following data gaps have been identified for toxaphene: mammalian germ cell genotoxicity, studies that investigate sensitive developmental toxicity endpoints including behavioral effects, epidemiological and animal studies of immunotoxicity, long-term neurotoxicity studies in animals using sensitive functional and neuropathological tests and behavioral effects on prenatally exposed animals, epidemiological studies evaluating multiple organ systems, and pharmacokinetic studies (ATSDR, 1996c).

5.3.11.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	2.5×10^{-4} mg/kg-d
Carcinogenicity	1.1 per mg/kg-d.

5.3.11.12 Major Sources—

ATSDR (1996c), HSDB (1993), IRIS (1999).

5.4 ORGANOPHOSPHATE PESTICIDES

Please note that these analytes are currently undergoing reassessment by the EPA under the provisions of the Food Quality Protection Act of 1996. This reassessment may result in changes in the RfD values. Contact EPA for the most current information.

5.4.1 Chlorpyrifos

5.4.1.1 Background—

Chlorpyrifos is an organophosphate insecticide first registered in 1965 and used throughout the United States. Chlorpyrifos is used to control foliar and soil insects for a wide variety of crops. While most use is agricultural, significant amounts of chlorpyrifos are used in urban settings for termite control and commercial landscape maintenance and pest control. Chlorpyrifos formulations (e.g., Dursban) are also used by the general public for home, lawn, and garden insect control.

5.4.1.2 Pharmacokinetics—

Chlorpyrifos accumulates in fat and has a longer half-life in fatty tissues than in other tissues. It has been detected in cows' milk (HSDB, 1993) and would be expected to occur in human milk of exposed mothers. This is of concern because organophosphates may have a higher toxicity for immature individuals than adults (e.g., malathion was more toxic to juveniles in three species tested) (U.S. EPA, 1992f). Chlorpyrifos is rapidly metabolized and excreted based on studies in animals (Hayes and Laws, 1991).

5.4.1.3 Acute Toxicity—

Effects commonly associated with acute high-level exposure to chlorpyrifos include the following: headache, dizziness, weakness, incoordination, muscle twitching, tremor, nausea, abdominal cramps, diarrhea, sweating, blurred or dark vision, confusion, tightness in the chest, wheezing, productive cough, pulmonary edema, slow heartbeat, salivation, tearing, toxic psychosis with manic or bizarre behavior, influenza-like illness with weakness, anorexia, malaise, incontinence, unconsciousness, and convulsions (HSDB, 1999).

5.4.1.4 Chronic Toxicity—

IRIS provides an oral RfD of 0.003 mg/kg-d based on a NOAEL in a 20-day study reported in 1972 that found cholinesterase inhibition in adult male humans after 9 days of exposure. There were four subjects per dosed group. An uncertainty factor of 10 was used to calculate the RfD (IRIS, 1999). There are limitations in the use of this study for a chronic toxicity RfD. Although effects were observed at levels lower than the NOAEL, they were discounted due to an inability to

achieve statistical significance; however, it is very difficult to achieve statistical significance with four subjects. No uncertainty factor was applied for the acute nature of the study. Most important, EPA is reviewing its methods for evaluating cholinesterase inhibitors. Cholinesterase inhibition alone is not necessarily considered an adverse effect in the absence of other effects. The value listed on IRIS was confirmed in 1993 by an Office of Pesticide Programs RfD Peer-Review Committee (U.S. EPA, 1993c).

Other chronic exposure effects have been observed in study animals. In a 1991 two-generation rat study, adrenal lesions were reported at 1 and 5 mg/kg-d. In a subchronic study at higher doses, the same effects were observed along with increased brain and heart weight (U.S. EPA, 1992f).

There are significant uncertainties regarding an appropriate threshold for effects of chlorpyrifos exposure. These include the very limited data on the recently identified adrenal and cardiac effects of chlorpyrifos and the utility of a cholinesterase endpoint. The IRIS value was used to calculate fish consumption limits shown in Section 4 for chronic toxicity. Future improvements in the database may result in alteration in this recommended value.

5.4.1.5 Reproductive and Developmental Toxicity—

Chlorpyrifos has been evaluated for developmental toxicity in mice, rats, and rabbits (U.S. EPA, 2000b). Most studies only show effects at doses that cause maternal toxicity due to cholinesterase inhibition (i.e., ≥ 5 mg/kg-d). However, in a study where observations were carried out to postnatal day 66, delayed alterations in brain development were noted in offspring of rats receiving 1.0 mg/kg-d. Decreases in measurements of the parietal cortex were observed in females. In addition, several studies show that neonates and young animals are more susceptible to chlorpyrifos-induced cholinesterase inhibition than adults (U.S. EPA, 2000b). For these reasons, a Population Adjusted Dose has been calculated to provide extra protection for infants, children, and women of childbearing age.

5.4.1.6 Mutagenicity—

Chlorpyrifos was not mutagenic in bacteria or mammalian cells. Slight genetic alterations in yeast and DNA damage in bacteria have been observed. Chlorpyrifos did not induce chromosome aberrations in vitro, was not clastogenic in the mouse micronucleus test in vivo, and failed to induce unscheduled DNA synthesis in isolated rat hepatocytes (U.S. EPA, 2000b).

5.4.1.7 Carcinogenicity—

Chlorpyrifos did not increase cancer incidence in 2-yr feeding studies in mice and rats (U.S. EPA, 1992f). EPA has classified chlorpyrifos as Group E (evidence of noncarcinogenicity for humans) (U.S. EPA, 1999c).

5.4.1.8 Special Susceptibilities—

There is a recognized human population that may be at high risk with respect to organophosphate exposure. Approximately 3 percent of the human population has an abnormally low plasma cholinesterase level resulting from genetic causes. These people are particularly vulnerable to cholinesterase-inhibiting pesticides. Others at greater risk include persons with advanced liver disease, malnutrition, chronic alcoholism, and dermatomyositis because they exhibit chronically low plasma cholinesterase activities. Red blood cell (RBC) acetylcholinesterase is reduced in certain conditions such as hemolytic anemias; people with these conditions may be at greater risk than the general population from exposure to organophosphates (U.S. EPA, 1999).

5.4.1.9 Interactive Effects—

No data were located. However, it is possible that coexposure to compounds with a similar mechanism of action (i.e., organophosphate and carbamate pesticides) may result in additive or synergistic effects.

5.4.1.10 Critical Data Gaps—

Data are needed on potential noncholinesterase effects of chronic exposure and on the mechanism of toxicity that underlies the alterations in brain development observed in the offspring of chlorpyrifos-treated rats. Additionally, toxicokinetic data are needed to explain the differential extent of cholinesterase inhibition between adult and young animals.

5.4.1.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	3×10^{-4} mg/kg-d (3×10^{-5} mg/kg-d for infants, children, and women ages 13-50)
Carcinogenicity	Group E (evidence of noncarcinogenicity for humans).

5.4.1.12 Major Sources—

HSDB (1993), IRIS (1999), U.S. EPA (1992f, 2000b).

5.4.2 Diazinon

5.4.2.1 Background—

Diazinon is an organophosphorus insecticide that has been used widely since its introduction in 1952. Most use is agricultural, although diazinon formulations are also used commercially and by the general public for home, lawn, and garden insect control.

5.4.2.2 Pharmacokinetics—

Diazinon is converted in the liver into its active form diazoxon. Both diazinon and diazoxon are rapidly deactivated by esterases in the blood and liver. Animal studies indicate that diazinon and its metabolites are cleared from all tissues in the body within 12 days after single exposures (ATSDR, 1996d). Human milk may contain trace amounts of diazinon based on the results of exposure in cows (HSDB, 1993).

5.4.2.3 Acute Toxicity—

Diazinon is highly toxic. The estimated adult oral fatal dose is approximately 25 g (HSDB, 1993). Toxic effects are seen in the central and peripheral nervous system due to inhibition of cholinesterase.

5.4.2.4 Chronic Toxicity—

There is currently no IRIS file for diazinon. However, OPP provides an RfD of 7×10^{-4} mg/kg-d based on a NOAEL of 0.025 mg/kg-d observed for plasma cholinesterase inhibition in a human study. The uncertainty factor was 30:10 for intraspecies variability and 3 for the protection of infants and children (U.S. EPA, 1998b).

Very little dose-response data are available on chronic systemic toxicity other than cholinesterase effects. Hematocrit depression was observed in a rat chronic feeding study at 50 mg/kg-d. Gastrointestinal disturbances were noted at 5 mg/kg-d with a NOEL of 0.05 mg/kg-d in a chronic monkey study (U.S. EPA, 1993d). If an alternative to cholinesterase inhibition is required, the monkey study can be used with standard uncertainty factors that take into consideration inter- and intraspecies variability.

5.4.2.5 Reproductive and Developmental Toxicity—

The reproductive/teratogenic studies listed in the tox one-liners report no adverse effects at the highest doses tested (U.S. EPA, 1993d).

HSDB reported multiple studies indicating diazinon is teratogenic; however, the relevance of these studies is questionable since they were not conducted using standard protocols and administration of diazinon was by parenteral routes. In a prenatal exposure study (dose not specified), multiple doses of diazinon resulted in a higher incidence of urinary malformations, hydronephrosis, and hydroureter. Diazinon was teratogenic in rats administered a single dose on day 11 of gestation. Decreased fetal body weight was the most sensitive indicator. No dose was specified in the database (HSDB, 1993). In chicks, diazinon exposure led to abnormal vertebral column development including a tortuous and shortened structure with abnormal vertebral bodies. In the neck region, the vertebral bodies had fused neural arches and lacked most intervertebral joints. More severe

effects on other elements of the skeleton were observed at higher doses (HSDB, 1993; Hayes, 1982). The dose (1 mg/egg) is not easily convertible to a mammalian dose.

Behavioral effects were observed in mice exposed prenatally at 0.18 and 9 mg/kg-d throughout gestation. The high-dose group showed decreased growth, several behavioral effects, and structural pathology of the forebrain. The low-dose group did not have brain pathology or growth abnormalities; however, they showed small but measurable defects in behavior and a delay in reaching maturity (ATSDR, 1996d)

5.4.2.6 Mutagenicity—

Most mutagenicity assays were negative; one positive sister chromatid exchange assay was noted (U.S. EPA, 1993d). A study on the effect of diazinon on mitosis in human lymphocytes reported chromosomal aberrations in 74 percent of the cells at 0.5 mg/mL (HSDB, 1993).

5.4.2.7 Carcinogenicity—

No evidence of carcinogenicity was observed in several long-term feeding studies with diazinon in rodents (ATSDR, 1996d). EPA has classified diazinon as "not likely" to be a human carcinogen (U.S. EPA, 1999c).

5.4.2.8 Special Susceptibilities—

There is a recognized human population that may be at high risk with respect to organophosphate exposure. Approximately 3 percent of the human population has an abnormally low plasma cholinesterase level resulting from genetic causes. These people are particularly vulnerable to cholinesterase-inhibiting pesticides. Others at greater risk include persons with advanced liver disease, malnutrition, chronic alcoholism, and dermatomyositis because they exhibit chronically low plasma cholinesterase activities. Red blood cell (RBC) acetylcholinesterase is reduced in certain conditions such as hemolytic anemias; people with these conditions may be at greater risk than the general population from exposure to organophosphates (U.S. EPA, 1999).

5.4.2.9 Interactive Effects—

MIXTOX has reported antagonistic effects between diazinon and toxaphene with exposure in rats via gavage (MIXTOX, 1992).

5.4.2.10 Critical Data Gaps—

OPP lists the following data gaps: reproduction study in rats, chronic feeding oncogenicity study in rats, and chronic feeding study in dogs (U.S. EPA, 1992d). A multigeneration reproductive study that evaluated developmental effects at low

doses and defined a NOAEL would be useful in establishing an appropriate RfD.

5.4.2.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	7×10^{-4} mg/kg-d based on cholinesterase inhibition
Carcinogenicity	"Not likely" to be a human carcinogen.

5.4.2.12 Major Sources—

ATSDR (1996d), Hayes (1982), HSDB (1993), U.S. EPA (1993d).

5.4.3 Disulfoton (Disyston)

5.4.3.1 Background—

Disulfoton is an organophosphate pesticide used on a wide variety of crops; major uses are on corn, wheat, potatoes, and cotton. It is also used on fruit and nut trees and ornamental plants.

5.4.3.2 Pharmacokinetics—

Disulfoton is readily absorbed after ingestion. Metabolism of disulfoton involves sequential oxidation of the thioether sulfur and/or oxidative desulfuration in addition to hydrolytic cleavage. The major metabolites are the sulfoxide acid sulfone analogs of the compound. These are toxic metabolites that are degraded rapidly to water-soluble nontoxic metabolites. Their estimated half-life is 30 to 32 hours (U.S. EPA, 1993f). Disulfoton is rapidly absorbed through the mucous membrane of the digestive system and conveyed by the blood to body tissues. The kidneys are the main route of elimination of the metabolites (HSDB, 1993).

5.4.3.3 Acute Toxicity—

The acute oral LD_{50} in animals ranges from 2 to 27.5 mg/kg (U.S. EPA, 1993f). Disulfoton is highly toxic to all mammals by all routes of exposure (HSDB, 1993).

5.4.3.4 Chronic Toxicity—

IRIS provides an RfD of 4.0×10^{-5} mg/kg-d based on an LOAEL of 0.04 mg/kg-d from a 2-year rat study that demonstrated cholinesterase inhibition and optic nerve degeneration (IRIS, 1999). An uncertainty factor of 100 was used to account for the interspecies differences and the spectrum of sensitivity in the human population, plus a 10-fold factor to account for the lack of a no-effect level.

Numerous other effects of disulfoton have been reported at doses within 1 order of magnitude of the LOAEL identified in the critical study. Toxicity, as reflected in changes in absolute and relative organ weights, has been observed at 0.1 mg/kg-d (the lowest dose tested) for the following systems: spleen, liver, pituitary, brain,

seminal vesicles, and kidneys (IRIS, 1999). In addition, at 0.65 mg/kg-d, rats exhibited atrophy of the pancreas, chronic inflammation and hyperplasia in the stomach, and skeletal muscle atrophy (U.S. EPA, 1993h).

5.4.3.5 Reproductive and Developmental Toxicity—

In a rat teratogenicity study, incomplete ossification of the parietals and sternebrae were noted at 1 mg/kg-d with a NOEL of 0.3 mg/kg-d in rats. In a 1966 three-generation reproduction study in rats, male offspring had juvenile hypoplasia in the testes, females had mild nephropathy in the kidneys, and both had preliminary stages of liver damage at 0.5 mg/kg-d. No NOAEL was obtained, and no data were provided on a number of critical parameters, including weight, growth rate, and number of stillborn animals. Insufficient histologic data and incomplete necropsy reports were identified by EPA reviewers (IRIS, 1999, U.S. EPA, 1993f).

A more recent two-generation rat study identified a NOAEL of 0.04 mg/kg-d with an LOAEL of 0.12 mg/kg-d based on decreased litter sizes, pup survival, and pup weights (U.S. EPA, 1993f).

5.4.3.6 Mutagenicity—

Disulfoton was not mutagenic in most assays; however, it was positive for unscheduled DNA synthesis without activation in human fibroblasts, in a reverse mutation assay in *Salmonella* (U.S. EPA, 1993f), and in other in vitro assays (HSDB, 1993).

5.4.3.7 Carcinogenicity—

Insufficient information is available to determine the carcinogenic status of disulfoton. Disulfoton has been classified as Group E (evidence of noncarcinogenicity for humans (U.S. EPA, 1999c)

5.4.3.8 Special Susceptibilities—

Based on the organ toxicities observed in animal studies, individuals with diseases or disorders of the following systems may be at greater risk from exposure to disulfoton: pancreas, stomach, spleen, liver, pituitary, brain, seminal vesicles, kidneys, musculoskeletal, and ocular. In addition, children who were exposed prenatally to disulfoton may be at risk, depending on the level of exposure.

5.4.3.9 Interactive Effects—

No data were located.

5.4.3.10 Critical Data Gaps—

The IRIS file notes that additional rat reproduction studies and studies to evaluate the ocular effects of disulfoton are needed (IRIS, 1999). HSDB notes that, because of data gaps, a full risk assessment cannot be completed. Major relevant data gaps noted under the Federal Insecticide Fungicide, and Rodenticide Act (FIFRA) heading in HSDB include chronic toxicity, oncogenicity, and mutagenicity data; animal metabolism; subchronic toxicity; and human dietary and nondietary exposures (some data gaps may have been filled, cited in HSDB, 1993). As noted above, additional studies are needed to identify the NOEL for sensitive measures of the testicular, liver, and kidney toxicity identified in the multigeneration study.

5.4.3.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	4×10^{-5} mg/kg-d
Carcinogenicity	Group E (evidence of noncarcinogenicity for humans).

5.4.3.12 Major Sources—

HSDB (1993), IRIS (1999), U.S. EPA (1993f).

5.4.4 Ethion

5.4.4.1 Background—

Ethion is an organophosphate pesticide used primarily on citrus crops (U.S. EPA, 1993a).

5.4.4.2 Pharmacokinetics—

Absorption of ethion is rapid by the oral route. Ethion is desulfurated by P-450 enzymes in the liver to its active form, ethion monooxon, which causes toxicity because of its potent inhibition of neural cholinesterase. Ethion and its oxon form are detoxified by the action of esterases in the blood and liver, producing diethyl phosphate and other metabolites that have not been characterized. Ethion and its metabolites were cleared from the body within 7 days after single dose experiments in animals (ATSDR, 1998a).

5.4.4.3 Acute Toxicity—

Effects commonly associated with acute high-level exposure to ethion include the following: headache, dizziness, weakness, incoordination, muscle twitching, tremor, nausea, abdominal cramps, diarrhea, sweating, blurred or dark vision, confusion, tightness in the chest, wheezing, productive cough, pulmonary edema,

slow heartbeat, salivation, tearing, toxic psychosis with manic or bizarre behavior, influenza-like illness with weakness, anorexia, malaise, incontinence, unconsciousness, and convulsions (HSDB, 1999).

5.4.4.4 Chronic Toxicity—

IRIS provides an RfD of 5×10^{-4} mg/kg-d based on two principal studies. A study of 10 men reported a NOAEL of 0.05 mg/kg-d for plasma cholinesterase inhibition. A second study in dogs reported a NOAEL of 0.06 and 0.07 mg/kg-day for males and females, respectively, for plasma and brain cholinesterase inhibition Uncertainty factors of 10 each were applied for intraspecies sensitivity and because of concern for the significant effect on brain cholinesterase observed at the next highest dose (0.71 mg/kg-d) in the dog study (IRIS, 1999, U.S. EPA, 1999d).

5.4.4.5 Reproductive and Developmental Toxicity—

In a rat developmental toxicity study, both the maternal and developmental toxicity NOAELs were 0.6 mg/kg-d. Both the maternal and developmental toxicity LOAELs were 2.5 mg/kg-d based on signs of hyperactivity in the parents. In a rabbit developmental toxicity study, the NOAEL and LOAEL for maternal toxicity were 2.4 and 9.6 mg/kg-d, respectively, based on weight loss, reduced food consumption, and orange colored urine. The NOAEL for developmental toxicity was 9.6 mg/kg-d, the highest dose tested (U.S. EPA, 1999d).

In a three-generation reproductive study in rats, the reproductive NOAEL was 1.25 mg/kg-d, the highest dose tested. The systemic toxicity NOAEL was 0.2 mg/kg-d and the LOAEL was 1.25 mg/kg-d based on decrease in serum cholinesterase activity in F_1 and F_2 female rats (U.S. EPA, 1999d).

5.4.4.6 Mutagenicity—

Ethion has shown no evidence of genotoxicity in several in vitro tests. Ethion was negative in tests for point mutations, DNA repair, recombination, sister chromatid exchange, and unscheduled DNA synthesis (ATSDR, 1998a). No in vivo tests of ethion genotoxicity were located.

5.4.4.7 Carcinogenicity—

In 2-yr feeding studies with ethion in rodents, no evidence of carcinogenicity was observed in rats (up to 2 mg/kg-d) or mice (up to 1.2 mg/kg-d) (ATSDR, 1998a). On this basis, ethion is classified as a Group E chemical, evidence of non-carcinogenicity for humans (U.S. EPA, 1999d).

5.4.4.8 Special Susceptibilities—

In the case of ethion, EPA's Office of Pesticide Programs considered that a 10X safety factor was not necessary for the protection of infants and children. This recommendation was based on the following weight of evidence: no evidence of enhanced susceptibility in fetuses in developmental studies in rats and rabbits, no enhanced susceptibility in pups in a two-generation reproductive study in rats, no evidence of developmental neurotoxicity, and completeness of the toxicology database to assess susceptibility to infants and children (U.S. EPA, 1999).

5.4.4.9 Interactive Effects—

Potentiation between ethion and malathion has been observed. In rats, the potentiation was approximately 2.9-fold. In dogs, there was very slight, if any, potentiation (U.S. EPA, 1993l).

5.4.4.10 Critical Data Gaps—

IRIS lists a chronic dog feeding study as a data gap (IRIS, 1999).

5.4.4.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	5×10^{-4} mg/kg-d
Carcinogenicity	Group E (evidence of noncarcinogenicity for humans).

5.4.4.12 Major Sources—

ATSDR (1998a), IRIS (1999), U.S. EPA (1999d).

5.4.5 Terbufos

5.4.5.1 Background—

Terbufos is an organophosphorus insecticide/nematicide applied to the soil to control insects in a variety of crops.

5.4.5.2 Pharmacokinetics—

After a single oral dose of terbufos in rats, 83 percent was eliminated in urine as metabolites and 3.5 percent in the feces over the following 7 days. No unusual distribution of terbufos or its metabolites was noted in tissues (U.S. EPA, 1995).

5.4.5.3 Acute Toxicity—

Terbufos has a high acute toxicity to humans. Animal studies yielded the following results: an oral LD_{50} in rats of 1.3 to 1.6 mg/kg (surveillance index) and an oral LD_{50} in mice of 1.3 to 6.6 mg/kg (U.S. EPA, 1992e).

5.4.5.4 Chronic Toxicity—

Limited information is available on terbufos toxicity, and the focus of most toxicity evaluations is on its cholinesterase inhibition properties. There is currently no IRIS file for terbufos. The OPP lists an RfD of 2×10^{-5} mg/kg-d based on a NOAEL of 0.005 mg/kg-d for plasma cholinesterase inhibition in a 28-day study in dogs (U.S. EPA, 1997h). An uncertainty factor of 300 (10 for interspecies variation, 10 for intraspecies variation, and 3 for protection of infants and children) was applied to the NOAEL.

Quantitative chronic toxicity information on cholinesterase inhibition is available. In rats, a 1974 lifetime oral study found a LOAEL of 0.0125 mg/kg-d (the lowest dose tested); a 1987 1-year oral study found a NOAEL of 0.025 mg/kg-d. In dogs, a 1972 6-month oral study found a NOAEL of 0.0025 mg/kg; a 1986 1-year study found a LOAEL of 0.015 mg/kg-d (the lowest dose tested); a 1987 28-d dog study identified a NOAEL of 0.00125 mg/kg-d (U.S. EPA, 1992e).

Quantitative data on chronic effects that are not directly related to cholinesterase inhibition are limited because of the lack of "no effect levels" from many studies and the need for specific information on some effects. Chronic exposure effects include: corneal cloudiness and opacity, eye rupture, alopecia, disturbances in balance, and exophthalmia noted in multiple studies and multiple species at 0.0125 mg/kg-d and above (U.S. EPA, 1992e). Increased liver weight and increased liver extramedullary hematopoiesis at 0.025 mg/kg-d and above, and mesenteric and mandibular lymph node hyperplasia at 0.05 mg/kg-d and above were noted in a subchronic (3-mo) rat study (animals were not examined for this lesion at lower exposure levels) (U.S. EPA, 1992e).

5.4.5.5 Reproductive and Developmental Toxicity—

Data currently available on developmental toxicity are limited because the endpoints identified were gross measures of toxicity (death) and the underlying causes of toxicity were not identified. The studies are not based on sensitive measures of developmental toxicity. Results from two developmental studies and one multigeneration study are available: a 1984 rat study found a NOAEL of 0.1 mg/kg-d with increased fetal resorptions at 0.2 mg/kg-d; a 1988 rabbit study identified a NOAEL of 0.25 mg/kg-d with fetal resorptions at 0.5 mg/kg-d. A 1973 multigeneration reproductive study found a NOAEL of 0.0125 mg/kg-d in rats, based on an increase in the percentage of deaths in offspring (U.S. EPA, 1992e).

5.4.5.6 Mutagenicity—

Terbufos was negative in most assays. It was positive in an in vivo dominant-lethal assay in rats; at 0.4 mg/kg, the numbers of viable implants was reduced (U.S. EPA, 1992e).

5.4.5.7 Carcinogenicity—

EPA has classified terbufos as Group E, evidence of noncarcinogenicity for humans (U.S. EPA, 1999c).

5.4.5.8 Special Susceptibilities—

There is a recognized human population that may be at high risk with respect to organophosphate exposure. Approximately 3 percent of the human population has an abnormally low plasma cholinesterase level resulting from genetic causes. These people are particularly vulnerable to cholinesterase-inhibiting pesticides. Others at greater risk include persons with advanced liver disease, malnutrition, chronic alcoholism, and dermatomyositis because they exhibit chronically low plasma cholinesterase activities. Red blood cell (RBC) acetylcholinesterase is reduced in certain conditions such as hemolytic anemias; people with these conditions may be at greater risk than the general population from exposure to organophosphates (U.S. EPA, 1999).

5.4.5.9 Interactive Effects—

No data were located.

5.4.5.10 Critical Data Gaps—

There are inconsistencies in the toxicity database for terbufos based on a comparison of acute study results and the results obtained in some chronic feeding studies, developmental studies, and the LD_{50}s. Some longer-term studies reported no effects at exposure levels above the LD_{50}s (U.S. EPA, 1992e).

The animal and human studies available on terbufos do not provide a complete and consistent basis for calculation of an alternative exposure limit. The identification of mesenteric and mandibular lymph node hyperplasia is problematic due to its potential oncogenic implications. A NOAEL for these effects was not identified and effects were not screened in low-dose groups. Other effects, which are not directly related to cholinesterase inhibition, were also noted with terbufos exposure, including optic damage at 0.0125 mg/kg-d in multiple species and studies. In addition, there is uncertainty regarding a safe exposure level to prevent adverse developmental effects, as discussed above. These results warrant further evaluation and may be considered, by some, to justify an additional modifying factor to deal with data gaps and uncertainties in the database.

5.4.5.11 Summary of EPA Health Benchmarks—

Chronic Toxicity	2×10^{-5} mg/kg-d.
Carcinogenicity	Group E (evidence of noncarcinogenicity for humans).

5.4.5.12 Major Sources—

HSDB (1993), U.S. EPA (1992e).

5.5 CHLOROPHENOXY HERBICIDES

5.5.1 Oxyfluorfen

5.5.1.1 Background—

Oxyfluorfen is a recently introduced diphenyl ether pesticide in the chlorophenoxy class. Limited data were located on this chemical.

5.5.1.2 Pharmacokinetics—

No data were located.

5.5.1.3 Acute Toxicity—

The acute oral LD_{50} in rats is greater than 5,000 mg/kg (Hayes and Laws, 1991).

5.5.1.4 Chronic Toxicity—

IRIS provides an RfD of 3×10^{-3} mg/kg-d based on a NOAEL of 0.3 mg/kg-d from a 1977 20-month mouse feeding study that identified nonneoplastic lesions in the liver and increased absolute liver weight. Uncertainty factors of 10 each for inter- and intraspecies sensitivity were applied (IRIS, 1999).

5.5.1.5 Reproductive and Developmental Toxicity—

A three-generation rat study provided a NOAEL of 0.5 mg/kg-d and an LOAEL of 5 mg/kg-d. A rat teratology study identified a NOAEL of 100 mg/kg-d. A rabbit study found fused sternebrae at 30 mg/kg-d and a NOEL of 10 mg/kg-d (IRIS, 1999, U.S. EPA, 1993j). A rabbit teratology study data gap is noted in the IRIS file (IRIS, 1999).

5.5.1.6 Mutagenicity—

Results of mutagenicity assays on oxyfluorfen are mixed (U.S. EPA, 1993j).

5.5.1.7 Carcinogenicity—

Oxyfluorfen has been classified as a possible human carcinogen (C) based on liver tumors identified in experimental animals. A cancer slope factor of 0.0732 mg/kg-d has been derived (EPA 1998c).

5.5.1.8 Interactive Effects—

No data were located.

5.5.1.9 Critical Data Gaps—

The IRIS file notes a rabbit teratology study as a data gap (IRIS, 1999).

5.5.1.10 Summary of EPA Health Benchmarks—

Chronic Toxicity	3×10^{-3} mg/kg-d
Carcinogenicity	7.32×10^{-2} mg/kg-d.

5.5.1.11 Major Sources—

IRIS (1999), U.S. EPA (1993j).

5.6 POLYCYCLIC AROMATIC HYDROCARBONS (PAHs)

5.6.1 Background

Polycyclic aromatic hydrocarbons (PAHs) are a group of organic chemicals that have a fused ring structure of two or more benzene rings. PAHs are also commonly referred to as polynuclear aromatic hydrocarbons (PNAs). They are formed during the incomplete combustion of organic materials. Industrial activities that produce PAHs include coal coking; production of carbon blacks, creosote, and coal tar; petroleum refining; synfuel production from coal; and the use of Soderberg electrodes in aluminum smelters and ferrosilicum and iron works. Domestic activities that produce PAHs include cigarette smoking, home heating with wood or fossil fuels, waste incineration, broiling and smoking foods, and use of internal combustion engines. PAHs are ubiquitous in the environment and usually occur as mixtures. PAHs with two to five benzene rings are generally of greatest concern for environmental and human health effects (U.S. EPA, 1999a). ATSDR (1995b) has identified the following PAHs as the most important with regard to human exposure:

- Acenaphthene
- Acenaphthylene
- Anthracene
- Benz[*a*]anthracene
- Benzo[*a*]pyrene
- Benzo[*e*]pyrene
- Benzo[*b*]fluoranthene
- Benzo[*k*]fluoranthene
- Benzo[*j*]fluoranthene
- Benzo[*g,h,i*]perylene
- Chrysene
- Dibenz[*a,h*]anthracene
- Fluoranthene
- Fluorene
- Indeno[*1,2,3-cd*]pyrene
- Phenanthrene
- Pyrene.

Although these and many other PAHs are present in the environment, benzo[*a*]pyrene is the chemical with most of the available health effects data.

5.6.2 Pharmacokinetics

PAHs may be absorbed through the lungs, the stomach, or the skin. The extent of absorption varies in both humans and animals with the individual compound and is influenced by vehicle. For instance, oral absorption increases with more lipophilic PAHs or in the presence of oils in the intestinal tract. After inhalation, oral, or dermal exposure of animals, the highest levels of PAHs were found in

highly perfused tissues, such as the lung, liver, gastrointestinal tract, and kidney. Animal studies also show that PAHs cross the placenta. PAHs are rapidly metabolized and excreted in humans and animals. The elimination half-life for benzo[*a*]pyrene in rodents is 20 to 30 hours (ATSDR, 1995b).

PAHs have been shown (ATSDR, 1995b) to be metabolized to reactive intermediates by enzyme systems commonly found in the lung, intestines, and liver. These intermediates then covalently bind to cellular macromolecules, leading to mutation and tumor development.

5.6.3 Acute Toxicity

Few data are available describing the acute toxicity of PAHs after inhalation exposure in humans or animals. Limited information is available on the effects of acute oral and dermal exposure in animals. However, benzo[*a*]pyrene is fatal to mice following oral exposure to 120 mg/kg-d, and the liver and the skin have been identified as target organs in animals after oral or dermal exposure, respectively (ATSDR, 1998b).

5.6.4 Chronic Toxicity

Few controlled epidemiological studies have been reported in humans on the effects of exposure to PAHs or to PAH-containing mixtures. However, available information describing chronic-duration dermal exposure of humans to PAHs indicates that PAHs have a high chronic exposure toxicity characterized by chronic dermatitis and hyperkeratosis (ATSDR, 1995b).

Chronic studies in animals exposed to PAHs by ingestion, intratracheal installation, or skin-painting have identified adverse effects on the cardiovascular, respiratory, gastrointestinal, immune, and central nervous systems and on the blood, liver, and skin (ATSDR, 1995b).

IRIS provides an RfD of 3×10^{-1} for anthracene based on a NOAEL of 1,000 mg/kg-d in a subchronic study in mice. Uncertainty factors of 10 each for inter- and intraspecies variability were applied, with an additional uncertainty factor of 30 for use of a subchronic study and the lack of reproductive/developmental data and adequate toxicity data in a second species. Confidence in the RfD is rated low (IRIS, 1999).

An RfD of 4×10^{-2} mg/kg-d was calculated for fluoranthene based on a subchronic study in mice, a NOAEL of 125 mg/kg-d, and critical effects on the liver, blood, and kidneys. The same uncertainty factors were applied as for anthracene, with confidence also rated as low (IRIS, 1999).

IRIS provides the same RfD for fluorene as for fluoranthene; a subchronic study in mice was also used with the same NOAEL, uncertainty factors, and confidence rating. For fluorene, the critical effect was on the blood (IRIS, 1999).

For pyrene, an RfD of 3 x 10^{-2} mg/kg-d was calculated. It was also based on a subchronic study in mice, with a NOAEL of 75 mg/kg-d and kidney effects noted. The same uncertainty factors and confidence rating were used (IRIS, 1999).

5.6.5 Reproductive and Developmental Toxicity

No information is available regarding the reproductive or developmental toxicity of PAHs in humans. Animal data describing reproductive and developmental effects of benzo[*a*]pyrene administered orally or parenterally and indicate that PAHs have the potential to induce adverse reproductive and developmental effects such as sterility, resorptions, and malformations (ATSDR, 1995b).

