

Comparative Dietary Risks: Balancing the Risks and Benefits of Fish Consumption

Results of a Cooperative Agreement between

The U.S. Environmental Protection Agency

and

Toxicology Excellence for Risk Assessment (*TERA*)

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Table of Contents	Page
List of Tables and Figures	vi
List of Abbreviations	ix
Foreword	xi
Authors and Contributors	xii
Acknowledgements	xiv
Executive Summary	xv
 1. INTRODUCTION	 1-1
1.1 References	1-5
 2. HEALTH BENEFITS FROM EATING FISH	 2-1
2.1 Introduction	2-1
2.2 Health Benefits Associated with Fish Consumption	2-2
2.2.1 Coronary Heart Disease (CHD) and Myocardial Infarction (MI)	2-2
2.2.1.1 Kromhout, Bosschieter and Coulander, 1985. "The Zutphen Study" (1)	2-9
2.2.1.2 Kromhout, Feskens and Bowles, 1995. General practice patients in Rotterdam, the Netherlands. (2)	2-9
2.2.1.3 Norell, Ahlbom, Feychting and, Pedersen, 1986. "Swedish Twins" (3)	2-9
2.2.1.4 Vollset, Heuch and, Bjelke, 1985. "Norway Postal Dietary Survey (4)	2-10
2.2.1.5 Curb and Reed, 1985. "Honolulu Heart Program" (5)	2-10
2.2.1.6 Fraser, Sabate, Beeson and, Strahan, 1992. "The Adventist Health Study" (6) ...	2-11
2.2.1.7 Morris, Manson, Rosner, Buring, Willett and Hennekens, 1995. "The US Physicians' Health Study: 4 years" (7)	2-11
2.2.1.8 Albert, Hennekens, O'Donnell, Ajani, Carey, Willett, Ruskin and Manson, 1998. "The US Physicians' Health Study: 12 years" (8)	2-12
2.2.1.9 Ascherio, Rimm, Stampfer, Giovannucci and Willett, 1995. "The Health Professionals Follow-Up Survey" (9)	2-12
2.2.1.10 Gramenzi, Gentile, Fasoli, Negri, Parazzine and La Vecchia, 1990 (10)	2-13
2.2.1.11 Siscovick <i>et al.</i> , 1995. Case-control Study in Seattle and King County, Washington. (11)	2-13
2.2.1.12 Burr, Gilbert, Holliday, Elwood, Fehily, Rogers, Sweetnam and Deadman, 1989. "The Diet and Reinfarction Trial (DART)" (12)	2-13
2.2.1.13 Daviglus <i>et al.</i> , 1997. "The Western Electric Study" (13)	2-14
2.2.1.14 Conclusions and Weight of Evidence for an Association between Coronary Heart Disease and Fish Consumption	2-14
2.2.2 Studies of Other Possible Health Effects of Fish Consumption	2-16
2.2.2.1 Smoking-Related Chronic Obstructive Pulmonary Disease (COPD)	2-19
2.2.2.2 Lung Damage from Smoking	2-19
2.2.2.3 Rheumatoid Arthritis	2-19
2.2.2.4 Childhood Asthma	2-20
2.2.2.5 Plaque Psoriasis	2-20
2.2.2.6 Colon Cancer	2-20
2.2.2.7 Gastrointestinal Disease	2-20

2.2.2.8	Dyslipidemia in Non-Insulin-Dependent Diabetes Mellitus.....	2-21
2.3	Antioxidant Levels	2-21
2.4	Health Benefits During Pregnancy, Lactation and Infancy.....	2-21
2.5	Health Benefits for Children Consuming Fish.....	2-22
2.6	Conclusions and Research Needs.....	2-23
2.7	References.....	2-24
3	NUTRITIONAL ASPECTS OF FISH COMPARED WITH OTHER PROTEIN SOURCES.....	3-1
3.1	Introduction	3-1
3.2	Per Capita Consumption of Fish (Finfish and Shellfish)	3-1
3.3	Nutritional Content and Contamination Levels for Fish and Other Protein Sources.....	3-3
3.3.1	Selection of Nutrients, Foods and Contaminants for Tables 3-1 and 3-2.....	3-3
3.3.2	Substituting Other Foods for Fish: Effects on Macronutrient Profiles.....	3-4
3.4	Fish as a Protein Source	3-5
3.4.1	Protein Quality	3-5
3.4.2	Fish Protein vs Other Dietary Protein Sources	3-5
3.5	Fish as a Source of Essential Fatty Acids	3-6
3.6	Cholesterol	3-7
3.7	Vitamins	3-7
3.7.1	Vitamins B3, B6, and B12	3-7
3.7.2	Vitamin A	3-8
3.7.3	Vitamin D	3-9
3.8	Minerals.....	3-9
3.8.1	Calcium.....	3-9
3.8.2	Iron.....	3-10
3.8.3	Zinc	3-10
3.8.4	Selenium	3-11
3.9	Effects of Food Preparation Methods on Nutritional Benefits.....	3-11
3.10	Effects of Food Preparation Methods on Contaminant Levels	3-12
3.11	Conclusions and Research Needs.....	3-12
3.12	References	3-22
4	HEALTH RISKS FROM EATING CONTAMINATED FISH	4-1
4.1	Introduction	4-1
4.2	Calculating Risk above the Reference Dose for Noncancer Endpoints.....	4-2
4.2.1	EPA/ChemRisk Model	4-3
4.2.2	Other Approaches to Calculate Risk above the RfD	4-5
4.3	Dose Response Information for the Six Selected Target Substances	4-6
4.3.1	DDT and Metabolites (DDE and DDD)	4-6
4.3.2	Methylmercury	4-7
4.3.3	Dioxin	4-10
4.3.4	Polychlorinated Biphenyls (PCBs)	4-11
4.3.5	Chlordane.....	4-13
4.3.6	Chlorpyrifos	4-16
4.4	Multigenerational Study of Great Lakes Salmon Fed to Rats.....	4-17

4.5	Breast Milk as a Source of Contaminants	4-18
4.6	Conclusions and Research Needs.....	4-19
4.7	References	4-19
5	SOCIO-CULTURAL CONSIDERATIONS OF FISH CONSUMPTION	5-1
5.1	Introduction	5-1
5.2	Asian-Americans and Fish	5-2
5.3	Native Americans and Fish	5-4
5.4	Subsistence Fishing.....	5-5
5.5	Low-Income, Urban Anglers	5-5
5.6	Conclusion and Research Needs	5-7
5.7	References	5-8
6	FRAMEWORK AND CASE STUDIES	6-1
6.1	Introduction	6-1
6.2	Goals of the Comparative Dietary Risk Framework.....	6-2
6.3	Inputs for the Comparative Dietary Risk Framework.....	6-3
6.3.1	Potential Health Benefits of Fish Consumption	6-3
6.3.2	Measuring Severity of Health Outcomes and Magnitude of Health Benefits	6-4
6.3.2.1	Introduction	6-4
6.3.2.2	Incorporation of Severity into the Framework.....	6-6
6.3.3	Estimates of Human Health Risk.....	6-8
6.3.4	Dietary Considerations	6-8
6.3.5	Cultural Considerations	6-12
6.4	The Benefit/Risk Framework.....	6-13
6.4.1	Algorithm for Health Benefits	6-17
6.4.2	Algorithm for Health Risk	6-19
6.4.3	Algorithm for the Fish Consumption Index (FCI).....	6-20
6.5	Demonstrating the Framework.....	6-20
6.5.1	Quantitative Example of the Framework.....	6-22
6.5.1.1	Calculations for Estimating Benefits	6-24
6.5.1.2	Calculations for Estimating Risks.....	6-25
6.5.1.2.1	Excess Lifetime Cancer Risk	6-25
6.5.1.2.2	Excess Lifetime Non-Cancer Risk	6-26
6.5.1.3	Estimating the FCI	6-28
6.5.2	Impacts from Changes in Contaminant Concentrations	6-28
6.5.3	Evaluation of Different Subgroups	6-32
6.5.4	Mixtures of Chemicals and Multiple Endpoints	6-34
6.5.5	Cultural Benefits.....	6-41
6.5.6	Personal Perception of Severity.....	6-43
6.6	Case Studies	6-44
6.6.1	Case Study: The Florida Everglades.....	6-44
6.6.1.1	Background	6-44
6.6.1.2	Summary of Existing Data	6-44
6.6.1.3	Exposure Assessment.....	6-45
6.6.1.4	Calculation of FCI.....	6-46

6.6.1.5	Discussion	6-48
6.6.1.6	A Method for Verifying Fish Consumption Estimates	6-51
6.6.2	Vietnamese Immigrant Women Consuming Lake Ontario Sportfish.....	6-52
6.6.2.1	Background	6-52
6.6.2.2	Summary of Existing Data	6-53
6.6.2.2.1	Descriptive Data	6-53
6.6.2.2.2	Biochemical Data	6-54
6.6.2.3	Exposure Assessment	6-55
6.6.2.4	Calculation of FCI.....	6-56
6.6.2.4.1	Salmon from Credit River	6-56
6.6.2.4.2	Rockbass and Smallmouth Bass from the Niagara River.....	6-60
6.6.2.5	Discussion	6-60
6.7	Overall Conclusions and Research Needs.....	6-61
6.8	References	6-69
7	USING AND COMMUNICATING THE COMPARATIVE DIETARY RISK FRAMEWORK.....	7-1
7.1	Overview of Risk Communication as a Process	7-1
7.2	Designing, Implementing, and Evaluating a Communication Program for the Comparative Dietary Risk Framework	7-2
7.2.1	Problem Analysis	7-5
7.2.2	Audience Identification and Needs Assessment	7-6
7.2.3	Communication Program Strategy Design and Implementation	7-7
7.2.4	Evaluation	7-10
7.3	Research Needs and Further Work	7-10
7.4	References	7-11
8	CONCLUSIONS AND RESEARCH NEEDS	8-1
8.1	Overall Conclusions and Research Needs.....	8-1
8.2	Chapter 2	8-1
8.3	Chapter 3	8-2
8.4	Chapter 4	8-3
8.5	Chapter 5	8-4
8.6	Chapter 6	8-5
8.7	Chapter 7	8-7
8.8	Final Comment.....	8-8
8.9	References	8-8

List of Tables and Figures

List of Tables

Table 2-1. Studies of Fish Consumption and Coronary Heart Disease (CHD).....	2-3
Table 2-2. Studies of Fish Consumption and Other Endpoints.....	2-17
Table 3-3. Percent of energy (calories) from macronutrients based upon one day's diet which included a 150 gram serving of fish, chicken or hotdogs. ¹ (calculations based on Candat, 1994)	3-4
Table 3-1 Nutrition Values and Contaminant Levels in Fish - values for 100 g edible portion.....	3-14
Table 3-2 Nutrition Values and Contaminant Levels in Other Protein Sources - values for 100 g edible portion.....	3-18
Table 4-1. Frequency of residue presence in fish, and the number of states that have issued advisories for the chosen chemicals.	4-2
Table 4-2: Methylmercury Responses at Multiples of the Reference Dose.....	4-10
Table 4-3: Chlordane Responses at Multiples of the Reference Dose.....	4-16
Table 6-1. Relative Risks for Various Endpoints listed in Table 2-1	6-4
Table 6-2. Severity Ranking of Effects and Benefits and Resulting Multipliers for the Framework	6-7
Table 6-3. Caveats with the Use of Severity Schemes Shown in Table 6-2 for Adjusting Quantitative Information on Risks and Benefits	6-8
Table 6-4. Input Parameters To Estimate Benefits	6-22
Table 6-5. Inputs Parameters To Estimate Risks	6-23
Table 6-6. Calculation of estimated daily doses using total hair Hg data from Fleming <i>et al.</i> (1995).....	6-45
Table 6-7. Dose-response estimates for methylmercury (Price <i>et al.</i> 1997).....	6-46
Table 6-8. Dose (mg/kg-day) as a Function of Fish Consumption Rate and RfDs for Contaminants from EPA (1999).....	6-57
Table 6-9. Hazard Indices Assuming Additive Toxicity for Salmon taken from the Credit River. Calculations for Individual, all Compounds, and by Target Organ or Critical Effect. HI > 1 Indicates Possibility of Toxic Effect.....	6-57
Table 6-10. Cancer Incidence, Cancer Risk (Including Severity Factor), Benefit (Including Magnitude) and FCI for Salmon Taken from the Credit River.	6-58
Table 6-11. Dose (mg/kg-day) of chemicals detected in smallmouth bass taken from the Niagara River as a function of fish consumption (g/day).....	6-59
Table 6-12 Dose (mg/kg-day) of chemicals detected in rockbass taken from the Niagara River as a function of fish consumption (g/day).	6-59
Table 6-13. FCI at 38 g/day for Salmon Rockbass and Smallmouth Bass.	6-61
Table 6-14. Hazard Index for PCBs at 38 g/day	6-61

List of Figures

Figure 4-1. Dose-Response Curves for Methylmercury	4-9
Figure 4-2. Dose-Response Curves for Chlordane.....	4-15
Figure 6-1. Disability as a Function of Protein Intake	6-10
Figure 6-2. Disability as a Function of Target Organ Impairment.....	6-11
Figure 6-3. Relative risk as a function of intake rate and source of protein	6-12
Figure 6-4. Relative risk of benefits and toxicity as a function of different amounts of fish consumed assuming contamination with 2.1 ppm methylmercury and 12 ppm chlordane.....	6-14
Figure 6-5. Health Scale as a Function of Fish Consumption Rate	6-21
Figure 6-6. Low Concentration Carcinogen.....	6-29
Figure 6-7. High Concentration Carcinogen.....	6-29
Figure 6-8. Low Concentration Non-Cancer.....	6-30
Figure 6-9. High Concentration Non-Cancer.....	6-30
Figure 6-10. Low Concentration Cancer and Non-Cancer	6-31
Figure 6-11. High Concentration Cancer and Non-Cancer.....	6-31
Figure 6-12. Low Concentration Non-Bioaccumulative.....	6-35
Figure 6-13. High Concentration Non-Bioaccumulative	6-35
Figure 6-14. Low Concentration Bioaccumulative	6-35
Figure 6-15. High Concentration Bioaccumulative	6-35
Figure 6-16. Change in FCI as more chemicals are evaluated for health risk in fish Figure 6-16.....	6-36
Figure 6-17. Non-critical effects begin to manifest themselves at doses much greater than the critical effect.	6-37
Figure 6-18. Non-critical effects manifested at doses similar to critical effect but dose response curves are shallower.	6-38
Figure 6-19. Non-critical effects begin at doses similar to the critical effect and their dose response curves are ~ similar.....	6-39
Figure 6-20. FCI changes when cultural benefits of fish consumption are added	6-42
Figure 6-21a Estimated Risk, Benefit, and FCI for Mercury Contaminated Fish from the Everglades for the General Population.	6-49
Figure 6.21b Estimated Risk to the Fetus As a Function of Everglades Fish Consumption	6-50
Figure 6-22. Risk, Benefit, and FCI as a Function of Consumption of Salmon from the Credit River.	6-62
Figure 6-23. Total Cancer Risk and Individual Components for Salmon Taken from the Credit River.	6-63
Figure 6-24 Hypothetical Risk, Benefit, and FCI Assuming that the Shape of the Noncancer Dose-Response Curve for PCBs is the Same as that for Methylmercury for Salmon from the Credit River.....	6-64
Figure 6-25. Risk, Benefit, and FCI as a Function of Niagara River Rockbass Consumption.	6-65
Figure 6-26. Risk, Benefit, and FCI as a Function of Niagara River Smallmouth Bass Consumption.....	6-66

Figure 7-1. The risk communication process, adapted from Velicer and Knuth (1994).	7-3
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List of Abbreviations

AA	Arachidonic Acid
ADI	Allowable Daily Intake
AFS	American Fisheries Society
AOC	Areas of Concern
ARIC	Arteriosclerosis Risk in Communities
AR	Attributable Risk
ATSDR	Agency for Toxic Substances and Disease Registry
ChE	Cholinesterase
CSF	Cancer Slope Factor
B _i	Background incidence of health endpoint i
BMD	Benchmark Dose
BMDL	Lower confidence limit on a benchmark dose
BMDL ₁₀	Lower bound on dose corresponding to 10% risk (used to be explicit that the lower bound and not the maximum likelihood estimate is being used)
BMI	Body Mass Index
BMR	Benchmark Response
BW	Body Weight
CHD	Coronary Heart Disease
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CSF	Cancer Slope Factor
CSFII	Continuing Survey of Food Intakes by Individuals
DHA	Docosahexanoic Acid
DL	Detection Limit
ECG	Electrocardiogram
ED	Effective Dose
EPA	Eicosapentanoic Acid
EPA	Environmental Protection Agency
FA	Fatty Acid
Trans-FA	Trans-fatty Acid
FCI	Fish Consumption Index
FDA	Food and Drug Administration
FEL	Frank Effect Level
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
HDL	High Density Lipoprotein
HHP	Honolulu Heart Program
HI	Hazard Index
IRIS	Integrated Risk Information System
LDL	Low Density Lipoprotein
LOAEL	Lowest Observed Adverse Effect Level
MeHg	Methylmercury
MI	Myocardial Infarction
MOE	Margin of Exposure

MRL	Minimal Risk Level
NEJM	New England Journal of Medicine
NIDDM	Non-insulin-dependent diabetes mellitus
NTP	National Toxicology Program
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
PAH(s)	Polyaromatic Hydrocarbon(s)
PCB(s)	Polychlorinated Biphenyl(s)
PCDD(s)	Polychlorinated dibenzodioxin(s)
PCDF(s)	Polychlorinated dibenzofurans(s)
ppm	Parts Per Million
PUFA	Polyunsaturated Fatty Acid
QALY	Quality Adjusted Life Years
R	Risk
RQ	Reportable Quantity
RR	Relative Risk
RR_i	Relative Risk of health endpoint i at a given consumption rate
RfC	Reference Concentration
RfD	Reference Dose
RSD	Risk Specific Dose
S	Severity
S_i	Severity of health endpoint i
SFA	Saturated Fatty Acid
UF	Uncertainty factor
WHO	World Health Organization

Foreword

This document is the result of a cooperative agreement between Toxicology Excellence for Risk Assessment (*TERA*) and the U.S. Environmental Protection Agency (U.S. EPA), Office of Water. *TERA* formed a Research Team of scientists to collectively develop knowledge of problems regarding assessing health risks and benefits posed by consumption of chemically contaminated fish and determine a method to evaluate both risks and benefits together. The final outcome of this cooperative agreement is this report, which summarizes what is known about health risks from consumption of contaminated fish, health benefits from consuming fish, and general problems associated with comparisons of these risks and benefits. Moreover, this report proposes a framework for comparing the health benefits and health risks in a quantitative fashion.

The results of this research are intended to lead to a better understanding of the relative health risks and benefits of consumption of contaminated fish. The authors of this report anticipate that the proposed framework will be used by local risk managers and fish consumers to further evaluate health benefits, health risks and other dietary information on contaminated fish. Furthermore, states and tribes may use the results of this or subsequent work in assessing local conditions and developing policies towards site-specific fish consumption advisories. An Advisory Committee of state, local, tribal, industry and environmental scientists provided input during the course of this research on the design and use of the framework. This Advisory Committee reviewed a draft of this document and suggested improvements.

Funding for this work was provided by the U.S. EPA under Cooperative Agreement number CX825499-01-0 and by *TERA*. Mr. Jeffrey Bigler of the U.S. EPA Office of Water was the Project Officer. Although the information in this document has been funded in large part by the United States Environmental Protection Agency, it does not necessarily reflect the views of the Agency and no official endorsement should be inferred.

We would welcome your comments on this document. Please contact Toxicology Excellence for Risk Assessment (*TERA*) at 513-542-7475 (RISK), or tera@tera.org (e-mail).

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To conduct this research and write this document, Toxicology Excellence for Risk Assessment (*TERA*) formed a Research Team of scientists from a number of key disciplines, including risk assessment, nutrition science, environmental anthropology, medicine and public health, risk communication and toxicology. The Research Team members each contributed knowledge and inspiration from their respective fields to write or contribute to specific chapters, as well as collaborate on the quantitative framework outline.

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An Advisory Committee was formed in 1997 at the beginning of this project to provide advice and assistance to *TERA* and the Research Team by identifying target and countervailing risks, suggesting case study ideas and providing comments on the practicality and usefulness of the framework. The Advisory Committee met in February 1999 to review a draft of this document. The Committee members provided many helpful and constructive suggestions for revisions; many of which are reflected in the final document. *TERA* and the Research Team greatly appreciated the input and suggestions of the Advisory Committee. Their comments have significantly strengthened this document.

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Executive Summary

A comparative dietary risk framework (hereafter referred to as the framework) has been developed under this Cooperative Agreement for comparing the possible health risks of consuming contaminated fish, while considering the potential health benefits lost by not eating fish. The result of using the framework is a crude quantitative representation of the risk and benefit associated with eating contaminated fish. The output of the framework is referred to as the fish consumption index (FCI).

The FCI is an estimate of relative risk. It is not an estimate of absolute risk. In other words, it does not provide users of the framework with an estimate of their increased or decreased incidence of a particular health outcome. It simply provides a mechanism by which users can weigh the possible health risks versus the possible health benefits of eating contaminated fish. Cultural benefits of catching and eating fish (or detriments of not being able to fish or consume fish) may also be considered, however the current version of the framework does not attempt to quantify these benefits.

Before considering risks and benefits, a determination should be made that alternatives to contaminated fish are not available. Perhaps lower contaminated fish sources are available sufficient to maintain the individual's desired level of fish consumption. Situations where the weighing of benefits and risks may be necessary may include subsistence populations where alternatives to contaminated locally caught fish are limited.

The framework is designed to provide information for a range of fish consumption rates, allowing a user to roughly estimate the range of consumption rates at which people may have a net benefit, a net risk, and the consumption rate at which no net change in the health index would be likely. However, the suggested framework has a number of significant data gaps. These gaps are sufficiently large so as to prevent any definitive conclusions. Moreover, these gaps prevent making any overall recommendations on the existing fish consumption advisory programs of the U.S. or other countries. Further study is needed to confirm and extend the preliminary findings discussed in this document.

Use of the framework and FCI does not imply the proper choice is simply achieving a situation in which the net risks and benefits are zero. Nor is it a justification for accepting fish consumption risks as long as there is a net benefit. Rather, the framework helps make the risks and benefits transparent. Decisions about acceptable risks and distribution of risks and benefits throughout society should be made collectively by the communities affected, and are not a focus of this text. That the FCI may demonstrate cases in which fish consumption benefits may outweigh the risks is not a license to pollute. Rather, society must determine policy about long-term goals for minimizing environmental pollution based on a range of ethical, economic, social, and other criteria. Again, the purpose of this text is to discuss the underlying scientific issues associated with comparing the risks and benefits of fish consumption. It does not address the social, economic or ethical considerations.

There is some evidence for an association between decreased risk of coronary heart disease (CHD) or myocardial infarction (MI) and consumption of small amounts of fish, including

mainly lean (non-fatty) fish. In addition, other health endpoints have been examined and some research suggests that eating fish may be associated with reduced incidences or severity of a number of other endpoints. This evidence, along with the superior nutritional value of fish, is strong enough that public health officials routinely encourage the public to eat more fish.

Consuming uncontaminated fish (or at least fish that are smaller, younger, or in general less contaminated) may provide health benefits as mentioned above, but without the potential health risks associated with contamination. The eating of such “cleaner” fish rather than more contaminated fish, would maximize the net benefit of fish consumption, as we show specifically for low versus high concentrations of chemicals in fish, for those chemicals that either bioaccumulate or not, or for fish contaminated with more than one chemical.

This framework is an initial attempt to evaluate risks and benefits (qualitatively and quantitatively) on a common scale. Constructing this framework has identified numerous areas that need further research and development. Two needs seem paramount. First, better estimations of benefits are needed for the general population and its sensitive subgroups. Although information in this text is highly suggestive of the protective effects of eating fish and allows some quantification, more definitive work is needed to support or modify our chosen quantitative values. Second, better risk information is needed on the chemicals that commonly contaminate fish. Sufficient knowledge on the toxicity of most of these pollutants exists, on which noncancer risks could be quantified. Both sets of information are essential for this framework to be most effective.

1 Introduction

Toxic chemicals from point sources such as industrial or municipal discharges, and from non-point sources such as agricultural runoff have contaminated some surface waters and their sediments across the United States (U.S. EPA, 1992; Schmitt and Brumbaugh, 1990; Schmitt et al., 1990). In addition, naturally occurring chemicals such as mercury can also contaminate waters and sediments. Many of these pollutants concentrate in fish tissues by accumulating in fat or binding to muscle. These contaminants found in fish may pose health risks to people eating the fish. Those eating higher than average amounts of fish, such as sport and subsistence anglers, are at a potential greater risk from eating contaminated fish than the general population. In an effort to protect public health, state, local, and federal agencies and tribes issue fish consumption advisories, when necessary, that usually recommend limits on the number of fish meals which can safely be consumed within a specified time period (U.S. EPA, 1997a; Reinert et al., 1996; Dourson and Clark, 1990). These advisories are often issued for certain species of fish from specific bodies of water, to address local contamination.

Fish consumption advisories are the current method for consumers to gain information on health risks of contaminated fish. It is States and Tribes that issue fish consumption advisories and they use varying methods and scientific judgments in reaching their conclusions. In addition, policy issues may also be considered in setting these advisories, leading to greater difficulties for individuals trying to determine their personal risks (Kamrin and Fischer, 1999).

While these advisories are generally based solely on considerations of the potential adverse effects posed by the chemicals in fish, these same fish are an excellent source of low-fat protein and may provide additional health benefits. Some recent publications have suggested that the health benefits of eating even contaminated fish may outweigh the potential risks caused by the presence of contaminants (e.g., Anderson and Weiner, 1995).

Fish consumption advisories, however, are not regulations and compliance with the governmental advice varies (e.g., May and Burger, 1996; Knuth, 1995). It is individuals who make the decision whether and how much fish to eat. Anglers, fishery experts, and health care experts have all identified the importance of having information about how risks change with different levels of fish consumption (Velicer and Knuth, 1994). Studies have demonstrated that some anglers do respond to health risk information by changing their fishing-related behavior. Changes include eating less sport-caught fish, changing fish-cleaning methods, changing fishing locations, changing species eaten, changing the size of fish eaten, and changing cooking methods (Connelly et al., 1992). Connelly et al. (1996) provided evidence that fish consumption suppression (anglers eating less fish than they would in the absence of health advisories) was prevalent among Lake Ontario anglers.

Studies of licensed anglers have indicated the perceived importance of health advisory information on potential health benefits and risks associated with fish consumption. These same studies also note that anglers recognize the importance of how risks change as more or less fish is eaten, and compare the health risks of eating fish with the risks from other protein sources (e.g., Connelly et al., 1992; Connelly and Knuth, 1993).

Evaluating the potential risks (and benefits) requires information on contamination levels and consumption rates. Surveys of anglers and their families have shown that rates of fish consumption vary widely among subpopulations by race or ethnicity, age, sex, income, fishing mode, region of the country and other demographic variables (CAL EPA, 1997). For example, regional surveys of sport fishing populations report overall mean rates for consumption of sport fish ranging from 12.3 to 63.2 g/day (CALEPA, 1997), while U.S. EPA estimates a fish consumption rate for the general population for all fish of 20.1 g/day (uncooked weight) (U.S. EPA, 1997b). Studies among tribal and subsistence fishing populations have found much higher levels of consumption (see for example Toy et al., 1996, CALEPA 1997 and U.S. EPA, 1997b). This wide variability in consumption rates and patterns reinforces the necessity of evaluating fish pollutants and consumption on a case-by-case or local basis.

While contaminants in fish pose a public health risk, fish is also an excellent source of protein and provides additional health benefits not available from other foods. It has been recognized for over a decade that a need exists to evaluate the benefits of fish as a food source, as well as the risks from contaminants, when setting fish consumption advisories (CDHS, 1988; Kimbrough 1991; Egeland and Middaugh, 1997). The California Department of Health Services sponsored a workshop in 1988 called "Balancing the Scales: Weighing the Benefits and Risks of Fish Consumption." Speakers addressed the nutritional composition of fish, cardiovascular effects from n-3FA and benefits of fish oil consumption, along with exposures and health risks. Over ten years later there is more scientific data on potential health benefits of eating fish. Putting risks into perspective is even more important when the fish are a part of a traditional subsistence diet, which is important to a group's cultural identity (Egeland et al., 1998). In addition, for some communities, alternate foods are not readily available or affordable.

The need to consider the beneficial aspects of fish consumption has also been recognized by the Federal-State-Tribal Fish Forum sponsored by EPA (AFS, 1997). This group of federal, state and tribal scientists and public health officials has identified consideration of benefits from fish as one of their top issues needing research and guidance. The research discussed in this document is a direct result of this group's request.

When advisories are issued and suggestions made to reduce consumption of contaminated fish, individuals may respond in a number of ways. They may follow the fish advisory and reduce their consumption of that particular type of fish, they may reduce exposure to contaminants by selecting a less-contaminated fish or preparation method, they may stop eating fish, or, they may ignore the advice and eat without regard to the advisory. Ideally, by selecting and eating the least contaminated species, one can enjoy fish and its benefits without the health risks of contaminants. However, if individuals do reduce their consumption of contaminated fish and replace it with other non-fish foods; depending on the food choices made, these dietary changes may not reduce overall health risks and may actually result in greater overall health risks. Situations of subsistence populations, who have limited alternatives to a contaminated fish source, may encounter this dilemma of needing to weigh the benefits and risks. To fully evaluate the risks and benefits, one needs to examine the target risk - that is the adverse health effect from eating fish with chemical contaminants - as well as the countervailing risks, such as the consequences of reducing fish consumption and the potentially reduced nutritional or health benefits of the substituted foods.

Graham and Wiener explore the issues of target and countervailing risks for a number of public health issues in their book *Risk vs. Risk: Tradeoffs in Protecting Health and the Environment* (1995). For example, if a fish consumption advisory recommends reducing consumption of fish contaminated with a particular chemical, and

- the fish in the diet is replaced with a large amount of fruits and vegetables, the consumer may trade a decreased cancer risk from contaminants in fish (the target risk, i.e., the risk the advisory is designed to reduce) for an increased cancer risk from increased ingestion of anthropogenic and natural pesticides (the countervailing risk, i.e., the risk that may increase as a result of the advisory).
- the fish in the diet is replaced with red meat, the consumer may be trading a decreased risk of mortality from cancer (target risk) for an increased risk of mortality from heart disease (countervailing risk), due to an increased consumption of saturated fat.
- the consumption of local fish high in PCBs, such as salmon, is replaced with an increased consumption of canned tuna high in methylmercury, the consumer may be trading increased risk of developmental toxicity and cancer from PCBs (target risk), for an increased risk of neurological disease from methyl mercury (countervailing risk).

In one chapter of this book Anderson and Wiener (1995) concluded that the protective effect of increasing fish consumption on chronic heart disease far outweighed the increased cancer risk posed by contaminants in fish. Using U.S. EPA's cancer slope factors and assuming that fish contained the FDA limits of 6 common fish contaminants¹, Anderson and Wiener (1995) found that the cancer risk associated with eating 1 gram of fish per day for a 70-year lifetime was 5×10^{-4} . Based on their analysis, increasing consumption of fish from 0 to 40 grams per day would increase the average American's risk of dying by 2 percent from cancer². However, the same increase in fish consumption would decrease the average American's risk of dying from heart disease by 35 percent. Thus, public health officials and consumers might want to evaluate a broad range of dietary information before making decisions regarding consumption of contaminated fish.

Countervailing risks can go beyond the health implications of food substitutions and include social, economic, religious and cultural impacts (Wheatley and Paradis, 1996). Harris and Harper (1997) have explored how to evaluate impacts other than direct risk to health. They have developed a Native American exposure scenario that identifies parameters for evaluating countervailing impacts on cultural and religious activities. These may affect quality of life, which in turn impacts both individual and community health and well-being.

The direct benefits of fish consumption can be thought of as arising from two sources. The first relates to the change in the incidence of a particular health outcome as related to fish consumption rate (e.g., decrease in heart disease with increasing fish consumption). The results

¹ Chlorpyrifos, Chlordane, DDT, Dioxin, PCBs and Methylmercury

² Anderson and Weber (1995) recognized that EPA's cancer risk method predicts upper bound incidence of cancer, but assumed that cancer incidence was the same as cancer mortality in order to err on the side of protecting public health

of these studies can be used to derive a dose-response relationship between fish consumption rate and the health outcome being investigated (within limits imposed by the data). The second relates to how general nutritional status changes as fish is substituted for some other source of protein or is removed from the diet.

There is some evidence for an association between decreased risk of coronary heart disease (CHD) or myocardial infarction (MI) and consumption of small amounts of fish, including mainly lean (non-fatty) fish. In addition, other health endpoints have been examined and some research suggests that eating fish may be associated with reduced incidences or severity of a number of other endpoints. The possible benefits in the form of reduced risk of particular diseases are discussed in Chapter 2.