5.6.6 Mutagenicity

Benzo[*a*]pyrene has been thoroughly studied in genetic toxicology test systems (ATSDR, 1995b). It induces genetic damage in prokaryotes, eukaryotes, and mammalian cells in vitro and produces a wide range of genotoxic effects, including gene mutations in somatic cells, chromosome damage in germinal and somatic cells, DNA adduct formation, unscheduled DNA synthesis, sister chromatid exchange, and neoplastic cell transformation. The genotoxic effects of the other PAHs have been investigated using both in vivo and in vitro assays. All but three of the PAHs (acenaphthene, acenaphthylene, and fluorene) were reported to be mutagenic in at least one in vitro assay with the bacterium *S. typhimurium*.

5.6.7 Carcinogenicity

Evidence indicates that mixtures of PAHs are carcinogenic in humans. This evidence comes primarily from occupational studies of workers exposed to mixtures containing PAHs as a result of their involvement in such processes as coke production, roofing, oil refining, or coal gasification (ATSDR, 1995b). Cancer associated with exposure to PAH-containing mixtures in humans occurs predominantly in the lung and skin following inhalation and dermal exposure, respectively. In animals, individual PAHs have been shown to be carcinogenic by the inhalation route (benzo[*a*]pyrene) and the oral route (e.g., benz[*a*]anthracene, benzo[*a*]pyrene, and dibenz[*a,h*]anthracene). Dermal exposure of animals to benz[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, chrysene, dibenz[*a,h*]anthracene, or indeno[*1,2,3-cd*]pyrene has been shown to be tumorigenic in mice.

EPA has performed weight-of-evidence evaluations of several PAHs. The carcinogenicity classifications are listed below (IRIS, 1999):

- Acenaphthylene — D (not classifiable as to human carcinogenicity)
- Anthracene — D
- Benz[*a*]anthracene — B2 (probable human carcinogen)
- Benzo[*a*]pyrene — B2
- Benzo[*b*]fluoranthene — B2

- Benzo[*k*]fluoranthene B2
- Benzo[*g,h,i*]perylene D
- Chrysene B2
- Dibenz[*a,h*]anthracene B2
- Fluoranthene D
- Fluorene D
- Indeno[*1,2,3-cd*]pyrene B2
- Phenanthrene D
- Pyrene D

EPA and others have developed a relative potency estimate approach for PAHs (Nisbet and LaGoy, 1992; U.S. EPA, 1993n). Using this approach, the cancer potency of the other carcinogenic PAHs can be estimated based on their relative potency to benzo[*a*]pyrene. Table 5-2 lists the toxicity equivalence factors (based on carcinogenicity) calculated by Nisbet and LaGoy (1992) for PAHs discussed above.

U.S. EPA (1993n) has derived relative potency estimates based on mouse skin carcinogenesis. These are shown in Table 5-3.

Table 5-2. Toxicity Equivalent Factors for Various PAHs

Compound	Toxicity Equivalency Factor (TEF)
Dibenz[*a,h*]anthracene	5
Benzo[*a*]pyrene	1
Benz[*a*]anthracene	0
Benzo[*b*]fluoranthene	0.1
Benzo[*k*]fluoranthene	0.1
Indeno[*1,2,3-cd*]pyrene	0.1
Anthracene	0.01
Benzo[*g,h,i*]perylene	0.01
Chrysene	0.01
Acenaphthene	0.001
Acenaphthylene	0.001
Fluoranthene	0.001
Fluorene	0.001
Phenathrene	0.001
Pyrene	0.001

Source: Nisbet and LaGoy (1992).

Table 5-3. Relative Potency Estimates for Various PAHs

Compound	Relative Potency[a]
Benzo[*a*]pyrene	1.0
Benz[*a*]anthracene	0.145
Benzo[*b*]fluoranthene	0.167
Benzo[*k*]fluoranthene	0.020
Chrysene	0.0044
Dibenz[*a,h*]anthracene	1.11
Indeno[*1,2,3-cd*]pyrene	0.055[b]

Source: U.S. EPA, 1993n.

[a] Model was $P(d)=1-\exp[-a(1+bd)^2]$ for all but indeno[1,2,3-c,d]pyrene.

[b] Simple mean of relative potencies (0.021 and 0.089); the latter derived using the one-hit model.

5.6.8 Special Susceptibilities

People with nutritional deficiencies, genetic diseases that influence the efficiency of DNA repair, and immunodeficiency due to age or disease may be unusually susceptible to the effect of PAHs. In addition, people who smoke, people with a history of excessive sun exposure, people with liver and skin diseases, and women, especially of reproductive age, may be at increased risk. Individuals with hepatic-metabolizing enzymes that can be induced by PAHs may be unusually susceptible to the toxic effects of PAH exposure by virtue of producing more toxic metabolites. Fetuses may be susceptible to the effects of toxic PAH metabolites produced by maternal exposure, because of increased permeability of the embryonic and fetal blood-brain barrier and the immaturity of the enzymatic systems that are responsible for elimination (ATSDR, 1995c).

5.6.9 Interactive Effects

Humans are usually exposed to PAHs in complex mixtures rather than to individual PAHs. Interactions may occur among chemicals in a mixture prior to exposure or may occur after exposure as a result of differing effects of the mixture components on the body. Synergistic and/or antagonistic interactions with regard to the development of health effects, particularly carcinogenesis, may occur. The interaction between noncarcinogenic and carcinogenic PAHs have been examined extensively in animals. Weakly carcinogenic or noncarcinogenic PAHs, including benzo[*e*]pyrene, benzo[*g,h,i*]perylene, fluoranthene, or pyrene exhibit co-carcinogenic potential and tumor-initiating and promoting activity when applied with benzo[*a*]pyrene to the skin of mice. In contrast, benzo[*a*]fluoranthene,

benzo[*k*]fluoranthene, chrysene, and a mixture of anthracene, phenathracene, and pyrene have been shown to significantly inhibit benzo[*a*]pyrene-induced sarcoma after injection in mice. Several experiments have indicated that mixtures of several PAHs are less potent with respect to carcinogenicity than the individual PAHs that constitute the mixture (ATSDR, 1995c).

The majority of human exposure to PAHs occurs in the presence of particles or other environmental pollutants that may influence the toxicity of the PAHs. For instance, inhalation exposure to PAHs in the presence of particulate matter greatly increases respiratory tract tumors in laboratory animals, due to the fact that the particles are cleared more slowly from the lungs, thus allowing the particle-bound PAHs to remain in the respiratory tract for longer periods of time. Similarly, concomitant exposure to asbestos increases bronchopulmonary cancers. Exposure to solvents or other environmental compounds that increase metabolism of the PAHs may increase or decrease toxicity, depending on whether the individual PAH must be transformed to toxic intermediates in order to exert its adverse effect (ATSDR, 1995c).

5.6.10 Critical Data Gaps

A joint team of researchers from ATSDR, NTP, and EPA have identified the following data gaps: human responses to acute, intermediate (14 to 365 days), and chronic exposure, subchronic reproductive tests in various species, developmental toxicity studies in two species, immunotoxicity studies of animals and humans, and neurotoxicity studies in humans and animals (ATSDR, 1995c).

5.6.11 Summary of EPA Health Benchmarks

Chronic Toxicity	(anthracene)	3×10^{-1} mg/kg-d
	(fluoranthene)	4×10^{-2} mg/kg-d
	(fluorene)	4×10^{-2} mg/kg-d
	(pyrene)	3×10^{-2} mg/kg-d
Carcinogenicity	(benzo[*a*]pyrene)	7.3 per mg/kg-d.

5.6.12 Major Sources

ATSDR (1998b), IRIS (1997c), U.S. EPA (1999a, 1993n).

5.7 POLYCHLORINATED BIPHENYLS (PCBs)

5.7.1 Background

Polychlorinated biphenyls (PCBs) are a mixture of chlorinated biphenyl chemicals comprised of various chlorine substitution patterns. There are 209 possible PCB congeners. Mixtures of PCBs were marketed in the United States under the trade name Aroclor, with a numeric designation that indicated their chlorine content. Although production and use of PCBs were banned in 1979, this chemical group is extremely persistent in the environment and bioaccumulates through the food chain. However, environmental mixtures of PCBs differ from the commercial mixtures because of partitioning, transformation, and bioaccumulation. There is evidence that some of the more toxic PCB congeners preferentially accumulate in higher organisms (Aulerich et al., 1986). Consequently, the aggregate toxicity of a PCB mixture may increase as it moves up the food chain (U.S. EPA, 1993a).

PCB exposure is associated with a wide array of adverse health effects in experimental animals, but the effects of PCB exposure in humans are less clear. Many effects have only recently been investigated (e.g., endocrine effects), and the implications of newer studies are not fully known. The health effects of PCBs are still under active evaluation and currently there is not sufficient information on the specific congeners to develop congener-specific quantitative estimates of health risk (ATSDR, 1998c; U.S. EPA, 1993a). Aroclor mixtures, rather than environmental mixtures or bioconcentrated PCB mixtures, have been used in laboratory animal studies to determine toxicity. The preferable studies would be those that utilize human dose-response data from populations who have consumed PCBs via fish or who have been exposed to PCBs in occupational settings. Because sufficient human data are lacking, animal data were used to develop RfDs and CSFs for PCBs. The Office of Water recommends that total PCBs, calculated as the sum of the concentrations of the congeners or homologue groups, be reported. Aroclor analysis is not recommended, except for screening studies, because environmental PCB mixtures cannot be characterized by any commercial Aroclor mixture (Cogliano, 1998). The first volume in this document series, *Sampling and Analysis*, contains a detailed discussion of analysis of this group of chemicals (U.S. EPA, 1993a).

5.7.2 Pharmacokinetics

PCBs are absorbed through the GI tract and distributed throughout the body. Studies of individual chlorobiphenyl congeners indicate, in general, that PCBs are readily absorbed, with an oral absorption efficiency of 75 percent to greater than 90 percent (ATSDR, 1998b). Because of their lipophilic nature, PCBs, especially the more highly chlorinated congeners (tetra- through hexachlorobiphenyl), tend to accumulate in lipid-rich tissues. Greater relative amounts of PCBs are usually found in the liver, adipose tissue, skin, and breast milk. It has been shown that absorption of tetra- and higher chlorinated congeners from breast milk by nursing

infants ranges from 90 to 100 percent of the dose (ATSDR, 1998b). Offspring can also be exposed to PCBs through placental transfer. PCBs have also been measured in other body fluids including plasma, follicular fluid, and sperm fluid.

The retention of PCBs in fatty tissues is linked to the degree of chlorination and also to the position of the chlorine atoms in the biphenyl ring. In general, higher chlorinated PCBs persist for longer periods of time. Pharmacokinetics modeling of PCB disposition indicates that PCB movement in the body is a dynamic process, with exchanges between various tissues that depend on fluctuating exposure levels to specific congeners. The result is elimination of congeners that are more easily metabolized and retention of those that resist metabolism (ATSDR, 1998c). In occupationally exposed individuals, lower chlorinated congeners had half-lives between 1 and 6 years, whereas higher chlorinated PCBs had half-lives ranging from 8 to 24 years (ATSDR, 1998b).

PCBs induce mixed function oxidases, and different congeners induce specific forms (isozymes) of the cytochrome P-450 system. Although the mechanisms of PCB toxicity have been investigated in many studies, a clear definition of the mechanisms for most congeners has not been identified. The congeners appear to act by a variety of mechanisms (ATSDR, 1998b). Some PCB congeners are similar to dioxins and bind to a cytosolic protein, the Ah receptor, which regulates the synthesis of a variety of proteins. The toxicity of these congeners is similar to dioxins. The toxicity of other PCB congeners seems to be unrelated to the Ah receptor. Ultimately, the toxicity of a PCB mixture depends on the toxicity of the individual congeners, their interactions, and interactions with other chemical contaminants such as pesticides and dioxins. For example, both synergistic and antagonistic interactions have been reported with mixtures containing PCBs and dioxins (Van den Berg et al., 1998).

5.7.3 Acute Toxicity

Acute high-level exposures of laboratory animals to PCBs have resulted in liver and kidney damage, neurological effects, developmental effects,endocrine effects, hematological effects, and death. LD_{50} values for various Aroclor mixtures range from about 1,000 mg/kg to more than 4,000 mg/kg. No human deaths have been associated with acute exposure to PCBs (ATSDR, 1998b).

5.7.4 Chronic Toxicity

In animal studies, numerous effects have been documented, including hepatic, gastrointestinal, hematological, dermal, body weight changes, endocrine, immunological, neurological, and reproductive effects (ATSDR, 1998b). Most of the studies have involved oral exposure. Despite the variety of adverse effects observed in animals exposed to PCBs, overt adverse effects in humans have been difficult to document. This has been attributed to the fact that, in most cases, the dosages tested in animals were considerably higher than those found in occupational exposures and to the difficulties with interpreting epidemiological

studies (James et al.,1993; Kimbrough, 1995). These include multiple confounding factors, uncertain exposure estimates, and statistical limitations. Skin rashes and a persistent and severe form of acne (chloracne) have been reported following exposures to PCBs. Occupational and accidental exposures have indicated that PCBs may affect many organs including the gastrointestinal, respiratory, immune, central nervous, and cardiovascular systems.

EPA has derived an RfD of 2×10^{-5} mg/kg-d for Aroclor 1254 (IRIS, 1999). The RfD was based on a LOAEL of 0.005 mg/kg-d for ocular and immunological effects in monkeys. The study reported ocular exudate and inflamed Meibomian glands, distorted growth of finger and toenails, and decreased antibody response (IgM and IgG) to injected sheep red blood cells at the lowest dose tested. Uncertainty factors of 10 for sensitive individuals, 3 for extrapolation from monkeys to humans, 3 for extrapolation from a subchronic exposure to a chronic RfD, and 3 for use of a minimal LOAEL were applied, resulting in a total uncertainty factor of 300. An uncertainty factory of 3 (rather than 10) for extrapolation from subchronic to chronic exposure was used, because the duration of the critical study continued for approximately 25 percent of the lifespan of monkeys, and the immunologic and clinical changes observed did not appear to be dependent upon duration.

EPA has medium confidence in the study used as the basis for the RfD for Aroclor 1254, in the database, and in the RfD. EPA based this rating on the fact that the database consisted of a large number of laboratory animal and human studies; however, there were some inconsistencies in the effect levels for reproductive toxicity and the results of an unpublished study were considered (IRIS, 1999).

5.7.5 Developmental Toxicity

PCB mixtures have been shown to cause adverse developmental effects in experimental animals (ATSDR, 1998c). Some human studies have also suggested that PCB exposure may cause adverse effects in children and in developing fetuses while other studies have not shown effects (U.S. EPA, 1999a). Reported effects include lower IQ scores (Jacobson and Jacobson, 1996), low birth weight (Rylander et al., 1998), and lower behavior assessment scores (Lonky et al., 1996). However, study limitations, including lack of control for confounding variables, and deficiencies in the general areas of exposure assessment, selection of exposed and control subjects, and the comparability of exposed and control samples. Different findings from different studies provide inconclusive evidence that PCBs cause developmental effects in humans (ATSDR, 1998b).

The RfD for Aroclor 1016 is based on reduced birth weights observed in monkeys in a 22-month study (discussed below under longer-term developmental studies). This study established a NOAEL of 0.007 mg/kg-d. Applying an uncertainty factor of 100 (3 for sensitive individuals [infants exposed transplacentally], 3 for interspecies extrapolation, 3 for database limitations [male reproductive effects

are not directly addressed and two-generation reproductive studies are not available], and 3 for extrapolation from subchronic to chronic) to the NOAEL yields an RfD of 7×10^{-5} mg/kg-d (IRIS, 1999). However, since the RfD for Aroclor 1254 is more conservative (2×10^{-5} mg/kg-d) and protects against adult toxicity concerns as well as the risk to the fetus and children, this RfD will be used to calculate the consumption limits for all populations (adults, women of reproductive age, and children).

EPA has medium confidence in the study, in the database, and in the RfD for Aroclor 1016. EPA based this rating on the fact that the critical study was well conducted in a sensitive animal species and the database for PCBs in general is extensive; however, since mixtures of PCBs found in the environment do not match the pattern of congeners found in Aroclor 1016, EPA felt that only a medium confidence ranking could be given. For those particular environmental applications where it is known that Aroclor 1016 is the only form of PCB contamination, EPA stated that the RfD could be considered to have a high confidence rating (IRIS, 1999).

A study was conducted of pregnancy outcomes in women who had consumed PCB-contaminated fish from Lake Michigan over an average of 16 years (exposure both prior to and during pregnancy). Consumption of contaminated fish and levels of total PCBs in cord serum correlated with lower birth weight, smaller head circumference, and shorter gestational age. Fish consumption, however, was correlated with delayed neuromuscular maturity, and, at 7 months, the children had subnormal visual recognition memory. Children from this cohort were examined at age 4 and 11 years. At age 4, cord serum PCB levels were associated with impaired short-term memory. Activity level was inversely related to 4-year serum PCB level and also to maternal milk PCB level. At age 11, prenatal exposure to PCBs was associated with lower full-scale and verbal IQ scores after controlling for potential confounding variables, such as socioeconomic status. The results from this series of studies were confounded by possible maternal exposure to other chemicals and by the fact that the exposed group, on average, drank more alcohol and caffeine, prior to and during pregnancy, weighed more, and took more cold medications during pregnancy, than the nonexposed group (Fein et al., 1984a, 1984b).

Other relevant studies generally found no significant differences between control groups and exposed groups concerning stillbirths, multiple births, preterm births, congenital anomalies, and low birth weight.

Information on chronic developmental toxicity is available from studies in Rhesus monkeys (ATSDR, 1998b). Exposure periods ranged from 12 to 72 months. Inflammation of tarsal glands, nail lesions, and gum recession were noted in offspring of monkeys exposed to Aroclor 1254. Adverse neurobehavioral effects were reported following exposure to Aroclor 1016 and Aroclor 1248. Other observed effects included reduction in birth weight and increased infant death for Aroclor 1248.

Exposure via lactation is a significant concern for neonates because PCBs concentrate in milk fat. Animal studies indicate that lactational exposure, in some cases, can be more significant than transplacental transfer. In monkeys, signs of intoxication have been observed in offspring exposed to PCBs in maternal milk (ATSDR, 1998b).

In summary, the results from some studies in humans suggest that exposure to PCBs may cause developmental effects. However, limitations of these studies diminished the validity of the results. Animal studies indicate that PCBs can cause some developmental effects following prenatal or postnatal exposure.

5.7.6 Mutagenicity

The majority of mutagenicity assays of PCBs have been negative (IRIS, 1999). However, an increase in the percentage of chromosomal aberrations in peripheral lymphocytes and an increase in the sister chromatid exchange rate were reported in a study of workers manufacturing PCBs for 10 to 25 years. Although workers and controls were matched for smoking and drinking, concurrent exposure to other known human genotoxic chemicals occurred (ATSDR, 1998b). Another study found an increased incidence of chromatid exchanges in lymphocytes from workers exposed to PCBs in an electric power substation fire compared to unexposed controls. It is possibile that toxic chlorinated dioxins and/or furans generated during the fire may have been responsible for the effects.

The weight of evidence from the in vitro and in vivo genotoxicity studies suggests that PCBs are not likely to be genotoxic to humans. However, exposure to PCBs may enhance the genotoxic activity of other chemicals (ATSDR, 1998b).

5.7.7 Carcinogenicity

PCBs are classified by EPA as Group B2; probable human carcinogens . This is based on studies that have found liver tumors in rats exposed to Aroclors 1260, 1254, 1242, and 1016. Evaluation of the animal data indicate that PCBs with 54 percent chlorine content induces a higher yield of liver tumors in rats than other PCB mixtures.

Human epidemiological studies of PCBs have not yielded conclusive results (Silberhorn et al.,1990). There is some suggestive evidence that xenoestrogens, including PCBs, may play a role in breast cancer induction (ATSDR, 1998c). Some studies have indicated an excess risk of several cancers, including: liver, biliary tract, gallbladder, gastrointestinal tract, pancreas, melanoma, and non-Hodgkin's lymphoma (IRIS, 1999, ATSDR, 1998c). As with all epidemiological studies, it is very difficult to obtain unequivocal results because of the long latency period required for cancer induction and the multiple confounders arising from concurrent exposures, lifestyle differences, and other factors. The currently available human evidence is considered inadequate but suggestive that PCBs may cause cancer in humans (IRIS, 1999).

The Agency's recent peer-reviewed reassessment published in a final report, *PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures* (U.S. EPA, 1996c), adopts an innovative approach that distinguishes among PCB mixtures by using information on environmental processes. It considers all cancer studies (which used commercial mixtures only) to develop a range of cancer slope factors, then uses information on environmental processes to provide guidance on choosing an appropriate slope factor for representative classes of environmental mixtures and different pathways. Depending on the specific application, either central estimates or upper bound estimates can be appropriate. Central estimates describe a typical individual's risk, while upper bounds provide greater assurance that the true risk is not likely to be underestimated. Central estimates are used for comparing or ranking environmental hazards, while upper bounds provide information about the precision of the comparison or ranking. In this reassessment, the use of the upper bound values was found to increase cancer potency estimates by only two- or threefold over those using central tendency. Upper bounds are useful for estimating risks or setting exposure-related standards to protect public health and are used by EPA in quantitative cancer risk assessment. Thus, the cancer potency of PCB mixtures is determined using a tiered approach based on environmental exposure routes with upper-bound slope factors ranging from 0.07 to 2 per mg/kg-d for average lifetime exposures to PCBs. It is noteworthy that bioaccumulated PCBs appear to be more toxic than commercial PCBs and appear to be more persistent in the body (IRIS, 1999). In addition, there is evidence that early-life exposures may result in an increased risk (U.S. EPA, 1996c). Therefore, the highest cancer slope factor is recommended for the following conditions: food chain exposure; sediment and soil ingestion; inhalation of dust or aerosols; dermal exposure (if an absorption factor has been applied); presence of dioxin-like, tumor- promoting, or persistent congeners; and early-life exposure.

Alternatively, if site-specific congener concentrations are available, the risk assessment can be supplemented by determining the dioxin-like toxicity (U.S. EPA, 1996c; Cogliano, 1998). Cogliano (1998) presents data showing the typical composition of several commercial Aroclor mixtures (Table 5-4). Aroclors 1016, 1242, 1254, and 1260 contained concentrations of dioxin-like concentrations ranging from 0.14 ppm to 46.4 ppm TEQs. Therefore, separate risk assessments should be conducted for the dioxin-like and nondioxin-like PCB congeners if the congener analysis indicates elevated concentrations of dioxin-like congeners relative to the typical commercial mixtures (IRIS, 1999; U.S. EPA, 1996c).

Table 5-4. Reported Concentrations (ppm) of Dioxin-Like Congeners in Commercial Aroclor Mixtures

	Aroclors			
Congener	**1016**	**1242**	**1254**	**1260**
PCB-77 (3,3',4,4'-tetraCB)	66	3340	918	31
PCB-126 (3,3,4,4',5-pentaCB)	0.95	44	134.3	0.0
PCB-169 (3,3,4,4',5,5[1]-hexaCB)	0.0	0.0	1.52	0.0
PCDFs	0.05	2.2	0.13	5.5
TEQ from PCBs	0.14	8.1	46.4	7.1
TEQ from PCDFs	0.002	0.1	0.01	0.08

Source: Cogliano, 1998.
CB = Chlorinated biphenyls

In a recent study conducted by the Delaware Department of Natural Resources and Environmental Control (Greene, 1999), dioxin-like PCBs, nondioxin-like PCBs, and dioxins/furans accounted for about 64.4, 26.9, and 5.6 percent of the total cancer risk, respectively, from ingesting fish caught from the Chesapeake and Delaware Canal. Data from this study are shown in Table 5-5 to illustrate the potential importance of the dioxin-like PCB congeners. The DDNREC noted that, had cancer risk been calculated according to the traditional method (i.e., not including a separate assessment for dioxin-like PCBs), the cancer risk estimate for PCBs would have been lower by a factor of 2.9. However, PCBs contributed about 93 percent of the total dioxin risk based on 2,3,7,8-TCDD TEQs. Therefore, failure to evaluate the dioxin-like PCB congeners could result in underestimating cancer risk.

Table 5-5. PCB and Dioxin Concentrations (ppb) in Channel Catfish

Parameter	**Median**	**Mean**	**Maximum**
Total PCBs	1,104.8	1,173	1,665.3
Nondioxin-like PCBs	943.8	1,024.9	1,474.7
Dioxin-like PCBs TEQs	0.0302	0.0303	0.0509
Dioxin/furan TEQs	0.0026	0.0024	0.0043
Total TEQs	0.0328	0.0327	0.0552

Source: Greene, 1999.

5.7.8 Special Susceptibilities

There is evidence that embryos, fetuses, and neonates are more susceptible to PCBs due to their underdeveloped enzymatic systems, which may lead to increased PCB accumulation in the body. Breast-fed infants may have an increased risk because of bioconcentration of PCBs in breast milk and high intake rates relative to body weights. In addition, there is evidence that a steroid present in human milk inhibits glucuronyl transferase activity, which could, in turn, inhibit glucuronidation and excretion of PCB metabolities. Other individuals with potentially greater risk include those with liver and blood diseases or those with syndromes associated with impairment to the metabolic systems that help eliminate PCBs from the body.

5.7.9 Interactive Effects

PCBs induce microsomal enzymes; therefore, the effects of exposure to PCBs or other compounds depends on the role of oxidative metabolism. For example, preexposure to PCBs may enhance the liver toxicity of some chemicals (trichloroethylene, mirex, kepone, carbon tetrachloride, tetrachloroethylene) but decrease the liver toxicity of 1,1-dichloroethylene. Other interactive effects include increased metabolism and excretion of pentobarbital, increased genotoxicity of numerous carcinogens, increased duodenal ulcerogenic activity of acrylonitrile, and increased kidney toxicity of trichloroethylene (ATSDR, 1998b).

5.7.10 Critical Data Gaps

The following studies could help fill in some of the key data gaps for PCBs: congener-specific PCB levels in human tissues; epidemiological studies of populations living near PCB-contaminated sites and occupational settings where exposure to PCBs still occurs; reproductive studies in humans and animals, including fertility studies in males of a sensitive species; developmental and neurodevelopmental studies, immunotoxicity studies in humans and animals; neurotoxicity studies in humans with high PCB body burdens and in animals; chronic studies to determine the most sensitive animal target organ and species; and comparative toxicity of Aroclors and bioaccumulated PCBs (ATSDR, 1998b).

5.7.11 Summary of EPA Health Benchmarks

Chronic Toxicity	2×10^{-5} mg/kg-d based on Aroclor 1254
Carcinogenicity	2.0 per mg/kg-d based on mixed PCBs.

5.7.12 Major Sources

ATSDR (1998b), Cogliano (1998), HSDB (1993), IRIS (1999), James et al. (1993), Kimbrough (1995), Silberhorn et al. (1990), U.S. EPA (1996c).

5.8 DIOXINS

5.8.1 Background

Dioxins are a group of synthetic organic chemicals that contain 210 structurally related individual chlorinated dibenzo-p-dioxins (CDDs) and chlorinated dibenzofurans (CDFs). Dioxin is a generic term that is used, in this case, to refer to the aggregate of all CDDs and CDFs. It is recommended that the 17 2,3,7,8-substituted tetra- through octa-chlorinated dibenzo-*p*-dioxins and dibenzofurans be considered together as a simplifying and interim approach until further guidance is available on this chemical group. In addition, 12 PCB congeners have been identified that exhibit dioxin-like activity (U.S. EPA, 1996c, Van den Berg et al., 1998). The reader may consult guidance on the use of a toxicity equivalency approach to refine the toxicity estimate and fish consumption limit calculations (Barnes and Bellin, 1989; U.S. EPA, 1991c; U.S. EPA, 1996c).

Dioxin has been undergoing extensive review within EPA for several years. Consequently, only a brief summary, is provided below. Currently, the EPA's dioxin reassessment document, which includes two reports entitled *Estimating Exposure to Dioxin-like Compounds* (three volumes) (U.S. EPA, 1994a) and *Health Assessment Document for 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and Related Compounds* (three volumes) (U.S. EPA, 1994b) is undergoing final review. The dioxin reassessment document is scheduled for final external peer review during the third quarter of fiscal year 2000. Following peer review, the document will be sent to the EPA Science Advisory Board for final review. The final dioxin reassessment document is scheduled for release by the end of the calendar year 2000.

5.8.2 Pharmacokinetics—

Dioxins are absorbed through the gastrointestinal tract, respiratory tract, and skin and distributed throughout the body. Absorption is congener-specific with decreased absorption of hepta- and octa-congeners compared to dioxins with fewer chlorines. Because of their lipophilic nature, dioxins tend to accumulate in fat and the liver. Dioxins are slowly metabolized by oxidation or reductive dechlorination and conjugation and the major routes of excretion are the bile and feces. Reported half-lives in the body range from 5 to 15 years. Small amounts may be eliminated in the urine. The current evidence indicates that metabolities are less toxic than the parent compounds (ATSDR, 1998c, U.S. EPA 1994a).

The predominant forms retained in the tissues are the 2,3,7,8-substituted congeners. Tissue deposition depends on the route of exposure, congeners present, dose, and age. Based on a study of a human volunteer, about 87 percent of a single dose of dioxins dissolved in corn oil was absorbed and about 90 percent of the absorbed dose was distributed to fatty tissue (ATSDR, 1998c).

The half-lives for various dioxin congeners in humans have been reported to range from 2.9 to 26.9 years. Some studies have suggested longer half-lives in individuals with higher body fat (ATSDR, 1998c).

Dioxins induce mixed function oxidases and hepatic aryl hydrocarbon hydroxylase (AHH). Dioxins bind to a cytosolic protein, the Ah receptor, which regulates the synthesis of a variety of proteins. The Ah receptor has been found in many human tissues, including the lung, liver, placenta, and lymphocytes. Although evidence indicates that the Ah receptor is involved in many biological response to dioxins, the diversity of biological effects observed cannot be accounted for by characteristics of this receptor alone (ATSDR, 1998c, U.S. EPA, 1994a).

5.8.3 Acute Toxicity

LD_{50} values for dioxins vary over several orders of magnitude, depending on the congener, species, and strain of animal tested. The most toxic congener is 2,3,7,8-TCDD with LD_{50} values ranging from 22 μg/kg to 340 μg/kg in various strains of laboratory rats. Guinea pigs are the most sensitive species tested (LD_{50}s from 0.6 to 2.1 μg/kg) and hamsters are the most resistant (LD_{50}s from 1,157 to 5,051 μg/kg). In all studies, the animals died from a pronounced wasting syndrome characterized by weight loss and depletion of body fat that lasted 1 to 6 weeks. By contrast, laboratory animals have survived acute doses of 1 to 4 g/kg of 2,7-DCDD and OCDD. Single exposures to dioxins have also affected the heart, liver, kidneys, blood, stomach, and endocrine systems of laboratory animals. No human deaths have been directly associated with exposure to dioxins. (ATSDR, 1998c).

5.8.4 Chronic Toxicity

In animal studies, numerous effects have been documented, including hepatic, gastrointestinal, hematological, dermal, body weight changes, endocrine, immunological, neurological, reproductive, and developmental effects. Most of the studies have involved oral exposure. Despite the variety of adverse effects observed in animals exposed to dioxins, adverse health effects in humans have generally been limited to highly exposed populations in industrial factories or following chemical accidents and contamination episodes. The adverse human health effect most commonly associated with high-level exposure to dioxin-like agents is the skin disease chloracne, a particularly severe and prolonged acne-like skin disorder. Adverse human health effects were also noted following consumption of heated rice oil contaminated with PCBs and CDFs. Conclusive evidence of other adverse human health effects at lower dioxin exposure levels is generally lacking because of incomplete exposure data, concomitant exposure to other compounds, and/or small numbers of study participants. Some epidemiological studies have suggested that dioxins may cause immuno-suppression, respiratory effects, cardiovascular effects, and liver effects in humans (ATSDR, 1998c, U.S. EPA, 1994a).

5.8.5 Reproductive and Developmental Toxicity

Dioxins have been shown to cause adverse developmental effects in fish, birds, and mammals at low exposure levels. Several studies in humans have suggested that dioxin exposure may cause adverse effects in children and in the developing fetus. These include effects on the skin, nails, and meibomian glands; psychomotor delay; and growth retardation. However, study limitations, including lack of control for confounding variables, and deficiencies in the general areas of exposure make it difficult to interpret these results. Overall, the human data are inconclusive; however, the animal data suggest that developmental toxicity is a concern (ATSDR, 1998c, U.S. EPA, 1994a).

In mammals, learning behavior and development of the reproductive system appear to be among the most sensitive effects following prenatal exposure. In general, the embryo or fetus is more sensitive than the adult to dioxin-induced mortality across all species (ATSDR, 1998c, U.S. EPA, 1994a).

5.8.6 Mutagenicity

The majority of mutagenicity assays of dioxins have been negative. An increased incidence of chromosomal aberrations was found in fetal tissue but not maternal tissue in a group of women exposed to dioxins following an industrial accident in Italy; however, cases treated for chloracne did not have an increased incidence of chromosomal aberrations. Animal studies also are inconclusive. The available data do not provide strong evidence that dioxins are genotoxic (ATSDR. 1998c, U.S. EPA, 1994a).

5.8.7 Carcinogenicity

Dioxins are classified by EPA as Group B2 (sufficient evidence in animals, insufficient evidence in humans) when considered alone and Group B1 (sufficient evidence in animals, limited evidence in humans) when considered in association with chlorophenols and phenoxyherbicides. This is based on studies that have found multiple-site sarcomas and carcinomas in rats and mice exposed to various dioxin mixtures and congeners. Epidemiological studies suggest an increased incidence of cancer mortality (all types of cancers combined) and of some specific cancers (soft-tissue sarcoma, non-Hodgkin's lymphoma, respiratory tract cancer, and gastrointestinal cancers). In addition, there is evidence that 2,3,7,8-TCDD acts as a tumor promoter. As with all epidemiological studies, it is very difficult to obtain clear unequivocal results because of the long latency period required for cancer induction and the multiple confounders arising from concurrent exposures, lifestyle differences, and other factors. The currently available evidence suggests that dioxins may cause cancer in humans (ATSDR, 1998c, U.S. EPA, 1994a). EPA has derived a cancer slope factor of 1.56×10^{5} $(mg/kg\text{-}d)^{-1}$ for 2,3,7,8-TCDD (HEAST, 1997).