There are many nutritional benefits associated with eating fish, regardless of the species type. Perhaps, unlike red meats, eggs and dairy products, fish provides very high quality protein and a "heart healthy" combination of fatty acids. Further, fish (both lean and fatty) is one of the few foods that contain omega-3 (n-3) fatty acids, a class of fatty acids that are essential for the development of the nervous system and that may have other beneficial health effects. Fish supplies a number of vitamins and minerals that tend to be low in the U.S. diet, including calcium, iron, zinc, vitamin A, niacin, vitamin B6 and vitamin D, in addition to others. The nutritional advantages of fish compared to other protein sources are discussed in Chapter 3.

Fish consumption advisory programs have traditionally focussed on assessing the potential human health risks from eating contaminated fish and estimating safe consumption limits. Chapter 4 discusses potential health risks for a number of common contaminants and discusses the methods for estimating risk used later in this document.

Food, and fish in particular, may also be an important part of a culture, serving economic, social, aesthetic, and religious functions. Specific foods are often seen as having special nutritional or medicinal qualities, and methods of food preparation are frequently part of one's cultural identity. These cultural factors may need to be considered in evaluating risks and benefits from consumption of contaminated fish for some subpopulations. Chapter 5 outlines the social and cultural importance of fish to particular groups of people.

Chapter 6 develops the comparative dietary risk framework which compares the possible health risks of consuming contaminated fish, while considering the potential health benefits lost by not eating fish. Example outputs using hypothetical data and two case studies with actual exposure scenarios are also included. The result of using the framework is the fish consumption index (FCI), which is a crude quantitative representation of the net risk (or benefit) associated with eating contaminated fish. It provides a mechanism by which users can weigh the possible health risks versus the possible health benefits of eating contaminated fish. Cultural benefits of catching and eating fish (or detriments of not being able to fish or consume fish) may also be considered, however the current version of the framework does not attempt to quantify these benefits.

Because of the data intense process and results of the FCI, a solid risk communication program is necessary to insure successful usage of the information generated. Chapter 7 summarizes key

elements of the risk communication process as applied to the comparative dietary risk framework, emphasizing that risk communication is a process of information exchange between the target audience and the risk communicator. Although the framework provides a mechanism for comparing risks and benefits associated with fish consumption, it is not a justification for accepting fish consumption risks as long as there is a net benefit. Decisions about acceptable risks and distribution of risks and benefits throughout society is a social decision, to be made collectively by the communities affected. Rather, the framework helps make the tradeoffs between risks and benefits more transparent.

When alternatives to consumption of contaminated fish are not available or desired, it may be appropriate to weigh the risks of eating less contaminated fish with the benefits gained from eating more of these same fish. The framework developed here can crudely compare these risks and benefits. However, this framework has a number of significant data gaps, which are discussed in Chapter 8. These gaps are sufficiently large so as to prevent any definitive conclusions from this study or any overall recommendations regarding existing fish consumption advisory programs of the U.S. or other countries. Further work is needed to confirm and extend these preliminary findings.

The purpose of the current research is to develop an understanding and framework by which to evaluate the comparative risks posed by dietary changes as a result of fish consumption advisories. This research builds upon previous work from a series of documents developed by the U.S. EPA on "Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories." The four-volume set includes Volume 1-Fish Sampling and Analysis (1995a), Volume 2-Risk Assessment and Fish Consumption Limits (1997a), Volume 3-Overview of Risk Management (1996), and Volume 4-Risk Communication (1995b). The results of this research can lead to a better understanding of the effects that fish consumption advisories have on diet and public health. We anticipate that public health officials and consumers may use this increased understanding to evaluate a broad range of dietary information before making decisions about whether or not to eat contaminated fish.

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2 Health Benefits From Eating Fish

2.1 Introduction

In addition to providing high quality protein, essential fatty acids, and other nutrients required daily in the human diet (discussed in Chapter 3: *Nutritional Benefits of Eating Fish Compared to Other Protein Food Sources*), fish consumption is also associated with certain health endpoints over the longer term. This chapter provides a brief overview of health endpoints that have been shown, or are hypothesized, to be associated with fish consumption. In some cases the weight of evidence supports the relationship between eating fish and a lowered risk of disease (e.g., coronary heart disease or CHD). For other health endpoints, the link is more controversial (e.g., arthritis) and more research studies are needed. This report refers to the changes in health endpoints associated with fish consumption as benefits, because they generally involve a reduction in the risk of chronic disease. The chapter begins with an overview of the major studies that have examined the association between fish consumption and CHD, both those studies that have found associations and those which have not. It then continues with a brief description of studies that have looked at fish consumption in relation to several other endpoints.

The concept that eating fish may reduce the risk of CHD apparently originated from reports on the small population of non-acclimated Eskimos in arctic Greenland, where high consumption of marine animals (e.g., seal, fish) was observed (Bang *et al.*, 1971, 1980). It was claimed that coronary rates were low, but available data were – and remained – limited and tenuous. The inhabitants of the Japanese island of Okinawa were also observed to have low CHD mortality rates, and they too consume high amounts of fish (Kagawa *et al.*, 1982). The "Seven Countries Study" (Keys, 1980) conducted by Dr. Keys found that rates of CHD and myocardial infarctions (MI) were lower in southern Italy, Spain and Greece than rates in the United States, the Netherlands, and other countries. This raised the question of whether the Mediterranean diet, which includes fish, red wine, olive oil, nuts and legumes, was partly responsible for the findings.

These observations prompted epidemiologic investigations -- the first from the Netherlands (Kromhout *et al.*, 1985) -- on the relationship of fish consumption to CHD and MI. When the results of the long-term, prospective studies became available in the mid-1980s and 1990s, they provided strong evidence that higher levels of fish consumption among middle-aged men, free of CHD at baseline examination, were associated with a lower risk of mortality from CHD. Early hypotheses on the protective biological mechanism of fish consumption focused on the very long chain, polyunsaturated fatty acids of the omega-3 class (n-3 FA), since fish are one of the few good dietary sources of these types of fatty acids. It was thought that the n-3 FA of fish contributed to more healthful ratios of blood lipids (fats, including cholesterol), and this reduced one of the major risk factors for CHD: high blood levels of cholesterol and saturated fats. Later studies focused on the factors that cause blood platelets and other materials to clump together and deposit on the inside of artery walls, and specifically, the role that n-3 FA have in the synthesis of prostaglandins, which reduce platelet aggregation.

The American Heart Association has issued a statement regarding fish consumption, fish oil, lipids, and CHD. The primary focus of this statement, however, is on the evidence of health

benefits from n-3 FAs. It concludes that it is premature to recommend general usage of fish oil supplements at this time, but that the "inclusion of marine sources of the n-3 PUFA in the diet seems reasonable because they are good sources of protein without the accompanying high saturated fat seen in fatty meat products" (American Heart Association 1996). For reasons that will be discussed further in this section, it is unlikely that n-3 FA are the primary factor responsible for the observed association between fish consumption and lowered risk of CHD.

In addition to the relationship between fish consumption and sudden death from CHD and MI, other health endpoints have been examined. Scientists have investigated possible associations between eating fish and inflammation-related diseases such as rheumatoid arthritis, since the n-3 FA in fish oils are believed to have anti-inflammatory effects (reviewed by Simopoulos, 1991). Relatively few studies have been done, however, and their findings are still controversial. Other research has suggested that eating fish may be associated with reduced incidences or severity of asthma, psoriasis, gastrointestinal diseases, as well as lung damage caused by smoking. (Of course, even if fish consumption does protect against these diseases, it may exert its protective effect through mechanisms other than the reduction of inflammation by n-3 FA.) Recently, possible associations between fish consumption and other health endpoints for pregnant women, unborn babies and young infants have been reported. For example, there is evidence that consuming substantial amounts of fish during pregnancy may lengthen gestation (Olsen, Hansen & Sorensen, 1986), thereby resulting in higher birthweights. The n-3 fatty acids that fish provide have important roles in the development of the retina, brain and other central nervous system tissues in the unborn and infant (up until 12 months of age), as well.

The following sections briefly review available results of research on the association between fish consumption and several endpoints, and the possible health benefits of eating fish for adults, pregnant women, developing fetuses and infants. The nutritional contributions of fish to the diets of children are also highlighted.

2.2 Health Benefits Associated with Fish Consumption

2.2.1 Coronary Heart Disease (CHD) and Myocardial Infarction (MI)

Table 2-1 presents a summary of the samples, designs and main findings of 13 published reports examining the association between fish consumption and CHD. Studies 1 to 9 and study 13 are prospective studies, a strong epidemiological study design in which individuals who have no observable symptoms of CHD are categorized according to their level of fish consumption, and then followed for long periods of time to observe who later develops CHD and who does not. Studies 10 and 11 are case-control designs, whereby those who already have CHD are matched on important characteristics with those who do not, and retrospective information about their diets is collected. Study 12 is a randomized, controlled, clinical trial, the only study included here that contains an intervention. A brief summary of the findings of each of these 13 reports follows the table.

Table 2-1. Studies of Fish Consumption and Coronary Heart Disease (CHD) {PRIVATE }

Study, Country, Type of Study, Reference No.	Year of Baseline & Follow-Up Duration	No. of Participants, Gender, Baseline Ages, Background	Diet Assessment Method	Stratification of Fish Intake (no. or % of persons, or person-years)	CHD End Points, Number of Events	Main Findings, Fish Intake and CHD
1- Zutphen, The Netherlands, prospective epidemiologic (Kromhout <i>et al.</i> , 1985)	1960 20 years	852 men ages 40-59; urban community general population	in-depth cross-check diet history	0 g/d (159), 1-14 (283), 15-29 (215), 30-44 (116), ≥ 45 (79), mean: 0, 8, 22, 36, 67 g/d, about 2/3 lean fish	CHD death; 78 deaths	significant independent inverse relationship; RR values for strata: 1.00, 0.60, 0.57, 0.46, 0.42, p for trend <0.05
2- Rotterdam, The Netherlands, prospective epidemiologic (Kromhout <i>et al.</i> , 1995)	1971 17 years	292 men and women (137 & 135) ages 64-85; urban general practitioner's list	in-depth cross-check diet history	non-consumers (about 40%) and consumers; for latter, mean: 24 g/d (21.6 g/d lean fish)	CHD death; 58 deaths	significant independent inverse relationship; RR = 0.51, 0.41 for men, 0.64 for women; no relation of fish intake to all causes death (RR = 0.96)
3- Swedish Twins, prospective epidemiologic (Norell <i>et al.</i> , 1986)	1967-68 14 years	10,966 men and women ages 40-70; nationwide population-based twin registry	self-administered questionnaire	none (few people) + low (12,315 p-y), moderate (70,848 p-y), high (57,084 p-y)	CHD and MI death; 800 and 395 deaths	CHD: age-sex adjusted RR (95% CI) -- 1.00, 0.94 (0.83-1.06), 0.85 (0.69-1.06); MI 1.00, 0.91 (0.76-1.08), 0.70 (0.50-0.98); results similar with multivariate adjustment, and for 2 sexes separately

Table 2-1. continued

Bergen, Norway, prospective epidemiologic (Norell <i>et al.</i> , 1986)	1967 14 years	11,000 men, 65% ages 55+, 30% ages 65+; urban community general population	postal questionnaire, including 3 questions on fish intake	Fish index approximating no. of times fish eaten/month; 0-4 (642), 5-9 (2242), 10-14 (4412), 15-19 (1726), 20-24 (1497), ≥ 25 (482)	CHD and MI death before age 80; 967 CHD deaths, 301 in healthy subcohort, 22 in men ages <45 at entry	CHD, MI (also all causes death): no relationship; for men ages <45 at entry, inverse relationship, fish and CHD death, $p = 0.058$
4- Honolulu Heart Program, Hawaii, U.S.A., prospective epidemiologic (Curb <i>et al.</i> , 1985)	1965-68 12 years	7,615 Japanese-American men ages 45-68; urban community general population	questionnaire on usual frequency of eating various foods; 24-hour dietary recall	from usual frequency questionnaire: almost never (32), <2 times/wk (4143), 2-4 times/wk (2884), almost daily (545), >once/day (10); from 24-h recall: 0 g/d (4232), 28-56 (1374), 84-112 (1092), 140-168 (505), >168 (412)	CHD incidence and CHD death; nos. of events not stated	no significant relationships

Table 2-1. continued

5- Adventist Health Study, California, U.S.A., prospective epidemiologic (Fraser <i>et al.</i> , 1992)	1976 6 years	26,473 non-Hispanic white Californian Seventh-Day Adventists ages 25+, 10,003 men, mean age 51, 16,470 women, mean age 53	65-item semi-quantitative food frequency questionnaire mailed to cohort	never (43%), <1/wk (47%), ≥1/wk (10%)	Definite Nonfatal MI, 134 events; Definite Fatal CHD (clinical, autopsy-based), 260 deaths; Fatal CHD (death certificate), 463 deaths	multivariate adjusted RR: 1.00, 1.11 (0.75-1.66), 1.04 (0.55-1.96); 1.00, 1.01 (0.76-1.35), 0.74 (0.42-1.33); 1.00, 1.10 (0.89-1.37), 1.09 (0.73-1.61)
6- Physician's Health Study, U.S.A., prospective epidemiologic (Morris <i>et al.</i> , 1995)	1982 4 years	21,185 U.S. male physicians nationwide, ages 40-84, free of history of major disease	self-administered semi-quantitative food frequency questionnaire	<1 meal/wk (4,501), 1 (8,156), 2-4 (7,455), ≥5 (1,073)	nonfatal MI and all MI; 259 and 281 events (i.e., 22 MI deaths)	multivariate adjusted RR, nonfatal MI: 1.0, 1.4, 1.2, 0.8; all MI 1.0, 1.5, 1.3, 0.9 -- nonsignificant; p for trend 0.78, 0.72

Table 2-1. continued

7- Physician's Health Study, U.S.A., (Albert <i>et al.</i> , 1998)	12 years	20,551 U.S. male physicians from above cohort	same	<1 meal/month and 1+; also, <1, 1-3, 1-<2/wk, 2-<5/wk, 5+wk	sudden death (within 1 hour of symptom onset); 115 deaths	<1 vs. 1+ meal/month: unadjusted RR 0.44 (0.22-0.91), p 0.03; multivariate adjusted RR 0.51 (0.25-1.05), p 0.07; age-adjusted RR for 5 strata: 1.00, 0.71 (0.29-1.77), 0.44 (0.20-0.94), 0.43 (0.15-0.98), 0.39 (0.15-0.98)
8- Health Professionals Follow-Up Study, U.S.A., prospective epidemiology (Ascherio <i>et al.</i> , 1995)	1986 6 years	44,895 male health professionals nationwide, ages 40-75, free of known CVD	self-administered semi-quantitative food frequency questionnaire	servings of fish <1/month, 0 g/d (2,042); 1-3/month, 7 g/d (3,314); 1/wk, 18 g/d (12,296); 2-3/wk, 37 g/d (16,920); 4-5/wk, 69 g/d (6,271); ≥6/wk, 119 g/d (4,052)	fatal CHD (264), nonfatal MI (554), any MI (811), CABG (735), any CHD (including CABG) (1543)	for fatal CHD, multivariate adjusted RR 1.00, 0.74, 0.86, 0.71, 0.54, 0.77, all 95% CIs include 1.00; for RR 0.54, 95% CI 0.29-1.00; p for trend 0.14; for CABG, 1.0, 1.31, 1.43, 1.40, 1.71, 1.65; all 95% CIs include 1.00; p for trend 0.02; for other end points, no significant relationship

Table 2-1. continued

9- Northern Italy hospital-based case-control study (Gramenzi <i>et al.</i> , 1990)	Jan. 1985-Feb. 1989	287 women ages 22-69 with MI identified in CCUs of 30 hospitals; 649 controls ages 21-69, in-hospital with acute disorders other than CHD	interview with use of structured questionnaire on frequency of consumption of individual foods and beverages	tertiles of portions consumed per week: <1, 1, >1- - for cases: 148, 81, 58; for controls: 270, 220, 159	nonfatal MI	age-adjusted odds ratio: 1.0, 0.7, 0.6, p <0.05
10- Seattle and suburban King Co., Washington case-control study (Siscovick <i>et al.</i> , 1995)	Oct. 1988 to July 1994	334 men and women with primary cardiac arrest, ages 25-74, mean age 59, 80% men, 493 population-based controls, age-sex matched	quantitative food frequency questionnaire, including 25 fish and 10 shellfish, consumption during prior month; spouse as proxy respondent	no seafood intake, and quartiles of long-chain n-3 polyunsaturated fat intake, equivalent to 0 servings/month of fresh salmon (0 g/m), 0.6 (15g), 2.0 (45g), 3.7 (84g), 9.1 (207g)	primary cardiac arrest	multivariate adjusted odds ratio (OR): 1.0, 0.9 (0.8-1.0), 0.7 (0.6-0.9), 0.5 (0.4-0.8), 0.4 (0.2-0.7)

Table 2-1. continued

11-DART secondary prevention randomized controlled trial, Wales, U.K., factorial design (Burr <i>et al.</i> , 1989)	2 years	2,033 men <70 years old, recovered from acute MI, diagnosed at 21 hospitals, randomly assigned to 1 of 8 groups, with no dietary advice, fat modification, increased fiber intake from cereals, increased intake of fatty fish	dietary counseling	1015 men, randomly assigned, asked to consume at least 2 portions per week (200-400 g) of fatty fish, plus advice on 2, 1, or no other dietary factors; intake of eicosapentanoic acid estimated for 2 groups to be 2.3 & 0.7 g/week	nonfatal + fatal CHD, fatal CHD	for CHD incidence end point, multivariate adjusted RR 0.84, 95% CI 0.66-1.07; for CHD death, unadjusted RR = 0.68, $p < 0.01$; for all causes death, 0.71 (0.54-0.93), $p < 0.05$
12- Chicago Western Electric Study, U.S.A. (Davignus <i>et al.</i> , 1997)	1957-58 30 years	1,822 men ages 40-55; urban workers	in-depth cross-check diet history	0 g/d (189), 1-17 (646), 18-34 (745), ≥ 35 (245)	Fatal CHD, (430), fatal MI (293), nonsudden death (> 12 hours of symptom onset)	significant independent inverse relationships; for fatal CHD, RR 1.00, 0.88, 0.84, 0.62, p for trend 0.040; for fatal MI, RR 1.00, 0.88, 0.76, 0.56 p for trend 0.017; for nonsudden MI, RR 1.00, 1.04, 0.76, 0.33, p for trend 0.007

2.2.1.1 Kromhout, Bosschieter and Coulander, 1985. "The Zutphen Study" (1)

This was the first prospective study to create great interest in the topic of fish consumption and CHD risk reduction. The investigators followed 852 men for 20 years; there were 78 CHD deaths with 100% follow-up. The results showed an inverse relationship between the amount of fish reported and the relative risk of death from CHD ($p < 0.05$). This association held even for the group reporting the lowest fish consumption (at 1-14 grams of fish/day, $RR = 0.6$, i.e., only 60% of the risk of death from CHD compared to the group which didn't eat fish.) A limitation of this study (and prospective cohort studies in general) is that it assumes the usual rate of fish consumption remains relatively unchanged over the period studied.

Up until this study was released, it was believed that the protective effects were associated with eating very large amounts of cold-water fatty fish and marine mammals, based on studies of Eskimo and Inuit populations. The Zutphen study was a landmark in three respects: it demonstrated that (1) eating as little as one or two meals of fish each week was associated with a lower risk of heart disease; (2) this was a dose-response relationship (the higher the usual fish consumption, the lower the risk of death from CHD); and (3) the effects could be obtained with lean fish (two-thirds of the fish eaten by this Dutch sample were lean fish such as cod) as well as fatty fish.

2.2.1.2 Kromhout, Feskens and Bowles, 1995. General practice patients in Rotterdam, the Netherlands. (2)

This study was undertaken in 1971 in an elderly population in Rotterdam, the Netherlands. Men and women ($n = 282$) born before 1907 were recruited from a general practice, and followed for 17 years. Dietary information, body mass index (an indication of body fatness), blood pressure, serum lipids, and smoking were recorded at baseline. The status of the study population was checked in 1988, and for those who had died, both primary and secondary causes of death were used because they can be difficult to distinguish in an elderly population.

The prevalence of myocardial infarction (MI) was higher ($p < 0.05$) among the group of men who ate no fish, compared to the group which consumed fish ($OR = 0.34$). A similar association between fish consumption and risk of MI was seen in all female participants. The risk of dying from CHD was also less than half for the group who consumed fish compared to those who did not ($RR = 0.47$). Survival analyses indicated that the difference in CHD mortality between fish eaters and non-fish eaters became evident after 5 years of follow-up. When men and women were separated in the analysis, the difference in RR was not significant. The results of this study showed an inverse relationship between fish intake and CHD mortality in an elderly population of men and women, an association previously reported with middle-aged men.

2.2.1.3 Norell, Ahlbom, Feychting, and Pedersen, 1986. "Swedish Twins" (3)

In this letter to the editor of the British Medical Journal, Norell and colleagues provided data on 10,966 Swedish men and women who had no angina, myocardial infarctions or other history of CHD in 1967, who had participated in a 14-year prospective study of twins. Information on fish consumption was collected using a self-administered questionnaire, and the subjects were then

classified as high, moderate or low fish consumers based on ratios of average amounts of fish eaten in relation to other foods. Individuals who reported that they did not eat fish were included in the "low consumption" group, a limitation of this study. By combining the "unexposed" subjects and "low exposure" subjects into one statistical group, this "may have led to an underestimation of the strength of the inverse relation between fish consumption and death from MI and CHD" (p.426).

The results showed that 800 people died of coronary heart disease, 395 of whom had fatal myocardial infarctions. When the relative risk of death from each was calculated, controlling for gender and age, there was a dose-response relationship: those in the highest category of fish consumption had a relative risk of .85 for CHD death, and .70 for MI death when compared to the low/no fish group. The investigators report that when the data were controlled using multivariate analysis techniques the results were similar.

2.2.1.4 Vollset, Heuch and Bjelke, 1985. "Norway Postal Dietary Survey" (4)

In a letter to the editor of the New England Journal of Medicine, Vollset and his colleagues reported findings from a subset of 11,000 middle-aged and older men from their Norwegian prospective study, who were followed for 14 years. These men reported their smoking and "selected cardiovascular symptoms" in 1964, and their fish consumption in 1967. The investigators used the latter information to construct "a fish index approximating the number of times fish was eaten per month" (p.820). Overall, there were 967 deaths, 301 of which were due to fatal myocardial infarctions. The distribution of deaths observed, according to six categories of number of fish meals per month, was not significantly different from the predicted distribution. When the analyses excluded men who had reported CHD symptoms (such as angina) in 1964 and used only data from the 301 who died from acute MIs, there was still no significant relation between fish consumption and CHD death. However, the analyses did not control for a number of possibly important confounding factors (e.g., level of physical activity level, body fatness, high blood pressure, parental history of early death from CHD, diabetes mellitus, etc.).

2.2.1.5 Curb and Reed, 1985. "Honolulu Heart Program" (5)

The NEJM letter by Vollset and colleagues was followed by another letter to the editor reporting the relationship between fish consumption and CHD. Curb and Reed provided the results of a 12-year study following 7,615 Japanese men participating in the Honolulu Heart Program. The ages of the men upon enrolment into the study were not given, but the men were "without prevalent atherosclerotic disease". The results showed few differences in the rates of CHD and of fatal CHD across the categories of frequency of fish meals and amounts eaten in the previous 24 hours, and there were no statistically significant trends. The authors did not mention if they controlled for other risk factors for CHD in their analyses. Given that this population had high mean levels of fish consumption (--44% reported eating fish during the previous 24 hrs, with portion sizes ranging from 28 to 476 grams--) with few subjects reporting that they never ate fish (n=32) compared to other similar studies, the authors wondered if "maximal benefit" from fish consumption was already being obtained.

2.2.1.6 Fraser, Sabate, Beeson, and Strahan, 1992. "The Adventist Health Study" (6)

A cohort of 26,473 non-Hispanic Caucasian Seventh Day Adventists aged 25 years or older in 1974, was followed for 6 years. The sample was well educated and concerned about health; participants tended to abstain from smoking and the use of alcohol, and follow lacto-ovo-vegetarian diets (i.e., diets that include dairy products and eggs, but exclude meat, fish and poultry). The criteria for participation in this study were stricter than most previously conducted: those with a known history of heart disease, or whose history for CHD had not been assessed, as well as individuals with diabetes, were excluded. Baseline data were collected using a mailed self-administered questionnaire in 1976, and unlike other prospective studies, yearly data on hospital admissions (with access to medical records) and the development of CHD symptoms were also collected. Death due to CHD was strictly defined and three end-points were used: definite nonfatal MI (134 events), definite fatal MI (260 cases), and confirmed fatal CHD (463 cases).

The adjusted relative risks from multivariate analyses for three levels of fish consumption (none, less than once/week, once a week or greater) suggested protective effects for those consumers eating fish once a week or more, only for death from MI (adjusted RR = 0.74; 95% C.I. = 0.42-1.33). The group eating fish less than once a week had similar adjusted relative risks to the group eating no fish, for all 3 end-points. Given that only 10% of the largely vegetarian sample ate fish once a week or more, and that the sample was followed for only 6 years and was still relatively young (mean age of 51.3 years for men and 53.2 years for women), these effects may have been underestimated.

2.2.1.7 Morris, Manson, Rosner, Buring, Willett and Hennekens, 1995. "The US Physicians' Health Study: 4 years" (7)

This prospective study followed 21,185 U.S. physicians aged 40-84 years, with no history of MI or other cardiovascular disease, cancer, liver or renal disease, peptic ulcer, gout or use of certain drugs (including aspirin), from 1983 to 1987. As with the previous study, information on CHD symptoms was collected annually. What is different from other prospective studies, however, is that annual information was also collected on fish consumption, foods high in saturated fats, and parental MI events; as well, use of aspirin and beta-carotene were controlled for in analyses. Several CHD endpoints were used, along with all stroke events, and these were confirmed by ECG and enzyme test records, other patient records or autopsy. The relative risk values for all cardiovascular and stroke events (fatal and nonfatal) for subjects who ate 1 meal, 2-4 meals, and 5 or more fish meals per week were not significantly different from values for subjects who ate less than 1 meal of fish weekly, and there were no statistically significant trends across the four levels of fish consumption. The number of subjects at each level of fish consumption for each of the cardiovascular disease outcomes was relatively small, though (e.g., stroke and cardiovascular deaths each had only 7 subjects who consumed 5 or more fish meals per week), and some confidence intervals were wide (e.g., 95% CI = 0.8-5.9). As with the Swedish Twins Study above, grouping low consumers with consumers who never ate fish may have underestimated the benefits of eating modest amounts of fish (one or two meals weekly, such as in the Zutphen Study). As well, four years is a relatively short period of follow-up.

2.2.1.8 Albert, Hennekens, O'Donnell, Ajani, Carey, Willett, Ruskin and Manson, 1998. "The US Physicians' Health Study: 12 years" (8)

This was a continuation of the previous study, and examined the association between fish consumption and the risk of sudden cardiac death in men over an 11-year period. Eighty percent of the sample consumed fish between 1 and 4 times/week; the high fish consumers tended to be those who were at risk for cardiovascular disease (e.g. family history of CHD) and, being physicians, were aware of this risk. After controlling for age, and aspirin and beta carotene use, risk of sudden cardiac death was inversely related to fish consumption, and showed a significant decline ($p < .05$) across the five levels of fish consumption. Physicians who ate 1-2 fish meals/week had a significantly lower risk ($RR=0.42$, $p=0.02$) of sudden death compared to those who ate fish <1 /month. The magnitude of difference in risk did not change significantly with higher consumption, suggesting a threshold effect. After adjusting for coronary risk factors and prior cardiovascular disease, the decline in risk was no longer significant across the five categories of fish consumption but remained significant across three of the categories (<1 /month, 1-3/month, and ≥ 1 /week). Although fish consumption was inversely associated with sudden cardiac death, it was not related to non-sudden cardiac death, risk of coronary heart disease or total cardiovascular death.

2.2.1.9 Ascherio, Rimm, Stampfer, Giovannucci and Willett, 1995. "The Health Professionals Follow-Up Survey" (9)

This six year prospective study followed a cohort of 44,895 male health professionals who were aged 40 to 75 in 1986. Men who reported MI, angina, stroke, transient ischemic attack, peripheral artery disease, coronary artery surgery, diabetes, high blood pressure, high blood cholesterol, or who knew their blood cholesterol at baseline (and thus may have altered their lifestyles or diets to reduce their 'high risk'), were excluded from analyses, as were men who had CHD events during the first 4 years of follow-up. Questionnaires were sent every 2 years to ask for recent information on CHD events. Follow-up was complete for 94% of subjects. Endpoints were fatal CHD, nonfatal MI, coronary-artery bypass grafting (CABG) and angioplasty, and were confirmed using international criteria, patient records (ECG & cardiac enzyme results), and autopsy in addition to death certificates.

This study assessed the association of both fish intake and n-3 FA intake in relation to CHD endpoints. For analyses, fish intake was divided into 6 categories ranging from less than once per month ($n=2,042$) to 6 or more times weekly ($n=4,052$) with sufficient numbers of subjects in each category for multivariate analyses by CHD endpoints. No association was found between n-3 FA intake or fish oil supplements and risk of CHD disease. Compared with men who ate little or no fish (less than 1 serving per month), the relative risk of fatal CHD (after adjusting for many potential confounders) for men who ate fish 1 to 3 times a month was 0.74. This relative risk remained fairly constant as fish consumption increased (ranging from 0.86 to 1 meal/week to 0.54 for 4-5 meals/week) but confidence levels were very wide. These results suggest that as little as one fish meal a week could have a protective effect against death from CHD, and increasing fish consumption above this would likely not confer additional benefits. For other CHD endpoints, there were no apparent relationships with fish consumption, and the authors

suggested that eating fish might reduce the likelihood of death from a myocardial infarction but not reduce the risk of a MI event.

2.2.1.10 Gramenzi, Gentile, Fasoli, Negri, Parazzine and La Vecchia, 1990. (10)

This retrospective case control study matched 287 Northern Italian women aged 22 to 69 years who had suffered acute myocardial infarctions, with 649 controls hospitalised for conditions unrelated to CHD, cancer, smoking, alcohol, or digestive, hormonal, or reproductive disorders. The investigators relied upon participants' assessments of their level of fish consumption (low, intermediate, high consumption). Age adjusted odds ratios using 'less than 1 fish meal weekly' as the reference category showed that the risk of MI was 0.7 for those eating 1 fish meal per week, and dropped to 0.6 for more than 1 fish meal weekly; this trend was statistically significant at $p < 0.05$.

2.2.1.11 Siscovick *et al.*, 1995. Case-control Study in Seattle and King County, Washington. (11)

In this case control study, the association between dietary intake of long-chain n-3 fatty acids from seafood and risk of cardiac arrest was examined, based on cases of out-of-hospital primary cardiac arrests. Cases ($n=334$) were identified by paramedics (death certificates, and medical examiner and autopsy reports were also reviewed) and were matched to randomly selected controls ($n=493$) from the community. Spouses of cases and controls were interviewed to determine dietary intake of n-3 fatty acids from seafood during the previous month, and blood samples were collected from 82 cases and 108 controls to determine red blood cell membrane fatty acid composition (thought to be a biomarker of dietary n-3 fatty acid intake). Using a conditional logistic regression model, an inverse association was found between dietary intake of n-3 fatty acids and the risk of primary cardiac arrest. An intake of 2.9 g of n-3 fatty acids per month (equivalent of 2 fatty fish meals/month) compared to no seafood meals resulted in a 30% reduction in the risk of primary cardiac arrest ($OR=0.70$). There was a further reduction of risk ($OR=0.50$) with consumption of 5.5 g of n-3 fatty acids (equivalent to one fish meal/week), after adjustment for many potential confounding variables. There was also an inverse relationship between red blood cell membrane-combined EPA and DHA levels and risk of cardiac arrest: when n-3 fatty acids comprised 3.3% of total fatty acids in red blood cells, there was a 50% reduction ($OR=0.50$) in risk of primary cardiac arrest; a level of n-3 fatty acids of 5.0% of total fatty acids was associated with a 70% reduction ($OR=0.30$). However, after taking into account the effect of red blood cell membrane levels, dietary intake of n-3 fatty acids was not related to the risk of primary cardiac arrest. This may suggest that the effect of dietary fatty acids occurs through changes in cell membrane fatty acid composition.