5.8.8 Special Susceptibilities

There is evidence that children are more susceptible than adults to the dermal toxicity of dioxins. Animal data suggest that the developing reproductive, immune, and nervous systems of the fetus are particularly sensitive to dioxin toxicity (ATSDR, 1998c).

5.8.9 Interactive Effects

Environmental exposure to dioxins includes various mixtures of CDDs, CDFs, and some PCBs. These mixtures of dioxin-like chemicals cause multiple effects that vary according to species susceptibility, congeners present, and interactions. Risk assessment of these complex mixtures is based on the assumption that effects are additive and there is some experimental evidence to support this. However, there also is evidence that some interactions may result in inhibition and others result in potentiation. Cotreatment of mice with various commercial PCB mixtures (Aroclors) and 2,3,7,8-TCDD has resulted in inhibiting some of the Ah receptor mediated responses. An increased incidence of cleft palate was reported when mice were treated with both 2,3,7,8-TCDD and hexachlorobiphenyl compared to treatment with 2,3,7,8-TCDD alone. Both synergistic and antagonistic responses have been observed following co-exposure of 2,3,7,8-TCDD with other chemicals as well (ATSDR, 1998c).

5.8.10 Critical Data Gaps

The following data gaps have been identified for dioxins: inhalation and dermal toxicity studies; toxicity studies of dioxin compounds other than 2,3,7,8-TCDD; continued medical surveillance of individuals with known past high exposures to dioxins; mechanistic studies; immune function tests in human cohorts; neurological tests in ongoing prospective studies of humans; congener-specific human toxicokinetic studies to better assess human dosimetry; and further studies to identify potential biomarkers for exposure and effects. Another critical data gap is the need to gather exposure data and conduct modeling for the purpose of linking human exposure to sources (ATSDR, 1998c).

5.8.11 Summary of EPA Health Benchmarks

Chronic Toxicity	Not available
Carcinogenicity	$1.56 \times 10^{+5}$ per mg/kg-d.

5.8.12 Major Sources

U.S. EPA (1994a), ATSDR (1998c), Heast (1997), Van den Berg et.al. (1998).

SECTION 6

MAPPING TOOLS FOR RISK ASSESSMENT AND RISK MANAGEMENT

6.1 OVERVIEW OF POPULATION AND CONTAMINANT MAPPING

Mapping is useful for displaying geographic data concerning chemical contaminants, consumer populations, risks, locations of consumption advisories, or other related information. Mapping allows risk assessors and risk managers to work with a visual display of data that is easily understood and that may show patterns of contamination and risk useful to risk managers. A variety of methods for using mapping in risk assessment and management are discussed in this section. Although presented in the risk assessment volume in this series, this information may be useful to state staff in planning and displaying sampling and analysis activities and results, as well as for risk management and risk communication. Additional assistance with mapping may be obtained from mapping software companies, university geography departments, and EPA Regional and Headquarters offices that often use geographic information systems (GISs).

6.2 OBJECTIVES OF MAPPING

Mapping can be useful at every stage in the fish advisory development process to

- Display sampling results with respect to fish species and chemical contaminant levels
- Display population and/or fisher population density
- Display locations of recreational and subsistence fish harvests
- Spatially locate populations at high risk, based on high fish consumption rates
- Delineate areas where fish consumption advisories have been issued
- Determine where data gaps exist for purposes of targeting data collection efforts appropriately.

Information can be mapped in various combinations to address specific concerns. For example, mapping information on fisher population density and on contaminant concentrations can be combined to produce an overview of populations that may be at risk. Risk managers may find particular use for maps showing locations where contamination exceeds screening levels or where a set risk level is estimated to occur (e.g., greater than 100 percent of the RfD for noncarcinogenic effects, greater than 1 in 1 million risk for carcinogens).

6.3 BASIC GIS CONCEPTS FOR POPULATION AND CONTAMINANT MAPPING

A GIS stores information about the world as a collection of thematic layers that can be linked together by geography. A GIS is commonly defined as a computer system designed to allow users to collect, manage, and analyze large volumes of spatially referenced files and associated data layers. GISs are used for solving complex research, planning, and management problems. The major components of a GIS are: a computer with software providing a special user interface designed to facilitate dealing with spatial databases (or layers); database management software that allows spatial data sets to be created and maintained, along with features for importing data from other computer systems; a set of software tools to carry out spatial data processing and analyses of the GIS layers; and a high-resolution display system (usually a graphics monitor and a high-quality printer or plotter) to create the maps that summarize the spatial analysis work.

Two technologies have been developed for taking information about features in the real world and converting these into a GIS data layer. Raster technologies were developed largely in working with satellite images, high-altitude aerial photographs, or other remote sensing data where the information is organized around small squares or pixels similar to the "dots" found in the photographs printed in books or newspapers. Vector technologies involve a richer set of objects for breaking down the real world into features. Instead of small pixel patches, vector technologies can organize data using a more intuitive set of polygons (e.g., the boundary of a town), lines or arcs (e.g., rivers or roads), and points (e.g., the location of a Superfund site). Figure 6-1 illustrates the underlying differences between raster and vector approaches for organizing aspects of the real world into the digitized features contained in GIS data layers. Table 6-1 compares the advantages and disadvantages and recommends uses of raster- and vector-based GIS programs.

Although there was formerly a major divergence between GIS systems designed to handle raster as opposed to vector data layers, most GIS packages now will either contain procedures for handling both data types or provide transformation programs that can convert one format to the other. While raster-based systems have advantages when dealing with information such as land cover or soil types over large geographic areas, vector approaches have become increasingly popular for most routine GIS analysis applications.

To convert real-world information into GIS data layers, important objects and features must be located precisely so that different data layers will overlay correctly. Geographic information contains either an explicit geographic reference, such as a latitude and longitude or national grid coordinate, or an implicit reference, such as an address, postal code, census tract name, or road name. An automated process called geocoding is used to create explicit geographic references from implicit references (descriptions such as addresses). These geographic references allow you to locate features, such as a Superfund site, and events, such as the location of a major chemical spill, on the earth's surface for analysis. In the vector model, information about points, lines, and

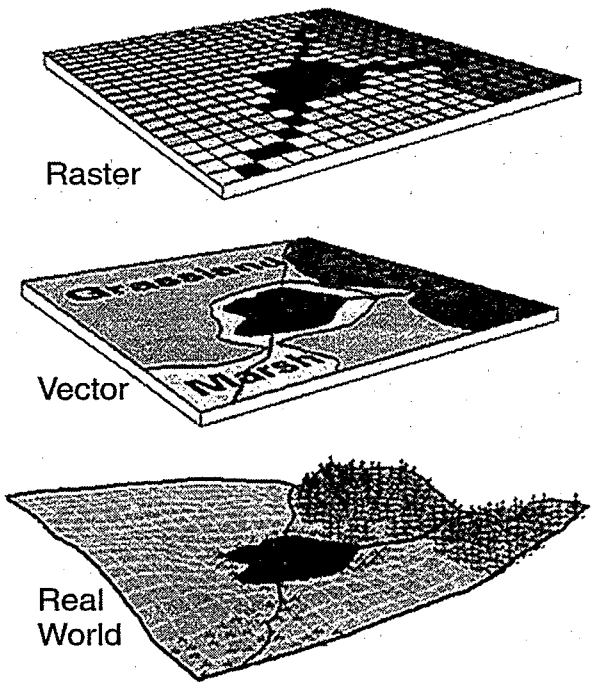


Figure 6-1. GIS data layers may use raster or vector representation techniques.

polygons is encoded and stored as a collection of *x,y* coordinates. The location of a point feature, such as a point source discharge, can be described by a single *x,y* coordinate. Linear features, such as roads and rivers, can be stored as a collection of point coordinates. Polygonal features, such as watershed catchments or the boundaries of political units, such as towns, can be stored as a closed loop of coordinates.

The geocoding process can be the most time-consuming and resource-intensive step in a GIS analysis and mapping process. Data layers involving point or polygon features can be especially difficult to digitize to high degrees of precision. On the other hand, point coverages are often much easier to create. For point coverage, the main requirements are an accurate set of latitude and longitude coordinates or locational information from global positioning satellite (GPS) tools. Point data layers (or coverages) can also be created using existing line or polygon coverages as base maps, from which the point locations can be supplied using software tools in a GIS.

A sensible strategy in conducting special risk analysis or risk management projects with GIS is to identify what data layers are already available and keep the coverages that must be created from scratch to a minimum. The new coverages, in many cases point coverages, would be based on site-specific information based on special surveys or data collections. For existing coverages or georeferenced data files, facilities accessible through the Internet

Table 6-1. Comparison of Raster- Versus Vector-Based GIS Programs

	Raster Method	Vector Method
Advantages	• Simple data structure • Overlay and combination of mapped data with remotely sensed data is easy • Various kinds of spatial analyses are easy • Simulation is easy because each spatial unit has the same size and shape • Technology is inexpensive and is being actively developed	• Good representation of phenomena (such as county and towns, or soil structure hierarchies) • Compact data structure • Topology can be described completely with network linkages • Retrieval, updating, and generalization of graphics and attributes are possible
Disadvantages	• Volumes of graphic data • Use of large cells to reduce data can lose important data, so frequently cannot simplify information • Raster map graphics are more crude than vector maps drawn with fine lines • Network linkages are difficult to establish • Projection transformations are time consuming unless special algorithms or hardware is used	• Complex data structures • Combination of several vector maps through overlay creates difficulties • Simulation is difficult because each unit has a different topological form • Display can be expensive, particularly for high quality, color, and cross-hatching • Technology is expensive, especially for more sophisticated software and hardware • Spatial analyses and filtering within areas are impossible
Recommended Uses	• Quick and inexpensive overlay, map combination and spatial analyses • Simulation and modeling when working with surfaces is necessary	• Data-archiving phenomena (e.g., soil areas, land use units) • Network analyses (e.g., telephone networks or transportation networks) • Compact digital terrain models

Source: Burrough (1991).

and the World Wide Web (WWW or Web) are making it easier to locate and obtain (often for free) a variety of useful data products. Major impetus for using the Internet to exchange GIS data has come from the federal initiative known as the National Spatial Data Infrastructure (NSDI). EPA has strongly supported this effort and, in partnership with other federal and state agencies, now offers a broad spectrum of valuable data products through its Web pages.

6.4 INTERNET SOURCES OF EXISTING DATA FILES AND GIS COVERAGES

A consortium of major governmental agencies cooperates through the Federal Geographic Data Committee (FGDC) to encourage the widest possible use of good quality spatial data products. The main mechanism for sharing these information products is through a series of special Internet facilities maintained by individual federal or state agencies, university research groups, and NSDI. The NSDI is conceived to be an umbrella of policies, standards, and procedures under which organizations and technologies interact to foster more efficient use, management, and production of geospatial data. The Clinton Administration has asked the FGDC to provide the federal leadership for evolving the NSDI in cooperation with state and local governments and the private sector.

The Internet provides a number of interactive software tools to share information, but the most popular tools center on the use of Web browsers that are available for computers of all types ranging from sophisticated workstations to personal computers. A growing number of private citizens use Web browsers at their homes. The URL providing general information for the entire NSDI is: <http://fgdc.er.usgs.gov/>.

This central hub for the NSDI provides Web links to a number of other major "nodes" in the NSDI system. Federal agencies such as the Census Bureau, the United States Geological Survey (USGS), the USDA, and EPA have their own NSDI Web pages with links to more specialized data items. EPA's link to the NSDI is at <http://nsdi.epa.gov/nsdi/>.

EPA has also established a number of Web pages to help provide background information or help access actual data products dealing with particular databases or EPA programs. Examples include a facility called "Surf Your Watershed," which acts as a gateway to information organized according to standard watershed catchments called Hydrologic Cataloging Units defined by the USGS, and an Internet data warehouse system called ENVIROFACTS that allows the retrieval of information dealing with permitted facilities (e.g., Permit Compliance Systems [PCS] for point source discharges to receiving waters), Superfund, or Comprehensive Environmental Response, Compensation, and Liability Act List of Sites (CERCLIS), and information from databases such as the TRI.

With the EPA Web facilities, data files or GIS coverages may be downloaded that could then be incorporated into risk assessment and management projects; the end user would then need access to a GIS to perform spatial analyses and produce the final GIS maps. EPA is also setting up Web facilities at which the user can provide inputs on the type of analysis to perform and then retrieve maps directly from the Internet link. An example is given in Figure 6-2 of a Web tool called BASININFO that can produce displays of the major types of permitted facilities within a USGS Cataloging Unit. Several WEB-based data retrieval and mapping tools are now part of EPA's Maps On Demand systems, which can be accessed at the following address:
<http://www.epa.gov/enviro/html/mod/index.html>.

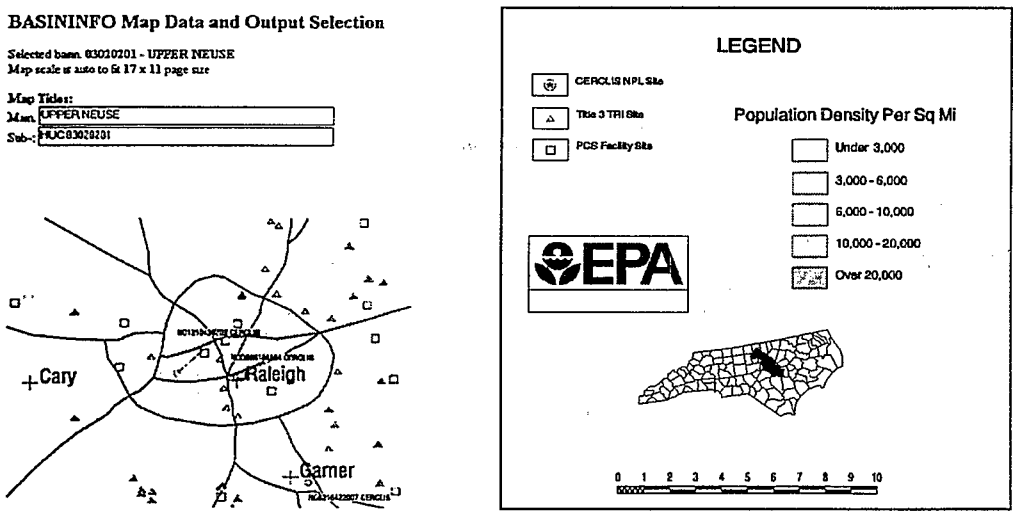


Figure 6-2. Examples of GIS displays from EPA's BASININFO Maps-on-Demand facility.

EPA's SURF YOUR WATERSHED facility provides an on-line set of maps derived from the Office of Science and Technology's National Listing of Fish and Wildlife Advisories (NLFWA) Database. Figure 6-3 shows a display depicting the locations of active advisories for the State of North Carolina. GIS maps showing the location of fish advisories in any of the 50 states, U.S. territories, and the District of Columbia can be viewed on this system.

6.5 DATA NEEDED FOR MAPPING

The information needed for a given map depends largely on the objective of the map itself. The following major categories of information are useful for mapping:

- Chemical contaminant type and concentration
- Consumer population
- Risk level.

Additional refinements may be desirable, including the relationship of chemical contaminants to various point or nonpoint sources, demographic characteristics of the consumer population, consumption patterns of population groups, and types and levels of human health risks. At a minimum, contaminant mapping is usually possible because sampling and analysis programs are basic to all fish advisory programs and generate the necessary data to map the locations where various contaminants are detected as well as the fish species and size (age class) in which the contaminant occurs. Individual maps for each contaminant may be generated, or maps of several contaminants can be displayed together if there is

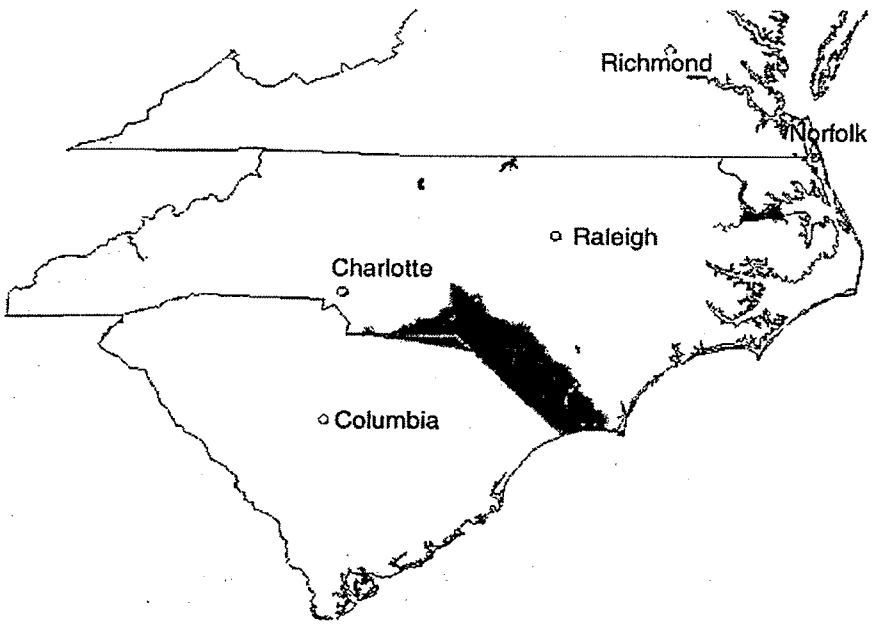


Figure 6-3. Map showing active fish and wildlife advisories for a state.

sufficient refinement in the system. Contaminant concentration can be indicated using different colors; through graphic patterning such as cross-hatching, lines, and dots; or through the use of different symbols (open, semiclosed, or closed circles or squares).

6.6 MAPPING PROGRAMS

Computerized mapping programs are useful aids; however, mapping programs take some time to learn and require data collection and organization prior to data entry. State and local agencies interested in digital mapping should consider the following:

- Availability of the data needed for each map
- Quality of the data to be used
- Amount of time and money available
- Type of program used to generate maps
- Purpose of each map or map series for developing consumption advisories.

It is important to evaluate the goals of the mapping effort and the resources available for the activity. Using a program that does more than is needed can result in unnecessary expenditures for staff training and developing maps for analysis. Data storage capacity is also an important consideration and may be a factor in choosing a mapping approach.

Many federal, regional, state, and tribal agencies already have some divisions that are using GIS programs for other purposes. It is cost- and time-effective to consult with staff already using this resource. Several mapping programs are available that are relatively uncomplicated and inexpensive. These programs are often called desktop mapping or desktop GIS packages. One example of a commercial desktop GIS package is ESRI's ArcView, which can be set up on a personal computer. Generally, PC-based programs can be used to digitize field map data onto a computer, but these programs often have limited capacity to accommodate large data sets. Although more sophisticated programs that usually require high-performance workstations as their computer platforms offer greater flexibility in data input and manipulation, they are often an expensive option and require more expertise to set up and operate. Most GIS programs can generate large volumes of data that need to be stored, so consider computer space in advance.

One cost-effective and sophisticated program, run as a nonprofit venture, has been used extensively by international nongovernmental organizations (NGOs) and intergovernmental organizations with great success. IDRISI (whose name is taken from a medieval Arabic geographer who lived in what is now Morocco) is available from the Geography Department of Clark University in Massachusetts. It consists of inexpensive software that can use and manipulate data easily and also be programmed to assist in selecting outlining criteria for management analyses. The University offers training workshops and other assistance for new users (including Applications in Forestry, Coastal Zone Research and Management, and Decision Making), which may be useful for fish advisory program staff. The IDRISI program is a raster-based system, so the analyses conducted by the program are performed rapidly, effectively, and relatively inexpensively. This particular program is sophisticated enough to accommodate some of the more complicated analyses that are normally difficult to perform without a vector-based program.

Mapping information for the development and management of fish advisories is a relatively new undertaking for most agencies. EPA welcomes ideas and recommendations on this topic. Examples of maps or mapping methods that are widely applicable are especially welcome.

6.7 NATIONAL LISTING OF FISH AND WILDLIFE ADVISORIES (NLFWA) DATABASE

Mapping information for the development and management of fish advisories is a relatively new undertaking that provides precise information to fish-consumers or those waterbodies where chemical contamination in fish may be of public health concern for most agencies.

The EPA Office of Science and Technology within the Office of Water has developed a new Internet Web-based platform for the NLFWA database. State, regional, and local governmental staff as well as members of the general public can now search this database to obtain narrative information on fish consumption advisories and bans. In addition, users can also electronically retrieve and print state, regional, and national maps showing the geographic location and extent of

the fish advisories in each of the states, District of Columbia, and the four U.S. territories.

Information on the geographic extent of the advisories and bans is provided to EPA by the states either as narrative information (e.g. advisory includes all waters of the Black River from its source to the stateline), as latitude and longitude coordinates, or hand-marked on USGS maps which can be digitized into the Geographic Information System (GIS). Other tools used to find the location of waterbodies under fish advisory include: searchable CD-ROMs of geographic information such as TopoUSA, digital tables of geographic sites provided by USGS, and other county maps or information (such as the county where an advisory occurs, or length of advisory) in state reports and memorandums. Tribal authorities also provided computer-generated maps in reports and an electronic GIS file of U.S. waterways include the names of waterbodies that can be searched and matched to information provided by the states.

This GIS mapping information related to fish consumption advisories and bans is available on the Internet at:

http://www.epa.gov/ost/fish

State, regional, and local agency staff may obtain additional information on the new Internet WEB-based database EPA now has available by contacting:

U.S. Environmental Protection Agency
Office of Science and Technology
National Fish and Wildlife Contamination Program 4305
1200 Pennsylvania Avenue, NW
Washington, DC 20460
PHONE: 202-260-7301
FAX: 202-260-9830
E-Mail: bigler.jeff@epa.gov

SECTION 7

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APPENDIX A

REVIEWERS OF FIRST EDITION OF GUIDANCE DOCUMENT

APPENDIX A

Reviewers of First Edition of Guidance Document

The following individuals, representing EPA Headquarters, EPA Regions, state and federal agencies, and Native American groups provided technical information, reviews, and recommendations throughout the preparation of the first edition. Participation in the review process does not imply concurrence by these individuals with all concepts and methods described in this document.

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APPENDIX B

POPULATION EXPOSURE ASSESSMENT—CONSUMPTION PATTERNS AND SURVEYS

APPENDIX B

POPULATION EXPOSURE ASSESSMENT—CONSUMPTION PATTERNS AND SURVEYS

Selecting appropriate population exposure data is critical in both risk estimation and in fish advisory program planning. Whenever possible, state agencies are encouraged to conduct local surveys to obtain information on consumption patterns. The time and resources required to conduct onsite surveys, however, can be prohibitive. If only limited local data are available, that information may be used and supplemented with the best available data from other sources. If local or regional data are not available and surveying is not feasible, other sources may be used to characterize the consumption patterns of a population.

B.1 HIERARCHY OF FISH CONSUMPTION INFORMATION

Table B-1 lists a hierarchy of information sources on fish consumption that may be considered in obtaining data for developing fish advisories. Care should be taken when selecting a matched population and consumption data set to use as "representative" of the target population. Matches should be made based on similar consumption patterns, rather than on generalizations about ethnic behavior or other attributes.

Matching groups with high consumption rates to previously studied groups having similar characteristics is particularly important. These groups with high consumption rates are often those of greatest concern due to their higher potential risks. They are at greater risk than the general population if their consumption is underestimated and may also be more severely jeopardized by losing their fish food sources than the general population if their consumption rates are overestimated.

Many studies are not appropriate for use in exposure assessment. Surveys may be based on only those fishers who apply for licenses through state agencies; this often underestimates consumption rates in some subpopulations. In some areas, the results may reflect a combination of commercially caught fish as well as subsistence- or sport-caught fish and may therefore provide an incomplete picture of fish consumption patterns in a particular region. Often, qualitative or anecdotal information is available to corroborate or challenge the results of older data; this can help to assess the need for additional data collection. For example, a survey may have been conducted in a state with a large urban Asian-American population, commonly known to eat large quantities of fish, yet only a small

Table B-1. Hierarchy of Data Sources[a]

1. Local fish consumption survey (creel surveys)
2. Local fish consumption survey with limited scope (e.g., acquired by fish licenses only)
3. Regional or state survey data from other areas having matching characteristics[b]
   - Behavioral Risk Surveillance Survey (BRSS)
   - Anecdotal information
4. National fish or food consumption data taking into consideration demographic data
   - *National Survey of Fishing, Hunting, and Wildlife Associated Recreation* (U.S. Fish and Wildlife Service, 1993)
   - U.S. Department of Agriculture Continuing Survey of Food Intake by Individuals (CSFII) studies
   - Other national surveys that estimate fish consumption patterns
   - Census data

[a] This hierarchy is generally applicable; however, the utility of any data source is dependent on the match between the population studied in the data source and that being considered by the risk managers. For example, when a better match is available through national or regional fish consumption data than can be found through limited local fish surveys, then the national, regional, or state data are preferable. Special care should be taken that data for highly exposed subpopulations are obtained from sources that considered populations with equally high exposures.

[b] Secondary data sources can be used most effectively in conjunction with qualitative data and anecdotal information (e.g., informal discussions with community groups, clerks, and other qualitative studies).

number of the survey respondents were Asian-American. If the survey was conducted by fishing license registration, it is likely that a large portion of the exposed population was unintentionally excluded from the survey and thus was not adequately represented in the consumption estimates.

B.1.1 Local Fish Consumption Data

B.1.1.1 Creel Surveys—

Another source of information concerning fishing habits (applicable indirectly to consumption estimates) is obtained through the creel surveys. Most state

agencies involved with fish and wildlife management perform creel surveys or censuses. These surveys consist of clerks interviewing fishers onsite and recording the size and species of fish they take home (and presumably eat). These surveys are performed to calculate fishing pressures and evaluate stocking programs for state lakes and streams. These surveys generally contain little demographic information beyond the fisher's home county, though they may be modified to ask additional questions about demographics and fish consumption.

Creel surveys are subject to reporting biases, which may include a reluctance of fishers to report a poor catch or a catch that exceeds allowable limits (see a discussion of data collection problems below). The clerks themselves know a great deal of anecdotal information about fishers because of their direct contact with these individuals. Clerks, area fisheries managers, and conservation officers are excellent sources of information on fisher demographics and should be contacted during research into most fisher populations (Shubat, 1993). Like surveys taken only from licensed fishers, however, this qualitative information may be restricted to certain fishers and fishing locations.

B.1.1.2 Fishing License Surveys—

Fishing license tracking may be a good source for obtaining demographic information for target populations. Fishing licenses include information on the name, age, and address of fishers, location where the license was sold, and the approximate length of the fishing trip (e.g., 4-day, seasonal). Although the information on the license is limited, some researchers have used the addresses on licenses to send out more detailed surveys. Several fish advisory programs, including those in Minnesota and Canada, insert detailed demographic and consumption surveys in their informational booklets, which fishers may fill out and return in exchange for receiving the following year's materials. These surveys by definition, however, reach only a portion of respondents already aware of the fish programs (Shubat, 1993). They also do not reach fishers who do not purchase licenses for economic or other reasons. In addition, Native American groups who are often legally entitled to fish on tribal waterbodies without licenses will not be accessed by this method.

B.1.2 Regional or State Consumption Data

B.1.2.1 Anecdotal Information—

Anecdotal information is vital in directing the search for data on fish consumption patterns. For example, anecdotal information suggests that urban and rural fishers often sell their products "informally" (i.e., without commercial licenses) in geographic areas near where they fish and have customers with "standing orders" for regular fish delivery. This practice has been observed in Missouri, Mississippi, Alaska, and in the Chicago and Milwaukee metropolitan areas and is common to both rural and urban areas (Carlson, 1994). Health officials have raised concerns that "customers," who tend to be from minority or low-income populations, may

be exposed to contaminant concentrations over a long period of time. These groups, while not composed entirely of fishers, may have exposure levels as high as those for subsistence fishers (Carlson, 1994). Another exposed group that may not be well-characterized in some surveys is made up of fishers' family members, including extended families to whom fish is supplied.

Under these circumstances of unlicensed distribution it is likely that

- Those consuming the fish are unaware of the fish advisories, even if the actual fisher is aware
- Contacting the fisher is often difficult and the fisher, once reached, may be very reluctant to provide data on fish catch rates for fear of prosecution.

To obtain an estimate of consumption occurring via these routes, information can be acquired through informal discussions with local community groups in areas of potential exposure.

B.1.2.2 Behavioral Risk Surveillance Surveys—

Most states already participate in random telephone surveys under the Behavioral Risk Surveillance System (BRSS). The BRSS surveys are often the only random, state-level survey information readily available to states. They are funded by the Agency for Toxic Substances and Disease Registry (ATSDR), a department within the Center for Disease Control and Prevention (CDC). Some states have already used federal grant money to add questions on fisher demographics and consumption to the BRSS surveys (Shubat, 1993).

B.1.3 National Consumption Data

B.1.3.1 National Survey of Fishing, Hunting and Wildlife—

The U.S. Fish and Wildlife Service (FWS) conducts a survey every 5 years that includes data on sport fishing. The most recent survey is entitled *1991 National Survey of Fishing, Hunting and Wildlife Associated Recreation* (U.S. FWS, 1993) and is available from the FWS. This survey provides information by state on fishers, broken down by age, sex, race/ethnic group, and state of residence. The FWS data can be used in combination with local data on the size of the fishing population overall to estimate the numbers of exposed individuals with relevant exposure characteristics. For example, using the FWS data, one could estimate the percentage of fishers in the state in a certain age group and apply this percentage to local fishing population data (from fishing licenses, for example) to estimate the number of local fishers in that age group.

B.1.3.2 U.S. Department of Agriculture (USDA) CSCFII Study—

The Continuing Survey of Food Intake by Individuals (CSFII) is a national food consumption survey conducted annually by the USDA. It consists of multistage, stratified-area probability samples from all states except Alaska and Hawaii. In the CSFIIs, dietary intake data collection is distributed over a year-long period. Survey participants provide 3 consecutive days of data. On the first day of the survey, participants provide information to an in-home interviewer. On the second and third days, data are taken from self-administered dietary records. Meals consumed both at home and away from home are recorded (U.S. EPA, 1998b).

B.2 FISH CONSUMPTION SURVEY METHODS

If time and money permit, researchers are encouraged to conduct their own surveys to characterize fisher populations. EPA's guidance manual, *Guidance for Conducting Fish and Wildlife Consumption Surveys* (U.S. EPA, 1998a) may be useful in planning demographic surveys. Researchers also may consider coordinating survey efforts with other existing programs. For example, many state agencies conduct educational outreach programs to provide information or explain new regulations to fishers. Health agencies and natural resource offices can combine efforts to target subpopulations not yet reached through other mechanisms.

B.2.1 Key Considerations

Table B-2 lists key considerations in conducting effective fish consumption surveys. Although surveying of a specific population can provide the most accurate exposure information about it, care must be taken in conducting the survey. The credibility of the survey results must be ensured through careful survey preparation, sample selection, and administration.

Population selection is one of the most significant components of an exposure assessment. A tiered approach is a logical recommendation for selecting populations of concern. First, examine the areas surrounding waterbodies that have been identified as contaminated or supporting potentially contaminated fish (e.g., anadromous fish arriving from contaminated estuaries).

Following this range identification, collect as much anecdotal information as possible from local populations surrounding these waterbodies. Qualitative data will indicate what communities are supported by the waterbodies, whether people are traveling long distances to fish in the waters, and other useful information to help direct further steps of the consumption evaluations. At this point, review the following information to determine whether a further investigation should be carried out:

- Anecdotal information suggesting high consumption rates
- Fish consumption patterns indicating potentially high exposure

Table B-2. Key Considerations for Effective Fish Consumption Surveys

Population Selection	What population is to be surveyed?
	Based on what criteria (e.g., jurisdictional region, region with known fish contamination)?
Population Access	How will the identified population be reached?
	Will separate methods be used for distinct subpopulations (e.g., fish licensing for sport fishers, community groups for urban subsistence fishers)?
Consumption Rates	What method will be used to estimate consumption rates (e.g., recall, recordkeeping, catch rate)?
	What assumptions are made in these estimations (e.g., meal size, household size)?
Consumption Patterns	How are variations in consumption patterns accommodated (e.g., preparation methods, type of fish eaten, parts of fish consumed)?
Duration of Study	Have consumption rates been estimated for each different season or generalized?
	Have large fish catches that have been frozen or preserved for nonfishing seasons been addressed?

- Subpopulations known to have high consumption rates living in the region or identified as fishing in the waters of concern, whether or not any anecdotal evidence exists to support high consumption or exposure rates.

Once the target population is selected, some method must be chosen to survey these individuals. As mentioned earlier, using fishing licenses as a survey tool may miss a large portion of the fishing population. It may be most useful to enlist the help of local agencies or community groups to help access some of the subpopulations at high risk, such as urban low-income populations or individuals of a particular ethnicity. Both identifying populations and collecting data may rely heavily on qualitative or anecdotal evidence on fishers to evaluate exposures of highly exposed populations. Consumption patterns affecting the overall consumption rate and toxicity must be discerned as well, including:

- Species of fish consumed
- Portions of fish that are consumed (fillet only or whole body)
- Preparation and cooking methods.

A determination must be made as to whether fish is a major source of protein in the diet of the subpopulation of concern. If advisories are developed based on the survey results, this information can provide some clue about the impact of fishing restrictions as one risk management option.

Several methods can be used to estimate a population's consumption rate. Actual recordkeeping for some period of time is the most accurate method, although a long-term commitment is needed from the respondents. Memory-recall is another method used to estimate consumption rates. This method can take the form of either "*how many meals of fish (or what amount of fish) have you (and household members) eaten in this past week*?" or "*how many meals of fish (or what amount of fish) do you (and household members) eat each week in general*?" While the length of recall can vary, long-term recall introduces uncertainties and inaccuracies. Individuals knowing the objective of the survey may be biased in their memory recall as well.

Meal size is another feature of determining consumption patterns. Many fish advisories are developed based on assumptions regarding meal size or specific consumption limits for a specific meal size. If information is not collected on meal size, risk managers may wish to use the average meal size assumption recommended by EPA of 227 g (8 oz) of fillet per 70 kg consumer body weight for adults. This value has been cited as appropriate in many documents on fish consumption (Anderson and Amrhein, 1993; Dourson and Clark, 1990; Minnesota Department of Health, 1992; Missouri Department of Health, 1992; U.S. EPA, 1988, 1995). This 8-oz fish meal weight may be considered an average meal size.

For those populations who consume fish whole, or who consume nonfilleted portions of the fish, meal sizes should be obtained from qualitative data or direct surveys. Readers are urged to collect information on meal size specific to their areas and populations of concern, especially if very large meals are known to be consumed during fishing trips, festivals, or under other circumstances. Information regarding maximum meal size may also be valuable in determining whether risks are likely to arise from large short-term exposures (bolus doses).

B.2.2 Data Collection Problems

Conducting surveys to assess the consumption of noncommercially caught fish can be particularly challenging. Numerous individuals involved with fish consumption surveys have raised issues not mentioned in prior guidance documents. Their most notable concern was that of assessing the consumption rates of urban fishers or minority groups that were not registered for fishing licenses. In addition, surveys were often returned with consumption rates that were inconsistent with observed habits and the available qualitative data.

Surveys conducted using traditional methods can exclude major portions of the fish-consuming population. Several localities have attempted to conduct surveys to more accurately reflect the true consumption patterns existing within each

subpopulation. However, they found that, in some cases, unregistered fish consumers were answering survey questions inaccurately for any number of reasons, including the following:

- Fishers associated the state or local agency conducting the survey with enforcement and provided responses they thought the surveyors wanted to hear.
- Individuals who run illegal fish markets and are afraid of being caught responded inaccurately.
- Fish consumers who purchased fish from illegal fish markets and believed them to be commercial fish responded with lower consumption values.
- Surveys were not conducted in the native languages, and the details of the survey were lost in translation when individuals had conversational English skills only.
- Individuals surveyed relied heavily on fish for basic nutritional needs due to economic necessity, or because of personal preference and/or cultural traditions, and were afraid of restrictions that might jeopardize their family.
- Fishers understood the implications of the survey and responded inaccurately out of pride.
- Surveys addressed only certain species of fish that were caught, yet fishers caught and consumed numerous species of bottomfish.
- Questions were asked that made assumptions about the parts of fish consumed when the whole fish, including organs, may have been consumed.

Each of these issues has been addressed in more than one recent fish consumption survey in the past 2 years. Many fisheries resources and health officials therefore believe that approaches that utilize community-level organizations facilitate the survey process. This approach builds on the established trust between the community organization and its members and enables surveyors to develop a more accurate representation of fish consumption patterns.

Fish catch rates have also been used to estimate consumption rates, but variations in preparation methods, illegal resale of fish, and catching and preserving fish for later consumption in other seasons and for extended families and friends all add significantly to the uncertainty of these estimates. The duration of the survey may include only times of high exposure or can be comprehensive and address consumption rates year round to include variations in catch rates and preservation and preparation methods.

Some specific concerns have arisen over the use of license survey methods. Performance exaggeration has been noted for sport fisher respondents, particularly for individuals who associate fishing with prestige or who travel greater distances to reach a particular fishing location. Nonresponse bias has also been noted with surveys conducted on licensed fishers: typically, fishers who traveled shorter distances to reach a fishing destination, or who fished less frequently or consumed smaller quantities of fish, were less likely to respond to surveys than were more frequent fishers. Consequently, consumption rates may have been overestimated somewhat from surveys conducted in this manner.

B.2.3 Intake Patterns and Bolus Dose

When characterizing the consumption patterns of fishers, it is important to consider the intake patterns. Patterns of exposure are critical to evaluating potential health risks. As discussed in Section 2.4.3.2, toxicity is related to both the overall exposure to a contaminant and the time over which the contaminant is consumed. Exposure durations and exposure frequency are important factors in estimating whether toxicity may occur. Consuming a few large meals over a very short period (a bolus dose) may cause acute exposure health effects, whereas consumption of the same total quantity spread over a month or year may cause chronic exposure effects, or no effects at all.

Bolus dose exposure may pose significant risks to:

- Children who
  - consume greater quantities in relation to their body weight than adults
  - have greater susceptibility to some contaminants
  - have less capability to detoxify some contaminants.

- Pregnant women, if the contaminant is known to cause fetal damage following prenatal exposure. Evidence from animal or human data presented in Section 5 shows that prenatal exposure to many of the target analytes may cause damage to offspring.

- Persons with special susceptibilities due to illness (e.g., persons with kidney, liver, or other diseases may be especially vulnerable to toxicants that attack those systems).

The reader is urged to review the toxicity data provided in Section 5 for contaminants of interest in their areas to determine if there are population subgroups requiring particular attention.

Fish consumption is often intermittent based on fish availability, cultural practices, weather, and other factors. Determining whether a large intake is likely to occur over a brief period of time is required to assess whether acute toxicity or developmental toxicity may occur. It is important to obtain descriptive or quantitative information on the timing of consumption over a calendar year.

B.2.4 Calculation of Intake

When information is collected on both consumption patterns and contaminant level, the contaminant exposure can be estimated. The contaminant exposure is calculated using the fish consumption estimates for a specified time period (e.g., 1 week, 1 month). The concentration of the contaminant in the fish (in milligrams of contaminant per gram of fish) is multiplied by the amount of fish consumed (in grams) during the time period to obtain the total contaminant exposure during that time period (in milligrams). For example, if the contaminant concentration is 0.01 mg/g of fish tissue, and 1,000 g of fish are consumed in 1 month, then 0.01 mg/g is multiplied by 1,000 g/mo to obtain a total exposure of 10 mg/mo.

To facilitate the risk assessment process, exposure is expressed in terms of the daily average. The average daily exposure is calculated by dividing the total amount of chemical contaminant ingested (in milligrams) during the specified period by the number of days in the time period. For example, when data are collected for a 1-month period, the following equation can be used to calculate daily exposure:

$$\text{average daily exposure (mg/d)} = \frac{\text{contaminant ingested over 1 month (mg/mo)}}{\text{days per month (d/mo)}} \quad \text{(D-1)}$$

Although this equation uses 1 month as an averaging period, other averaging periods could be used by changing the time periods in both the numerator and denominator of the equation (e.g., 1 week).

Toxicity and risk values are expressed as intake in milligrams of chemical contaminant per kilogram of body weight per day (mg/kg-d). To adapt the exposure data to these units, the average daily exposure (in milligrams) is divided by the body weight of the consumer (in kilograms):

$$\text{average daily intake (mg/kg-d)} = \frac{\text{average daily exposure (mg/d)}}{\text{body weight of consumer (kg)}} \quad \text{(D-2)}$$

The most accurate body weight information is obtained directly from the local population. Table 3-5 in Section 3 of this volume provides body weights for men, women, and children of various ages from a national survey for use when local data are not available.

To determine the potential for acute or prenatal toxicity, the total intake over a short period of time (e.g., 3 days, 1 week) can be calculated. Depending on the toxicity data being used, the time period of interest will vary (see Section 5 for

chemical-specific information). The total intake is expressed as milligrams per kilogram of body weight, as in the following equation:

$$\text{total intake (mg/kg)} = \text{average daily intake (mg/kg-d)} \times \text{number of days (d)} . \quad \text{(D-3)}$$

Information regarding the duration and periodicity of exposure is needed for both determining potential risks and identifying the most appropriate consumption limits. It should be described when exposure information is presented for use in risk assessment.

B.3 FISH CONSUMPTION DATA FOR VARIOUS POPULATIONS

This section describes the results of fish consumption surveys. If state agencies cannot conduct local surveys of fish consumption, these surveys can be used to estimate fish consumption rates for the populations that an agency wishes to target when issuing fish advisories. To use these data appropriately, it is important to match the population surveyed in the reported studies as closely as possible to the local fisher population. This section contains tables summarizing consumption data for sport and subsistence fishers from studies conducted in various regions of the United States. If a study is to be used as the basis for risk assessment and setting advisory limits, agencies are strongly encouraged to review the actual study data to determine its applicability to their local conditions.

Two categories of fisher survey data are discussed: sport fishers and subsistence fishers. In these groups there is wide variability in consumption patterns. Although the surveys are divided into these two categories for ease of presentation, these two categories cannot be strictly defined. The results of many of these surveys are summarized in Tables B-3 through B-6. They are presented by Region, proceeding from east to west across the United States.

Tables B-3 and B-5 present consumption rate data for sport and subsistence fishers, respectively. The tables list consumption in grams per day; however, it should be noted that these values are estimates that are generally obtained by recall, not strict log-keeping. In addition, surveys generally ask about the number of meals eaten in a given time frame, but the size of these meals is generally imprecisely estimated. In addition to quantitative data, information regarding the types of fish included in the consumption rates is included with the consumption rate, because it directly impacts the quantitative data presented in the rate tables. These distinctions include

- Inclusion of freshwater fish, saltwater fish, or both
- Inclusion of sport and/or commercially caught fish.

Survey methods used to collect the data reported in Tables B-3 and B-5 are listed in Tables B-4 and B-6. The methods of conducting fish consumption surveys and the reporting of information from these surveys may differ among studies and many of the differences are highlighted in the survey methods tables.

Methods of averaging fish consumption information also differ among studies. Some studies average the consumption rates over all individuals, regardless of whether they ate fish, while other surveys average the information only for those individuals who reported eating fish. For example, Cox et al. (1993) report consumption rates averaged for the fish-eating population, whereas the Alabama Department of Environmental Management (ALDEM, 1993) reports a rate averaged for both the fish-consuming and nonconsuming populations. Although some of the survey characteristics are noted in the tables, agencies should consult the individual surveys to obtain the most complete descriptions of the study and resulting consumption rates.

In addition to the studies of sport and subsistence fishers, national survey results are discussed at the end of this section. In the absence of local data, national fish consumption data may be used.

B.3.1 Sport Fishers

As noted previously, sport fishers differ with respect to their catch and consumption habits. Some may fish for 1 week during a year or for several weekends each year. Others may fish for much longer periods during a year or may fish year-round. Surveys of the general sport fishing population may include those who primarily fish for recreational purposes or eat fish for a small portion of the year but may also include some individuals who eat fish as a main staple in their diets. Fish consumption data obtained from sport fisher surveys are summarized in Table B-3 and the survey methods used to collect the data are summarized in Table B-4.

Table B-3. Sport Fishers[a] Consumption Data

Fisher Group	Consumption Rates (g/d) Mean	Median	80th Percentile	90th Percentile	95th Percentile	Fish Type
Alabama fishers[1]	45.8				50.7	F+S, F+C
Louisiana (coastal) fishers[2]		65				F+S, F+C
New York fishers[3]	28.1					F+S, R+C
New York (Hudson River) fishers[4]	40.9					F+S, R
Michigan fishers[5]	14.5		30	62	80	F+S, R
Michigan fishers[6]	18.3			≈50		F+S, R+C
Michigan fishers[7]	44.7					F, R
Wisconsin fishers (10 counties)[8]	12.3				37.3	F, R
Wisconsin fishers (10 counties)[8]	26.1				63.4	F, R+C
Ontario fishers[9]	22.5					F, R
Los Angeles Harbor fishers[10]		37		225		S, R
Washington State (Commencement Bay) fishers[11]		23		54		S, R
Washington State (Columbia River) fishers[12]	7.7					F+S, R+C
Maine fishers (inland waters)[13]	6.4	2.0		13	26	F, R

F = freshwater, S = saltwater, R = recreationally caught, C = commercially caught.

[a] Sport fishers may include individuals who eat sport-caught fish as a large portion of their diets.

SOURCES:

1 ALDEM (1993).
2 Dellenbarger et al. (1993).
3 Connelly et al. (1990).
4 Barclay (1993).
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7 Humphrey (1976).
8 Fiore et al. (1989).
9 Cox et al. (1993).
10 Puffer et al. (1982).
11 Pierce et al. (1981).
12 Honstead et al. (1971).
13 Ebert et al. (1993).

Table B-4. Sport Fishers[a] Survey Description

Fisher Group	Number Surveyed	Contact Method/ Instrument	Reporting Method[b]	Catch vs. Consumption[c]	Individual vs. Household	Data Available	Duration
Alabama fishers[1]	1,586	Onsite/personal interview	Log	Catch	Individual	Age, ethnicity, income, region, sex	12 mo
Louisiana (coastal) fishers[2]	1,100	Random/telephone	Recall	Consumption	Household	Age, education, ethnicity, income, other	1 mo
New York fishers[3]	4,530	Fish license/mail/ followup by telephone	Recall	Catch	Individual	Age, income, region	12 mo
New York (Hudson River) fishers[4]	336	Onsite/personal interview	Recall	Consumption	NA	NA	NA
Michigan fishers[5]	2,684	Fish license/mail	Recall	Consumption	Household	Age, education, ethnicity, income, region, sex	12 mo
Michigan fishers[6]	1,104	Fish license/mail	Recall	Consumption	Household	Age, education, ethnicity, income, region, sex	6 mo
Michigan fishers[7]	182	Fish license/NA	Log	Catch	Individual	NA	24 mo
Wisconsin fishers (10 counties)[8]	801	Fish license/mail	Recall	Consumption	Individual	Age, education, ethnicity, region, sex	NA
Ontario fishers[9]	494	Fish license/mail	Recall	Consumption	Individual	Age, region, sex	Summer, fall
Los Angeles Harbor fishers[10]	1,059	Onsite/personal interview	Recall	Catch	Individual	Age, ethnicity	12 mo
Washington State (Commencement Bay) fishers[11]	508	Fish license/personal interview/followup by telephone	Recall	Catch	Individual	NA	Summer, fall
Washington State (Columbia River) fishers[12]	10,900	Fish license/personal interview	Recall	Consumption	Household	NA	12 mo
Maine fishers (inland waters)[13]	1,612	Fish license/mail/ followup by mail	Recall	Consumption	Individual **and** household	NA	12 mo

NA = Not available.

[a] Sport fishers may include some individuals who eat fish as a large portion of their diets.

[b] Respondents recorded consumption information in a log or recalled consumption information during interview.

[c] Catch: Original data from catch rates extrapolated to consumption rates. Consumption: Data obtained on consumption patterns.

SOURCES:

[1] ALDEM (1993).
[2] Dellenbarger et al. (1993).
[3] Connelly et al. (1990).
[4] Barclay (1993).
[5] West et al. (1993).
[6] West et al. (1989).

Table B-5. Subsistence Fishers[a] Consumption Data

Fisher Group	Consumption Rates (g/d) Mean	95th percentile	Max	Fish Type
Great Lakes tribes[1]	351		1,426	F
Columbia River tribes[2]	58.7	170		F
High-end Caucasian consumers on Lake Michigan[3]	48[b] 27[c]		144 132	F F
Native Alaskan adults[4]	109			F+S

F = fish, S = shellfish.

[a] Subsistence fishers include individuals who may eat sport-caught fish at high rates but do not subsist on fish as a large part of their diet.

[b] Data from 1982 survey of fish eaters.

[c] Data from 1989 survey of fish eaters.

SOURCES:

[1] Kmiecik and Ngu (1994).

[2] CRITFC (1994).

[3] Hovinga et al. (1992, 1993).

[4] Nobman et al. (1992).

B.3.2 Subsistence Fishers

Subsistence fishers consume fish as a major staple of their diet. These fishers rely on fish to meet nutritional needs, as an inexpensive food source, and, in some cases, because of their cultural traditions. Subsistence fishers often have higher consumption rates than other fisher groups; however, consumption rates vary considerably among subsistence fishers. Consequently, generalizations should not be made about this fisher group. If studies contained in this section are used to estimate exposure patterns for a subsistence population of concern, care should be taken to match the dietary and population characteristics of the two populations as closely as possible.

Subsistence fishers include a wide variety of people who differ in many respects. This section is not suggesting that similarities exist between populations, other than in their consumption of a relatively large quantity of fish. Information is provided below on some qualitative characteristics of specific subsistence population groups.

Table B-6. Subsistence Fishers[a] Survey Description

Fisher Type[b]	Number Surveyed	Contact Method/ Instrument	Reporting Method[b]	Catch vs. Consumption[c]	Individual vs. Household	Data Available	Duration (months)
Great Lakes tribes[1]	69	Tribe/mail	Recall	Consumption	Individual	NA	2
Columbia River tribes[2]	717	Tribe/random/personal interview	Recall	Consumption	Individual	Age, ethnicity, region, sex	12
High-end Caucasian consumers on Lake Michigan[3]	115	Other[d]/personal interview	Recall	Consumption	Individual	Age, sex, education, other	7
Native Alaskan adults[4]	351	Tribe/random/personal interview	Recall	Consumption	Individual	Age, ethnicity, sex, other	18

NA = Not available.

[a] Subsistence fishers include individuals who may eat sport-caught fish at high rates but do not subsist on fish as a large part of their diets.

[b] Respondents recorded consumption information in a log or recalled consumption information during interview.

[c] Catch: Original data from catch rates extrapolated to consumption rates. Consumption: Data obtained on consumption patterns.

[d] Fishers identified in a Michigan Department of Health study in 1982.

SOURCES:

1 Kmiecik and Ngu (1994).

2 CRITFC (1994).

3 Hovinga et al. (1992, 1993).

4 Nobman et al. (1992).

Subsistence fishers may consume different types or portions of fish than sport fishers (e.g., organs, whole fish), although individual tastes will vary. Their consumption patterns in this regard may result in greater exposure to contaminants. For example, many Asian-American subsistence fishers eat raw fish, liver, hepatopancreas, kidneys, brains, and eyes of bottom-dwelling fish such as carp and catfish that bioaccumulate more toxicants due to the scavenging habits). They may use whole fish in soup stocks and consume seaweed and other aquatic species that may contain the same contaminants as fish. Fish advisory programs have only recently begun to address concerns associated with this subpopulation, and some studies are underway to evaluate consumption patterns. Current information is primarily qualitative; however, differing patterns have been identified among the populations considered: Laotians, Hmong, Cambodian, and Vietnamese (Allbright, 1994; Cung, 1994; Den, 1994; Lorenzano, 1994; Nehls-Lowe, 1994; Pestana, 1994; Shubat et al., 1996; University of Wisconsin Sea Grant, 1994; Young, 1994).

Native American groups in some areas include fish extensively in their cultural, ceremonial, and dietary patterns. Many of the surveys of Native American groups indicate a high fish consumption rate. Most of the study information is recent and many studies are still ongoing.

Rural fishers make up a large segment of subsistence fishers. For example, more than half the noncommercial fishing in Idaho is conducted in Washington County, Idaho. Within Washington County, a community considered by some researchers to be subsistence fishers is located in the area surrounding Brownlee Reservoir, a major fishing location. The local community has a high unemployment rate, with over 40 percent of the population on public assistance. The sport and subsistence fishers in the area often catch 100 to 300 lb of crappies during a fishing trip and freeze much of the catch for year-long consumption. Many fishers are dependent on fish as a major source of protein for themselves and their families. Fishing activities also bring needed economic resources to the area. However, elevated pollutant levels have been found in the reservoir. Community leaders have concerns regarding tradeoffs between fish advisories developed to reduce health risks and the negative economic and nutritional impacts the advisories might have on the fisher population (Richter and Rondinelli, 1989).

Several surveys evaluating the consumption patterns of subsistence fishers have been initiated in the past several years. Some of these have been completed and many more are currently being carried out, with results expected in the near future. Although many of these surveys provide only a range of consumption rates, a great deal of qualitative information has been gained through these surveys, both about the individual populations that were studied and about effective survey methods for different groups of subsistence fishers. The consumption rates reported by these surveys are presented in Table B-5 and the survey methods used to collect the data are summarized in Table B-6.

B.3.3 General Population

For the purposes of risk assessment or risk management, the consumption rates derived from national surveys can provide a useful picture of the distribution of fish consumption for the U.S. population. However, since sport and subsistence fishers generally have higher consumption rates than the national rates, the distributions for these groups will differ. That is, the point estimates of the mean and upper percentiles of fish consumption will generally be higher for the sport and subsistence fishers than for the general U.S. population. National survey data are the least preferred for use in developing local advisories.

Fish consumption data from three national studies are reported in Table B-7. The details of the survey methods used in these studies are summarized in Table B-8. Note that two of the three studies (National Purchase Diary [NPD] and Market Facts) were conducted more than 20 years ago. Also, study results conflict in some respects. For example, the NPD study found the lowest consumption rate in New England, and the Market Facts study found the highest rates in New England. There is also concern that the reported rates in these dated studies do not reflect current consumption patterns.

B.3.4. Sensitive Subpopulations

States with consumption rate information specific to sensitive subpopulations (e.g., women of reproductive age and children) may wish to use such information when assessing exposure. For example, a recent study was conducted to determine fish consumption patterns among the Umatilla, Nez Perce, Yakama, and Warm Springs Tribes of the Columbia River Basin in Washington and Oregon (CRITFC, 1994). This study found that adults in these four tribes consume an average of 58.7 g/d and that children (5 years and younger) from these four tribes consumed 19.6 g/d. Mean fish consumption was more than nine times higher among adults and over three times higher among children in these tribes than for adults in the general population (assuming a consumption rate of 6.5 g/d). Many of the contaminants examined in Section 5 of this volume have develop-mental effects of particular concern to women of reproductive age and children.

If data are available for only the general population, however, the consumption rates for the populations of interest may be calculated by using values for meal size and body weights specific to those subgroups using the methods described in Section 3 of this volume. In cases where studies do not separate consumption rates by age and gender, an exposure assessment based on these rates would reflect exposure to the general population only.

Population size estimates may need to be adjusted to include family members of fishers who share their catch. While children may not constitute a large fraction of fishers, they may be exposed by eating fish that their parents or older siblings catch. Site-specific data on family size can be used to make this estimate, if

Table B-7. National Studies Consumption Data

Population	Consumption Rates (g/d)				Fish Type
	Mean	90th Percentile	95th Percentile	99th Percentile	
US[1]	6.6	NA	47.3	NA	F+E, C+R
US[2]	6.5	NA	NA	NA	F+E, C+R
US[2]	14.3	NA	41.7	NA	F+S, C+R
US[3]	16.7	NA	NA	NA	F+S, C+R
US[4]	20.1	70.1	102.0	173.2	F+S+E, C+R
US[4]	5.9	15.9	40.0	107.6	F+E, C+R

F = Freshwater, S = Saltwater, E = Estuarine, C = Commercial, R = Recreational.

SOURCES:
[1] Continuing Survey of Food Intake by Individuals (CSFII) conducted by USDA (1991).
[2] National Purchase Diary (NPD) Fish Consumption Survey (as cited in Javitz, 1980; Rupp et al., 1980).
[3] Market Facts Survey (as cited in Javitz, 1980).
[4] Continuning Survey of Food Intake by Individuals (CSFII) conducted by USDA, 1988, 1990, 1991, U.S. EPA (1998b).

available. In the absence of these data, U.S. census data on average family size can be used.

Other susceptible subpopulations among the fisher populations should be considered as well. The presence of these groups will depend on local demographics and the nature of the contaminants present in fish. Section 5 of this volume provides information on especially susceptible subgroups for many of the target analytes. Some chemical contaminants interfere or act synergistically with pharmaceuticals; others attack particular organ systems and may cause people with related illnesses to be at elevated risk. Information on any susceptible subgroup should be considered both in estimating risks and establishing health-based exposure limits.

Table B-8. National Studies Survey Description

Population	Number Surveyed	Contact Method/ Instrument	Reporting Method[a]	Catch vs. Consumption[b]	Individual vs. Household	Data Available	Duration
US[1]	11,912	Census/personal interview	Log/recall	Consumption	Individual	Age, sex	12 mo (3 d recall/ person)
US[2]	23,213	Census/NA	Log	Consumption	Household	Age, sex, region	12 mo
US[3]	4,864	Census/NA	Log	Consumption	Household	Education, ethnicity, income	12 mo
US[4]	11,912	Census/personal interview	Log/recall	Consumption	Individual	Age, sex	12 mo (3 d recall/ person)

NA = Not available.

[a] Respondents recorded consumption information in a log or recalled consumption information during interview.

[b] Catch: Original data from catch rates extrapolated to consumption rates. Consumption: Data obtained on consumption patterns.

SOURCES:

[1] Continuing Survey of Food Intake by Individuals (CSFII) conducted by USDA (1991).

[2] National Purchase Diary (NPD) Survey (as cited in Javitz, 1980; Rupp et al., 1980).

[3] Market Facts Survey (as cited in Javitz, 1980).

[4] Continuing Survey of Food Intake by Individuals (CSFII) conducted by USDA, 1989,1990, 1991, U.S. EPA (1998b).

B.4. CONSUMPTION SURVEY DATA ORGANIZATION

In assembling the exposure data, it is most appropriate to build a population exposure database in the form of data groupings for each waterbody and population subgroup (e.g., population consumption characteristics for individuals living around or using a particular lake, river, etc.). Because most contamination data are maintained for specific waterbodies, they serve as a natural unit for evaluating exposure.

Further subdividing of a population may be necessary, depending on population size and the area being considered. If a large or diverse population of concern (e.g., a city or large geographic area) is to be evaluated, subgroups within the population of interest may need to be identified. These subgroups, which may have higher than average exposures, can include groups of subsistence fishers or sport fishers known to fish in contaminated waters. If attention is focused on smaller groups (e.g., sport fishers at a single lake, subsistence fishers from a particular tribe), further subdividing the population into subgroups may not be necessary for purposes of evaluating exposures.

A template is provided in Section 2, Table 2-4, of this volume on which exposure data may be entered. It is located in that section because risk managers are encouraged to evaluate other aspects of exposure in addition to consumption patterns. These factors include exposure modifications that may be associated with fish cleaning (skinning and trimming) and cooking fish procedures (discussed in Appendix C) and additional exposures to the contaminant of concern that may arise from other sources such as air, water, other foods, and soil (discussed in Section 2.4.5.6 of this volume).

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APPENDIX C

DOSE MODIFICATIONS DUE TO FOOD PREPARATION AND COOKING

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DOSE MODIFICATIONS DUE TO FOOD PREPARATION AND COOKING

C.1 DOSE MODIFICATIONS OF FISH CONTAMINANT EXPOSURE

Fish preparation and cooking procedures can modify the amount of contaminant ingested by fish consumers. Consequently, exposure and dose are modified. Incorporating a dose modification factor into the exposure equation to account for loss of chemical contaminants from fish tissue during preparation and cooking requires two types of information:

- Methods used by fish consumers to prepare (trimming, skinning) and cook (broiling, baking, , charbroiling, canning, deep frying, pan frying, microwaving, poaching, roasting, salt boiling, smoking) their catch.

- The extent to which a particular contaminant concentration is likely to be decreased by these culinary methods.

To adjust contaminant concentrations appropriately, the dose modification factors must be matched to the type of sample from which the fish contaminant concentration was measured. For example, it would be inappropriate to apply a dose modification factor for removing skin if the contaminant concentrations in the fish were based on the analysis of a skin-off fillet. To select the correct approach for evaluating exposure, information on both the distribution of chemicals in fish tissue and alterations due to food preparation and cooking must be used. The modified contaminant concentration (based on preparation and cooking losses) is used to modify the exposure estimates used in the risk equations. This information is also useful in development of fish advisories and risk communication activities.

C.1.1 Contaminant Distribution in Fish Tissues

Chemical contaminants are not distributed uniformly in fish. Fatty tissues, for example, will concentrate organic chemicals more readily than muscle tissue. Muscle tissue and viscera will preferentially concentrate other contaminants. This information has important implications for fish analysis and for fish consumers. Depending on how fish are prepared and what parts are eaten, consumers may have significantly differing exposures to chemical contaminants. This section is meant as an overview; states should consult primary research studies for more information. In general, contaminant concentrations differ among

- Fatty tissues, muscle tissue, and internal organs
- Different species of fish
- Different age or size classes of fish
- Type of chemical contaminant present in the fish.

C.1.2 Fish Tissue Types

Lipophilic chemicals accumulate mainly in fatty tissues, including the belly flap, lateral line, subcutaneous and dorsal fat, and the dark muscle, gills, eyes, brain, and internal organs. Some heavy metals, such as cadmium, concentrate more in the liver and kidneys. Muscle tissue often contains lower organic contaminant concentrations than fatty tissues (Great Lakes Sport Fish Advisory Task Force, 1993), but contains more mercury, which binds to muscle proteins (Minnesota Department of Health, 1992).

Many people remove the internal organs before cooking fish and trim off fat and skin before eating, thus decreasing exposure to lipophilic and other contaminants. Removing the fat, however, will not decrease exposure to other contaminants, such as mercury, that are concentrated in muscle and other protein-rich tissues (Gutenmann and Lisk, 1991; Minnesota Department of Health, 1992). Concentrations of mercury have been shown to be higher per gram of fillet in skin-off than in skin-on fillets contaminated with mercury (Gutenmann and Lisk, 1991). Certain populations, including some Asian-Americans and Native American groups, eat parts of the fish other than the fillet and may consume the whole fish. Recipes from many cultures employ whole fish for making soups or stews. As a result, more of the fish contaminants are consumed.

States should take preparation methods of local fisher populations into account when assessing exposure levels and when assessing whether use of a dose modification factor is appropriate for their target fish-consuming population.

C.1.3 Fish Species

Fish accumulate contaminants from the water column, from suspended sediment and organic matter in the water, and from their food. Depending on their propensity to bioaccumulate contaminants (largely a function of their feeding habits, ability to metabolize contaminants, and fat content), different fish species living in the same area may contain very different contaminant concentrations. Due to biomagnification, higher trophic level species are more likely to have higher contaminant concentrations. The tissues of the top predators can contain contaminant levels exceeding those in ambient water or sediments by several orders of magnitude.

Where a fish feeds in the water column also determines its relative bioaccumulation potential. Bottom feeders, such as carp or catfish, are exposed to

more sediments than are fish that feed in mid-water or near the surface of the water column. Bottom feeders, therefore, have a tendency to accumulate more of the dense, hydrophobic contaminants, such as chlordane or polychlorinated biphenyls (PCBs), that are adsorbed to the sediment particles. In addition, fish species vary widely in their fat content. Fish low in fat, such as bass, sunfish, crappies, yellow perch, and walleyes, are less likely to accumulate lipophilic contaminants than fattier fish such as bluefish, rainbow trout, lake trout, some salmon, catfish, and carp. Even within the same species, great differences in fat content may occur. Zabik et al. (1996) reported the average fat content of Lake Michigan lean lake trout (*Salvelinus namaycush namaycush)* was 9.1 percent, which was significantly lower than that of the fat Lake Superior siscowets (*Salvelinus namaycush siscowet*) (20.5 percent). Aquatic organisms also differ in their abilities to metabolize and excrete contaminants. For example, one study found fish more readily able to metabolize benzo[*a*]pyrene than shrimp, amphipod crustaceans, and clams, respectively (U.S. EPA, 1995a). The ability to break down and excrete chemical contaminants may also differ among fish species.

This differential accumulation of contaminants produces very different exposure levels for individuals eating different species of fish. An individual who eats primarily fatty fish species will receive higher exposures of organic chemical contaminants than an individual who eats primarily leaner fish species. Thus, states should consider multiple species exposure in their decision to issue fish consumption advisories.

C.1.4 Fish Size or Age Class

Larger size classes of fish within the same species generally contain higher concentrations of bioaccumulative contaminants, especially the more persistent chemicals such as mercury, DDT, PCBs, and toxaphene (Gutenmann et al. 1992; U.S. EPA, 1995a). Because larger fish are older, they have had more time to accumulate chemicals from their food and they are more likely to catch larger prey, which themselves have had a longer time to bioaccumulate chemicals (Minnesota Department of Health, 1992). Older fish also concentrate more contaminants in their muscle tissues, which are fattier than muscle tissue in younger fish, particularly along the backbone and lateral lines (Kleeman et al., 1986a). States may choose to issue size-specific consumption advisories and/or explain this correlation of increasing contaminant residues in larger fish within a given species in their public education efforts.

C.1.5 Chemical Contaminants

Many of the target chemicals examined in this guidance series are lipophilic and accumulate in the fatty tissues. Some contaminants (and their congeners) bioaccumulate in fish more readily than others or are more resistant to metabolism and excretion once accumulated than others (Bruggeman et al., 1984; Stern et al., 1992). Thus, fish exposed to the same concentrations of a contaminant may accumulate different levels of contaminants in their tissues

based on their ability to bioaccumulate the contaminant directly from solution or via preconcentration on prey species coupled with their ability to metabolize and excrete the contaminant.

States may wish to use this chemical-specific information on distribution of contaminants in fish tissues to assess whether a local population may be exposed unreasonably to a given contaminant, due to particular eating habits such as eating only one species of fish, eating specific parts (whole fish or organs) of the fish, or eating fish species with a high fat content in contrast to eating leaner species.

C.1.5.1 Heavy Metals—

Several studies indicate that mercury, cadmium, and selenium bind to different tissues in fish than do organochlorines. Mercury, for example, binds strongly to proteins, thereby concentrating in muscle tissues of fish (Gutenmann and Lisk, 1991; Minnesota Department of Health, 1992). Mercury also concentrates in the liver and kidneys, though at generally lower rates (Harrison and Klaverkamp, 1990; Marcovecchio et al., 1988). Thus, trimming and gutting can actually result in a greater average concentration of mercury in the remaining fillet tissues compared with the concentration in the whole untrimmed fish proteins, thereby concentrating in muscle tissues of fish (Gutenmann and Lisk, 1991).

Cadmium concentrates largely in the liver, followed by the kidneys and gills, and less so in the muscle tissue (Harrison and Klaverkamp, 1990; Marcovecchio et al., 1988; Norey et al., 1990), indicating that cadmium concentrations could be decreased by trimming and gutting fish before consumption.

Selenium was shown to concentrate in both the liver and muscle tissues at similar rates (Harrison and Klaverkamp, 1990). Consumers would be likely to receive a lower exposure if they consumed a fillet only rather than consuming the whole fish (including fillet tissue and the liver tissue).