2.2.1.12 Burr, Gilbert, Holliday, Elwood, Fehily, Rogers, Sweetnam and Deadman, 1989. "The Diet and Reinfarction Trial (DART)" (12)

The purpose of this randomised, controlled clinical trial was to determine if changes in fat, fish and dietary fiber intakes of men who had had nonfatal myocardial infarctions could affect the incidence of second MIs. A total of 2033 men were randomised to receive dietary counselling to reduce their fat intakes, eat at least 2 servings a week of fatty fish (e.g., mackerel, salmon, trout),

or eat more dietary fiber. Those in the fish group who disliked fish were given 3 fish oil capsules daily instead. A subset of 25 study participants completed 7 day weighed food records, and subjects in the fat and fish advice groups had serum cholesterol and fatty acid profiles done, as cross-checks for compliance. After two years, the groups receiving fat and fiber advice showed no significant differences in death rates. Although there is a confounding of fish consumption with fish oil consumption, the fish advice group showed a 29% lower risk of death from all causes than the group which received no fish advice, even after analyses were adjusted for 10 potentially confounding factors. This was the first randomised, controlled trial to investigate the effectiveness of increased fish consumption on the secondary prevention of MI.

2.2.1.13 Daviglus *et al.*, 1997. "The Western Electric Study" (13)

The relationship between baseline fish consumption and the 30-year risk of CHD was assessed in 1822 men aged 40 to 55 years, as part of the Chicago Western Electric Study. Fish consumption was determined from a detailed diet history and was stratified into 4 categories: 0, 1-17 g/day, 18-34 g/day, and >35 g/day. Annual examinations, conducted for the first 10 years, and mailed questionnaires or telephone interviews done over the next 15 years, were used to obtain information on the status of the study participants. Dietary information was collected at the first and second annual examination. During the 31st year vital status was determined from the National Death Index, the Health Care Financing Administration, and surviving participants. Deaths due to CHD were classified as death from MI (sudden or nonsudden) or death from other coronary causes. Cox proportional hazards regression was used to estimate the RR of death for each of the four levels of fish consumption, after controlling for 13 possible confounders. Age-adjusted death rates from MI, coronary heart disease, cardiovascular disease, and all causes were the lowest in men who had the highest consumption of fish. The relative risks of death from any MI (sudden or nonsudden), sudden MI, and nonsudden MI were 0.56, 0.68, and 0.33 respectively for men who consumed >35 g of fish per day, compared to the group who consumed no fish. There was a significant trend towards a lower relative risk as the level of fish in the diet for nonsudden MI ($p=0.007$) and all CHD ($p=0.040$) but not for sudden MI. The results of this study indicated a significant inverse relationship between fish consumption and 30-year risk of death from coronary heart disease, including nonsudden MI.

2.2.1.14 Conclusions and Weight of Evidence for an Association between Coronary Heart Disease and Fish Consumption

The 13 studies chosen for this review included 1 clinical (randomised, controlled) trial and 12 epidemiological studies (2 case-control and 10 prospective cohort studies) with strong designs and large sample sizes. All the prospective studies had good rates of follow-up (i.e., they had few study dropouts), although there were large differences in the lengths of follow-up. Earlier studies relied upon information on death certificates; later studies used international guidelines for diagnostic criteria, autopsies, physician and hospital records (ECG results, cardiac enzymes, blood lipid profiles), and interviews with relatives, to improve the accuracy of CHD endpoints diagnosed. Later studies also expanded their exclusion criteria and did not recruit subjects with pre-existing or early symptoms of CHD (e.g., angina pectoris, angioplasty procedures, coronary artery bypass grafting, ischemic stroke, strokes due to injury or tumors, silent infarctions, etc.). More recent prospective studies have collected information during the follow-up period, not just

at baseline, to determine if and when health conditions, family history, or diet changes. They also controlled for substances and lifestyle factors believed to lower CHD risk, such as aspirin, anti-oxidant vitamins, alcohol, and regular exercise, in addition to other potential confounding health and socio-demographic variables. Dietary assessment methods have improved as well, with the use of instruments with known validity and reliability, and crosschecks for assessing the accuracy of recalls or compliance with dietary advice.

Findings from five (of eight) prospective population studies B Zutphen (Kromhout *et al.*, 1985), Rotterdam (Kromhout, 1995), Sweden (Norell *et al.*, 1985), U.S. physicians 12-year study (Albert *et al.*, 1998), and Chicago Western Electric (Daviglus *et al.*, 1997) are broadly concordant in showing a significant inverse relation between fish intake and risk of CHD mortality, as are also results from the two case-control studies (Gramenzi *et al.*, 1990, Siscovick *et al.*, 1995) and the one intervention trial (Burr *et al.*, 1989). For the specific endpoints of non-sudden vs. sudden CHD death, findings in the Physicians' Health Study (Albert *et al.*, 1998) and the Seattle Study (Siscovick *et al.*, 1995), appear different from those in the Chicago Western Electric Study (Daviglus *et al.*, 1997). Both of the former found an association between reported fish intake and rate of sudden death, whereas the Chicago Western Electric data found a lower rate of non-sudden MI death (not sudden MI death).

Three prospective studies, the Bergen Norway (Vollset *et al.*, 1985), Hawaii (Curb & Reed, 1985), and U.S. Health Professionals (Ascherio *et al.*, 1995) studies, did not find a relationship between fish intake and CHD-MI. There were many differences among the prospective epidemiologic investigations, one or more of which may account for this apparent inconsistency in results:

1. different methods to assess diet and to array men by fish intake;
2. different distributions of reported fish intake, such that in some cohorts (e.g., Bergen and Hawaii) there were few or no people in the group consuming little or no fish; hence, there was no fully suitable reference group;
3. different study sites and times, with populations that have quite different diets (resulting in different dietary intakes of cholesterol, saturated fats, antioxidants, fiber, etc.). For example, the cohorts of Norwegian, Hawaiian Japanese-American and U.S. health professionals were studied during the 1980s and 1990s, at a time of widespread awareness of general dietary advice about 'heart healthy eating', as well as some awareness of the idea that fish may "protect" against CHD;
4. the possibility of bias due to this recent awareness, i.e., people who know they have some risk factors for CHD may have differentially become greater fish eaters in the 1980s. This could potentially cause an inversion of the fish-CHD relationship, i.e., the people who eat more fish have higher relative risks of death from CHD (e.g., the Health Professionals Follow-Up Study finding re: fish and CABG?);

5. different durations of follow-up, ranging from decades to 4-6 years (e.g., findings in Physicians' Health Study with 4- and with 12-year follow-up, compared to findings in the Chicago Western Electric Study with 30 year follow-up -- Table 2-1);
6. different CHD endpoints, with only a few studies reporting on fish and fatal MI, and only two prospective studies (Chicago Western Electric Study and Physicians' Health Study) reporting on fish and the suddenness of CHD death;
7. differences in the interpretation of findings (e.g., in the Health Professionals Follow-up Study, are data on CHD death more soundly interpreted as indicating no relation or an inverse relation of fish intake to this end point?);
8. chance, that is, random variation across studies in results.

Although the data available at this time do not allow us to say definitively that these factors account for the apparent discrepancies in findings, the 'weight of evidence' supports an association between fish consumption and lower risk of CHD in men with no previous history or symptoms of CHD. It appears that this relation is evident with as little as one to two meals of fish (lean or fatty) per week.

This inverse relation seems unlikely to be due to n-3 FA content of fish, for several reasons. First, lean fish have lower levels of n-3 FA than fatty fish, yet both appear to protect against sudden cardiac death. Second, fish oil supplementation trials have observed effects at high doses, the equivalent of enormous amounts of fish in the diet; however, there is evidence of an association between a reduced risk of sudden death from CHD and MI when as little as one meal of fish a week is consumed. It is possible that a component or combination of substances in fish, through some mechanism not yet discovered, confers the cardio-protective benefits.

With the exception of the DART study (Burr *et al.*, 1989), a randomised controlled clinical trial which examined the effects of three different interventions on the secondary prevention of MI, studies have not been designed to suggest a 'cause and effect' relationship between eating fish and rates of CHD. These epidemiological studies can indicate associations between variables, but randomised controlled clinical trials are needed in order to answer the question, 'Does eating fish lead to a lower risk of CHD?'

2.2.2 Studies of Other Possible Health Effects of Fish Consumption

The following sections briefly describe investigations of benefits of fish consumption with respect to other health endpoints (Table 2-2). These endpoints have not been studied as well as coronary heart disease. Table 2-2 summarizes this research.

Table 2-2. Studies of Fish Consumption and Other Endpoints

Condition	Key Studies	Evidence to Date
Smoking-Related Chronic Obstructive Pulmonary Disease	ARIC Study (Shahar <i>et al.</i> , 1994)	fish consumption associated with better lung function for Whites who currently or formerly smoked, but not Blacks
Lung Damage from Smoking	ARIC Study (Shahar <i>et al.</i> 1994) and Honolulu Heart Program (Sharp <i>et al.</i> , 1994)	frequent fish consumption may protect the lungs of 35+ yr. smokers from damage; smokers of 30+ cigarettes daily not protected though
Rheumatoid Arthritis	Shapiro <i>et al.</i> , 1996	2 or more servings of broiled/baked fish/week reduced risk of rheumatoid arthritis (OR=0.57); no association for other types of fish (fried, shellfish, canned tuna)
Childhood Asthma	Hodge <i>et al.</i> , 1996 (fish) Hodge <i>et al.</i> , 1998 (n-3 oil) Thien 1996	1996 study of 71 children with asthma found 1+ meals of oily fish/month reduced risk of asthma (OR=0.26); not supported by Nurses' Health Study (Thien, 1996); 1998 study using n-3 oil found no effect on severity of asthma
Plaque Psoriasis	Collier <i>et al.</i> , 1993	small clinical trial (cross-over design) with diets including 6 oz oily or 6 oz lean fish/day; 11-15% improvement of psoriasis symptoms with oily fish
Colon Cancer	Nurses Health Study (Willett <i>et al.</i> , 1990)	no association with fish alone, but ratio of ≥ 5.2 red meat:fish + chicken was 2.5 x more likely to get colon cancer than ratio of < 1.2 red meat: fish + chicken
Gastrointestinal Disease	[reviewed in O'Keefe, 1996]	ulcerative colitis and adenomatous polyps successfully treated with fish oil supplements; no data re: intake of fish and incidence/severity

Condition	Key Studies	Evidence to Date
Dyslipidemia in Non-Insulin-Dependent Diabetes Mellitus	<i>Dunston et al.</i> , 1997	NIDDM patients who ate 1 fish meal/day as part of a low fat diet had reduced triglyceride and increased HDL levels, but poorer glycemic control; when exercise was added, glycemic control was maintained
Antioxidant Levels	<i>Anttolainen et al.</i> , 1996	comparison of 82 Finns with very high fish consumption to group eating <1 meal/month showed similar levels of antioxidants (beta-carotene & vitamin E)

2.2.2.1 Smoking-Related Chronic Obstructive Pulmonary Disease (COPD)

Shahar *et al.* (1994) looked at COPD in current and former smokers participating in the Atherosclerosis Risk in Communities (ARIC) study. They defined COPD as chronic bronchitis, physician-diagnosed emphysema, or spirometrically detected COPD. Current or former smokers in the third and fourth quartiles of fish consumption (≥ 1.5 servings/week) were significantly less likely to have COPD than those who ate little or no fish. Fish consumption was also associated with improved lung function (greater forced expiratory volume in one second [FEV₁] and greater FEV₁/Forced vital capacity [FVC]) in white current and former smokers. Oddly, this relationship was not seen in black participants. Fish consumption was not related to lung function in ARIC participants who had never smoked, suggesting that fish consumption does not actually improve lung function directly, but rather protects the lungs from damage caused by smoking.

2.2.2.2 Lung Damage from Smoking

Like the results of the ARIC study summarized above, the results of the Honolulu Heart Program (HHP) study (Sharp *et al.*, 1994) suggest that frequent fish consumption may protect the lungs of long-term cigarette smokers from damage. Male cigarette smokers who reported eating fish at least 2 times/week showed less of a relationship between duration of tobacco exposure and reduced FEV₁ than did smokers who ate fish less frequently. However, fish consumption only seemed to be protective among smokers who had smoked for more than 35 years. There was also some evidence that 'heavy smokers (> 30 cigarettes/day) were not protected by frequent fish consumption.

The authors of both the ARIC and the HHP studies speculate that fish consumption may exert its protective effect by inhibiting the production of various mediators of lung inflammation, some of which have been associated with cigarette smoking. Supplementation of the diet with fish oil has been shown to inhibit the production of a number of known and putative mediators of lung inflammation, and fish itself might produce similar effects. However, the average intake of n-3 fatty acids by study participants was much lower than the dosage contained in fish oil supplements, so some factor other than n-3 fatty acids may be at work.

2.2.2.3 Rheumatoid Arthritis

In a case-control study by Shapiro *et al.* (1996), consumption of broiled or baked fish was associated with a decreased risk of rheumatoid arthritis in women. The adjusted OR for ≥ 2 servings of broiled or baked fish/week, compared with <1 serving, was 0.57 (95%CI=0.35-0.93). However, consumption of other types of fish (fried fish, canned tuna, and shellfish) was not associated with rheumatoid arthritis, and neither was a combined measure including all types of fish consumed. In addition, there was no significant association between the estimated amounts of n-3 fatty acids in the participants' diets and rheumatoid arthritis when all cases were included in the analysis. When the analysis was restricted to cases who were rheumatoid factor positive (RF+), the association with consumption of broiled or baked fish remained significant, and there was also an association between n-3 fatty acid consumption and reduced risk of arthritis.

However, the latter association appeared to be weaker than the former; the association between n-3 fatty acid consumption and rheumatoid arthritis was only statistically significant when participants in the top 10% of n-3 consumption were compared to those in the first quartile.

2.2.2.4 Childhood Asthma

In a study of 71 children with asthma and 263 controls, Hodge *et al.* (1996) found that consumption of fresh, oily fish was associated with a reduced risk of current asthma. The adjusted OR for those who ate oily fish at least monthly versus those who never ate oily fish was 0.26, with a 95% C.I. of (0.09-0.72). There was no statistically significant association between asthma and consumption of non-oily fish or of canned or processed fish. Thien *et al.* (1996) were somewhat dubious about these results, since other studies had suggested that fish in the diet would have no effect on risk of asthma or on reducing the severity of asthma. For instance, the Nurses' Health Study had shown no relationship between adult-onset asthma and fish in the diet, and most clinical trials of fish oil supplements as a treatment for asthma had yielded disappointing results. In fact, a small clinical trial by Hodge *et al.* (1998) showed that n-3 oil supplements had no effect on the severity of symptoms in asthmatic children. However, it is possible that the association observed in the 1996 study was genuine, and that some compound in fish other than n-3 fatty acids was responsible for the protective effect.

2.2.2.5 Plaque Psoriasis

Collier *et al.* (1993) carried out a small clinical trial to examine whether a diet containing 6 oz. of oily fish/day could improve psoriasis symptoms; the control diet contained 6 oz. of white fish/day. Patients on the oily fish diet showed a small (between 11% and 15%) but statistically significant improvement after 6 weeks on the diet, and symptoms worsened again when patients switched from the oily fish diet to the white fish diet. The oily fish diet contained high levels of both vitamin D and n-3 fatty acids, and the authors speculated that one or both of these factors might have been responsible for the beneficial effect of the diet.

2.2.2.6 Colon Cancer

There was no significant relationship between fish consumption and colon cancer among the Nurses' Health Study cohort (Willett *et al.*, 1990). However, the total amount of chicken and fish in the diet was associated with a reduced risk of colon cancer, and the ratio of red meat to chicken and fish in the diet was associated with an increased risk of colon cancer. Women who ate ≥ 5.2 times more red meat than chicken and fish (the highest quintile) were 2.5 times more likely to have colon cancer than women in the lowest quintile (< 1.2 times more red meat than chicken and fish). In this case, it seems likely that fish and chicken exerted their protective effect by substituting for red meat, thus decreasing the amount of animal fat and other potentially hazardous components of red meat in the diet.

2.2.2.7 Gastrointestinal Disease

O'Keefe (1996) cites a number of studies in which fish oil supplements were successfully used to treat patients with ulcerative colitis or adenomatous polyps. However, there seem to be no

published studies of the effect of fish in the diet on the incidence or severity of colitis or other gastrointestinal disorders.

2.2.2.8 Dyslipidemia in Non-Insulin-Dependent Diabetes Mellitus

Dunston *et al.* (1997) conducted a small clinical trial to test whether fish consumption (1 meal/day) could improve serum lipid levels in dyslipidemic NIDDM patients without increasing levels of plasma glucose and glycated hemoglobin. The addition of one fish meal per day to a low-fat diet ($\leq 30\%$ of energy intake) did cause triglyceride levels to fall and HDL₂ levels to rise, but it also caused glycated hemoglobin and serum glucose to rise. However, in patients who ate one fish meal per day and participated in an exercise program (riding a stationary bicycle for 30' at 55-65% of V_{O2max}), plasma lipid levels improved with no deterioration in glycemic control.

2.3 Antioxidant Levels

Several researchers have speculated that a high-fish diet might reduce antioxidant levels in the diet or in the blood, since n-3 fatty acids have a tendency to oxidize *in vitro*, and since fish oil contains less of the antioxidant vitamin E than vegetable oils. Anttolainen *et al.* (1996) studied 82 Finns to determine whether men and women with very high levels of fish consumption do in fact have lower levels of antioxidants in their diet and in their plasma than people who eat little or no fish. When compared to participants who ate fish less than once per month, participants who ate fish every day or almost every day had equivalent or higher levels of vitamin E, vitamin C, β -carotene, and selenium in their diets. Similarly, levels of plasma tocopherol (vitamin E) and β -carotene were very similar in the high-fish and low-fish groups. Although this study could not measure the vitamin E stored in tissue, the results do suggest that a diet high in fish does not dangerously reduce antioxidant levels.

2.4 Health Benefits During Pregnancy, Lactation and Infancy

As mentioned earlier, fish is a good dietary source of the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). DHA is incorporated into the cell membranes of the retina, brain and other parts of the central nervous system. Several animal studies have demonstrated that if DHA levels are low when these tissues are developing, vision and learning problems may result (see Neuringer, Reisbick and Janowsky, 1994 for a review). This is most important during the third trimester of pregnancy when the brain of the unborn child is rapidly developing, but is also important during the first year after birth when the brain continues to grow. Thus, there has been an interest in the possible health benefits of consuming fish during pregnancy. The unborn child may benefit from the omega-3 fatty acids from fish the mother consumes during pregnancy, and may be born with greater body stores of these fatty acids to draw upon during the first year of life.

Human milk contains many long-chain polyunsaturated fatty acids, including DHA and arachidonic acid (AA). DHA accounts for 0.1% to 1.5% of total fatty acids in human milk depending upon the amount of pre-formed n-3 fatty acids, the main source of which is fish, in the mother's diet. Currently, commercial infant formulas in the U.S. contain the n-6 fatty acid linoleic acid (precursor to arachidonic acid), and the n-3 fatty acid linolenic acid (precursor to

DHA & EPA), but do not contain AA, DHA or EPA (Auestad *et al.*, 1997). Thus, mothers who consume fish while provide pre-formed n-3 fatty acids to their infants through breast milk, during the first year of life when the brain is still developing.

In the Faroe Islands study, women who ate high amounts of marine fish and marine animals during their pregnancies were observed to have longer gestations and correspondingly heavier babies (Olsen, Hansen and Sorensen, 1986). A subsequent study of Danish women hypothesized that it was the n-3 fatty acids in marine fish and animals that conferred these benefits; indeed, the results showed that women who received fish oil supplements in their third trimesters had pregnancies that were an average of four days longer than women who received olive oil supplements or no supplements (Olsen, *et al.*, 1992). Comparisons among the three groups of mothers showed that those given fish oil supplements had significantly higher levels of n-3 fatty acids, particularly docosahexaenoic acid (DHA), in their umbilical cord blood than the two other groups (Van Houwelingen, Sorensen, Hornstra *et al.*, 1995). Thus, the extra n-3 fatty acids consumed by the supplemented pregnant mothers led to higher n-3 fatty acid levels in their babies at birth. The authors concluded that "it is, indeed, possible to interfere with the DHA status at birth: children born to mothers supplemented with fish oil in the last trimester of pregnancy start with a better DHA status at birth, which may be beneficial to neonatal neurodevelopment" (Van Houwelingen *et al.*, 1995, p.723).

A study of 300 Canadian Inuit women provides some preliminary evidence that consuming marine fish and mammals during pregnancy may reduce the likelihood of pregnancy-induced hypertension for women at risk (Popeski *et al.*, 1991). Women from communities harvesting large amounts of marine foods had significantly lower diastolic blood pressure levels in the last six hours of their pregnancies, compared with women from communities where less marine fish and sea animals, and more caribou, were eaten. Among the 53 women who developed hypertension, 12 were from communities with high fish and sea mammal consumption and 41 from communities eating lower amounts. Although these differences in blood pressure levels could reflect other dietary differences not assessed in this study (e.g., sodium intake), levels of the n-3 fatty acids eicosapentaenoic acid (EPA) and DHA in cord blood were higher in the communities with more marine foods in their diets, lending support to the hypothesis that the differences were related to diet.

2.5 Health Benefits for Children Consuming Fish

All fish is a good source of high-quality protein, essential fatty acids, and minerals such as iron and zinc (see Chapter 3 *Nutritional Benefits of Eating Fish Compared to Other Protein Sources*), and thus is an important food in the diets of growing children. Consuming other protein foods, particularly fast foods that are popular among children and teens, can result in more saturated fats in a meal. Given the increasing rates of obesity among American children, and the evidence that obese children tend to become obese adults, high dietary fat intakes among children are a public health concern. Learning to enjoy a healthful diet and to maintain an appropriate body weight during childhood may help children to reduce their risks of cardiovascular disease, Type II diabetes mellitus, and some forms of diet-related cancers, as adults.

Some children and adolescents follow strict vegetarian (vegan) diets, or variations that include dairy products and eggs (lacto-ovo-vegetarians), or dairy products, eggs and fish (lacto-ovo-pesco-vegetarians or semi-vegetarians). A recent Slovakian study examined the fatty acid profiles of children following such diets and children who were omnivores (Krajcovicova-Kudlackova *et al.*, 1997). The children following semi-vegetarian, lacto-ovo-vegetarian, and vegan diets had significantly lower blood levels of saturated fatty acids compared to the omnivore children. The semi-vegetarians, who consumed fish but not poultry or meats, had significantly higher levels of EPA and DHA than lacto-ovo-vegetarians; vegans had the lowest levels of both n-3 fatty acids. There were no significant differences among the groups in the long-chain n-6 AA or in monounsaturated fatty acids. The authors warned that the "significantly reduced n-3 fatty acid content and significantly higher ratio n-6/n-3 may represent a health risk in vegans," with respect to cardiovascular diseases. However, the high EPA and DHA levels and low n-6/n-3 ratio found in semi-vegetarians, who reported eating an average of 1.9 fish meals weekly, was considered important for the prevention of cardiovascular diseases.

While children in our culture seem to love hamburgers, hot dogs, and macaroni and cheese by an early age, they may not appear to have the same preference for a lower-fat meal of baked, broiled or steamed fish. Leann Birch (1996), an authority in children's food acceptance patterns, notes that some taste preferences are "built-in" and "unlearned," infants have a preference for sweet and salty tastes, and an aversion to sour and bitter tastes. Other food likes, such as for fatty, crunchy, or creamy foods, get established through repeated experiences with the food. Therefore, "early experiences have a profound effect on food preferences" and "repeated opportunities to taste the food enhance food acceptance" (Birch, 1996; p.235). Children can learn to accept and like fish (or any other new food) if they are introduced to it at an early age and are given time to become familiar with its taste and texture. If children have ample opportunities to become familiar with fish while they are young, chances are greater they will learn to like it and continue eating it as an adult. Thus, if we are interested in promoting the cardiovascular and other nutritional/health benefits of eating fish to adults, we should encourage parents to serve fish to young children so they can develop a liking for it and a willingness to include it in their diets at an early age.

2.6 Conclusions and Research Needs

The above data provide some evidence for an association between decreased risk of CHD or MI and consumption of small amounts of fish, including mainly lean (non-fatty) fish. However, it seems unlikely that decades-long intake of small amounts of fish protect, if fish is indeed etiologically protective, via the very small amounts of omega-3 long-chain polyunsaturated fatty acids so ingested. The resolution of this issue has important implications for public health and nutritional recommendations. Thus, further studies -- observational and interventional, particularly trials -- are needed to resolve whether there is an etiologically significant protection against CHD or MI afforded by regular ingestion of modest amounts of fish. Similarly, more research is needed on the relationship of fish intake and health endpoints other than CHD or MI.

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3 Nutritional Aspects of Fish Compared with Other Protein Sources

3.1 Introduction

This chapter presents an overview of the consumption rates and nutritional benefits of eating fish. While its specific contributions to the nutritional quality of the diet depend upon the amount of fish (versus other foods) and species (fatty versus lean) consumed, it is most valued as a "protein food". The Biological Value and Protein Efficiency Ratio, indices of the amino acid profile and ability to support growth, are higher for fish than for beef, pork, chicken and milk proteins. In addition, the types and proportions of dietary fats are generally more "heart healthy" than the fats found in other protein foods. Approximately 50% of the fatty acids in lean fish (e.g., walleye and yellow perch) and 25% in fattier fish (e.g., channel catfish and rainbow trout) are polyunsaturated fatty acids. The amount of saturated fatty acids, associated with increased risk of heart disease, tends to be relatively constant across fish species, at about 25% (Sabry, 1990). In contrast, the polyunsaturated and saturated fatty acids in beef are 4-10% and 40-45%, respectively, of the total fatty acids present. Fish is also valued as a source of omega-3 (n-3) fatty acids, very long chain polyunsaturated fatty acids which are critical for the development of the brain and retina, and which may be protective of some chronic diseases. Eicosapentanoic acid (EPA) (20:5 n-3) and docosahexanoic acid (DHA) (22:6 n-3), which account for approximately 90% of the polyunsaturated fatty acids in fish species from the North Atlantic and North Pacific (Sabry, 1990), are absent or present in much lower amounts in other foods. The amount of cholesterol found in fish is comparable to levels in beef, pork, and chicken. Fish is an excellent source of the B vitamins niacin and B12, and in general is a better source of Vitamins D and A than beef, pork or chicken. Fish can also contribute appreciable amounts of dietary calcium, heme iron and zinc, nutrients that tend to be low in people's diets. Fish is among the best sources of dietary selenium.

These nutritional benefits are examined from a population health perspective (i.e., what is relevant to the healthy 'general population'), rather than a high-risk approach (which is primarily interested in individuals at highest risk of disease). The nutrient profiles of commonly consumed sport-caught fish are also compared with those of other protein sources, and discussed in terms of current population intakes and recommendations. A table that summarizes the nutrient content and contaminant concentrations of various species of fish and other foods is found at the end of this chapter. Finally, a brief discussion of the effects on nutritional quality and contaminant levels from how the fish is prepared and cooked is provided.

3.2 Per Capita Consumption of Fish (Finfish and Shellfish)

In the Continuing Survey of Food Intakes by Individuals (CSFII), the USDA regularly collects information from large numbers of respondents across the United States, about foods eaten. These consumption data (recorded as weights of the food item consumed for three consecutive days) provide estimates of the average amounts of finfish and shellfish eaten daily by various population sub-groups.

In 1996, the U.S. EPA published *Daily Average Per Capita Fish Consumption Estimates Based on the Combined USDA 1989, 1990, and 1991 CSFII* in their *Exposure Factors Handbook* (U.S.

EPA, 1997a). It contains summaries and weighted population estimates based on data collected from the 11,912 participants in these three national surveys. The U.S. EPA considers this "the key study for estimating mean fish intake" (U.S. EPA, 1997a), stating that the data "are probably adequate for assessing fish ingestion exposure for current populations."

These food consumption data are summarized for the survey respondents and weighted for extrapolation to the U.S. general population. Estimates of both uncooked fish weights and cooked fish weights are provided. The average cooked weight of fish (finfish and shellfish) eaten from freshwater and estuaries was estimated to be 4.7 grams (90% C.I. = 4.2-5.3) per person per day for the U.S. population. Among the 18.5% of survey participants who reported eating freshwater and estuarine fish, the average cooked weight consumed was estimated to be 68.0 g/day (90% C.I. = 61.9-74.1; Tables 10-11 and 10-21, p.10-38 and 10-44). The average per capita intake of marine fish is 10.9 g/day (cooked weight; 90% C.I. = 10.1-11.7) for the U.S. population, and 87.8 g/day (90% C.I. = 83.7-91.8) among those 30.1% of survey participants who reported eating marine fish (Tables 10-11 and 10-22, p. 10-38 and 10-44). Overall, 37% of individuals reported eating fish (from all sources); on average, they ate an estimated 100.6 grams of (cooked) fish a day (Table 10-23, p.10-45). Perhaps not surprisingly, males ate higher amounts of freshwater/estuarine, marine and all fish (77.5 g/day, 98.6 g/day, and 114.2 g/day respectively) than females (58.8 g/day freshwater/estuarine; 78.5 g/day marine; 88.5 g/day all fish).

The U.S. per capita consumption of fish since 1977/78 has been approximately 11 g/day (U.S. EPA, 1997a, p.10-5), ranging from 4 g/day for children aged 0-5 years, to 12 g/day and 15 g/day among females and males aged 20 and older, respectively (Table 10-46, p.10-56). Geographically, slightly higher rates of fish consumption are found in New England and the Atlantic states, than in the rest of the U.S.

Preliminary analyses conducted on data from the most recent CSFII survey (1994-96) suggest that the per capita consumption of fish may have fallen slightly, from 11 to 9 g/day (Borrud et al., 1996). This is, on average, about the same as pork with a per capita consumption rate of 11 g/day (down considerably from 20 g/day in 1977/78). Beef consumption has declined dramatically over the past 20 years, from 52 g/per person/per day to 24; this is approximately the same as chicken, with an average per capita consumption rate of 23 g/day.

These shifts in dietary patterns have led to a drop in the percentage of energy (calories) from fat (from 40% in 1977-78 to 34%) and saturated fat (from 12 to 11%), and an increase in the percentage of energy from carbohydrates (from 43 to 51%). While these changes still do not meet current recommendations for "no more than 30% of energy from fat, 10% of energy from saturated fat, and at least 55% of energy from carbohydrates", they are important and healthful changes. However, the same data suggest that average intakes of vitamin B6, calcium, iron, zinc, and some other nutrients are below the Recommended Daily Intakes (RDAs). As the study authors explain, "as the percentage of the population with intakes below 100% of a given RDA increases, so does the likelihood that some people are at nutritional risk. Only 21% of the women in the 1994 CSFII had diets that met the RDA for calcium... and 17% for zinc" (Borrud et al, 1996, p.17).

3.3 Nutritional Content and Contaminant Levels for Fish and Other Protein Sources

3.3.1 Selection of Nutrients, Foods and Contaminants for Tables 3-1 and 3-2

Tables 3-1 and 3-2 (found at the end of this chapter on pages 3-14 and 3-18) were designed to facilitate the comparison of the nutritional components and contaminant levels in several fish species, to levels present in other commonly consumed foods of high protein quality. Ocean fish and seafood species were chosen to represent commonly consumed store-bought fish (e.g. halibut and tuna) as well as species commercially or sport caught in specific geographical regions (e.g., crab). Freshwater fish species selected represent commonly consumed sport-caught fish occurring in various geographical locations across the United States, and include species of varying fat content. Other foods present in the table, such as beef tenderloin, pork loin, and chicken breast, were chosen as lean protein sources that could be compared with lean fish species (e.g. walleye). Fast foods and processed foods such as fried chicken, hamburgers, hotdogs, and fish sticks are important sources of protein for a large segment of the population. Other foods, such as tofu and refried beans, were included because they may be important protein sources for specific ethnic groups.

The nutrients listed in Tables 3-1 and 3-2 represent the most important nutrients commonly obtained from fish, which could be regarded as public health concerns. In other words, fish would be considered good sources of these nutrients, which, according to U.S. population surveys, are often not consumed in recommended amounts. Fish do supply other important micronutrients and compounds, such as fluorine and copper, which are not currently public health nutrition concerns in the U.S. A detailed discussion of specific nutrients can be found in subsequent sections of this chapter. By comparing the protein (and associated indices such as protein efficiency ratio), vitamin, mineral and lipid (e.g. omega-3 fatty acids) levels in fish to those of other protein food sources, the nutritional benefits of consuming various protein sources can be assessed.

The nutrient compositions of the foods listed in the table were obtained from the USDA's food composition database (USDA, 1998). To create a nutrition profile for a given food, data are compiled from several sources. For example, the data on fish are obtained from the scientific literature, government agencies outside the USDA, USDA contracts, and industry and trade associations (J. Exler, personal communication, 26 April, 1999). Several sources of data are compiled to help make the samples more representative of fish obtained throughout the U.S. Values for cooked fish were calculated from data on raw fish. Fish species that are listed as "wild" were obtained from commercial sources or, if the wild form of the species was not available, the fish was caught by the group contracted to provide the sample. All values for the fish listed in the tables are for the "wild" form. For processed fish and other foods, data are available on the most popular brand names.