C.1.5.2 Organochlorines—

Organochlorine pesticides, PCBs, dioxins/furans tend to concentrate in fatty tissues (Armbruster et al. 1989; Branson et al., 1985; Bruggeman et al. 1984; Gutenmann et al. 1992; Kleeman et al., 1986a, 1986b; Ryan et al., 1983; Skea et al., 1979; Sanders and Hayes 1988; U.S. EPA, 1995a). Many of these compounds are neither readily metabolized nor excreted and thus tend to biomagnify through the food web (Gardner and White, 1990; Lake et al., 1995; Metcalf and Metcalf, 1997; Muir et al., 1986; Niimi and Oliver, 1989; Oliver and Niimi, 1988; U.S. EPA, 1995a). Because different fish species store fat differently, contain different amounts of body fat, and metabolize these compounds at slightly different rates, each species will also concentrate organochlorine-based contaminants somewhat differently. In general, however, trimming away fatty

tissues, including the skin, are the most effective ways to reduce exposure to these chemicals.

C.1.5.3 Other Contaminants—

The other chemicals examined in this exposure assessment (organophosphate pesticides and oxyfluorfen) have also been found to bioaccumulate in fish, but to a much lower extent than the organochlorine pesticides. Little information is available, however, on the distribution of these chemicals in specific fish tissues. After feeding chlorpyrifos to channel catfish in a laboratory study, the highest concentrations were found in the liver tissue, while less than 5 percent of the dose was found in muscle tissue (Barron et al., 1991). No information was located on the tissue distribution of any of the other organophosphates in feral fish populations. Organophosphates as a group are lipophilic and would be expected to distribute to body fat like the organochlorine compounds. However, the organophosphates are much less persistent in both the environment (U.S. EPA, 1995a) and in aquatic organisms because these compounds are vulnerable to hydrolysis in water and to metabolic breakdown by esterases.

C.2 ESTIMATING DOSE MODIFICATION BASED ON PREPARATION METHODS

This section presents data on the effects of various preparation methods on contaminant concentrations in fish tissue. In the absence of specific data on fish preparation methods, the U.S. Environmental Protection Agency (EPA) recommends using fillets as the standard sample type for analyzing chemical contaminants. Readers are referred to Volume 1, 3rd edition, of this series for a more complete discussion of sample analysis (U.S. EPA, 1999). The sample type should consist of the portion of the individual organism commonly consumed by the general fish-consuming population or a specific target population of concern (e.g., pregnant or nursing women, young children, recreational or subsistence fishers). EPA recommends analyzing skin-on fillets (including the belly flap) for most scaled finfish. Conversely, skin-off fillets may be more appropriate for target species without scales (e.g., catfish). State or local agencies, however, are advised to select the sample type most appropriate for each target species based on consumption patterns of local populations and should sample the whole body of the fish if a local target population typically consumes whole fish. Following these guidelines, states may have concentration data from fillet samples with skin-on, fillet samples with skin-off, or from whole fish.

When states have data on the preparation methods of the target fish-consuming populations, appropriate dose modification factors from these studies can be used to adjust assumed fish chemical contaminant concentrations. Without food preparation data, however, states should not assume that specific preparation methods are employed, since fish preparation and cooking techniques frequently vary among individuals and often depend on the type of fish consumed. As noted earlier, many groups known to consume large quantities of fish, including Native American and Asian American fishers, often consume most of the whole fish and

may do very little trimming. Consequently, assuming a dose reduction in chemical contaminants based on fillet samples may lead to an underestimate of the exposure and risk for these groups that consume whole fish.

EPA recommends the use of dose modification factors for setting health-based intake limits only when data on local methods of preparation and their impact on contaminant concentrations are available.

EPA recommends that all fish advisories emphasize the importance of skinning and trimming fish (including gutting) and certain ways of cooking as effective means to minimize the risks from chemical contaminant residues in fish tissue. To achieve the best results, all three techniques should be used together. States are encouraged to include illustrations in their fish advisories showing the location of fatty tissue in fish and describing the parts of of the fish tissue to be trimmed. This type of information could be provided to fish consumers as part of a fish advisory program through risk communication efforts. Further information on risk communication is included in Volume 4 in this series of guidance documents (U.S. EPA, 1995b).

The degree of preparation-related reduction in contaminant concentration depends on

- Fish species and size (age class)
- Chemical contaminant residues present
- Specific food preparation and cooking techniques used.

Consumer concern about the presence of toxic chemicals in fish has focused research on quantitating the effects of processing and cooking on the possible reduction of chemical contaminant levels in fish. Several generalizations about specific food preparation and cooking techniques can be made based on several detailed studies conducted using primarily Great Lakes fish.

- Trimming fish is an important consideration in reducing the levels of PCBs and other organochlorine pesticides ingested by consumers (Hora 1981; Sanders and Haynes, 1988; Zabik et al., 1995b; Zabik and Zabik, 1996). For example, in a recent study, raw skin-off fillets had an average of 50 percent of the residues found in raw skin-on fillets. The skin-off fillets had both the belly flap and the lateral line and its associated fat trimmed off, while the skin-on fillet had only the belly flap removed. Zabik et al. (1995b) also established that this contaminant reduction was carried over to cooked fillets.

- Cooking methods that allow the separation of the cooked muscle from the skin (pan frying, poaching, broiling, baking) reduce the amount of chemical contaminants the consumer would ingest over such cooking methods as deep frying where both the skin and cooked muscle are consumed together (Zabik et al., 1995a).

- As a cooking process, smoking resulted in significantly greater reductions (40 to >50 percent) of organochlorine pesticides (DDT,DDE, DDD, chlordane complex, HCB, dieldrin, heptachlor epoxide, toxaphene), total PCBs, and dioxin residues (TCDD) than other cooking methods (baking, charbroiling, salt boiling, deep fat frying, canning) tested, but polynuclear aromatic compounds (PAHs) showed significant formation during the smoking process especially in fish species with higher body fat levels (siscowet) (Zabik et al., 1996).

- For dioxins, several organochlorine pesticides, and PCBs, increasing the internal temperature of the cooked fish from 60 to 80°C (Stachiw et al.,1988), increasing the surface area exposed to the cooking process by scoring the fillets (Stachiw et al.,1988: Zabik et al., 1994), or increasing the cooking time or cooking temperature enhances the loss of contaminant residues in the fish (Zabik and Zabik, 1996).

- For PCBs, residue reductions during cooking (baking and charbroiling) of the homologues with the lowest and the highest numbers of chlorines (trichloro-, tetrachloro- and octachloro-PCBs) tended to be less than residue reductions for the pentachloro-, hexachloro- and heptachloro-PCBs, which typically make up the major portion of the PCBs found in fish samples (Zabik and Zabik, 1996).

- In general for heavy metals, tissue residues are not significantly reduced by processing or cooking methods (Gutenmann and Lisk, 1991; Zabik and Zabik, 1996).

The results of a number of fish preparation and cooking studies are presented in Tables C-1 and C-2 for a variety of fish species. The data are relevant primarily to concentrations in the standard fillet. Dose modification will depend on how the dose is determined initially (i.e., what portion of the fish was analyzed to determine contamination concentrations). Note that contaminants distributed throughout the fish muscle tissue, such as mercury, will not be substantially reduced through most fish preparation or cooking methods.

Table C-1 summarizes various study results where specific activities reduce contaminants in standard fillets of fish species. Study citations are provided for readers who wish to obtain more information on study methods and results. Similar information obtained from studies of standard fillet, whole fish, or other fillet types is presented in Table C-2. Both show that a high level of variability should be expected in the effectiveness of skinning, trimming, and cooking fish. The average reductions are reported for each study. Although significant variability in percent reductions was found within each study, the mean reduction data suggest that significant reductions can occur with food preparation and cooking (Voiland et al., 1991). The cooked weight of fish tissue is always less than the uncooked weight. On average, cooking reduces the fish weight by about one-third (Great Lakes Sport Fish Advisory Task Force, 1993); therefore, the standard

meal of 1/2 pound of raw fillet weighs about 1/3 pound after cooking. Most of the weight reduction is due to water loss, but fat liquification and volatilization also contribute to weight reduction (Great Lakes Sport Fish Advisory Task Force, 1993). The actual weight loss depends on the cooking technique used.

The results of studies shown in Tables C-1 through C-3 do not address chemical degradation due to heat applied in cooking. Zabik et al. (1994) found that smoking lake trout reduced pesticides and total PCBs significantly more than other cooking methods, but this cooking method resulted in the formation of PAHs. Until there is more information about the toxicity of the byproducts generated during the degradation of PCBs, dioxins/furans, organochlorine pesticides, or the other chemicals of concern, EPA recommends that no dose modification be assumed due to degradation alone.

Zabik et al. (1994) found similarities in the percentage of pesticide and total PCB reductions (ranging from 27.9 to 36.5 percent) attributed to cooking for Great Lakes carp, salmon, lake trout, walleye, and white bass analyzed (Table C-3). However, they assessed only lipophilic chlorinated hydrocarbons. Similarities in their chemical behavior may be responsible for the similarities observed in the study results listed in Table C-3. The information provided in this table is not species-specific, which may limit the situations to which it is applicable.

Table C-1. Summary of Contaminant Reductions Due to Skinning, Trimming, and Cooking (Based on Standard Fillet)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Brown Trout	DDE	Trimming	52	Skea et al. (1979)
	DDE	Smoking	27	Skea et al. (1979)
	DDE	Broiling	20	Skea et al. (1979)
	Mirex	Trimming	44	Voiland et al. (1991)
	Mirex	Trimming	45	Skea et al. (1979)
	Mirex	Smoking	39	Skea et al. (1979)
	Mirex	Broiling	26	Skea et al. (1979)
	Mirex	Trimming & cooking	74	Skea et al. (1979)
	PCB	Trimming	46	Voiland et al. (1991)
	PCB	Trimming	43	Skea et al. (1979)
	PCB	Smoking	27	Skea et al. (1979)
	PCB	Broiling	0	Skea et al. (1979)
	PCB	Trimming & cooking	78	Skea et al. (1979)
Carp	α-Chlordane	Skin-off & deep frying	44	Zabik et al. (1994)
	α-Chlordane	Skin-off & pan frying	17	Zabik et al. (1994)
	α-Chlordane	Skin-on & deep frying	38	Zabik et al. (1994)
	α-Chlordane	Skin-on & pan frying	51	Zabik et al. (1994)
	Dieldrin	Skin-off & deep frying	76	Zabik et al. (1994)
	Dieldrin	Skin-off & pan frying	58	Zabik et al. (1994)
	Dieldrin	Skin-on & deep frying	56	Zabik et al. (1994)
	Dieldrin	Skin-on & pan frying	59	Zabik et al. (1994)
	Heptachlor epoxide	Skin-on & pan frying	82	Zabik et al. (1994)
	PCB	Skin-off & deep frying	37	Zabik et al. (1994)
	PCB	Skin-off & pan frying	25	Zabik et al. (1994)
	PCB	Skin-on & deep frying	38	Zabik et al. (1994)
Carp	TCDD	skin-on & cooked	approx. 37	Zabik & Zabik 1995
(Great Lakes)	TCDD	skin off & cooked	approx. 54	Zabik & Zabik 1995
(Lake Erie)	p,p'-DDE	skin-on & deep fried	28	Zabik et al. 1995b
Carp	p,p'-DDE	skin off & deep fried	45	Zabik et al. 1995b
(Lake Erie)	p,p'-DDD	skin-on & deep fried	30	Zabik et al. 1995b
	p,p'-DDD	skin off & deep fried	35	Zabik et al. 1995b
	α- chlordane	skin-on & deep fried	37	Zabik et al. 1995b
	α- chlordane	skin off & deep fried	56	Zabik et al. 1995b
	γ- chlordane	skin-on & deep fried	32	Zabik et al. 1995b
	γ- chlordane	skin off & deep fried	41	Zabik et al. 1995b
	cis-nonachlor	skin-on & deep fried	34	Zabik et al. 1995b
	cis-nonachlor	skin off & deep fried	53	Zabik et al. 1995b
	trans-nonachlor	skin-on & deep fried	54 *	Zabik et al. 1995b
	trans-nonachlor	skin off & deep fried	27	Zabik et al. 1995b
	HCB	skin-on & deep fried	14	Zabik et al. 1995b
	HCB	skin off & deep fried	54	Zabik et al. 1995b
	dieldrin	skin-on & deep fried	52	Zabik et al. 1995b
	dieldrin	skin off & deep fried	53	Zabik et al. 1995b
	Total PCBs	skin-on & deep fried	16	Zabik et al. 1995b

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Carp (con.)	Total PCBs	skin off & deep fried	32	Zabik et al. 1995b
(Lake Erie)	p,p'-DDE	skin-on & pan fried	36	Zabik et al. 1995b
	p,p'-DDE	skin off & pan fried	17	Zabik et al. 1995b
	p,p'-DDD	skin-on & pan fried	54	Zabik et al. 1995b
	p,p'-DDD	skin off & pan fried	40	Zabik et al. 1995b
	α- chlordane	skin-on & pan fried	43	Zabik et al. 1995b
	α- chlordane	skin off & pan fried	26	Zabik et al. 1995b
	γ- chlordane	skin-on & pan fried	20	Zabik et al. 1995b
	oxychlordane	skin-on & pan fried	38	Zabik et al. 1995b
	cis-nonachlor	skin-on & pan fried	42	Zabik et al. 1995b
	trans-nonachlor	skin-on & pan fried	7	Zabik et al. 1995b
	trans-nonachlor	skin off & pan fried	3 *	Zabik et al. 1995b
	HCB	skin-on & pan fried	138 *	Zabik et al. 1995b
	dieldrin	skin-on & pan fried	27	Zabik et al. 1995b
	dieldrin	skin off & pan fried	19	Zabik et al. 1995b
	heptachlor epoxide	skin-on & pan fried	8	Zabik et al. 1995b
	Total PCBs	skin-on & pan fried	22	Zabik et al. 1995b
	Total PCBs	skin off & pan fried	19	Zabik et al. 1995b
Carp	p,p'-DDE	skin-on & deep fried	46	Zabik et al. 1995b
(Lake Huron)	p,p'-DDE	skin off & deep fried	39	Zabik et al. 1995b
	p,p'-DDD	skin-on & deep fried	31	Zabik et al. 1995b
	p,p'-DDD	skin off & deep fried	51	Zabik et al. 1995b
	α- chlordane	skin-on & deep fried	32	Zabik et al. 1995b
	α- chlordane	skin off & deep fried	33	Zabik et al. 1995b
	γ- chlordane	skin-on & deep fried	29	Zabik et al. 1995b
	cis-nonachlor	skin-on & deep fried	54	Zabik et al. 1995b
	trans-nonachlor	skin-on & deep fried	13 *	Zabik et al. 1995b
	trans-nonachlor	skin off & deep fried	27	Zabik et al. 1995b
	HCB	skin-on & deep fried	33	Zabik et al. 1995b
	HCB	skin off & deep fried	27	Zabik et al. 1995b
	dieldrin	skin-on & deep fried	44	Zabik et al. 1995b
	Total PCBs	skin-on & deep fried	67	Zabik et al. 1995b
	Total PCBs	skin off & deep fried	32	Zabik et al. 1995b
	p,p'-DDE	skin-on & pan fried	48	Zabik et al. 1995b
	p,p'-DDE	skin off & pan fried	50	Zabik et al. 1995b
	p,p'-DDD	skin-on & pan fried	38	Zabik et al. 1995b
	p,p'-DDD	skin off & pan fried	17	Zabik et al. 1995b
	α- chlordane	skin-on & pan fried	55	Zabik et al. 1995b
	α- chlordane	skin off & pan fried	35	Zabik et al. 1995b
	γ- chlordane	skin-on & pan fried	50	Zabik et al. 1995b
	cis-nonachlor	skin-on & pan fried	54	Zabik et al. 1995b
	trans-nonachlor	skin-on & pan fried	35	Zabik et al. 1995b
	trans-nonachlor	skin off & pan fried	39	Zabik et al. 1995b
	HCB	skin-on & pan fried	19	Zabik et al. 1995b
	HCB	skin off & pan fried	10 *	Zabik et al. 1995b
	dieldrin	skin-on & pan fried	93	Zabik et al. 1995b
	Total PCBs	skin-on & pan fried	42	Zabik et al. 1995b

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Carp (con.)	Total PCBs	skin off & pan fried	37	Zabik et al. 1995b
(Lake Huron)	PCB	Skin-on & pan frying	31	Zabik et al. (1994)
Chinook	α-Chlordane	Skin-off & baking	44	Zabik et al. (1994)
Salmon	α-Chlordane	Skin-off & charbroiling	41	Zabik et al. (1994)
	α-Chlordane	Skin-off & charbroiling after scoring	45	Zabik et al. (1994)
	α-Chlordane	Skin-off & canning	37	Zabik et al. (1994)
	α-Chlordane	Skin-on & baking	27	Zabik et al. (1994)
	α-Chlordane	Skin-on & charbroiling	42	Zabik et al. (1994)
	α-Chlordane	Skin-on & charbroiling after scoring	51	Zabik et al. (1994)
	Dieldrin	Skin-off & baking	30	Zabik et al. (1994)
	Dieldrin	Skin-off & charbroiling	31	Zabik et al. (1994)
	Dieldrin	Skin-off & charbroiling after scoring	40	Zabik et al. (1994)
	Dieldrin	Skin-off & canning	40	Zabik et al. (1994)
	Dieldrin	Skin-on & baking	29	Zabik et al. (1994)
	Dieldrin	Skin-on & charbroiling	40	Zabik et al. (1994)
	Dieldrin	Skin-on & charbroiling after scoring	50	Zabik et al. (1994)
	Heptachlor epoxide	Skin-off & baking	52	Zabik et al. (1994)
	Heptachlor epoxide	Skin-off & charbroiling	40	Zabik et al. (1994)
	Heptachlor epoxide	Skin-off & charbroiling after scoring	42	Zabik et al. (1994)
	Heptachlor epoxide	Skin-off & canning	37	Zabik et al. (1994)
	Heptachlor epoxide	Skin-on & baking	23	Zabik et al. (1994)
	Heptachlor epoxide	Skin-on & charbroiling	45	Zabik et al. (1994)
	Heptachlor epoxide	Skin-on & charbroiling after scoring	48	Zabik et al. (1994)
	PCB	Skin-off & baking	38	Zabik et al. (1994)
	PCB	Skin-off & charbroiling	44	Zabik et al. (1994)
	PCB	Skin-off & charbroiling after scoring	46	Zabik et al. (1994)
	PCB	Skin-off & canning	36	Zabik et al. (1994)
	PCB	Skin-on & baking	33	Zabik et al. (1994)
	PCB	Skin-on & charbroiling	40	Zabik et al. (1994)
	PCB	Skin-on & charbroiling after scoring	49	Zabik et al. (1994)
	Toxaphene	Skin-off & baking	34	Zabik et al. (1994)
	Toxaphene	Skin-off & charbroiling	30	Zabik et al. (1994)
	Toxaphene	Skin-off & charbroiling after scoring	34	Zabik et al. (1994)
	Toxaphene	Skin-off & canning	74	Zabik et al. (1994)
	Toxaphene	Skin-on & baking	22	Zabik et al. (1994)
	Toxaphene	Skin-on & charbroiling	37	Zabik et al. (1994)
	Toxaphene	Skin-on & charbroiling after scoring	47	Zabik et al. (1994)
Chinook Salmon	TCDD	skin-on & cooked	approx. 43	Zabik & Zabik 1995
(Great Lakes)	TCDD	skin off & cooked	approx. 57	Zabik & Zabik 1995
Chinook Salmon	p,p'-DDT	skin-on & baked	23	Zabik et al. 1995b
(Lake Huron)	p,p'-DDT	skin-off & baked	26	Zabik et al. 1995b
	p,p'-DDE	skin-on & baked	35	Zabik et al. 1995b
	p,p'-DDE	skin-off & baked	47	Zabik et al. 1995b
	p,p'-DDD	skin-on & baked	27	Zabik et al. 1995b
	p,p'-DDD	skin-off & baked	4	Zabik et al. 1995b
	α- chlordane	skin-on & baked	33	Zabik et al. 1995b
	α- chlordane	skin-off & baked	51	Zabik et al. 1995b

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Chinook Salmon	γ - chlordane	skin-on & baked	33	Zabik et al. 1995b
(Lake Huron)	γ - chlordane	skin-off & baked	43	Zabik et al. 1995b
(con.)	oxychlordane	skin-on & baked	42	Zabik et al. 1995b
	oxychlordane	skin-off & baked	50	Zabik et al. 1995b
	cis-nonachlor	skin-on & baked	31	Zabik et al. 1995b
	cis-nonachlor	skin-off & baked	46	Zabik et al. 1995b
	trans-nonachlor	skin-on & baked	43	Zabik et al. 1995b
	trans-nonachlor	skin-off & baked	41	Zabik et al. 1995b
	HCB	skin-on & baked	48	Zabik et al. 1995b
	HCB	skin-off & baked	60	Zabik et al. 1995b
	dieldrin	skin-on & baked	38	Zabik et al. 1995b
	dieldrin	skin-off & baked	35	Zabik et al. 1995b
	heptachlor epoxide	skin-on & baked	36	Zabik et al. 1995b
	heptachlor epoxide	skin-off & baked	44	Zabik et al. 1995b
	toxaphene	skin-on & baked	38	Zabik et al. 1995b
	toxaphene	skin-off & baked	49	Zabik et al. 1995b
	Total PCBs	skin-on & baked	49	Zabik et al. 1995b
	Total PCBs	skin-off & baked	48	Zabik et al. 1995b
	p,p'-DDT	skin-on & charbroiled	35	Zabik et al. 1995b
	p,p'-DDT	skin-off & charbroiled	50	Zabik et al. 1995b
	p,p'-DDE	skin-on & charbroiled	41	Zabik et al. 1995b
	p,p'-DDE	skin-off & charbroiled	61	Zabik et al. 1995b
	p,p'-DDD	skin-on & charbroiled	39	Zabik et al. 1995b
	p,p'-DDD	skin-off & charbroiled	62	Zabik et al. 1995b
	α- chlordane	skin-on & charbroiled	44	Zabik et al. 1995b
	α- chlordane	skin-off & charbroiled	63	Zabik et al. 1995b
	γ - chlordane	skin-on & charbroiled	38	Zabik et al. 1995b
	γ - chlordane	skin-off & charbroiled	48	Zabik et al. 1995b
	oxychlordane	skin-on & charbroiled	62	Zabik et al. 1995b
	oxychlordane	skin-off & charbroiled	59	Zabik et al. 1995b
	cis-nonachlor	skin-on & charbroiled	45	Zabik et al. 1995b
	cis-nonachlor	skin-off & charbroiled	61	Zabik et al. 1995b
	trans-nonachlor	skin-on & charbroiled	45	Zabik et al. 1995b
	trans-nonachlor	skin-off & charbroiled	61	Zabik et al. 1995b
	HCB	skin-on & charbroiled	47	Zabik et al. 1995b
	HCB	skin-off & charbroiled	49	Zabik et al. 1995b
	dieldrin	skin-on & charbroiled	47	Zabik et al. 1995b
	dieldrin	skin-off & charbroiled	51	Zabik et al. 1995b
	heptachlor epoxide	skin-on & charbroiled	45	Zabik et al. 1995b
	heptachlor epoxide	skin-off & charbroiled	55	Zabik et al. 1995b
	toxaphene	skin-on & charbroiled	41	Zabik et al. 1995b
	toxaphene	skin-off & charbroiled	47	Zabik et al. 1995b
	Total PCBs	skin-on & charbroiled	40	Zabik et al. 1995b
	Total PCBs	skin-off & charbroiled	62	Zabik et al. 1995b
	p,p'-DDT	skin-on, scored & charbroiled	58	Zabik et al. 1995b
	p,p'-DDT	skin-off , scored & charbroiled	59	Zabik et al. 1995b
	p,p'-DDE	skin-on, scored & charbroiled	59	Zabik et al. 1995b

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Chinook Salmon (con.) (Lake Huron)	p,p'-DDE	skin-off , scored & charbroiled	51	Zabik et al. 1995b
	p,p'-DDD	skin-on, scored & charbroiled	54	Zabik et al. 1995b
	p,p'-DDD	skin-off , scored & charbroiled	57	Zabik et al. 1995b
	α- chlordane	skin-on, scored & charbroiled	63	Zabik et al. 1995b
	α- chlordane	skin-off , scored & charbroiled	54	Zabik et al. 1995b
	oxychlordane	skin-on, scored & charbroiled	49	Zabik et al. 1995b
	oxychlordane	skin-off, scored & charbroiled	50	Zabik et al. 1995b
	cis-nonachlor	skin-on, scored & charbroiled	49	Zabik et al. 1995b
	cis-nonachlor	skin-off, scored & charbroiled	50	Zabik et al. 1995b
	trans-nonachlor	skin-on, scored & charbroiled	63	Zabik et al. 1995b
	trans-nonachlor	skin-off, scored & charbroiled	54	Zabik et al. 1995b
	HCB	skin-on, scored & charbroiled	50	Zabik et al. 1995b
	HCB	skin-off , scored & charbroiled	46	Zabik et al. 1995b
	dieldrin	skin-on, scored & charbroiled	62	Zabik et al. 1995b
	dieldrin	skin-off , scored & charbroiled	43	Zabik et al. 1995b
	heptachlor epoxide	skin-on, scored & charbroiled	57	Zabik et al. 1995b
	heptachlor epoxide	skin-off, scored & charbroiled	56	Zabik et al. 1995b
	toxaphene	skin-on, scored & charbroiled	56	Zabik et al. 1995b
	toxaphene	skin-off, scored & charbroiled	48	Zabik et al. 1995b
	Total PCBs	skin-on, scored & charbroiled	61	Zabik et al. 1995b
	Total PCBs	skin-off, scored & charbroiled	52	Zabik et al. 1995b
	p,p'-DDT	canned with skin-off	80	Zabik et al. 1995b
	p,p'-DDE	canned with skin-off	38	Zabik et al. 1995b
	p,p'-DDD	canned with skin-off	8 *	Zabik et al. 1995b
	α- chlordane	canned with skin-off	51	Zabik et al. 1995b
	γ - chlordane	canned with skin-off	56	Zabik et al. 1995b
	oxychlordane	canned with skin-off	47	Zabik et al. 1995b
	cis-nonachlor	canned with skin-off	46	Zabik et al. 1995b
	trans-nonachlor	canned with skin-off	53	Zabik et al. 1995b
	HCB	canned with skin-off	27	Zabik et al. 1995b
	dieldrin	canned with skin-off	88	Zabik et al. 1995b
	toxaphene	canned with skin-off	77	Zabik et al. 1995b
	Total PCBs	canned with skin-off	33	Zabik et al. 1995b
Chinook Salmon (Lake Michigan)	p,p'-DDT	skin-on & baked	23	Zabik et al. 1995b
	p,p'-DDT	skin-off & baked	26	Zabik et al. 1995b
	p,p'-DDE	skin-on & baked	16	Zabik et al. 1995b
	p,p'-DDE	skin-off & baked	26	Zabik et al. 1995b
	p,p'-DDD	skin-on & baked	10	Zabik et al. 1995b
	p,p'-DDD	skin-off & baked	30	Zabik et al. 1995b
	α- chlordane	skin-on & baked	29	Zabik et al. 1995b
	α- chlordane	skin-off & baked	31	Zabik et al. 1995b
	γ- chlordane	skin-on & baked	28	Zabik et al. 1995b
	γ- chlordane	skin-off & baked	22	Zabik et al. 1995b
	oxychlordane	skin-on & baked	2810	Zabik et al. 1995b
	oxychlordane	skin-off & baked	2236	Zabik et al. 1995b
	cis-nonachlor	skin-on & baked	32	Zabik et al. 1995b
	cis-nonachlor	skin-off & baked	33	Zabik et al. 1995b

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Chinook Salmon	trans-nonachlor	skin-on & baked	28	Zabik et al. 1995b
(Lake Michigan)	trans-nonachlor	skin-off & baked	28	Zabik et al. 1995b
(con.)	HCB	skin-on & baked	34	Zabik et al. 1995b
	HCB	skin-off & baked	27	Zabik et al. 1995b
	dieldrin	skin-on & baked	21	Zabik et al. 1995b
	dieldrin	skin-off & baked	25	Zabik et al. 1995b
	heptachlor epoxide	skin-on & baked	14	Zabik et al. 1995b
	heptachlor epoxide	skin-off & baked	32	Zabik et al. 1995b
	toxaphene	skin-on & baked	7	Zabik et al. 1995b
	toxaphene	skin-off & baked	22	Zabik et al. 1995b
Chinook Salmon (Lake Huron)	Total PCBs	skin-on & baked	25	Zabik et al. 1995b
Chinook Salmon	Total PCBs	skin-off & baked	29	Zabik et al. 1995b
(Lake Michigan)	p,p'-DDT	skin-on & charbroiled	48	Zabik et al. 1995b
	p,p'-DDT	skin-off & charbroiled	23	Zabik et al. 1995b
	p,p'-DDE	skin-on & charbroiled	41	Zabik et al. 1995b
	p,p'-DDE	skin-off & charbroiled	30	Zabik et al. 1995b
	p,p'-DDD	skin-on & charbroiled	48	Zabik et al. 1995b
	p,p'-DDD	skin-off & charbroiled	20	Zabik et al. 1995b
	α- chlordane	skin-on & charbroiled	43	Zabik et al. 1995b
	α- chlordane	skin-off & charbroiled	27	Zabik et al. 1995b
	γ- chlordane	skin-on & charbroiled	43	Zabik et al. 1995b
	γ- chlordane	skin-off & charbroiled	29	Zabik et al. 1995b
	oxychlordane	skin-on & charbroiled	46	Zabik et al. 1995b
	oxychlordane	skin-off & charbroiled	21	Zabik et al. 1995b
	cis-nonachlor	skin-on & charbroiled	49	Zabik et al. 1995b
	cis-nonachlor	skin-off & charbroiled	31	Zabik et al. 1995b
	trans-nonachlor	skin-on & charbroiled	43	Zabik et al. 1995b
	trans-nonachlor	skin-off & charbroiled	21	Zabik et al. 1995b
	HCB	skin-on & charbroiled	53	Zabik et al. 1995b
	HCB	skin-off & charbroiled	40	Zabik et al. 1995b
	dieldrin	skin-on & charbroiled	39	Zabik et al. 1995b
	dieldrin	skin-off & charbroiled	12	Zabik et al. 1995b
	heptachlor epoxide	skin-on & charbroiled	48	Zabik et al. 1995b
	heptachlor epoxide	skin-off & charbroiled	29	Zabik et al. 1995b
	toxaphene	skin-on & charbroiled	33	Zabik et al. 1995b
	toxaphene	skin-off & charbroiled	16	Zabik et al. 1995b
Chinook Salmon (Lake Huron)	Total PCBs	skin-on & charbroiled	44	Zabik et al. 1995b
Chinook Salmon	Total PCBs	skin-off & charbroiled	33	Zabik et al. 1995b
(Lake Michigan)	p,p'-DDT	skin-on, scored, & charbroiled	54	Zabik et al. 1995b
	p,p'-DDT	skin-off , scored, & charbroiled	45	Zabik et al. 1995b
	p,p'-DDE	skin-on, scored, & charbroiled	35	Zabik et al. 1995b
	p,p'-DDE	skin-off , scored, & charbroiled	34	Zabik et al. 1995b
	p,p'-DDD	skin-on, scored, & charbroiled	34	Zabik et al. 1995b
	p,p'-DDD	skin-off , scored, & charbroiled	42	Zabik et al. 1995b
	α- chlordane	skin-on, scored, & charbroiled	46	Zabik et al. 1995b

See footnotes at end of table. (continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Chinook Salmon	α- chlordane	skin-off , scored, & charbroiled	39	Zabik et al. 1995b
(Lake Michigan)	γ- chlordane	skin-on, scored, & charbroiled	47	Zabik et al. 1995b
(con.)	γ- chlordane	skin-off , scored, & charbroiled	32	Zabik et al. 1995b
	oxychlordane	skin-on, scored, & charbroiled	34	Zabik et al. 1995b
	oxychlordane	skin-off , scored, & charbroiled	33	Zabik et al. 1995b
	cis-nonachlor	skin-on, scored, & charbroiled	51	Zabik et al. 1995b
	cis-nonachlor	skin-off , scored, & charbroiled	41	Zabik et al. 1995b
	trans-nonachlor	skin-on, scored, & charbroiled	37	Zabik et al. 1995b
	trans-nonachlor	skin-off , scored, & charbroiled	44	Zabik et al. 1995b
	HCB	skin-on, scored, & charbroiled	31	Zabik et al. 1995b
	HCB	skin-off , scored, & charbroiled	43	Zabik et al. 1995b
	dieldrin	skin-on, scored, & charbroiled	42	Zabik et al. 1995b
	dieldrin	skin-off , scored, & charbroiled	41	Zabik et al. 1995b
	heptachlor epoxide	skin-on, scored, & charbroiled	42	Zabik et al. 1995b
	heptachlor epoxide	skin-off , scored, & charbroiled	31	Zabik et al. 1995b
	toxaphene	skin-on, scored, & charbroiled	37	Zabik et al. 1995b
	toxaphene	skin-off , scored, & charbroiled	22	Zabik et al. 1995b
Chinook Salmon				
(Lake Huron)	Total PCBs	skin-on, scored, & charbroiled	37	Zabik et al. 1995b
Chinook Salmon	Total PCBs	skin-off , scored, & charbroiled	44	Zabik et al. 1995b
(Lake Michigan)	p,p'-DDT	canned with skin-off	141 *	Zabik et al. 1995b
	p,p'-DDE	canned with skin-off	37	Zabik et al. 1995b
	p,p'-DDD	canned with skin-off	34 *	Zabik et al. 1995b
	α- chlordane	canned with skin-off	35	Zabik et al. 1995b
	γ- chlordane	canned with skin-off	35	Zabik et al. 1995b
	oxychlordane	canned with skin-off	30	Zabik et al. 1995b
	cis-nonachlor	canned with skin-off	28	Zabik et al. 1995b
	trans-nonachlor	canned with skin-off	43	Zabik et al. 1995b
	HCB	canned with skin-off	33	Zabik et al. 1995b
	dieldrin	canned with skin-off	43	Zabik et al. 1995b
	heptachlor epoxide	canned with skin-off	28	Zabik et al. 1995b
	toxaphene	canned with skin-off	72	Zabik et al. 1995b
	Total PCBs	canned with skin-off	39	Zabik et al. 1995b
Lake Trout	α-Chlordane	Skin-off & baking	26	Zabik et al. (1994)
	α-Chlordane	Skin-off & charbroiling	41	Zabik et al. (1994)
	α-Chlordane	Skin-off & salt boiling	6	Zabik et al. (1994)
	α-Chlordane	Skin-on & smoking	53	Zabik et al. (1994)
	DDT	Skin-off & baking	14	Zabik et al. (1994)
	DDT	Skin-off & charbroiling	21	Zabik et al. (1994)
	DDT	Skin-off & salt boiling	1	Zabik et al. (1994)
	DDT	Skin-on & smoking	60	Zabik et al. (1994)
	Dieldrin	Skin-off & baking	8	Zabik et al. (1994)
	Dieldrin	Skin-off & charbroiling	15	Zabik et al. (1994)
	Dieldrin	Skin-off & salt boiling	16	Zabik et al. (1994)
	Dieldrin	Skin-on & smoking	43	Zabik et al. (1994)
	Heptachlor epoxide	Skin-off & baking	39	Zabik et al. (1994)
	Heptachlor epoxide	Skin-off & charbroiling	39	Zabik et al. (1994)

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Lake Trout (con.)	Heptachlor epoxide	Skin-off & salt boiling	3	Zabik et al. (1994)
	Heptachlor epoxide	Skin-on & smoking	59	Zabik et al. (1994)
	PCB	Skin-off & baking	13	Zabik et al. (1994)
	PCB	Skin-off & charbroiling	29	Zabik et al. (1994)
	PCB	Skin-off & salt boiling	10	Zabik et al. (1994)
	PCB	Skin-on & smoking	46	Zabik et al. (1994)
	Toxaphene	Skin-off & baking	31	Zabik et al. (1994)
	Toxaphene	Skin-off & charbroiling	40	Zabik et al. (1994)
	Toxaphene	Skin-off & salt boiling	5	Zabik et al. (1994)
	Toxaphene	Skin-on & smoking	51	Zabik et al. (1994)
Lake Trout (Great Lakes)	TCDD	skin-off & cooked	61	Zabik & Zabik 1995
Lake Trout / Lean (Lake Huron)	p,p'-DDT	skin-off & baked	17	Zabik et al. 1996
	p,p'-DDT	skin-off & charbroiled	34	Zabik et al. 1996
	p,p'-DDE	skin-off & baked	18	Zabik et al. 1996
	p,p'-DDE	skin-off & charbroiled	9	Zabik et al. 1996
	p,p'-DDD	skin-off & baked	6	Zabik et al. 1996
	p,p'-DDD	skin-off & charbroiled	16	Zabik et al. 1996
	α- chlordane	skin-off & baked	7	Zabik et al. 1996
	α- chlordane	skin-off & charbroiled	18	Zabik et al. 1996
	γ- chlordane	skin-off & baked	83	Zabik et al. 1996
	γ- chlordane	skin-off & charbroiled	38	Zabik et al. 1996
	oxychlordane	skin-off & baked	6	Zabik et al. 1996
	oxychlordane	skin-off & charbroiled	12	Zabik et al. 1996
	cis-nonachlor	skin-off & baked	17	Zabik et al. 1996
	cis-nonachlor	skin-off & charbroiled	18	Zabik et al. 1996
	trans-nonachlor	skin-off & baked	19	Zabik et al. 1996
	trans-nonachlor	skin-off & charbroiled	16	Zabik et al. 1996
	HCB	skin-off & baked	15	Zabik et al. 1996
	HCB	skin-off & charbroiled	23	Zabik et al. 1996
	dieldrin	skin-off & baked	8	Zabik et al. 1996
	dieldrin	skin-off & charbroiled	30	Zabik et al. 1996
	heptachlor epoxide	skin-off & baked	4	Zabik et al. 1996
	heptachlor epoxide	skin-off & charbroiled	12	Zabik et al. 1996
	toxaphene	skin-off & baked	18 *	Zabik et al. 1996
	toxaphene	skin-off & charbroiled	13	Zabik et al. 1996
	Total PCBs	skin-off & baked	18	Zabik et al. 1996
	Total PCBs	skin-off & charbroiled	15	Zabik et al. 1996
Lake Trout / Lean (Lake Michigan)	p,p'-DDT	skin-off & baked	11	Zabik et al. 1996
	p,p'-DDT	skin-off & charbroiled	19	Zabik et al. 1996
	p,p'-DDE	skin-off & baked	9	Zabik et al. 1996
	p,p'-DDE	skin-off & charbroiled	14	Zabik et al. 1996
	p,p'-DDD	skin-off & baked	11	Zabik et al. 1996
	p,p'-DDD	skin-off & charbroiled	9	Zabik et al. 1996
	α- chlordane	skin-off & baked	4	Zabik et al. 1996
	α- chlordane	skin-off & charbroiled	3	Zabik et al. 1996
	γ- chlordane	skin-off & baked	2	Zabik et al. 1996

See footnotes at end of table. (continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Lake Trout / Lean (Lake Michigan) (con.)	γ- chlordane	skin-off & charbroiled	3	Zabik et al. 1996
	oxychlordane	skin-off & baked	11	Zabik et al. 1996
	oxychlordane	skin-off & charbroiled	11	Zabik et al. 1996
	cis-nonachlor	skin-off & baked	18	Zabik et al. 1996
	cis-nonachlor	skin-off & charbroiled	10	Zabik et al. 1996
	trans-nonachlor	skin-off & baked	2	Zabik et al. 1996
	trans-nonachlor	skin-off & charbroiled	9	Zabik et al. 1996
	HCB	skin-off & baked	19	Zabik et al. 1996
	HCB	skin-off & charbroiled	15	Zabik et al. 1996
	dieldrin	skin-off & baked	18	Zabik et al. 1996
	dieldrin	skin-off & charbroiled	7	Zabik et al. 1996
	heptachlor epoxide	skin-off & baked	12	Zabik et al. 1996
	heptachlor epoxide	skin-off & charbroiled	5	Zabik et al. 1996
	toxaphene	skin-off & baked	13	Zabik et al. 1996
	toxaphene	skin-off & charbroiled	15	Zabik et al. 1996
	Total PCBs	skin-off & baked	10	Zabik et al. 1996
	Total PCBs	skin-off & charbroiled	7	Zabik et al. 1996
	p,p'-DDT	skin-off & baked	12	Zabik et al. 1996
	p,p'-DDE	skin-off & baked	9	Zabik et al. 1996
	p,p'-DDD	skin-off & baked	11	Zabik et al. 1996
	α- chlordane	skin-off & baked	4	Zabik et al. 1996
	γ- chlordane	skin-off & baked	3 *	Zabik et al. 1996
	oxychlordane	skin-off & baked	11	Zabik et al. 1996
	cis-nonachlor	skin-off & baked	18	Zabik et al. 1996
	trans-nonachlor	skin-off & baked	2	Zabik et al. 1996
	HCB	skin-off & baked	19	Zabik et al. 1996
	dieldrin	skin-off & baked	18	Zabik et al. 1996
	heptachlor epoxide	skin-off & baked	12	Zabik et al. 1996
	toxaphene	skin-off & baked	13	Zabik et al. 1996
	Total PCBs	skin-off & baked	10	Zabik et al. 1996
	p,p'-DDT	skin-off & charbroiled	19	Zabik et al. 1996
	p,p'-DDE	skin-off & charbroiled	14	Zabik et al. 1996
	p,p'-DDD	skin-off & charbroiled	9	Zabik et al. 1996
	α- chlordane	skin-off & charbroiled	3	Zabik et al. 1996
	γ- chlordane	skin-off & charbroiled	3	Zabik et al. 1996
	oxychlordane	skin-off & charbroiled	11	Zabik et al. 1996
	cis-nonachlor	skin-off & charbroiled	10	Zabik et al. 1996
	trans-nonachlor	skin-off & charbroiled	9	Zabik et al. 1996
	HCB	skin-off & charbroiled	15	Zabik et al. 1996
	dieldrin	skin-off & charbroiled	7	Zabik et al. 1996
	heptachlor epoxide	skin-off & charbroiled	5	Zabik et al. 1996
	toxaphene	skin-off & charbroiled	15	Zabik et al. 1996
	Total PCBs	skin-off & charbroiled	7	Zabik et al. 1996
	p,p'-DDT	skin-off & salt boiled	1 *	Zabik et al. 1996
	p,p'-DDE	skin-off & salt boiled	7	Zabik et al. 1996
	p,p'-DDD	skin-off & salt boiled	5	Zabik et al. 1996
	α- chlordane	skin-off & salt boiled	5	Zabik et al. 1996

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Lake Trout / Lean (Lake Michigan) (con.)	γ- chlordane	skin-off & salt boiled	1	Zabik et al. 1996
	oxychlordane	skin-off & salt boiled	3	Zabik et al. 1996
	cis-nonachlor	skin-off & salt boiled	10	Zabik et al. 1996
	trans-nonachlor	skin-off & salt boiled	13	Zabik et al. 1996
	HCB	skin-off & salt boiled	7	Zabik et al. 1996
	dieldrin	skin-off & salt boiled	16	Zabik et al. 1996
	heptachlor epoxide	skin-off & salt boiled	3	Zabik et al. 1996
	toxaphene	skin-off & salt boiled	5	Zabik et al. 1996
	Total PCBs	skin-off & salt boiled	10	Zabik et al. 1996
	p,p'-DDT	skin-off & smoked	58	Zabik et al. 1996
	p,p'-DDE	skin-off & smoked	47	Zabik et al. 1996
	p,p'-DDD	skin-off & smoked	61	Zabik et al. 1996
	α- chlordane	skin-off & smoked	50	Zabik et al. 1996
	γ- chlordane	skin-off & smoked	49	Zabik et al. 1996
	oxychlordane	skin-off & smoked	57	Zabik et al. 1996
	cis-nonachlor	skin-off & smoked	51	Zabik et al. 1996
	trans-nonachlor	skin-off & smoked	55	Zabik et al. 1996
	HCB	skin-off & smoked	53	Zabik et al. 1996
	dieldrin	skin-off & smoked	42	Zabik et al. 1996
	heptachlor epoxide	skin-off & smoked	59	Zabik et al. 1996
	toxaphene	skin-off & smoked	49	Zabik et al. 1996
	Fluoranthene	skin-off & smoked	6782 *	Zabik et al. 1996
	Total PCBs	skin-off & smoked	41	Zabik et al. 1996
	Benzo[b]fluorene	skin-off & smoked	1170 *	Zabik et al. 1996
	3,6-Dimethylphenanthrene	skin-off & smoked	1245 *	Zabik et al. 1996
	Benz[a]anthacene	skin-off & smoked	5582 *	Zabik et al. 1996
	Chrysene	skin-off & smoked	4086 *	Zabik et al. 1996
	Total PAHs	skin-off & smoked	10058 *	Zabik et al. 1996
Lake Trout / Lean (Lake Ontario)	p,p'-DDT	skin-off & baked	12	Zabik et al. 1996
	p,p'-DDT	skin-off & charbroiled	8	Zabik et al. 1996
	p,p'-DDE	skin-off & baked	12	Zabik et al. 1996
	p,p'-DDE	skin-off & charbroiled	12	Zabik et al. 1996
	p,p'-DDD	skin-off & baked	85	Zabik et al. 1996
	p,p'-DDD	skin-off & charbroiled	88	Zabik et al. 1996
	HCB	skin-off & baked	10	Zabik et al. 1996
	HCB	skin-off & charbroiled	17	Zabik et al. 1996
	dieldrin	skin-off & baked	4	Zabik et al. 1996
	dieldrin	skin-off & charbroiled	8	Zabik et al. 1996
	toxaphene	skin-off & baked	71	Zabik et al. 1996
	Total PCBs	skin-off & baked	11	Zabik et al. 1996
	Total PCBs	skin-off & charbroiled	12	Zabik et al. 1996
Lake Trout Siscowet/ High Fat Content (Lake Superior)	p,p'-DDT	skin-off & baked	42	Zabik et al. 1996
	p,p'-DDT	skin-off & charbroiled	72	Zabik et al. 1996
	p,p'-DDE	skin-off & baked	20	Zabik et al. 1996
	p,p'-DDE	skin-off & charbroiled	10	Zabik et al. 1996
	p,p'-DDD	skin-off & baked	20	Zabik et al. 1996

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Lake Trout	p,p'-DDD	skin-off & charbroiled	14	Zabik et al. 1996
Siscowet/	α- chlordane	skin-off & baked	10	Zabik et al. 1996
High Fat Content	α- chlordane	skin-off & charbroiled	6	Zabik et al. 1996
(Lake Superior)	γ- chlordane	skin-off & baked	12	Zabik et al. 1996
(con.)	γ- chlordane	skin-off & charbroiled	29 *	Zabik et al. 1996
	oxychlordane	skin-off & baked	9	Zabik et al. 1996
	oxychlordane	skin-off & charbroiled	18	Zabik et al. 1996
	cis-nonachlor	skin-off & baked	17	Zabik et al. 1996
	cis-nonachlor	skin-off & charbroiled	21	Zabik et al. 1996
	trans-nonachlor	skin-off & baked	9	Zabik et al. 1996
	trans-nonachlor	skin-off & charbroiled	18	Zabik et al. 1996
Lake Trout	HCB	skin-off & baked	16	Zabik et al. 1996
High Fat Content/	HCB	skin-off & charbroiled	24	Zabik et al. 1996
Siscowet	dieldrin	skin-off & baked	15	Zabik et al. 1996
(Lake Superior)	dieldrin	skin-off & charbroiled	16	Zabik et al. 1996
(con.)	heptachlor epoxide	skin-off & baked	57	Zabik et al. 1996
	heptachlor epoxide	skin-off & charbroiled	3 *	Zabik et al. 1996
	toxaphene	skin-off & baked	28	Zabik et al. 1996
	toxaphene	skin-off & charbroiled	45	Zabik et al. 1996
	Total PCBs	skin-off & baked	18	Zabik et al. 1996
	Total PCBs	skin-off & charbroiled	32	Zabik et al. 1996
	p,p'-DDT	skin-off & baked	42	Zabik et al. 1996
	p,p'-DDE	skin-off & baked	20	Zabik et al. 1996
	p,p'-DDD	skin-off & baked	17	Zabik et al. 1996
	α- chlordane	skin-off & baked	10	Zabik et al. 1996
	γ- chlordane	skin-off & baked	12	Zabik et al. 1996
	oxychlordane	skin-off & baked	9	Zabik et al. 1996
	cis-nonachlor	skin-off & baked	17	Zabik et al. 1996
	trans-nonachlor	skin-off & baked	9	Zabik et al. 1996
	HCB	skin-off & baked	16	Zabik et al. 1996
	dieldrin	skin-off & baked	15	Zabik et al. 1996
	heptachlor epoxide	skin-off & baked	57	Zabik et al. 1996
	toxaphene	skin-off & baked	28	Zabik et al. 1996
	Total PCBs	skin-off & baked	18	Zabik et al. 1996
	p,p'-DDT	skin-off & charbroiled	72	Zabik et al. 1996
	p,p'-DDE	skin-off & charbroiled	10	Zabik et al. 1996
	p,p'-DDD	skin-off & charbroiled	14	Zabik et al. 1996
	α- chlordane	skin-off & charbroiled	6	Zabik et al. 1996
	γ- chlordane	skin-off & charbroiled	29 *	Zabik et al. 1996
	oxychlordane	skin-off & charbroiled	18	Zabik et al. 1996
	cis-nonachlor	skin-off & charbroiled	21	Zabik et al. 1996
	trans-nonachlor	skin-off & charbroiled	18	Zabik et al. 1996
	HCB	skin-off & charbroiled	24	Zabik et al. 1996
	dieldrin	skin-off & charbroiled	16	Zabik et al. 1996
	heptachlor epoxide	skin-off & charbroiled	3 *	Zabik et al. 1996
	toxaphene	skin-off & charbroiled	45	Zabik et al. 1996

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Lake Trout	Total PCBs	skin-off & charbroiled	32	Zabik et al. 1996
Siscowet/	p,p'-DDT	skin-off & salt boiled	16	Zabik et al. 1996
High Fat Content	p,p'-DDE	skin-off & salt boiled	25	Zabik et al. 1996
(Lake Superior)	p,p'-DDD	skin-off & salt boiled	18	Zabik et al. 1996
(con.)	α- chlordane	skin-off & salt boiled	24	Zabik et al. 1996
	γ- chlordane	skin-off & salt boiled	28	Zabik et al. 1996
	oxychlordane	skin-off & salt boiled	22	Zabik et al. 1996
	cis-nonachlor	skin-off & salt boiled	11	Zabik et al. 1996
	trans-nonachlor	skin-off & salt boiled	13	Zabik et al. 1996
	HCB	skin-off & salt boiled	38	Zabik et al. 1996
	dieldrin	skin-off & salt boiled	12	Zabik et al. 1996
	heptachlor epoxide	skin-off & salt boiled	10	Zabik et al. 1996
	toxaphene	skin-off & salt boiled	17	Zabik et al. 1996
	Total PCBs	skin-off & salt boiled	19	Zabik et al. 1996
	p,p'-DDT	skin-off & smoked	61	Zabik et al. 1996
	p,p'-DDE	skin-off & smoked	42	Zabik et al. 1996
	p,p'-DDD	skin-off & smoked	44	Zabik et al. 1996
	α- chlordane	skin-off & smoked	43	Zabik et al. 1996
	γ- chlordane	skin-off & smoked	40	Zabik et al. 1996
	oxychlordane	skin-off & smoked	63	Zabik et al. 1996
	cis-nonachlor	skin-off & smoked	45	Zabik et al. 1996
	trans-nonachlor	skin-off & smoked	45	Zabik et al. 1996
	HCB	skin-off & smoked	46	Zabik et al. 1996
	dieldrin	skin-off & smoked	41	Zabik et al. 1996
	heptachlor epoxide	skin-off & smoked	35	Zabik et al. 1996
	toxaphene	skin-off & smoked	44	Zabik et al. 1996
	Total PCBs	skin-off & smoked	37	Zabik et al. 1996
	Phenathrene	skin-off & smoked	10771 *	Zabik et al. 1996
	Anthracene	skin-off & smoked	2677 *	Zabik et al. 1996
	Fluoranthene	skin-off & smoked	29654 *	Zabik et al. 1996
	Pyrene	skin-off & smoked	5928 *	Zabik et al. 1996
	Benzo[b]fluorene	skin-off & smoked	255 *	Zabik et al. 1996
	3,6-Dimethylphenanthrene	skin-off & smoked	1260 *	Zabik et al. 1996
	Benz[a]anthacene	skin-off & smoked	915 *	Zabik et al. 1996
	Dibenz[ac]anthracene	skin-off & smoked	259 *	Zabik et al. 1996
	Dibenzo[ae]pyrene	skin-off & smoked	157 *	Zabik et al. 1996
	Dibenzo[ah]pyrene	skin-off & smoked	8 *	Zabik et al. 1996
	Chrysene	skin-off & smoked	421 *	Zabik et al. 1996
	Total PAHs	skin-off & smoked	4173 *	Zabik et al. 1996
Smallmouth Bass	DDE	Trimming	54	Skea et al. (1979)
	DDE	Baking	16	Skea et al. (1979)
	DDE	Frying	75	Skea et al. (1979)
	Mirex	Trimming	64	Skea et al. (1979)
	Mirex	Baking	21	Skea et al. (1979)
	Mirex	Frying	75	Skea et al. (1979)
	Mirex	Trimming & cooking	80	Skea et al. (1979)

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Smallmouth Bass (con.)	PCB	Trimming	64	Skea et al. (1979)
	PCB	Baking	16	Skea et al. (1979)
	PCB	Frying	74	Skea et al. (1979)
	PCB	Trimming & cooking	80	Skea et al. (1979)
White Bass (Great Lakes)	TCDD	skin-on & cooked	approx. 80	Zabik & Zabik 1995
Walleye	DDT	Skin-on & baking	4	Zabik et al. (1994)
	DDT	Skin-on & charbroiling	16	Zabik et al. (1994)
	DDT	Skin-on & deep frying	11	Zabik et al. (1994)
	α-Chlordane	Skin-on & baking	32	Zabik et al. (1994)
	α-Chlordane	Skin-on & charbroiling	33	Zabik et al. (1994)
	α-Chlordane	Skin-on & deep frying	-25	Zabik et al. (1994)
	Dieldrin	Skin-on & baking	3	Zabik et al. (1994)
	Dieldrin	Skin-on & charbroiling	3	Zabik et al. (1994)
	Dieldrin	Skin-on & deep frying	26	Zabik et al. (1994)
	PCB	Skin-on & baking	17	Zabik et al. (1994)
	PCB	Skin-on & charbroiling	24	Zabik et al. (1994)
	PCB	Skin-on & deep frying	14	Zabik et al. (1994)
	Toxaphene	Skin-on & baking	45	Zabik et al. (1994)
Walleye (Great Lakes)	TCDD	skin-on & cooked	approx. 44	Zabik & Zabik 1995
Walleye (Lake Erie)	Chlordane Complex	skin-on & baked	33	Zabik et al. 1995a
	DDT Complex	skin-on & baked	33	Zabik et al. 1995a
	Dieldrin	skin-on & baked	21	Zabik et al. 1995a
	Total PCBs	skin-on & baked	13	Zabik et al. 1995a
	Chlordane Complex	skin-on & charbroiled	60	Zabik et al. 1995a
	DDT Complex	skin-on & charbroiled	25	Zabik et al. 1995a
	Dieldrin	skin-on & charbroiled	29	Zabik et al. 1995a
	Total PCBs	skin-on & charbroiled	20	Zabik et al. 1995a
Walleye (Lake Huron)	Chlordane Complex	skin-on & baked	44	Zabik et al. 1995a
	DDT Complex	skin-on & baked	26	Zabik et al. 1995a
	Dieldrin	skin-on & baked	10	Zabik et al. 1995a
	Total PCBs	skin-on & baked	20	Zabik et al. 1995a
	Chlordane Complex	skin-on & charbroiled	25	Zabik et al. 1995a
	DDT Complex	skin-on & charbroiled	17	Zabik et al. 1995a
	Dieldrin	skin-on & charbroiled	37	Zabik et al. 1995a
	Total PCBs	skin-on & charbroiled	29	Zabik et al. 1995a
Walleye (Lake Michigan)	Chlordane Complex	skin-on & baked	9	Zabik et al. 1995a
	DDT Complex	skin-on & baked	22	Zabik et al. 1995a
	Dieldrin	skin-on & baked	26	Zabik et al. 1995a
	Total PCBs	skin-on & baked	23	Zabik et al. 1995a
	Chlordane Complex	skin-on & charbroiled	33	Zabik et al. 1995a
	DDT Complex	skin-on & charbroiled	33	Zabik et al. 1995a
	Dieldrin	skin-on & charbroiled	12	Zabik et al. 1995a
	Total PCBs	skin-on & charbroiled	27	Zabik et al. 1995a
	Chlordane Complex	skin-on & deep fat fried	3	Zabik et al. 1995a
	DDT Complex	skin-on & deep fat fried	3	Zabik et al. 1995a

See footnotes at end of table.

(continued)

Table C-1. (Continued)

Species	Contaminant	Activity[a]	Reduction (%)[b]	Reference
Walleye (con.)	Dieldrin	skin-on & deep fat fried	27	Zabik et al. 1995a
(Lake Michigan)	Total PCBs	skin-on & deep fat fried	15	Zabik et al. 1995a
Five species	trichloro-PCB	skin-on & baked	approx. 15	Zabik & Zabik 1996
(Great Lakes)	trichloro-PCB	skin-off & baked	approx. 20	Zabik & Zabik 1996
	tetrachloro-PCB	skin-on & baked	approx. 26	Zabik & Zabik 1996
	tetrachloro-PCB	skin-off & baked	approx. 26.5	Zabik & Zabik 1996
	pentachloro-PCB	skin-on & baked	approx. 32	Zabik & Zabik 1996
	pentachloro-PCB	skin-off & baked	approx. 29	Zabik & Zabik 1996
	hexachloro-PCB	skin-on & baked	approx. 34	Zabik & Zabik 1996
	hexachloro-PCB	skin-off & baked	approx. 34.5	Zabik & Zabik 1996
	heptachloro-PCB	skin-on & baked	approx. 34.75	Zabik & Zabik 1996
	heptachloro-PCB	skin-off & baked	approx. 33	Zabik & Zabik 1996
	octachloro-PCB	skin-on & baked	approx. 27	Zabik & Zabik 1996
	octachloro-PCB	skin-off & baked	approx. 25	Zabik & Zabik 1996
	Total PCBs	skin-on & baked	approx. 34	Zabik & Zabik 1996
	Total PCBs	skin-off & baked	approx. 33	Zabik & Zabik 1996
	trichloro-PCB	skin-on & charbroiled	approx. 28	Zabik & Zabik 1996
	trichloro-PCB	skin-off & charbroiled	approx. 26	Zabik & Zabik 1996
	tetrachloro-PCB	skin-on & charbroiled	approx. 32	Zabik & Zabik 1996
	tetrachloro-PCB	skin-off & charbroiled	approx. 34	Zabik & Zabik 1996
	pentachloro-PCB	skin-on & charbroiled	approx. 36	Zabik & Zabik 1996
	pentachloro-PCB	skin-off & charbroiled	approx. 33	Zabik & Zabik 1996
	hexachloro-PCB	skin-on & charbroiled	approx. 40	Zabik & Zabik 1996
	hexachloro-PCB	skin-off & charbroiled	approx. 35	Zabik & Zabik 1996
	heptachloro-PCB	skin-on & charbroiled	approx. 40	Zabik & Zabik 1996
	heptachloro-PCB	skin-off & charbroiled	approx. 37	Zabik & Zabik 1996
	octachloro-PCB	skin-on & charbroiled	approx. 28	Zabik & Zabik 1996
	octachloro-PCB	skin-off & charbroiled	approx. 31	Zabik & Zabik 1996
	Total PCBs	skin-on & charbroiled	approx. 37	Zabik & Zabik 1996
	Total PCBs	skin-off & charbroiled	approx. 36	Zabik & Zabik 1996

[a] Skin-on refers to the trimming of only the belly flap; skin-off refers to the removal of the belly flap as well as the lateral line and associated fat tissue.

[b] Data from the Zabik et al. (1994) study were condensed by averaging contaminant reductions across lakes whenever a fish species was sampled from more than one of the Great Lakes.

Table C-2. Summary of Contaminant Reductions Due to Skinning, Trimming, and Cooking (Based on Standard Fillet, Whole Fish or Other Fillet)

Species	Contaminant	Activity	Reduction (%)[a]	Reference
American Shad	DDT/DDE	Trimming	40	NYSDEC (1981)
	PCB	Trimming	44	NYSDEC (1981)
Bluefish	PCB	Trimming	59	Armbruster et al. (1989)[c]
	PCB	Baking	8	Armbruster et al. (1989)[c]
	PCB	Broiling	8	Armbruster et al. (1989)[c]
	PCB	Frying	8	Armbruster et al. (1989)[c]
	PCB	Poaching	8	Armbruster et al. (1989)[c]
	PCB	Trimming & cooking	67	Armbruster et al. (1989)[c]
Chinook Salmon	Mirex	Trimming	15	NYSDEC (1981)
	PCB	Trimming	25	NYSDEC (1981)
	PCB (1248)	Trimming & baking	15	Smith et al. (1973)
	PCB (1248)	Trimming & poaching	-1	Smith et al. (1973)
	PCB (1254)	Trimming and baking	-1	Smith et al. (1973)
	PCB (1254)	Trimming & poaching	2	Smith et al. (1973)
Coho Salmon	DDT	Trimming	62	Reinert et al. (1972)
	DDT/DDE	Trimming	53	NYSDEC (1981)
	DDT	Dressing	0	Reinert et al. (1972)
	Mirex	Trimming	21	NYSDEC (1981)
	PCB	Trimming	32	NYSDEC (1981)
	PCB (1248)	Trimming & baking	4	Smith et al. (1973)
	PCB (1248)	Trimming & poaching	-9	Smith et al. (1973)
	PCB (1254)	Trimming & baking	-10	Smith et al. (1973)
	PCB(1254)	Trimming & poaching	-14	Smith et al. (1973)
	Dieldrin	Roasted	25	Zabik et al. (1994)
	Dieldrin	Microwave	47	Zabik et al. (1994)
Lake Trout	DDT	Trimming	54	Reinert et al. (1972)
	DDT/DDE	Trimming	46	NYSDEC (1981)
	DDT	Dressing	0	Reinert et al. (1972)
	DDT	Frying	64-72	Reinert et al. (1972)
	DDT	Broiling	64-72	Reinert et al. (1972)
	DDT	Broiling	39	Zabik et al. (1994)
	DDT	Roasted	30	Zabik et al. (1994)
	DDT	Microwave	54	Zabik et al. (1994)
	Dieldrin	Broiling	48	Zabik et al. (1994)
	Mirex	Trimming	50	NYSDEC (1981)
	PCB	Trimming	50	NYSDEC (1981)
Perch	DDT	Dressing	90	Reinert et al. (1972)
Winter Flounder (Seafish)	PCB	Deep frying	47	EPA (1992)
	PCB	Pan frying	-15	EPA (1992)
	PCB	Broiling	-17	EPA (1992)

[a] It could not be positively determined that reduction figures were calculated as changes in contaminant concentrations from the standard fillet.

[b] Average of findings reported in New York State Department of Environmental Conservation (1981) and White et al. (1985).

[c] Averages of findings reported in Armbruster et al. (1989).

Table C-3. Average Contaminant Reductions Due to Cooking in Great Lakes Fish [a]

Chemical Contaminant	Reduction (%)
p,p'-DDT	34.0
p,p'-DDE	29.4
p,p'-DDD	29.0
α-Chlordane	34.8
γ-Chlordane	33.0
Oxychlordane	35.6
cis-Nonachlor	35.7
trans-Nonachlor	27.9
Dieldrin	28.7
Heptachlor epoxide	35.6
Toxaphene	36.5
Total PCBs	30.3

[a] Processing involved trimming the belly flap area for skin-on fillets and skinning and removing fatty tissue from the belly flap area and the lateral line for skin-off fillets.

Source: Zabik et al. (1994).

C.3 REFERENCES

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APPENDIX D

GUIDANCE FOR RISK CHARACTERIZATION

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

THE ADMINISTRATOR

MAR 2 1 1995

MEMORANDUM

SUBJECT: EPA Risk Characterization Program

TO Assistant Administrators
Associate Administrators
Regional Administrators
General Counsel
Inspector General

EPA has achieved significant pollution reduction over the past 20 years, but the challenges we face now are very different from those of the past. Many more people are aware of environmental issues today than in the past and their level of sophistication and interest in understanding these issues continues to increase. We now work with a populace which is not only interested in knowing what EPA thinks about a particular issue, but also how we come to our conclusions.

More and more key stakeholders in environmental issues want enough information to allow them to independently assess and make judgments about the significance of environmental risks and the reasonableness of our risk reduction actions. If we are to succeed and build our credibility and stature as a leader in environmental protection for the next century, EPA must be responsive and resolve to more openly and fully communicate to the public the complexities and challenges of environmental decisionmaking in the face of scientific uncertainty.

As the issues we face become more complex, people both inside and outside of EPA must better understand the basis for our decisions, as well as our confidence in the data, the science policy judgments we have made, and the uncertainty in the information base. In order to achieve this better understanding, we must improve the way in which we characterize and communicate environmental risk. We must embrace certain fundamental values so that we may begin the process of changing the way in which we interact with each other, the public, and key stakeholders on environmental risk issues. I need your help to ensure that these values are embraced and that we change the way we do business.

First, we must adopt as values transparency in our decisionmaking process and clarity in communication with each other and the public regarding environmental risk and the uncertainties associated with our assessments of environmental risk. This means that we must fully, openly, and clearly characterize risks. In doing so, we will disclose the scientific analyses, uncertainties, assumptions, and science policies which underlie our decisions as they are made throughout the risk assessment and risk management processes. I want to be sure that key science policy issues are identified as such during the risk assessment process, that policy makers are fully aware and engaged in the selection of science policy options, and that their choices and the rationale for those choices are clearly articulated and visible in our communications about environmental risk.

I understand that some may be concerned about additional challenges and disputes. I expect that we will see more challenges, particularly at first. However, I strongly believe that making this change to a more open decisionmaking process will lead to more meaningful public participation, better information for decisionmaking, improved decisions, and more public support and respect for EPA positions and decisions. There is value in sharing with others the complexities and challenges we face in making decisions in the face of uncertainty. I view making this change as essential to the long-term success of this Agency.

Clarity in communication also means that we will strive to help the public put environmental risk in the proper perspective when we take risk management actions. We must meet this challenge and find legitimate ways to help the public better comprehend the relative significance of environmental risks.

Second, because transparency in decisionmaking and clarity in communication will likely lead to more outside questioning of our assumptions and science policies, we must be more vigilant about ensuring that our core assumptions and science policies are consistent and comparable across programs, well grounded in science, and that they fall within a "zone of reasonableness."

While I believe that the American public expects us to err on the side of protection in the face of scientific uncertainty, I do not want our assessments to be unrealistically conservative. We cannot lead the fight for environmental protection into the next century unless we use common sense in all we do.

These core values of transparency, clarity, consistency, and reasonableness need to guide each of us in our day-to-day work; from the toxicologist reviewing the individual cancer study, to the exposure and risk assessors, to the risk manager, and through to the ultimate decisionmaker. I recognize that issuing this memo will not by itself result in any change. You need to believe in the importance of this change and convey your beliefs to your managers and staff through your words and actions in order for the change to occur. You also need to play an integral role in developing the implementing policies and procedures for your programs.