For the development of the framework, six chemical contaminants were chosen to represent toxic substances that may be present in various protein sources. By comparing the levels of contaminants in commonly consumed fish species to those in other commonly consumed protein food sources, the relative risk of exposure to contaminants through the consumption of various foods can be assessed. Contaminant levels in foods, including wild fish species, are monitored to

identify foods that may contain unsafe levels. While published reports of contaminant levels in fish and other foods have been released as recently as 1998, the data used for many of these reports were collected in the late 1970s and early 1980s. Since the level of many of these contaminants in foods declined during those years (and the decline most likely continued throughout the 1990s) references that contained data collected in the late 1970s and early 1980s were not used in Tables 3-1 and 3-2. Data for a number of these chemical contaminants was not available.

3.3.2 Substituting Other Foods for Fish: Effects on Macronutrient Profiles

While it can be useful to compare the nutrients found in equal weights of various foods, it is the impact of substituting one for food another on the *total diet* that is important. For example, 24-hour food record for a 45 year old female of Asian descent, who had eaten 150 grams of rainbow trout for dinner was analyzed by a nutrient software program (Candat, 1994), and the results are shown in Table 3-3. Her total protein intake (from the fish and other foods eaten) on that particular day accounted for 24% of her energy intake (calories), while 37% of her calories came from fat and 39% came from carbohydrates. (Although this dietary profile does not meet current recommendations for diets composed of 30% or less of energy from fat and 55% or more of energy from carbohydrates, it is a typical North American dietary profile). Table 3-3 shows the effect of substituting 150 grams of perch (a lean herbivorous fish), skinless chicken breast, or hot dogs for the rainbow trout. The rainbow trout, a fattier fish species, and the skinless chicken breast produce daily dietary profiles that are similar. The best macronutrient profile is obtained with perch (i.e., the lowest % of energy from fat, highest % of energy from carbohydrates, and lowest total number of kcal), while substituting 150 grams of hot dogs produces the worst dietary profile. Thus, substituting a fatty or a lean species of fish for hot dogs at one meal can make a noticeable improvement in the profile of the whole day's diet, even if no other dietary changes are made.

Table 3-3. Percent of energy (calories) from macronutrients based upon one day's diet which included a 150 gram serving of fish, chicken or hotdogs.¹ (calculations based on Candat, 1994)

	Rainbow Trout	Perch Mixed Species	Chicken Breast (no skin)	Hotdog
% energy from Protein	24%	26%	27%	15%
% energy from Fat	37%	33%	34%	52%
% energy from Carbohydrates	39%	41%	39%	33%
Total energy intake for 24-hr	1148 kcal	1099 kcal	1171 kcal	1396 kcal

¹ based upon an actual 24-hr food record of a 45-year-old female

3.4 Fish as a Protein Source

3.4.1 Protein Quality

As Groff et al. (1995) states, "The importance of protein in nutrition and health cannot be overemphasized." Protein is composed of amino acids; nine of these (leucine, isoleucine, valine, lysine, tryptophan, threonine, methionine, phenylalanine, and histidine) are considered nutritionally essential or "indispensable" in the human diet, because they cannot be synthesized by the body. Protein also supplies nitrogen, for the internal synthesis of other amino acids required by the body. Different categories of proteins include enzymes, required as catalysts in most of the body's chemical reactions, peptide hormones (such as insulin, thyroid hormones, and the growth hormone somatotropin), structural proteins (in muscle and connective tissue), transport proteins (e.g., albumin, transferrin, hemoglobin), and immunoproteins or antibodies.

The quality of a protein is mainly determined by the specific amounts and relative proportions of its essential amino acids, their availability to the body, and to a lesser extent, the protein's digestibility. While the amount of protein required by individuals depends on their body weight and height, energy (calorie) intake, and physiologic condition (e.g., infancy, pregnancy), it is the quality of the protein which is most important in determining daily requirements.

3.4.2 Fish Protein vs. Other Dietary Protein Sources

There are many ways of evaluating the quality of the protein provided by different foods, for comparison purposes. In general, protein from animal foods (e.g., dairy products, eggs, meats, fish, and poultry) is of higher quality than protein from plant foods (e.g., pasta, rice, fruits, and vegetables).

The Chemical Score or Amino Acid Score compares a food's amino acid pattern to that of whole egg protein (with a score of 100), considered to be have the 'ideal' reference composition. The Chemical Score of finfish is 70, an indication of its high quality; beef is 69 and cow's milk is 60 (Sabry, 1990).

The Biological Value (BV) of a protein is calculated by measuring the body's nitrogen balance--nitrogen ingested (from the protein of interest), absorption and use for synthesizing new amino acids, and losses (through urine and feces). The percentage of the absorbed nitrogen which is retained by the body for tissue growth and maintenance, is the BV:

$$BV = (\text{nitrogen retained} / \text{nitrogen absorbed}) \times 100$$

As shown in Tables 3-1 and 3-2, the BV of fish (76%) is slightly higher than that of beef (74.3), pork (74.0) and chicken (74.3), but all are somewhat lower than egg (93.7).

The Protein Efficiency Ratio (PER) is another measure of protein quality, usually calculated by putting young animals on diets with various test proteins, and monitoring their growth. The PER

is a ratio of the gain in weight divided by the weight of the protein consumed:

$$\text{PER} = \text{gain in body weight (in grams)} / \text{grams of protein consumed}$$

The PER of fish (3.55) is higher than beef (2.30) and milk proteins (casein = 2.50), and close to that of egg (3.92).

3.5 Fish as a Source of Essential Fatty Acids

Although high fat intakes have been associated with an increase in the risk of several chronic diseases, a certain amount of fat is necessary for the body to function normally. Triglycerides provide the body with a continuous fuel source, supply heat to the body, protect the body from mechanical shock, and certain fatty acid components are important building blocks for several hormone regulators (Whitney and Rolfes, 1996). Phospholipids and sterols are a major component of cell membranes, and sterol cholesterol provides the building blocks for some hormones, Vitamin D, and bile.

Food is composed of saturated, monounsaturated and polyunsaturated fatty acids. In lean finfish (e.g., walleye and yellow perch) polyunsaturated fatty acids account for approximately 50% of the total fatty acid content in the flesh. Saturated and monounsaturated fatty acids each comprise approximately 25% of the total fatty acid content. For fattier finfish (e.g., channel catfish and rainbow trout) polyunsaturated and saturated fatty acids each constitute approximately 25% of the total fatty acid content. The amount of saturated fatty acids tends to be relatively constant across fish species with proportions of polyunsaturated fatty acids being lower in fish with higher levels of monounsaturated fatty acids (Sabry, 1990).

Finfish tend to have higher levels of polyunsaturated fatty acids and lower levels of saturated fatty acids than other meat sources of protein. The proportion of saturated, monounsaturated and polyunsaturated fatty acids found in beef and pork are, respectively, approximately 40-45%, 50%, and 4-10% (Sabry, 1990). The fatty acid profile of chicken (30-35% saturates, 35-40% monounsaturates, and 25-30% polyunsaturates) falls between that of fish and beef and pork. Dairy products (e.g., cheese and eggs) have a much higher saturated fat component (40-65%), similar monounsaturated levels (30-45%), and much lower polyunsaturated levels (5%) than fish.

Fish also contain long chain polyunsaturated fatty acids of the n-3 (or omega-3) series which are not commonly found in other food sources (Sabry, 1990). Eicosapentanoic acid (EPA) (20:5n-3) and docosahexanoic acid (DHA) (22:6n-3) are the most common n-3 fatty acids, and account for approximately 90% of the total polyunsaturated fatty acids in fish species from the North Atlantic and North Pacific (Sabry, 1990). Linolenic acid (18:3n-3), linoleic acid (18:2n-6) and arachidonic acid (20:4n-6) are also present in fish, although in much smaller proportions (i.e., 1-2%). In lean and lower fat fish (e.g., walleye and yellow perch), the n-3 fatty acid content (EPA + DHA) is often less than 0.5g/100g fish. For higher fat fish (e.g., coho salmon and rainbow trout) the fatty acid content is often between 0.8-1.0g/100g fish. These fatty acid components are absent or present in much smaller amounts in other protein food sources.

Linoleic and linolenic acid are essential fatty acids that are not produced in the body and must be obtained from dietary sources (Whitney and Rolfes, 1996). These fatty acids are an important part of the structural component of cell membranes, and are necessary for the formation of eicosanoids which assist in blood pressure regulation, blood clot formation, maintenance of blood lipid levels, and assist in the body's immune response.

Because studies have linked the type and amount of dietary fat to various diseases (e.g., cardiovascular disease), the fatty acid composition of fish has been of great interest to researchers for the past several years. The benefits of consuming the various types of fatty acids (and their component parts) found in fish are discussed in Chapter 2.

3.6 Cholesterol

Cholesterol forms the building blocks of several compounds (e.g., bile, sex hormones, adrenal hormones, and Vitamin D) with important physiological functions, and is a major structural component of cell membranes (Whitney and Rolfes, 1996). Although food provides an important source of cholesterol, endogenous sources contribute much higher amounts. Cholesterol is synthesized in the liver, through the production of bile, and in the intestine by *de novo* synthesis and desquamation of mucosal cells. The amount of endogenous cholesterol produced in the liver is dependent on the amount of raw materials available (i.e., carbohydrate, protein, and fat), the extent of bile production and availability of regulating hormones (e.g., insulin).

The amount of cholesterol found in finfish varies from approximately 50-100 mg/100 gram portion. This is comparable to the amounts found in beef (84 mg), pork (79 mg), and chicken (85 mg), and is somewhat lower than the levels found in cheddar cheese (105mg) and eggs (424 mg). The method of food preparation will also affect cholesterol levels. Deep frying, compared with dry heat cooking, increased the cholesterol level of channel catfish by approximately 10% (USDA, 1998).

3.7 Vitamins

3.7.1 Vitamins B3, B6, and B12

Vitamins B3 (niacin, nicotinic acid, nicotinamide) and B6 (pyridoxine, pyridoxal, and pyridoxamine) are water soluble organic compounds that are absorbed into the portal blood and stored only briefly in the body; thus, they must be supplied in the human diet every day. Vitamin B12 (cyanocobalamin), also water-soluble, is available from animal foods and can also be re-absorbed into the bloodstream from bile and secretions in the small intestine (i.e., via enterohepatic circulation). It can be stored in the liver and other tissues for years.

Niacin is involved in hydrogen transfer reactions (as part of coenzymes NAD and NADP) and a deficiency results in diarrhea, dermatitis and dementia, a condition known as Pellagra. Adults require approx. 15-19 mg per day, according to the 1989 US Recommended Dietary Allowances. Sixty milligrams of the amino acid tryptophan are considered to be equivalent to 1 mg niacin and expressed as a niacin equivalent (NE).

Fish is an excellent source of niacin. A 100 gram portion of canned tuna supplies 13.280 mg of niacin, which compares favorably with another good source, chicken (13.712 mg). The same portion size of channel catfish or coho salmon supplies 7.95 mg of niacin, in contrast to beef tenderloin (3.92 mg), pork loin (5.243 mg), fortified pasta (1.672 mg), or egg (0.064 mg).

Vitamin B6 exists as several different chemical structures and their phosphorylated forms. Different forms of Vitamin B6 serve as important co-enzymes in transamination, decarboxylation, and transulfhydration and desulfhydration reactions. The RDAs for adult males and females are 2.0 mg and 1.6 mg, respectively, and deficiencies are rare in North America.

The pyridoxine forms are found only in plant foods (especially bananas, navy beans, and walnuts), while the phosphorylated pyridoxal and pyridoxamine forms are found in animal foods, particularly coho salmon (0.568 mg/100 g) and roast chicken breast (0.600 mg/100 g). As shown in Table 3-1, 100 grams of fresh-water drum and rainbow trout (both 0.346 mg), halibut (0.397 mg) or canned tuna (0.350 mg) contain about the same amount of Vitamin B6 as pork (0.277 mg for a shoulder cut and 0.492 mg for a loin cut), beef (0.440 mg for tenderloin), ham (0.340 mg) or fast food chicken (0.350 mg). Even fish with lower amounts, such as channel catfish (0.106 mg) and northern pike (0.135 mg), compare favorably with the Vitamin B6 content of egg (0.121 mg) and are better sources than hot dogs (0.050 mg), cheddar cheese (0.074 mg), pasta (0.035 mg), and rice (0.093 mg).

Vitamin B12 or cyanocobalamin is produced by microorganisms in animals, and does not occur naturally in plant foods. It is important in three enzymatic reactions: the conversion of (1) homocysteine into methionine; (2) L-methylmalonyl CoA to succinyl CoA; and (3) the formation of leucine aminomutase. Little Vitamin B12 is lost through urine or feces; most is excreted into bile and then re-absorbed in the ileum. A deficiency occurs if absorption is impaired (e.g., with doses of 500 mg or more of Vitamin C), or after many years on a strict vegan diet, and results in megaloblastic anemia and neuropathy.

Sport-caught fish are among the best dietary sources of Vitamin B12; e.g., rainbow trout, coho salmon and channel catfish (6.3 ug, 5 ug, and 2.9 ug per 100 gram portions, respectively) provide more than beef (2.57 ug), pork (1.06 ug), chicken (0.34 ug), or egg (1.10 ug).

3.7.2 Vitamin A

Vitamin A (retinol, retinal, retinoic acid) is a fat-soluble vitamin, meaning that its absorption, transport and storage are linked to lipids (i.e., it requires bile salts for absorption, is transported as chylomicrons, and stored in fatty tissues). It is critical for good vision, growth, bone development and maintenance, T-lymphocyte function and antibody response, among other things.

Provitamin A refers to carotenoids found in plants and converted into retinol. Carotenoids such as lycopene and beta-carotene, which function as anti-oxidants, are thought to play a role in the prevention of some cancers. One Retinol Equivalent (RE) is the same as 1 microgram of all-trans retinol, 6 micrograms of all-trans beta-carotene, 12 micrograms of other provitamin A carotenoids and 3.33 International Units (IU) of pre-formed Vitamin A. According to the 1989

RDAs, adult males and females require 1,000 and 800 micrograms RE, respectively, each day. The vitamin A content of sport-caught fish depends on the fattiness of the species and the type of preparation for cooking (i.e., skin on vs. off, internal organs consumed). Relatively lower-fat species, such as yellow perch, contain smaller amounts of Vitamin A (10 RE per 100 g portion) in comparison with higher-fat species, such as coho salmon (39 RE), bass (35 RE) and freshwater drum (59 RE). In general, fish is a better source of this vitamin than beef, pork, or chicken.

3.7.3 Vitamin D

Vitamin D is a fat-soluble sterol that occurs naturally in many forms. It is ergosterol when found in plants, while in animals and humans, it is synthesized in the skin as 7-dehydrocholesterol and upon exposure to sunlight is subsequently converted to precalciferol, then cholecalciferol. This is later converted by the liver to the active form, calcitriol. Vitamin D behaves like a steroid hormone to control blood levels of calcium, and thus has effects on bone, kidney, and intestinal tissues. A deficiency of Vitamin D interferes with the body's absorption of calcium and perhaps also phosphorus, which results in bone demineralization.

Fish is among the best food sources of Vitamin D, but few data are available in food composition tables. A 100 g portion of herring and tuna provide 22 and 6 micrograms, respectively, of Vitamin D. In contrast, the same amount of Vitamin D-fortified milk and liver provide only 1 and 0.1-0.2 micrograms, respectively.

3.8 Minerals

While fish is known to contain many important trace elements, only those minerals that are frequently lacking in the diets of healthy populations are presented here.

3.8.1 Calcium

An estimated 99% of the body's calcium resides in the teeth and bones, where it is extracted and re-deposited as needed to keep blood levels of calcium constant. The one percent found in the blood, lymph and other body fluids is critical to the intracellular and extracellular environments of all living cells. The parathyroid hormone, calcitonin, calcitriol (Vitamin D) and other hormones help to regulate levels by releasing calcium from bone and controlling its absorption from the intestine and excretion in urine, feces and sweat. Bone loss occurs naturally with age, in both males and females; therefore, it is important that children and young adults achieve their optimum bone density so that age-related losses will not result in osteoporosis.

Many dietary factors affect the bioavailability of calcium; dietary fiber, phytic acid, uronic acid and oxalic acid are believed to reduce intestinal absorption. Calcium is poorly absorbed (5%) from spinach, for example, which is high in oxalic acid, but more readily available from kale, which is low in oxalic acid. Dairy products provide about one-half of dietary calcium in the U.S. Fish with soft bones can also be important dietary sources; for example, walleye, bass and yellow perch provide 141, 103 and 102 mg of calcium, respectively, in a 100 gram portion. Small fish eaten whole, such as sardines and smelts, as well as canned fish with bones, such as salmon, also contribute appreciable amounts of dietary calcium.