I am issuing the attached EPA Risk Characterization Policy and Guidance today. I view these documents as building blocks for the development of your program-specific policies and procedures. The Science Policy Council (SPC) plans to adopt the same basic approach to implementation as was used for Peer Review. That is, the Council will form an Advisory Group that will work with a broad Implementation Team made up of representatives from every Program Office and Region. Each Program Office and each Region will be asked by the Advisory Group to develop program and region-specific policies and procedures for risk characterization consistent with the values of transparency, clarity, consistency, and reasonableness and consistent with the attached policy and guidance.

I recognize that as you develop your Program-specific policies and procedures you are likely to need additional tools to fully implement this policy. I want you to identify these needed tools and work cooperatively with the Science Policy Council in their development. I want your draft program and region-specific policies, procedures, and implementation plans to be developed and submitted to the Advisory Group for review by no later than May 30, 1995. You will be contacted shortly by the SPC Steering Committee to obtain the names of your nominees to the Implementation Team.

Carol M. Browner

Attachments

March 1995

POLICY FOR RISK CHARACTERIZATION

at the U.S. Environmental Protection Agency

INTRODUCTION

Many EPA policy decisions are based in part on the results of risk assessment, an analysis of scientific information on existing and projected risks to human health and the environment. As practiced at EPA, risk assessment makes use of many different kinds of scientific concepts and data (e.g., exposure, toxicity, epidemiology, ecology), all of which are used to "characterize" the expected risk associated with a particular agent or action in a particular environmental context. Informed use of reliable scientific information from many different sources is a central feature of the risk assessment process.

Reliable information may or may not be available for many aspects of a risk assessment. Scientific uncertainty is a fact of life for the risk assessment process, and agency managers almost always must make decisions using assessments that are not as definitive in all important areas as would be desirable. They therefore need to understand the strengths and the limitations of each assessment, and to communicate this information to all participants and the public.

This policy reaffirms the principles and guidance found in the Agency's 1992 policy (Guidance on Risk Characterization for Risk Managers and Risk Assessors, February 26, 1992). That guidance was based on EPA's risk assessment guidelines, which are products of peer review and public comment. The 1994 National Research Council (NRC) report, "Science and Judgment in Risk Assessment," addressed the Agency's approach to risk assessment, including the 1992 risk characterization policy. The NRC statement accompanying the report stated, "... EPA's overall approach to assessing risks is fundamentally sound despite often-heard criticisms, but the Agency must more clearly establish the scientific and policy basis for risk estimates and better describe the uncertainties in its estimates of risk."

This policy statement and associated guidance for risk characterization is designed to ensure that critical information from each stage of a risk assessment is used in forming conclusions about risk and that this information is communicated from risk assessors to risk managers (policy makers), from middle to upper management, and from the Agency to the public. Additionally, the policy will provide a basis for greater clarity, transparency, reasonableness, and consistency in risk assessments across Agency programs. While most of the discussion and examples in this policy are drawn from health risk assessment, these values also apply to ecological risk assessment. A parallel effort by the Risk Assessment Forum to develop EPA ecological risk assessment guidelines will include guidance specific to ecological risk characterization.

Policy Statement

Each risk assessment prepared in support of decision-making at EPA should include a risk characterization that follows the principles and reflects the values outlined in this policy. A

risk characterization should be prepared in a manner that is clear, transparent, reasonable and consistent with other risk characterizations of similar scope prepared across programs in the Agency. Further, discussion of risk in all EPA reports, presentations, decision packages, and other documents should be substantively consistent with the risk characterization. The nature of the risk characterization will depend upon the information available, the regulatory application of the risk information, and the resources (including time) available. In all cases, however, the assessment should identify and discuss all the major issues associated with determining the nature and extent of the risk and provide commentary on any constraints limiting fuller exposition.

Key Aspects of Risk Characterization

Bridging risk assessment and risk management. As the interface between risk assessment and risk management, risk characterizations should be clearly presented, and separate from any risk management considerations. Risk management options should be developed using the risk characterization and should be based on consideration of all relevant factors, scientific and nonscientific.

Discussing confidence and uncertainties. Key scientific concepts, data and methods (e.g., use of animal or human data for extrapolating from high to low doses, use of pharmacokinetics data, exposure pathways, sampling methods, availability of chemical-specific information, quality of data) should be discussed. To ensure transparency, risk characterizations should include a statement of confidence in the assessment that identifies all major uncertainties along with comment on their influence on the assessment, consistent with the Guidance on Risk Characterization (attached).

Presenting several types of risk information. Information should be presented on the range of exposures derived from exposure scenarios and on the use of multiple risk descriptors (e.,g., central tendency, high end of individual risk, population risk, important subgroups, if known) consistent with terminology in the Guidance on Risk Characterization, Agency risk assessment guidelines, and program-specific guidance. In decision-making, risk managers should use risk information appropriate to their program legislation.

EPA conducts many types of risk assessments, including screening-level assessments of new chemicals, in-depth assessments of pollutants such as dioxin and environmental tobacco smoke, and site-specific assessments for hazardous waste sites. An iterative approach to risk assessment, beginning with screening techniques, may be used to determine if a more comprehensive assessment is necessary. The degree to which confidence and uncertainty are addressed in a risk characterization depends largely on the scope of the assessment. In general, the scope of the risk characterization should reflect the information presented in the risk assessment and program-specific guidance. When special circumstances (e.g., lack of data, extremely complex situations, resource limitations, statutory deadlines) preclude a full

assessment, such circumstances should be explained and their impact on the risk assessment discussed.

Risk Characterization in Context

Risk assessment is based on a series of questions that the assessor asks about scientific information that is relevant to human and/or environmental risk. Each question calls for analysis and interpretation of the available studies, selection of the concepts and data that are most scientifically reliable and most relevant to the problem at hand, and scientific conclusions regarding the question presented. For example health risk assessments involve the following questions:

> Hazard Identification—What is known about the capacity of an environmental agent for causing cancer or other adverse health effects in humans, laboratory animals, or wildlife species? What are the related uncertainties and science policy choices?
>
> Dose-Response Assessment—What is known about the biological mechanisms and dose-response relationships underlying any effects observed in the laboratory or epidemiology studies providing data for the assessment? What are the related uncertainties and science policy choices?
>
> Exposure Assessment—What is known about the principal paths, patterns, and magnitudes of human or wildlife exposure and numbers of persons or wildlife species likely to be exposed? What are the related uncertainties and science policy choices?

Corresponding principles and questions for ecological risk assessment are being discussed as part of the effort to develop ecological risk guidelines.

Risk characterization is the summarizing step of risk assessment. The risk characterization integrates information from the preceding components of the risk assessment and synthesizes an overall conclusion about risk that is complete, informative and useful for decisionmakers.

Risk characterizations should clearly highlight both the confidence and the uncertainty associated with the risk assessment. For example, numerical risk estimates should always be accompanied by descriptive information carefully selected to ensure an objective and balanced characterization of risk in risk assessment reports and regulatory documents. In essence, a risk characterization conveys the assessor's judgment as to the nature and existence of (or lack of) human health or ecological risks. Even though a risk characterization describes limitations in an assessment, a balanced discussion of reasonable conclusions and related uncertainties enhances, rather than detracts, from the overall credibility of each assessment.

"Risk characterization" is not synonymous with "risk communication." This risk characterization policy addresses the interface between risk assessment and risk management. Risk communication, in contrast, emphasizes the process of exchanging information and opinion with the public—including individuals, groups, and other institutions. The development of a risk assessment may involve risk communication. For example, in the case of site-specific assessments for hazardous waste sites, discussions with the public may influence the exposure pathways included in the risk assessment. While the final risk assessment document (including the risk characterization) is available to the public, the risk communication process may be better served by separate risk information documents designed for particular audiences.

Promoting Clarity, Comparability and Consistency

There are several reasons that the Agency should strive for greater clarity, consistency and comparability in risk assessments. One reason is to minimize confusion. For example, many people have not understood that a risk estimate of one in a million for an "average" individual is not comparable to another one in a million risk estimate for the "most exposed individual." Use of such apparently similar estimates without further explanation leads to misunderstandings about the relative significance of risks and the protectiveness of risk reduction actions.

EPA's Exposure Assessment Guidelines provide standard descriptors of exposure and risk. Use of these terms in all Agency risk assessments will promote consistency and comparability. Use of several descriptors, rather than a single descriptor, will enable EPA to present a fuller picture of risk that corresponds to the range of different exposure conditions encountered by various individuals and populations exposed to most environmental chemicals.

Legal Effect

This policy statement and associated guidance on risk characterization do not establish or affect legal rights or obligations. Rather, they confirm the importance of risk characterization as a component of risk assessment, outline relevant principles, and identify factors Agency staff should consider in implementing the policy.

The policy and associated guidance do not stand alone; nor do they establish a binding norm that is finally determinative of the issues addressed. Except where otherwise provided by law, the Agency's decision on conducting a risk assessment in any particular case is within the Agency's discretion. Variations in the application of the policy and associated guidance, therefore, are not a legitimate basis for delaying or complicating action on Agency decisions.

Applicability

Except where otherwise provided by law and subject to the limitations on the policy's legal effect discussed above, this policy applies to risk assessments prepared by EPA and to risk assessments prepared by others that are used in support of EPA decisions.

EPA will consider the principles in this policy in evaluating assessments submitted to EPA to complement or challenge Agency assessments. Adherence to this Agency-wide policy will improve understanding of Agency risk assessments, lead to more informed decisions, and heighten the credibility of both assessments and decisions.

Implementation

Assistant Administrators and Regional Administrators are responsible for implementation of this policy within their organizational units. The Science Policy Council (SPC) is organizing Agency-wide implementation activities. Its responsibilities include promoting consistent interpretation, assessing Agency-wide progress, working with external groups on risk characterization issues and methods, and developing recommendations for revisions of the policy and guidance, as necessary.

Each Program and Regional office will develop office-specific policies and procedures for risk characterization that are consistent with this policy and the associated guidance. Each Program and Regional office will designate a risk manager or risk assessor as the office representative to the Agency-wide Implementation Team, which will coordinate development of office-specific policies and procedures and other implementation activities. The SPC will also designate a small cross-Agency Advisory Group that will serve as the liaison between the SPC and the Implementation Team.

In ensuring coordination and consistency among EPA offices, the Implementation Team will take into account statutory and court deadlines, resource implications, and existing Agency and program-specific guidance on risk assessment. The group will work closely with staff throughout Headquarters and Regional offices to promote development of risk characterizations that present a full and complete picture of risk that meets the needs of the risk managers.

APPROVED: DATE: MAR 2 1 1995

Carol M. Browner, Administrator

ELEMENTS TO CONSIDER WHEN DRAFTING EPA RISK CHARACTERIZATIONS
March 1995

Background—Risk Characterization Principles

There are a number of principles which form the basis for a risk characterization:

- Risk assessments should be transparent, in that the conclusions drawn from the science are identified separately from policy judgements, and the use of default values or methods and the use of assumptions in the risk assessment are clearly articulated.

- Risk characterizations should include a summary of the key issues and conclusions of each of the other components of the risk assessment, as well as describe the likelihood of harm. The summary should include a description of the overall strengths and the limitations (including uncertainties) of the assessment and conclusions.

- Risk characterizations should be consistent in general format, but recognize the unique characteristics of each specific situation.

- Risk characterizations should include, at least in a qualitative sense, a discussion of how a specific risk and its context compares with other similar risks. This may be accomplished by comparisons with other chemicals or situations in which the Agency has decided to act, or with other situations which the public may be familiar with. The discussion should highlight the limitations of such comparisons.

- Risk characterization is a key component of risk communication, which is an interactive process involving exchange of information and expert opinion among individuals, groups and institutions.

Conceptual Guide for Developing Chemical-Specific Risk Characterizations

The following outline is a guide and formatting aid for developing risk characterizations for chemical risk assessments. Similar outlines will be developed for other types of risk characterizations, including site-specific assessments and ecological risk assessments. A common format will assist risk managers in evaluating and using risk characterization.

The outline has two parts. The first part tracks the risk assessment to bring forward its major conclusions. The second part draws all of the information together to characterize risk. The outline represents the expected findings for a typical complete chemical assessment for a single chemical. However, exceptions for the circumstances of individual assessments exist and should be explained as part of the risk characterization. For example, particular statutory requirements, court-ordered deadlines, resource limitations, and other specific factors may be described to explain why certain elements are incomplete.

This outline does not establish or affect legal rights or obligations. Rather, it confirms the importance of risk characterization, outlines relevant principles, and identifies factors Agency staff should consider in implementing the policy. On a continuing basis, Agency management is expected to evaluate the policy as well as the results of its application throughout the Agency and undertake revisions as necessary. Therefore, the policy does not stand alone; nor does it establish a binding norm that is finally determinative of the issues addressed. Minor variations in its application from one instance to another are appropriate and expected; they thus are not a legitimate basis for delaying or complicating action on otherwise satisfactory scientific, technical, and regulatory products.

PART ONE

SUMMARIZING MAJOR CONCLUSIONS IN RISK CHARACTERIZATION

I. Characterization of Hazard Identification

A. What is the key toxicological study (or studies) that provides the basis for health concerns?
- How good is the key study?
- Are the data from laboratory or field studies? In single species or multiple species?
- If the hazard is carcinogenic, comment on issues such as: observation of single or multiple tumor sites; occurrence of benign or malignant tumors; certain tumor types not linked to carcinogenicity; use of the maximum tolerated dose (MTD).
- If the hazard is other than carcinogenic, what endpoints were observed, and what is the basis for the critical effect?
- Describe other studies that support this finding.
- Discuss any valid studies which conflict with this finding.

B. Besides the health effect observed in the key study, are there other health endpoints of concern?
- What are the significant data gaps?

C. Discuss available epidemiological or clinical data. For epidemiological studies:
- What types of studies were used, i.e., ecologic, case-control, cohort?
- Describe the degree to which exposures were adequately described.
- Describe the degree to which confounding factors were adequately accounted for.
- Describe the degree to which other causal factors were excluded.

D. How much is known about how (through what biological mechanism) the chemical produces adverse effects?
   - Discuss relevant studies of mechanisms of action or metabolism.
   - Does this information aid in the interpretation of the toxicity data?
   - What are the implications for potential health effects?

E. Comment on any non-positive data in animals or people, and whether these data were considered in the hazard identification.

F. If adverse health effects have been observed in wildlife species, characterize such effects by discussing the relevant issues as in A through E above.

G. Summarize the hazard identification and discuss the significance of each of the following:
   - confidence in conclusions;
   - alternative conclusions that are also supported by the data;
   - significant data gaps; and
   - highlights of major assumptions.

II. Characterization of Dose-Response

A. What data were used to develop the dose-response curve? Would the result have been significantly different if based on a different data set?
   - If animal data were used;
     - which species were used? most sensitive, average of all species, or other?
     - were any studies excluded? why?
   - If epidemiological data were used:
     - Which studies were used? only positive studies, all studies, or some other combination?
     - Were any studies excluded? why?
     - Was a meta-analysis performed to combine the epidemiological studies? what approach was used? were studies excluded? why?

B. What model was used to develop the dose-response curve? What rationale supports this choice? Is chemical-specific information available to support this approach?
   - For non-carcinogenic hazards:
     - How was the RfD/RfC (or the acceptable range) calculated?
     - What assumptions or uncertainty factors were used?
     - What is the confidence in the estimates?
   - For carcinogenic hazards:
     - What dose-response model was used? LMS or other linear-at-low dose model, a biologically based model based on metabolism data, or data about possible mechanisms of action?

- What is the basis for the selection of the particular dose-response model used? Are there other models that could have been used with equal plausibility and scientific validity? What is the basis for selection of the model used in this instance?

C. Discuss the route and level of exposure observed, as compared to expected human exposures.
   - Are the available data from the same route of exposure as the expected human exposures? If not, are pharmacokinetic data available to extrapolate across route of exposure?
   - How far does one need to extrapolate from the observed data to environmental exposures (one to two orders of magnitude? multiple orders of magnitude)? What is the impact of such an extrapolation?

D. If adverse health effects have been observed in wildlife species, characterize dose response information using the process outlined in A-C.

III. Characterization of Exposure

A. What are the most significant sources of environmental exposure?
   - Are there data on sources of exposure from different media? What is the relative contribution of different sources of exposure?
   - What are the most significant environmental pathways for exposure?

B. Describe the populations that were assessed, including as the general population, highly exposed groups, and highly susceptible groups.

C. Describe the basis for the exposure assessment, including any monitoring, modeling, or other analyses of exposure distributions such as Monte-Carlo or krieging.

D. What are the key descriptors of exposure?
   - Describe the (range of) exposures to: "average" individuals, "high end" individuals, general population, high exposure group(s), children, susceptible populations.
   - How was the central tendency estimate developed? What factors and/or methods were used in developing this estimate?
   - How was the high-end estimate developed?
   - Is there information on highly exposed subgroups? Who are they? What are their levels of exposure? How are they accounted for in the assessment?

E. Is there reason to be concerned about cumulative or multiple exposures because of ethnic, racial, or socioeconomic reasons?

F. If adverse health effects have been observed in wildlife species, characterize wildlife exposure by discussing the relevant issues as in A through E above.

G. Summarize exposure conclusions and discuss the following:
- results of different approaches, i.e., modeling, monitoring, probability distributions;
- limitations of each, and the range of most reasonable values; and
- confidence in the results obtained, and the limitations to the results.

PART TWO
RISK CONCLUSIONS AND COMPARISONS

IV. Risk Conclusions

A. What is the overall picture of risk, based on the hazard identification, dose-response and exposure characterizations?

B. What are the major conclusions and strengths of the assessment in each of the three main analyses (i.e., hazard identification, dose-response, and exposure assessment)?

C. What are the major limitations and uncertainties in the three main analyses?

D. What are the science policy options in each of the three major analyses?
- What are the alternative approaches evaluated?
- What are the reasons for the choices made?

V. Risk Context

A. What are the qualitative characteristics of the hazard (e.g., voluntary vs. involuntary, technological vs. natural, etc.)? Comment on findings, if any, from studies of risk perception that relate to this hazard or similar hazards.

B. What are the alternatives to this hazard? How do the risks compare?

C. How does this risk compare to other risks?
1. How does this risk compare to other risks in this regulatory program, or other similar risks that the EPA has made decisions about?
2. Where appropriate, can this risk be compared with past Agency decisions, decisions by other federal or state agencies, or common risks with which people may be familiar?
3. Describe the limitations of making these comparisons.

D. Comment on significant community concerns which influence public perception of risk.

VI. Existing Risk Information

Comment on other risk assessments that have been done on this chemical by EPA, other federal agencies, or other organizations. Are there significantly different conclusions that merit discussion?

VII. Other Information

Is there other information that would be useful to the risk manager or the public in this situation that has not been described above?

GUIDANCE
FOR
RISK CHARACTERIZATION

U.S. Environmental Protection Agency
Science Policy Council
February 1995

CONTENTS

I. The Risk Assessment-Risk Management Interface

II. Risk Assessment and Risk Characterization

III. Exposure and Risk Descriptors

PREFACE

This guidance contains principles for developing and describing EPA risk assessments, with a particular emphasis on risk characterization. The current document is an update of the guidance issued with the Agency's 1992 policy (Guidance on Risk Characterization for Risk Managers and Risk Assessors, February 26, 1992). The guidance has not been substantially revised, but includes some clarifications and changes to give more prominence to certain issues, such as the need to explain the use of default assumptions.

As in the 1992 policy, some aspects of this guidance focus on cancer risk assessment, but the guidance applies generally to human health effects (e.g., neurotoxicity, developmental toxicity) and, with appropriate modifications, should be used in all health risk assessments. This document has not been revised to specifically address ecological risk assessment; however, initial guidance for ecological risk characterization is included in EPA's Framework for Ecological Risk Assessments (EPA/630/R-92/001). Neither does this guidance address in detail the use of risk assessment information (e.g., information from the Integrated Risk Information System (IRIS)) to generate site- or media-specific risk assessments. Additional program-specific guidance will be developed to enable implementation of EPA's Risk Characterization Policy. Development of such guidance will be overseen by the Science Policy Council and will involve risk assessors and risk managers from across the Agency.

I. THE RISK ASSESSMENT-RISK MANAGEMENT INTERFACE

Recognizing that for many people the term risk assessment has wide meaning, the National Research Council's 1983 report on risk assessment in the federal government distinguished between risk assessment and risk management.

> "Broader uses of the term [risk assessment] than ours also embrace analysis of perceived risks, comparisons of risks associated with different regulatory strategies, and occasionally analysis of the economic and social implications of regulatory decisions—functions that we assign to risk management (emphasis added). (l)

In 1984, EPA endorsed these distinctions between risk assessment and risk management for Agency use (2), and later relied on them in developing risk assessment guidelines (3). In 1994, the NRC reviewed the Agency's approach to and use of risk assessment and issued an extensive report on their findings (4). This distinction suggests that EPA participants in the process can be grouped into two main categories, each with somewhat different responsibilities, based on their roles with respect to risk assessment and risk management.

A. Roles of Risk Assessors anal Risk Managers

Within the Risk Assessment category there is a group that develops chemical-specific risk assessments by collecting, analyzing, and synthesizing scientific data to produce the hazard identification, dose-response, and exposure assessment portion of the risk assessment and to characterize risk. This group relies in part on Agency risk assessment guidelines to address science policy issues and scientific uncertainties. Generally, this group includes scientists and statisticians in the Office of Research and Development; the Office of Prevention, Pesticides and Toxics and other program offices; the Carcinogen Risk Assessment Verification Endeavor (CRAVE); and the Reference Dose (RfD) and Reference Concentration (RfC) Workgroups

Another group generates site- or media-specific risk assessments for use in regulation development or site-specific decision-making. These assessors rely on existing databases (e.g., IRIS, ORD Health Assessment Documents, CRAVE and RfD/RfC Workgroup documents, and program-specific toxicity information) and media- or site-specific exposure information in developing risk assessments. This group also relies in part on Agency risk assessment guidelines and program-specific guidance to address science policy issues and scientific uncertainties. Generally, this group includes scientists and analysts in program offices, regional offices, and the Office of Research and Development.

Risk managers, as a separate category, integrate the risk characterization with other considerations specified in applicable statutes to make and justify regulatory decisions. Generally, this group includes Agency managers and decision-makers. Risk managers also play a role in determining the scope of risk assessments. The risk assessment process involves regular interaction between risk assessors and risk managers, with overlapping responsibilities

at various stages in the overall process. Shared responsibilities include initial decisions regarding the planning and conduct of an assessment, discussions as the assessment develops, decisions regarding new data needed to complete an assessment and to address significant uncertainties. At critical junctures in the assessment, such consultations shape the nature of, and schedule for, the assessment. External experts and members of the public may also play a role in determining the scope of the assessment; for example, the public is often concerned about certain chemicals or exposure pathways in the development of site-specific risk assessments.

B. Guiding Principles

The following guidance outlines principles for those who generate, review, use, and integrate risk assessments for decision-making.

1. Risk assessors and risk managers should be sensitive to distinctions between risk assessment and risk management.

The major participants in the risk assessment process have many shared responsibilities. Where responsibilities differ, it is important that participants confine themselves to tasks in their areas of responsibility and not inadvertently obscure differences between risk assessment and risk management.

For the generators of the assessment, distinguishing between risk assessment and risk management means that scientific information is selected, evaluated, and presented without considering issues such as cost, feasibility, or how the scientific analysis might influence the regulatory or site-specific decision. Assessors are charged with (1) generating a credible, objective, realistic, and scientifically balanced analyst; (2) presenting information on hazard, dose-response, exposure and risk; and (3) explaining confidence in each assessment by clearly delineating strengths, uncertainties and assumptions, along with the impacts of these factors (e.g., confidence limits, use of conservative/non-conservative assumptions) on the overall assessment. They do not make decisions on the acceptability of any risk level for protecting public health or selecting procedures for reducing risks.

For users of the assessment and for decision-makers who integrate these assessments into regulatory or site-specific decisions, the distinction between risk assessment and risk management means refraining from influencing the risk description through consideration of other factors—e.g., the regulatory outcome—and from attempting to shape the risk assessment to avoid statutory constraints, meet regulatory objectives, or serve political purposes. Such management considerations are often legitimate considerations for the overall regulatory decision (see next principle), but they have no role in estimating or describing risk. However, decision-makers and risk assessors participate in an Agency process that establishes policy directions that determine the overall nature and tone of Agency risk assessments and, as appropriate, provide policy guidance on difficult and controversial risk assessment issues. Matters such as risk assessment priorities, degree of conservatism, and acceptability of

particular risk levels are reserved for decision-makers who are charged with making decisions regarding protection of public health.

2. **The risk assessment product, that is, the risk characterization, is only one of several kinds of information used for regulatory decision-making.**

Risk characterization, the last step in risk assessment, is the starting point for risk management considerations and the foundation for regulatory decision-making, but it is only one of several important components in such decisions. As the last step in risk assessment, the risk characterization identifies and highlights the noteworthy risk conclusions and related uncertainties. Each of the environmental laws administered by EPA calls for consideration of other factors at various stages in the regulatory process. As authorized by different statutes, decision-makers evaluate technical feasibility (e.g., treatability, detection limits), economic, social, political, and legal factors as part of the analysis of whether or not to regulate and, if so, to what extent. Thus, regulatory decisions are usually based on a combination of the technical analysis used to develop the risk assessment and information from other fields.

For this reason, risk assessors and managers should understand that the regulatory decision is usually not determined solely by the outcome of the risk assessment. For example, a regulatory decision on the use of a particular pesticide considers not only the risk level to affected populations, but also the agricultural benefits of its use that may be important for the nation's food supply. Similarly, assessment efforts may produce an RfD for a particular chemical, but other considerations may result in a regulatory level that is more or less protective than the RfD itself.

For decision-makers, this means that societal considerations (e.g., costs and benefits) that, along with the risk assessment, shape the regulatory decision should be described as fully as the scientific information set forth in the risk characterization. Information on data sources and analyses, their strengths and limitations, confidence in the assessment, uncertainties, and alternative analyses are as important here as they are for the scientific components of the regulatory decision. Decision-makers should be able to expect, for example, the same level of rigor from the economic analysis as they receive from the risk analysis. Risk management decisions involve numerous assumptions and uncertainties regarding technology, economics and social factors, which need to be explicitly identified for the decision-makers and the public.

II. RISK CHARACTERIZATION

A. Defining Risk Characterization in the Context of Risk Assessment

EPA risk assessment principles and practices draw on many sources. Obvious sources include the environmental laws administered by EPA, the National Research Council's 1983 report on risk assessment (l), the Agency's Risk Assessment Guidelines (3), and various program specific guidance (e.g., the Risk Assessment Guidance for Superfund). Twenty years of EPA experience in developing, defending, and enforcing risk assessment-based regulation is another. Together these various sources stress the importance of a clear explanation of Agency processes for evaluating hazard, dose-response, exposure, and other data that provide the scientific foundation for characterizing risk.

This section focuses on two requirements for full characterization of risk. First, the characterization should address qualitative and quantitative features of the assessment. Second, it should identify the important strengths and uncertainties in the assessment as part of a discussion of the confidence in the assessment. This emphasis on a full description of all elements of the assessment draws attention to the importance of the qualitative, as well as the quantitative, dimensions of the assessment. The 1983 NRC report carefully distinguished qualitative risk assessment from quantitative assessments, preferring risk statements that are not strictly numerical.

The term risk assessment is often given narrower and broader meanings than we have adopted here. For some observers, the term is synonymous with quantitative risk assessment and emphasizes reliance on numerical results. Our broader definition includes quantification, but also includes qualitative expressions of risk. Quantitative estimates of risk are not always feasible, and they may be eschewed by agencies for policy reasons. (1)

EPA's Exposure Assessment Guidelines define risk characterization as the final step in the risk assessment process that:

- Integrates the individual characterizations from the hazard identification, dose-response, and exposure assessments;
- Provides an evaluation of the overall quality of the assessment and the degree of confidence the authors have in the estimates of risk and conclusions drawn;
- Describes risks to individuals and populations in terms of extent and severity of probable harm; and
- Communicates results of the risk assessment to the risk manager. (5)

Particularly critical to full characterization of risk is a frank and open discussion of the uncertainty in the overall assessment and in each of its components. The uncertainty discussion is important for several reasons.

1. Information from different sources carries different kinds of uncertainty and knowledge of these differences is important when uncertainties are combined for characterizing risk.

2. The risk assessment process, with management input, involves decisions regarding the collection of additional data (versus living with uncertainty); in the risk characterization, a discussion of the uncertainties will help to identify where additional information could contribute significantly to reducing uncertainties in risk assessment.

3. A clear and explicit statement of the strengths and limitations of a risk assessment requires a clear and explicit statement of related uncertainties.

A discussion of uncertainty requires comment on such issues as the quality and quantity of available data, gaps in the data base for specific chemicals, quality of the measured data, use of default assumptions, incomplete understanding of general biological phenomena, and scientific judgments or science policy positions that were employed to bridge information gaps.

In short, broad agreement exists on the importance of a full picture of risk, particularly including a statement of confidence in the assessment and the associated uncertainties. This section discusses information content and uncertainty aspects of risk characterization, while Section III discusses various descriptors used in risk characterization.

B. Guiding Principles

1. The risk characterization integrates the information from the hazard identification, dose-response, and exposure assessments, using a combination of qualitative information, quantitative information, and information regarding uncertainties.

Risk assessment is based on a series of questions that the assessor asks about the data and the implications of the data for human risk. Each question calls for analysis and interpretation of the available studies, selection of the data that are most scientifically reliable and most relevant to the problem at hand, and scientific conclusions regarding the question presented. As suggested below, because the questions and analyses are complex, a complete characterization includes several different kinds of information, carefully selected for reliability and relevance.

a. *Hazard Identification*—What is known about the capacity of an environmental agent for causing cancer (or other adverse effects) in humans and laboratory animals?

Hazard identification is a qualitative description based on factors such as the kind and quality of data on humans or laboratory animals, the availability of ancillary information (e.g., structure-

activity analysis, genetic toxicity, pharmacokinetics) from other studies, and the weight-of-the-evidence from all of these data sources. For example, to develop this description, the issues addressed include:

1) the nature, reliability, and consistency of the particular studies in humans and in laboratory animals;

2) the available information on the mechanistic basis for activity; and

3) experimental animal responses and their relevance to human outcomes.

These issues make clear that the task of hazard identification is characterized by describing the full range of available information and the implications of that information for human health.

b. *Dose-Response Assessment*—What is known about the biological mechanisms and dose-response relationships underlying any effects observed in the laboratory or epidemiology studies providing data for the assessment?

The dose-response assessment examines quantitative relationships between exposure (or dose) and effects in the studies used to identify and define effects of concern. This information is later used along with "real world" exposure information (see below) to develop estimates of the likelihood of adverse effects in populations potentially at risk. It should be noted that, in practice, hazard identification for developmental toxicity and other non-cancer health effects is usually done in conjunction with an evaluation of dose-response relationships, since the determination of whether there is a hazard is often dependent on whether a dose response relationship is present. (6) Also, the framework developed by EPA for ecological risk assessment does not distinguish between hazard identification and dose-response assessment, but rather calls for a "characterization of ecological effects." (7)

Methods for establishing dose-response relationships often depend on various assumptions used in lieu of a complete database, and the method chosen can strongly influence the overall assessment. The Agency's risk assessment guidelines often identify so-called "default assumptions" for use in the absence of other information. The risk assessment should pay careful attention to the choice of a high-to-low dose extrapolation procedure. As a result, an assessor who is characterizing a dose-response relationship considers several key issues:

1) the relationship between extrapolation models selected and available information on biological mechanisms;

2) how appropriate data sets were selected from those that show the range of possible potencies both in laboratory animals and humans;

3) the basis for selecting interspecies dose scaling factors to account for scaling doses from experimental animals to humans;

4) the correspondence between the expected route(s) of exposure and the exposure route(s) utilized in the studies forming the basis of the dose-response assessment, as well as the interrelationships of potential effects from different exposure routes;

5) the correspondence between the expected duration of exposure and the exposure durations in the studies used in forming the basis of the dose-response assessment, e.g., chronic studies would be used to assess long-term, cumulative exposure concentrations, while acute studies would be used in assessing peak levels of exposure; and

6) the potential for differing susceptibilities among population subgroups.

The Agency's Integrated Risk Information System (IRIS) is a repository for such information for EPA. EPA program offices also maintain program-specific databases, such as the OSWER. Health Effects Assessment Summary Tables (HEAST). IRIS includes data summaries representing Agency consensus on specific chemicals, based on a careful review of the scientific issues listed above. For specific risk assessments based on data from any source, risk assessors should carefully review the information presented, emphasizing confidence in the data and uncertainties (see subsection 2 below). Specifically, when IRIS data are used, the IRIS statement of confidence should be included as an explicit part of the risk characterization for hazard and dose-response information.

c. *Exposure Assessment*—What is known about the principal paths, patterns, and magnitudes of human exposure and numbers of persons who may be exposed?

The exposure assessment examines a wide range of exposure parameters pertaining to the environmental scenarios of people who may be exposed to the agent under study. The information considered for the exposure assessment includes monitoring studies of chemical concentrations in environmental media, food, and other materials; modeling of environmental fate and transport of contaminants; and information on different activity patterns of different population subgroups. An assessor who characterizes exposure should address several issues:

1) The basis for the values and input parameters used for each exposure scenario. If the values are based on data, there should be a discussion of the quality, purpose, and representativeness of the database. For monitoring data, there should be a discussion of the data quality objectives as they are relevant to risk assessment, including the appropriateness of the analytical detection limits. If models are applied, the appropriateness of the models and information on their validation should be

presented. When assumptions are made, the source and general logic used to develop the assumptions (e.g., program guidance, analogy, professional judgment) should be described.

2) The confidence in the assumptions made about human behavior and the relative likelihood of the different exposure scenarios.

3) The major factor or factors (e.g., concentration, body uptake, duration/frequency of exposure) thought to account for the greatest uncertainty in the exposure estimate, due either to sensitivity or lack of data.

4) The link between the exposure information and the risk descriptors discussed in Section III of this Appendix. Specifically, the risk assessor needs to discuss the connection between the conservatism or non-conservatism of the data/assumptions used in the scenarios and the choice of descriptors.

5) Other information that may be important for the particular risk assessment. For example, for many assessments, other sources and background levels in the environment may contribute significantly to population exposures and should be discussed.

2. The risk characterization includes a discussion of uncertainty and variability.

In the risk characterization, conclusions about hazard and dose response are integrated with those from the exposure assessment. In addition, confidence about these conclusions, including information about the uncertainties associated with each aspect of the assessment in the final risk summary, is highlighted. In the previous assessment steps and in the risk characterization, the risk assessor must distinguish between variability and uncertainty.

Variability arises from true heterogeneity in characteristics such as dose-response differences within a population, or differences in contaminant levels in the environment. The values of some variables used in an assessment change with time and space, or across the population whose exposure is being estimated. Assessments should address the resulting variability in doses received by members of the target population. Individual exposure, dose, and risk can vary widely in a large population. The central tendency and high end individual risk descriptors (discussed in Section III below) are intended to capture the variability in exposure, lifestyles, and other factors that lead to a distribution of risk across a population.

Uncertainty, on the other hand, represents lack of knowledge about factors such as adverse effects or contaminant levels which may be reduced with additional study. Generally, risk assessments carry several categories of uncertainty, and each merits consideration. Measurement uncertainty refers to the usual error that accompanies scientific measurements—standard statistical techniques can often be used to express measurement uncertainty. A

substantial amount of uncertainty is often inherent in environmental sampling, and assessments should address these uncertainties. There are likewise uncertainties associated with the use of scientific models, e.g., dose-response models, models of environmental fate and transport. Evaluation of model uncertainty would consider the scientific basis for the model and available empirical validation.

A different kind of uncertainty stems from data gaps—that is, estimates or assumptions used in the assessment. Often, the data gap is broad, such as the absence of information on the effects of exposure to a chemical on humans or on the biological mechanism of action of an agent. The risk assessor should include a statement of confidence that reflects the degree to which the risk assessor believes that the estimates or assumptions adequately fill the data gap. For some common and important data gaps, Agency or program-specific risk assessment guidance provides default assumptions or values. Risk assessors should carefully consider all available data before deciding to rely on default assumptions. If defaults are used, the risk assessment should reference the Agency guidance that explains the default assumptions or values.

Often risk assessors and managers simplify discussion of risk issues by speaking only of the numerical components of an assessment. That is, they refer to the alphanumeric weight-of-the-evidence classification, unit risk, the risk-specific dose or the q_1* for cancer risk, and the RfD/RfC for health effects other than cancer, to the exclusion of other information bearing on the risk case. However, since every assessment carries uncertainties, a simplified numerical presentation of risk is always incomplete and often misleading. For this reason, the NRC (1) and EPA risk assessment guidelines (2) call for "characterizing" risk to include qualitative information, a related numerical risk estimate and a discussion of uncertainties, limitations, and assumptions—default and otherwise.

Qualitative information on methodology, alternative interpretations, and working assumptions (including defaults) is an important component of risk characterization. For example, specifying that animal studies rather than human studies were used in an assessment tells others that the risk estimate is based on assumptions about human response to a particular chemical rather than human data. Information that human exposure estimates are based on the subjects' presence in the vicinity of a chemical accident rather than tissue measurements defines known and unknown aspects of the exposure component of the study.

Qualitative descriptions of this kind provide crucial information that augments understanding of numerical risk estimates. Uncertainties such as these are expected in scientific studies and in any risk assessment based on these studies. Such uncertainties do not reduce the validity of the assessment. Rather, they should be highlighted along with other important risk assessment conclusions to inform others fully on the results of the assessment.

In many cases, assessors must choose among available data, models, or assumptions in estimating risks. Examining the impact of selected, plausible alternatives on the conclusions of the assessment is an important part of the uncertainty discussion. The key words are "selected"

and "plausible"; listing all alternatives to a particular assumption, regardless of their merits would be superfluous. Generators of the assessment, using best professional judgment, should outline the strengths and weaknesses of the plausible alternative approaches.[1]

An adequate description of the process of alternatives selection involves several aspects.

a. A rationale for the choice.
b. Discussion of the effects of alternatives selected on the assessment.
c. Comparison with other plausible alternatives, where appropriate.

The degree to which variability and uncertainty are addressed depends largely on the scope of the assessment and the resources available. For example, the Agency does not expect an assessment to evaluate and assess every conceivable exposure scenario for every possible pollutant, to examine all susceptible populations potentially at risk, or to characterize every possible environmental scenario to estimate the cause and effect relationships between exposure to pollutants and adverse health effects. Rather, the discussion of uncertainty and variability should reflect the type and complexity of the risk assessment, with the level of effort for analysis and discussion of uncertainty corresponding to the level of effort for the assessment.

3. Well-balanced risk characterizations present risk conclusions and information regarding the strengths and limitations of the assessment for other risk assessors, EPA decision-makers, and the public.

The risk assessment process calls for identifying and highlighting significant risk conclusions and related uncertainties partly to assure full communication among risk assessors and partly to assure that decision-makers are fully informed. Issues are identified by acknowledging noteworthy qualitative and quantitative factors that make a difference in the overall assessment of hazard and risk, and hence in the ultimate regulatory decision. The key word is "noteworthy." Information that significantly influences the analysis is explicitly noted—in all future presentations of the risk assessment and in the related decision. Uncertainties and assumptions that strongly influence confidence in the risk estimate also require special attention.

Numerical estimates should not be separated from the descriptive information that is integral to risk characterization. Documents and presentations supporting regulatory or site-specific decisions should include both the numerical estimate and descriptive information; in short reports, this information can be abbreviated. Fully visible information assures that important features of the assessment are immediately available at each level of review for evaluating whether risks are acceptable or unreasonable.

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[1]In cases where risk assessments within an Agency program routinely address similar sets of alternatives, program guidance may be developed to streamline and simplify the discussion of these alternatives.

III. EXPOSURE ASSESSMENT AND RISK DESCRIPTORS

A. Presentation of Risk Descriptors

The results of a risk assessment are usually communicated to the risk manager in the risk characterization portion of the assessment. This communication is often accomplished through risk descriptors which convey information and answer questions about risk, each descriptor providing different information and insights. Exposure assessment plays a key role in developing these risk descriptors since each descriptor is based in part on the exposure distribution within the population of interest.

The following guidance outlines the different descriptors in a convenient order that should not be construed as a hierarchy of importance. These descriptors should be used to describe risk in a variety of ways for a given assessment, consistent with the assessment's purpose, the data available, and the information the risk manager needs. Use of a range of descriptors instead of a single descriptor enables Agency programs to present a picture of risk that corresponds to the range of different exposure conditions encountered for most environmental chemicals. This analysis, in turn, allows risk managers to identify populations at greater and lesser risk and to shape regulatory solutions accordingly.

Agency risk assessments will be expected to address or provide descriptions of (1) individual risk that include the central tendency and high end portions of the risk distribution, (2) population risk, and (3) important subgroups of the population, such as highly exposed or highly susceptible groups. Assessors may also use additional descriptors of risk as needed when these add to the clarity of the presentation. With the exception of assessments where particular descriptors clearly do not apply, some form of these three types of descriptors should be routinely developed and presented for Agency risk assessments.[2] In other cases, where a descriptor would be relevant, but the program lacks the data or methods to develop it, the program office should design and implement a plan, in coordination with other EPA offices, to meet these assessment needs. While gaps continue to exist, risk assessors should make their best efforts to address each risk descriptor, and at a minimum, should briefly discuss the lack of data or methods. Finally, presenters of risk assessment information should be prepared to routinely answer questions by risk managers concerning these descriptors.

It is essential that presenters not only communicate the results of the assessment by addressing each of the descriptors where appropriate, but that they also communicate their confidence that these results portray a reasonable picture of the actual or projected exposures. This task will

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[2]Program-specific guidance will need to address these situations. For example, for site-specific assessments, the utility and appropriateness of population risk estimates will be determined based on the available data and program guidance.

usually be accomplished by frankly commenting on the key assumptions and parameters that have the greatest impact on the results, the basis or rationale for choosing these assumptions/ parameters, and the consequences of choosing other assumptions.

B. Relationship Between Exposure Descriptors and Risk Descriptors

In the risk assessment process, risk is estimated as a function of exposure, with the risk of adverse effects increasing as exposure increases. Information on the levels of exposure experienced by different members of the population is key to understanding the range of risks that may occur. Risk assessors and risk managers should keep in mind, however, that exposure is not synonymous with risk. Differences among individuals, in absorption rates, susceptibility, or other factors mean that individuals with the same level of exposure may be at different levels of risk. In most cases, the state of the science is not yet adequate to define distributions of factors such as population susceptibility. The guidance principles below discuss a variety of risk descriptors that primarily reflect differences in estimated exposure. If a full description of the range of susceptibility in the population cannot be presented, an effort should be made to identify subgroups that, for various reasons, may be particularly susceptible.

C. Guiding Principles

1. Information about the distribution of individual exposures is important to communicating the results of a risk assessment.

The risk manager is generally interested in answers to questions such as the following:

- Who are the people at the highest risk?
- What risk levels are they subjected to?
- What are they doing, where do they live, etc., that might be putting them at this higher risk?
- What is the average risk for individuals in the population of interest?

Individual exposure and risk descriptors are intended to provide answers to these questions so as to illuminate the risk management decisions that need to be made. In order to describe the range of risks, both high end and central tendency descriptors are used to convey the variability in risk levels experienced by different individuals in the population.

a. High end descriptor

For the Agency's purposes, high end risk descriptors are plausible estimates of the individual risk for those persons at the upper end of the risk distribution. Given limitations in current

understanding of variability in individuals' sensitivity to toxins, high end descriptors will usually address high end exposure or dose (herein referred to as exposure for brevity). The intent of these descriptors is to convey estimates of exposure in the upper range of the distribution, but to avoid estimates which are beyond the true distribution. Conceptually, high end exposure means exposure above about the 90th percentile of the population distribution, but not higher than the individual in the population who has the highest exposure. When large populations are assessed, a large number of individuals may be included within the "high end" (e.g., above 90th or 95th percentile) and information on the range of exposures received by these individuals should be presented.

High end descriptors are intended to estimate the exposures that are expected to occur in small, but definable, "high end" segments of the subject population.[3] The individuals with these exposures may be members of a special population segment or individuals in the general population who are highly exposed because of the inherent stochastic nature of the factors which give rise to exposure. Where differences in sensitivity can be identified within the population, high end estimates addressing sensitive individuals or subgroups can be developed.

In those few cases in which the complete data on the population distributions of exposures and doses are available, high end exposure or dose estimates can be represented by reporting exposures or doses at a set of selected percentiles of the distributions, such as the 90th, 95th, and 98th percentile. High end exposures or doses, as appropriate, can then be used to calculate high end risk estimates.

In the majority of cases where the complete distributions are not available, several methods help estimate a high end exposure or dose. If sufficient information about the variability in chemical concentrations, activity patterns, or other factors are available, the distribution may be estimated through the use of appropriate modeling (e.g., Monte Carlo simulation or parametric statistical methods). The determination of whether available information is sufficient to support the use of probabilistic estimation methods requires careful review and documentation by the risk assessor. If the input distributions are based on limited data, the resulting distribution should be evaluated carefully to determine whether it is an improvement over more traditional estimation techniques. If a distribution is developed, it should be described with a series of percentiles or population frequency estimates, particularly in the high end range. The assessor and risk manager should be aware, however, that unless a great deal is known about exposures and doses at the high end of the distribution, these estimates will involve considerable

[3]High end estimates focus on estimates of exposure in the exposed populations. Bounding estimates, on the other hand, are constructed to be equal to or greater than the highest actual risk in the population (or the highest risk that could be expected in a future scenario). A "worst case scenario" refers to a combination of events and conditions such that, taken together, produces the highest conceivable risk. Although it is possible that such an exposure, dose, or sensitivity combination might occur in a given population of interest, the probability of an individual receiving this combination of events and conditions is usually small, and often so small that such a combination will not occur in a particular, actual population.

uncertainty which the exposure assessor will need to describe. Note that in this context, the probabilistic analysis addresses variability of exposure in the population. Probabilistic techniques may also be applied to evaluate uncertainty in estimates (see section 5, below). However, it is generally inappropriate to combine distributions reflecting both uncertainty and variability to get a single overall distribution. Such a result is not readily interpretable for the concerns of environmental decision-making.

If only limited information on the distribution of the exposure or dose factors is available, the assessor should approach estimating the high end by identifying the most sensitive variables and using high end values for a subset of these variables, leaving others at their central values.[4] In doing this, the assessor needs to avoid combinations of parameter values that are inconsistent (e.g., low body weight used in combination with high dietary intake rates), and must keep in mind the ultimate objective of being within the distribution of actual expected exposures and doses, and not beyond it.

If very little data are available on the ranges for the various variables, it will be difficult to estimate exposures or doses and associated risks in the high end with much confidence. One method that has been used in such cases is to start with a bounding estimate and "back off" the limits used until the combination of parameter values is, in the judgment of the assessor, within the distribution of expected exposure, and still lies within the upper 10% of persons exposed. Obviously, this method results in a large uncertainty and requires explanation.

b. Central tendency descriptor

Central tendency descriptors generally reflect central estimates of exposure or dose. The descriptor addressing central tendency may be based on either the arithmetic mean exposure (average estimate) or the median exposure (median estimate), either of which should be clearly labeled. The average estimate, used to approximate the arithmetic mean, can often be derived by using average values for all the exposure factors.[5] It does not necessarily represent a particular individual on the distribution. Because of the skewness of typical exposure profiles, the arithmetic mean may differ substantially from the median estimate (i.e., 50th percentile estimate, which is equal to the geometric mean for a log normal distribution). The selection of which descriptor(s) to present in the risk characterization will depend on the available data and the goals of the assessment. When data are limited, it may not be possible to construct true

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[4]Maximizing all variables will in virtually all cases result in an estimate that is above the actual values seen in the population. When the principal parameters of the dose equation, e.g., concentration (appropriately integrated over time), intake rate, and duration, are broken out into sub-components, it may be necessary to use maximum values for more than two of these sub-component parameters depending on a sensitivity analysis.

[5]This holds true when variables are added (e.g., exposures by different routes) or when independent variables are multiplied (e.g., concentration x intake). However, it would be incorrect for products of correlated variables, variables used as divisors, or for formulas involving exponents.

median or mean estimates, but it is still possible to construct estimates of central tendency. The discussion of the use of probabilistic techniques in Section 1(a) above also applies to estimates of central tendency.

2. Information about population exposure leads to another important way to describe risk.

Population risk refers to an assessment of the extent of harm for the population as a whole. In theory, it can be calculated by summing the individual risks for all individuals within the subject population. This task, of course, requires a great deal more information than is normally, if ever, available.

The kinds of questions addressed by descriptors of population risk include the following:

- How many cases of a particular health effect might be probabilistically estimated in this population for a specific time period?
- For non-carcinogens, what portion of the population is within a specified range of some reference level; e.g., exceedance of the RfD (a dose), the RfC (a concentration), or other health concern level?
- For carcinogens, what portion of the population is above a certain risk level, such as 10^{-6}?

These questions can lead to two different descriptors of population risk.

a. Probabilistic number of cases

The first descriptor is the probabilistic number of health effect cases estimated in the population of interest over a specified time period. This descriptor can be obtained either by (a) summing the individual risks over all the individuals in the population, e.g. using an estimated distribution of risk in the population, when such information is available, or (b) through the use of a risk model that assumes a linear non-threshold response to exposure, such as many carcinogenic models. In these calculations, data will typically be available to address variability in individual exposures. If risk varies linearly with exposure, multiplying the mean risk by the population size produces an estimate of the number of cases.[6] At the present time, most cancer potency values represent plausible upper bounds on risk. When such a value is used to estimate

[6]However, certain important cautions apply (see EPA's Exposure Assessment Guidelines). Also, this is not appropriate for non-carcinogenic effects or for other types of cancer models. For non-linear cancer models, an estimate of population risk must be calculated using the distribution of individual risks

numbers of cancer cases, it is important to understand that the result is also an upper bound. As with other risk descriptors, this approach may not adequately address sensitive subgroups for which different dose-response curve or exposure estimates might be needed.

Obviously, the more information one has, the more certain the estimate of this risk descriptor, but inherent uncertainties in risk assessment methodology place limitations on the accuracy of the estimate. The discussion of uncertainty involved in estimating the number of cases should indicate that this descriptor is not to be confused with an actuarial prediction of cases in the population (which is a statistical prediction based on a great deal of empirical data).

In general, it should be recognized that when small populations are exposed, population risk estimates may be very small. For example, if 100 people are exposed to an individual lifetime cancer risk of 10^{-4}, the expected number of cases is 0.01. In such situations, individual risk estimates will usually be a more meaningful parameter for decision-makers.

b. Estimated percentage of population with risk greater than some level

For non-cancer effects, we generally have not developed the risk assessment techniques to the point of knowing how to add risk probabilities, so a second descriptor is usually more appropriate: An estimate of the percentage of the population, or the number of persons, above a specified level of risk or within a specified range of some reference level, e.g., exceedance of the RfD or the RfC, LOAEL or other specific level of interest. This descriptor must be obtained through measuring or simulating the population distribution.

3. Information about the distribution of exposure and risk for different subgroups of the population are important components of a risk assessment.

A risk manager might also ask questions about the distributor of the risk burden among various segments of the subject population such as the following: How do exposure and risk impact various subgroups?; and, what is the population risk of a particular subgroup? Questions about the distribution of exposure and risk among such population segments require additional risk descriptors.

a. Highly exposed

Highly exposed subgroups can be identified, and where possible, characterized and the magnitude of risk quantified. This descriptor is useful when there is (or is expected to be) a subgroup experiencing significantly different exposures or doses from that of the larger population. These sub-populations may be identified by age, sex, lifestyle, economic factors, or other demographic variables. For example, toddlers who play in contaminated soil and high fish consumers represent sub-populations that may have greater exposures to certain agents.

b. Highly susceptible

Highly susceptible subgroups can also be identified, and if possible, characterized and the magnitude of risk quantified. This descriptor is useful when the sensitivity or susceptibility to the effect for specific subgroups is (or is expected to be) significantly different from that of the larger population. In order to calculate risk for these subgroups, it will sometimes be necessary to use a different dose-response relationship; e.g., upon exposure to a chemical, pregnant women, elderly people, children, and people with certain illnesses may each be more sensitive than the population as a whole. For example, children are thought to be both highly exposed and highly susceptible to the effects of environmental lead. A model has been developed that uses data on lead concentrations in different environmental media to predict the resulting blood lead levels in children. Federal agencies are working together to develop specific guidance on blood lead levels that present risks to children

It is important to note, however, that the Agency's current methodologies for developing reference doses and reference concentrations (RfDs and RfCs) are designed to protect sensitive populations. If data on sensitive human populations are available (and there is confidence in the quality of the data), then the RfD is set at the dose level at which no adverse effects are observed in the sensitive population (e.g., RfDs for fluoride and nitrate). If no such data are available (for example, if the R is developed using data from humans of average or unknown sensitivity), then an additional 10-fold factor is used to account for variability between the average human response and the response of more sensitive individuals.

Generally selection of the population segments is a matter of either a priori interest in the subgroup (e.g., environmental justice considerations), in which case the risk assessor and risk manager can jointly agree on which subgroups to highlight, or a matter of discovery of a sensitive or highly exposed subgroup during the assessment process. In either case, once identified, the subgroup can be treated as a population in itself, and characterized in the same way as the larger population using the descriptors for population and individual risk.

4. Situation-specific information adds perspective on possible future events or regulatory options.

"What if...?" questions can be used to examine candidate risk management options. For example, consider the following:

- What if a pesticide applicator applies this pesticide without using protective equipment?
- What if this site becomes residential in the future?
- What risk level will occur if we set the standard at 100 ppb?

Answering these "What if...?" questions involves a calculation of risk based on specific combinations of factors postulated within the assessment.[7] The answers to these "What if...?" questions do not, by themselves, give information about how likely the combination of values might be in the actual population or about how many (if any) persons might be subjected to the potential future risk. However, information on the likelihood of the postulated scenario would also be desirable to include in the assessment.

When addressing projected changes for a population (either expected future developments or consideration of different regulatory options), it is usually appropriate to calculate and consider all the risk descriptors discussed above. When central tendency or high end estimates are developed for a future scenario, these descriptors should reflect reasonable expectations about future activities. For example, in site-specific risk assessments, future scenarios should be evaluated when they are supported by realistic forecasts of future land use, and the risk descriptors should be developed within that context.

5. An evaluation of the uncertainty in the risk descriptors is an important component of the uncertainty discussion in the assessment.

Risk descriptors are intended to address variability of risk within the population and the overall adverse impact on the population. In particular, differences between high end and central tendency estimates reflect variability in the population, but not the scientific uncertainty inherent in the risk estimates. As discussed above, there will be uncertainty in all estimates of risk. These uncertainties can include measurement uncertainties, modeling uncertainties, and assumptions to fill data gaps. Risk assessors should address the impact of each of these factors on the confidence in the estimated risk values.

Both qualitative and quantitative evaluations of uncertainty provide useful information to users of the assessment. The techniques of quantitative uncertainty analysis are evolving rapidly and both the SAB (8) and the NRC (4) have urged the Agency to incorporate these techniques into its risk analyses. However, it should be noted that a probabilistic assessment that uses only the assessor's best estimates for distributions of population variables addresses variability, but not uncertainty. Uncertainties in the estimated risk distribution need to be separately evaluated.

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[7]Some programs routinely develop future scenarios as part of developing a risk assessment. Program-specific guidance may address future scenarios in more detail than they are described here.

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APPENDIX E

ADDITIONAL DEVELOPMENTAL TOXICITY ISSUES

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Several chemicals, including lead, PCBs, methylmercury, and some pharmaceuticals, are known to cause developmental toxicity in humans. This information comes from large-scale poisoning incidents that resulted in serious developmental effects in a large number of offspring. Human dose-response studies cannot be carried out with planned dosing for developmental toxicants. However, developmental toxicity studies have been carried out on many environmental contaminants in animals. Many of these have yielded positive results (U.S. EPA, 1991). It is difficult to specifically interpret the dose-response relationship between effects in animal studies and anticipated observable effects in the human population. Research has been conducted to evaluate the relationship between known human developmental toxicants and animal testing results; many similarities in response were found. Alternatively, chemicals that caused developmental effects in animals were studied for effects in humans. These evaluations have yielded mixed results. It has been theorized that the lack of concurrence in results may be due in part to the limited nature of the human data differences in exposure route and the timing and duration of exposure (U.S. EPA, 1991). Further analysis has indicated that:

> The minimally effective dose for the most sensitive animal species was generally higher than that for humans usually within 10-fold of the human effective dose, but sometimes was 100 times or more higher (U.S. EPA, 1991).

The Guidelines go on to state that:

> Thus, the experimental animal data were generally predictive of adverse developmental effects in humans, but in some cases, the administered dose or exposure level required to achieve these adverse effects was much higher than the effective dose in humans. (U.S. EPA, 1991)

A number of assumptions are made in approaching developmental toxicity risk assessment in the absence of specific information:

- Adverse effects in experimental animals may pose a hazard to humans.
- The four manifestations of developmental toxicity (death, structural abnormalities, growth alterations, and functional deficits) are all of concern rather

than only malformations and death, which were the primary effects considered in the past.

- The type of developmental effects seen in animals is **not** necessarily the same as that produced in humans.
- The most appropriate species is used to estimate human risk when data are available (e.g., pharmacokinetic). In the absence of such data, the most sensitive species is used.
- A threshold is assumed based on the capacity of the developing organism to repair or compensate for some amount of damage (U.S. EPA, 1991).

Although it is assumed there is a threshold for developmental toxicity, EPA has stated that:

> . . . a threshold for a population of individuals may or may not exist because of other endogenous or exogenous factors that may increase the sensitivity of some individuals in the population (U.S. EPA, 1991).

The Agency is currently sponsoring research to better characterize the dose-response relationship for developmental toxicants. This includes an evaluation of the threshold concept (U.S. EPA, 1991). The process of risk assessment, as recommended in the 1991 EPA guidelines, generally follows the four-step process described in this document. However, hazard identification and dose-response evaluation are combined in the developmental toxicity guidelines because "the determination of hazard is often dependent on whether a dose-response relationship is present" (U.S. EPA, 1991).

E. 1 DEFINITIONS

There is no one consistent definition of developmental toxicity (U.S. EPA, 1986a). Developmental toxicity may include the range of effects from early pregnancy loss to cognitive disorders detectable only long after birth. The severity of developmental effects ranges from minor alterations in enzyme levels, with no known associated pathology, to death. Developmental toxicity also encompasses health endpoints having genetic and nongenetic bases. EPA's 1986 guidelines (U.S. EPA, 1986a) provide useful definitions that are used in this document to classify different types of developmental effects and to define the scope of effects included under the overall heading of developmental effects.

- **Developmental Toxicology**—The study of adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the lifespan of the organism. The major manifestations of developmental toxicity include: (1) death of the developing organism, (2)

structural abnormality, (3) altered growth (defined below), and (4) functional deficiency.

- **Functional Developmental Toxicology**—The study of alterations or delays in the physiological and/or biochemical functioning of the individual during critical pre- or postnatal development periods.

- **Embryotoxicity and Fetotoxicity**—Any toxic effect on the conceptus as a result of prenatal exposure. The distinguishing feature between the two terms is the stage of development during which the injury occurs (the embryonic stage lasts until approximately 8 weeks postconception followed by the fetal stage). The terms include malformations and variations, altered growth, and in utero death.

- **Altered Growth**—An alteration in offspring organ or body weight or size. These alterations may or may not be accompanied by a change in crown-rump length and/or in skeletal ossification. Altered growth can be induced at any stage of development and may be reversible or may result in a permanent change.

- **Malformations**—Permanent structural changes that may adversely affect survival, development, or function. The term teratogenicity is used to describe only structural abnormalities.

- **Variations**—Divergences beyond the usual range of structural constitution that may not adversely affect survival or health. Distinguishing between variations and malformations is difficult because responses form a continuum from normal to extremely deviant. (U.S. EPA, 1986a, 1991).

Other terminology is often used (e.g., anomalies, deformations, and aberrations) but definitions may vary.

For purposes of this guidance document, the definition of developmental toxicology given above will be used to describe the range of effects considered in this section. This provides a broad scope for evaluation of developmental effects, including those resulting from both prenatal and preconception exposures and effects that are observable pre- and postnatally. This section does **not** include a discussion of reproductive system effects (i.e., damage to the reproductive system), such as sterility, that result from exposure **during** adulthood and that may prevent conception from occurring but that do not affect the development of another individual. This type of toxicity is included under the Chronic Toxicity heading in each profile in Section 5.

Carcinogenic effects occurring prior to adulthood may be considered developmental effects under some circumstances. These can be evaluated using the methods described in the previous section on carcinogenicity in keeping with EPA recommendations (U.S. EPA, 1986b, 1996) and, similarly, mutagenic effects

can be evaluated using criteria discussed in *Guidelines for Mutagenicity Risk Assessment* (U.S. EPA, 1986c), as described in Appendix D.

E.2 SPECIAL ISSUES IN EVALUATING DEVELOPMENTAL TOXICANTS

Studies of developmental toxicants that are most useful in quantitative risk assessment include human epidemiological studies and animal toxicology studies. Epidemiological studies have been conducted on very few chemicals. Animal studies, which are more readily available, pose problems related to interspecies extrapolation (see statements in Sections 2.3.5 and 5 regarding uncertainty). The *Guidelines for the Health Assessment of Suspect Developmental Toxicants* (U.S. EPA, 1991) provides guidance on evaluating various types of developmental toxicity studies.

Some aspects of the evaluation of developmental toxicity studies differ from the approaches and data that would be sought from most other types of toxicity studies. One area of concern is the need to ascertain overall reproductive performance, not only adverse effects on developing individuals. Exposure to a toxicant often results in developmental damage at a very early stage of growth. This may prevent implantation or lead to very early fetal loss. Such losses are usually only detectable in animal studies by comparing the number of individuals per litter or the number of litters produced to the same outcomes in control populations. Very early losses are often absorbed and are not identifiable via other means. In human studies such losses are not usually identified, although prospective studies have used the monitoring of pregnancy markers, such as human chorionic gonadotropic (HCG) hormone, to identify very early post-implantation pregnancy losses (see U.S. EPA, 1991, for further discussion).

Another area of concern in developmental toxicity studies that is not usually of significant interest in other types of toxicity studies is the importance of weight changes. According to the federal guidelines, "A change in offspring body weight is a sensitive indicator of developmental toxicity . . ." (U.S. EPA, 1991). A relatively small weight change is not generally considered important in toxicological studies of adult subjects; however, this is considered an important effect during development. For example, the human corollary to decreased weight in animals may be low birth weight, although this cannot be directly implied from animal studies. Low birth weight in infants is a significant and often serious public health problem. Weight gain or loss may also be organ-specific and may be indicative of organ toxicity. For example, decreased brain weight may be indicative of retarded or neurological development.

An issue that is often raised in developmental toxicity studies is maternal toxicity. Although some researchers have suggested that the presence of maternal toxicity undermines the validity of results observed in offspring, some level of maternal toxicity should be observed in this type of study at the high end of the dose regimen (U.S. EPA, 1991). The EPA health assessment guidelines describe appropriate endpoints of maternal toxicity. One reason that identification of

maternal toxicity is an important component of a developmental toxicity study is that it can provide information on the likelihood of developing individuals being more or less susceptible than adults to an agent. Agents that produce developmental toxicity in offspring at doses that do not cause maternal toxicity are of greatest concern because these dynamics suggest that developing individuals are more sensitive or selectively affected (U.S. EPA, 1991). Those that produce effects in parent and offspring at the same dose are also of concern; it should not be assumed that offspring toxicity results from maternal toxicity because both may be sensitive to the given dose level (U.S. EPA, 1991).

E.3 REFERENCES

U.S. EPA (U.S. Environmental Protection Agency). 1986a. Guidelines for the health assessment of suspect developmental toxicants. *Federal Register* 51(185):34028-34040.

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U.S. EPA (U.S. Environmental Protection Agency). 1986c. Guidelines for mutagenicity risk assessment. *Federal Register* 51(185):34006-34012.

U.S. EPA (U.S. Environmental Protection Agency). 1991. Guidelines for the health assessment of suspect developmental toxicants. *Federal Register* 56:63798-63826.

U.S. EPA (U.S. Environmental Protection Agency). 1996. *Proposed Guidelines for Carcinogen Risk Assessment.* EPA/600/P-92/003C, Office of Research and Development, Washington, DC.

APPENDIX F

SUMMARY OF LIMITS OF DETECTION FOR THE RECOMMENDED TARGET ANALYTES

Table F-1. Summary of Limits of Detection for the Recommended Target Analytes[a]

Target Analyte	Detection Limits[b] (ppb)
Metals	
Arsenic (inorganic)[c]	5
Cadmium[d]	5
Mercury[e]	1.3
Selenium[f]	17
Tributyltin[g]	2
Organochlorine Pesticides[h]	
Chlordane (total)	1
cis-Chlordane	
trans-Chlordane	
cis-Nonachlor	
trans-Nonachlor	
Oxychlordane	
DDT (Total)	
4,4'-DDT	0.1
1,4'-DDT	
4,4'-DDD	
2,4'-DDD	
4,4'-DDE	
2,4'-DDE	
Dicofol	1
Dieldrin	0.1
Endosulfan (Total)	5
Endosulfan I	
Endosulfan II	
Endrin	0.1
Heptachlor epoxide	0.1
Hexachlorobenzene	0.1
Lindane	0.1
Mirex	0.1
Toxaphene	3
Organophosphate Pesticides[i]	
Chlorpyrifos	2
Diazinon	2
Disulfoton	2
Ethion	2
Turbufos	2

(continued)

Table F-1 (continued)

Target Analyte	Detection Limits[b] (ppb)
Chlorophenoxy Herbicides[h]	
Oxyfluorfen	10
PAHs[j]	1 ppt
PCBs (Total Aroclors)[h]	20
Dioxins/Furans (Total)[k]	1 ppt

PAHs = Polycyclic aromatic hydrocarbons.
PCBs = Polychlorinated biphenyls.

[a] Detection limit provided for analysis of tissue on a wet weight basis.
[b] Limit of detection shown is lowest value identified. For further information, see Table 8-4, Volume 1, of this series.
[c] Analysis by hydride generation atomic absorption spectrophotometry (HAA) with preconcentration (E. Crecelius, Battelle Pacific Northwest Laboratories, Marine Sciences Laboratory, Sequim, WA, personal communication, July 1999).
[d] Analysis by graphite furnace atomic absorption spectrophotometry (GFAA).
[e] Analysis by cold vapor atomic absorption spectrophotometry (CVAA).
[f] Analysis by hydride generation on atomic absorption spectrophotometry (HAA).
[g] Analysis by gas chromatography/flame photometric detection (GC/FPD) (E. Crecelius, Battelle Pacific Northwest Laboratories, Marine Sciences Laboratory, Sequim, WA, personal communication, July 1999).
[h] Analysis by gas chromatography/electron capture detection (GC/ECD), except where otherwise noted. GC/ECD does not provide definitive compound identification, and false positives due to interferences are commonly reported. Confirmation by an alternative GC column phase (with ECD), or by GC/MS with selected ion monitoring, is required for positive identification of PCBs, organochlorine pesticides, and chlorophenoxy herbicides.
[i] Analysis by gas chromatography/nitrogen-phosphorus detection (GC/NPD).
[j] Analysis by gas chromatography/mass spectrometry (GC/MS). Detection limits of ≤1 ppb can be achieved using high-resolution gas chromatography/mass spectrometry (HRGC/HRMS).
[k] Analysis by high-resolution GC/high-resolution mass spectrometry (HRGC/HRMS).

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