3.8.2 Iron

In North America and worldwide, iron deficiency is the most prevalent nutritional deficiency (Yip and Dallman, 1996), particularly among young children and premenopausal women. Men typically have approximately 3.8 grams of iron in their bodies, one-third of which is stored as ferritin and hemosiderin in the liver, bone marrow and spleen, and two-thirds of which is functional iron, mostly in the form of hemoglobin and myoglobin. Women's bodies have about 2.3 grams of iron, and only about one-eighth (0.3 grams) is in storage. The body's increased demand for iron in pregnancy (1.0 gram) is much greater than the average woman's iron stores. In situations such as this, when the body's functional needs for iron outstrip bodily stores, iron deficiency may result. Measures of serum ferritin indicate when body stores of iron are low or depleted (iron depletion). When transferrin saturation falls, erythrocyte protoporphyrin levels rise, but hemoglobin levels are normal, resulting in iron deficiency without anemia. Iron-deficiency anemia occurs when blood hemoglobin levels have also dropped below normal values.

On average, men absorb only 6% of the dietary iron they consume; the rest is not soluble and thus not bioavailable. Premenopausal women absorb about 13% of their dietary iron, which helps to offset their smaller body stores. Fish and other animal foods contain heme iron, which only accounts for about 15% of dietary iron (85% is nonheme) but which is absorbed at over twice the rate of nonheme iron. Further, the presence of fish, meat, or poultry in a meal greatly increases the bioavailability of the nonheme iron provided by plant foods.

As seen in Table 3-1, fish species differ in the amount of dietary iron they provide--channel catfish has 0.35 mg/100 grams while the same size portion of bass contains 1.91 mg. In general, fish contains less iron than beef, but comparable levels to pork and chicken. Although dietary iron levels are similar in eggs, the iron has poor bioavailability.

3.8.3 Zinc

Zinc is part of many enzymes, biomembranes, and is involved in RNA transcription, among other activities too numerous to mention here. It has held tremendous public health significance in developing countries since the 1960s, when zinc deficiency was linked to stunted growth and delayed sexual maturation. Inadequate intakes of zinc are common in North America, particularly among vegetarians and adult women (e.g., Borrud et. al, 1996). While quite widely distributed among plant and animal foods, zinc often has low bioavailability because of its interactions with copper, iron, and other food components such as phytates.

Animal foods provide approximately 70% of the dietary zinc in the U.S., and in general, foods rich in protein are also good sources of zinc. As shown in Tables 3-1 and 3-2, sport-caught fish contain from 0.51-1.43 mg of zinc per 100 gram edible portions, comparable to levels in eggs, tofu, refried beans, pasta and rice.

3.8.4 Selenium

Selenium is found in different forms in plants (mainly as selenomethionine) and animals (mainly as selenocysteine). Animals and humans rely exclusively on dietary sources of the mineral, which is an important component of the enzyme glutathione peroxidase and some transfer RNAs, and functions as an anti-oxidant. There is also some evidence that it may form complexes with mercury, cadmium, and other toxic heavy metals (Levander & Burk, 1991).

Seafood and organ meats (e.g., liver) are the best dietary sources of selenium (40-150 micrograms per 100 gram portions). Beef and pork have lower levels (10-40 micrograms), and are followed by cereals and grains, <10 to >80 depending upon the soil content; dairy products, <10 to 30; and fruits and vegetables <10 (Levander & Burk, 1991).

3.9 Effects of Food Preparation Methods on Nutritional Benefits

The type of cooking method may affect some nutritional components, while other components remain unaffected. During the cooking process fish flesh loses moisture, with the amount lost dependent on the fish species, the size of the piece and cooking method (Sabry, 1990). For finfish, cooking with dry heat results in a moisture loss of 22% of the original weight compared to a 21% loss with moist heat, or an eight percent loss with bread-fried cooking. Microwave cooking results in even higher moisture losses (i.e. 30-35%) than dry or moist heat cooking. Because the proportion of solids is increased with moisture loss, the concentrations of certain nutrients tend to be higher in cooked relative to raw fish. After adjustments for water loss have been made, however, cooking does not appear to affect the protein or total lipid levels. With the exception of poaching, which may cause a loss of some dissolved minerals when cooking water is discarded, the mineral content of cooked fish is usually not affected by the cooking process. Some vitamins may be destroyed during the cooking process but this is dependent on the method, duration, and temperature of cooking. For the B vitamins (i.e. thiamin, riboflavin, niacin, B6, and B12) a loss in the range of 0- 30% has been reported (Sabry, 1990). For vitamin A, a loss of 5-15% has been observed due to the cooking process. In general, cooking with high temperatures for long periods of time tends to cause the greatest loss of vitamins.

The fat content of fish may also be altered depending upon how it is prepared and cooked. A 100-gram portion of channel catfish that was breaded and fried had twice the amount of energy (calories), and four times the amount of fat than a similar portion that was cooked using dry heat (USDA, 1998). Breading and frying also significantly altered the proportions of lipids. The amount of saturated fat, monounsaturated fats, and polyunsaturated fats increased by 400 - 500% in the breaded and fried fish. Levels of omega-3 fatty acids also increased in the breaded and fried fish, although not as dramatically (i.e. 10-100%). When comparing the nutritional benefits of consuming various types of fish and other protein sources, it is important to consider the method of food preparation and any additional ingredients (e.g., oil for frying) that may be added to the final cooked product.

3.10 Effects of Food Preparation Methods on Contaminant Levels

The way fish is prepared and cooked can modify the amount of chemical contaminants consumed. Appendix E of *the U.S. EPA Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories, Volume 2* (U.S. EPA, 1997b) discusses the available data; some of this information is presented here.

The degree to which contaminants bioaccumulate in different fish species is dependent on their methods of feeding, the ability of the fish to metabolize the contaminants and the fat content of the fish (U.S. EPA, 1997b). Trimming the fat, and removing the skin and the internal organs will help decrease the amount of lipophilic contaminants but will not reduce exposure to those contaminants that concentrate in muscle and other protein-rich tissues (e.g. mercury).

The method of preparing the fish for cooking and eating appears to be a major factor in reducing the amount of certain contaminants in standard fish fillets. For example, trimming and cooking brown trout reduced the Mirex and PCB content by 74% and 78%, respectively (U.S. EPA, 1997b). However, broiling reduced the Mirex content by 26% but resulted in no reduction in the PCB levels. Removing the skin before cooking also resulted in a further 17% reduction in alpha-chlordane levels in chinook salmon fillets, compared to fillets baked with the skin on. Toxaphene levels were reduced by 40% when lake trout fillets had the skin removed and were charbroiled. For smallmouth bass, DDE levels were reduced by 54% when the fillets were trimmed. For certain ocean fish such as bluefish, the PCB content of the fillets was decreased by 27% after cooking and removal of skin and oil drippings (Trotter et al., 1988). For five fish species from the Great Lakes region, Zabik and Zabik (1995) found a 30-100% reduction in dioxin levels depending on the type of cooking method used. Smoking removed the greatest amount of dioxin (i.e. 100%) while salt boiling resulted in the smallest reduction (i.e. 30%). Preparation methods have a significant influence on the amount of various contaminants present in a cooked fish fillet.

3.11 Conclusions and Research Needs

There are many nutritional benefits associated with eating fish, regardless of the species type. Unlike red meats, eggs and dairy products, fish provides very high quality protein *and* a 'heart healthy' combination of fatty acids. Further, fish (both lean and fatty) is one of the few foods that contain n-3 (omega-3) fatty acids, a class of fatty acids that are essential for the development of the nervous system and that may have other beneficial health effects. Calcium, iron, zinc, vitamin A, niacin, vitamin B6, and vitamin D tend to be low in U.S. diets; fish supplies all of these vitamins and minerals, in addition to others.

Fish is known to be a good dietary source of selenium, but few reference data are published; more research into the role of selenium in human health is also needed. Nutrient databases contain a wide range of fish species, but samples used to obtain nutrient values are composites of cooked fish from various unknown locations. Nutrient values are generally expressed on the basis of a 100 gram cooked fish portion. This limits the extent to which comparisons can be made with contaminant data, which are usually based on raw tissue samples of wild fish gathered from specific geographic areas, and expressed as concentrations rather than on a weight basis.

We know that different methods of preparing and cooking fish will alter some of the organochlorine contaminant levels. Ideally, the same samples of prepared and cooked fish would be sent for both contaminant and nutrient analysis, and weighed records of amounts of the fish consumed would be kept to enable researchers to better assess the physiological risks and benefits to humans.

Cooperative Agreement with U S EPA on Comparative Dietary Risk

Table 3-1 Nutrition Values and Contaminant Levels in Fish - values for 100 g edible portion

	Coho Salmon	Rainbow Trout	Northern Pike	Walleye	Rainbow Smelt	Fresh-water Drum	Bass Mixed Species	Channel Catfish	Sunfish	Perch Mixed Species
Protein	23.4 g	22.9 g	24.7 g	24.5 g	22.6 g	22.5 g	24.2 g	18.5 g	24.8 g	24.9 g
Protein Efficiency Ratio ¹	3.55	3.55	3.55	3.55	3.55	3.55	3.55	3.55	3.55	3.55
Biological Value ²	76.0	76.0	76.0	76.0	76.0	76.0	76.0	76.0	76.0	76.0
Calories	139 kcal	150 kcal	113 kcal	119 kcal	124 kcal	153 kcal	146 kcal	105 kcal	114 kcal	117 kcal
Total fat	4.3 g	5.8 g	0.9 g	1.6 g	3.1 g	6.3 g	4.7 g	2.9 g	0.9 g	1.2 g
Saturated fat	1.1 g	1.6 g	0.2 g	0.3 g	0.6 g	1.4 g	1.0 g	0.7 g	0.2 g	0.2 g
MUFA=s	1.6 g	1.8 g	0.2 g	0.4 g	0.8 g	2.8 g	1.8 g	1.1 g	0.2 g	0.2 g
PUFA=s	1.3 g	1.8 g	0.3 g	0.6 g	1.1 g	1.5 g	1.4 g	0.6 g	0.3 g	0.5 g
18:2 Linoleic	0.056 g	0.288 g	0.041 g	0.033 g	0.058 g	0.199 g	0.112 g	0.142 g	0.019 g	0.014 g
18:3 Linolenic	0.055 g	0.187 g	0.027 g	0.018 g	0.063 g	0.146 g	0.142 g	0.096 g	0.013 g	0.015 g
20:4 AA	0.022 g	0.120 g	0.036 g	0.074 g	0.071 g	0.287 g	0.185 g	0.087 g	0.101 g	0.067 g
20:5 EPA	0.401 g	0.468 g	0.042 g	0.110 g	0.353 g	0.295 g	0.305 g	0.100 g	0.047 g	0.101 g
22:6 DHA	0.658 g	0.520 g	0.095 g	0.288 g	0.536 g	0.368 g	0.458 g	0.137 g	0.092 g	0.223 g
Cholesterol	55 mg	69 mg	50 mg	110 mg	90 mg	82 mg	87 mg	72 mg	86 mg	115 mg
Zinc	0.560 mg	0.510 mg	0.860 mg	0.79 mg	2.12 mg	0.850 mg	0.83 mg	0.61 mg	1.99 mg	1.43 mg

Cooperative Agreement with U S EPA on Comparative Dietary Risk

Iron	0 610 mg	0 380 mg	0 710 mg	1 67 mg	1 15 mg	1 15 mg	1.91 mg	0 35 mg	1 54 mg	1 16 mg
Calcium	45 mg	86 mg	73 mg	141 mg	77 mg	77 mg	103 mg	11 mg	103 mg	102 mg
Vitamin A	39 RE	15 RE	24 RE	24 RE	17 RE	59 RE	35 RE	15 RE	17 RE	10 RE
Vitamin B ₃	7 950 mg	5 770 mg	2.800 mg	2.810 mg	1 766 mg	2 862 mg	1 522 mg	7 950 mg	1.460 mg	1 900 mg
Vitamin B ₆	0 568 mg	0 346 mg	0 135 mg	0 138 mg	0.170 mg	0 346 mg	0 138 mg	0.106 mg	0.138 mg	0.140 mg
Vitamin B ₁₂	5 00 ug	6 30 ug	2.30 ug	2 31 ug	3.97 ug	2.31 ug	2.31 ug	2.90 ug	2 30 ug	2 20 ug
Chordane	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DDT	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chlorpyrifos	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dioxins	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lindane	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PCBs	NA	NA	NA	9 2-193 3 ng/g wet wt. ³	NA	NA	NA	NA	NA	NA
Mercury	NA	NA	NA	187-793 ng/g wet wt. ³	NA	NA	NA	NA	NA	NA

¹Protein Efficiency Ratio - gain in weight divided by weight of protein consumed

²Biological Value - the percentage of absorbed nitrogen retained

³Dellinger, J A et al. 1996 The Ojibwa Health Study fish residue comparisons for Lakes Superior, Michigan, and Huron Tox. Ind Health 12 393-402
NA indicates Not Available

Cooperative Agreement with U.S. EPA on Comparative Dietary Risk

Table 3-1 (Cont.) Nutrition Values and Contaminant Levels in Fish - values for 100 g edible portion, cont.

	Tuna Canned in water	Cod (Atlantic)	Halibut	Flatfish (Flounder & Sole)	Haddock	Mackerel Mixed Species	Orange Roughy	Ocean Perch	Sardines	Blue Crab	Northern Lobster
Protein	25.5 g	22.8 g	26.7 g	24.2 g	24.2 g	25.7 g	18.9 g	23.9 g	24.6 g	20.2 g	20.5 g
Protein Efficiency Ratio ¹	3.55	3.55	3.55	3.55	3.55	3.55	3.55	3.55	3.55	NA	NA
Biological Value ²	76.0	76.0	76.0	76.0	76.0	76.0	76.0	76.0	76.0	NA	NA
Calories	116 kcal	105 kcal	140 kcal	117 kcal	112 kcal	201 kcal	89 kcal	121 kcal	208 kcal	102 kcal	98 kcal
Total fat	0.8 g	0.9 g	2.9 g	1.5 g	0.9 g	10.1 g	0.9 g	2.1 g	11.5 g	1.8 g	0.6 g
Saturated fat	0.2 g	0.2 g	0.4 g	0.4 g	0.2 g	2.9 g	0.02 g	0.3 g	1.5 g	0.2 g	0.107 g
MUFA=s	0.2 g	0.1 g	1.0 g	0.2 g	0.2 g	3.4 g	0.6 g	0.8 g	3.9 g	0.3 g	0.160 g
PUFA=s	0.3 g	0.3 g	0.9 g	0.6 g	0.3 g	2.5 g	0.02 g	0.5 g	5.1 g	0.7 g	0.091 g
18:2 Linoleic	0.009 g	0.006 g	0.038 g	0.014 g	0.012 g	0.149 g	0.009 g	0.036 g	3.543 g	0.028 g	0.005 g
18:3 Linolenic	0.002 g	0.001 g	0.083 g	0.016 g	0.003 g	0.064 g	0.002 g	0.073 g	0.498 g	0.021 g	0
20:4 AA	0.034 g	0.028 g	0.178 g	0.048 g	0.029 g	0.104 g	0.002 g	0.005 g	0	0.084 g	0
20:5 EPA	0.047 g	0.004 g	0.091 g	0.243 g	0.076 g	0.653 g	0.002 g	0.103 g	0.473 g	0.243 g	0.053 g
22:6 DHA	0.223 g	0.154 g	0.374 g	0.258 g	0.162 g	1.195 g	NA	0.271 g	0.509 g	0.231 g	0.031 g
Cholesterol	30 mg	55 mg	41 mg	68 mg	74 mg	60 mg	26 mg	54 mg	142 mg	100 mg	72 mg
Zinc	0.77 mg	0.58 mg	0.53 mg	0.63 mg	0.48 mg	0.86 mg	0.96 mg	0.61 mg	1.31 mg	4.22 mg	2.92 mg
Iron	1.53 mg	0.49 mg	1.07 mg	0.34 mg	1.35 mg	1.49 mg	0.23 mg	1.18 mg	2.92 mg	0.91 mg	0.39 mg

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Table 3-1 (Cont.) Nutrition Values and Contaminant Levels in Fish - values for 100 g edible portion, cont.

Calcium	11 mg	14 mg	60 mg	18 mg	42 mg	29 mg	38 mg	137 mg	382 mg	104 mg	61 mg
Vitamin A	17 RE	14 RE	54 RE	11 RE	19 RE	14 RE	24 RE	14 RE	67 RE	2 RE	26 RE
Vitamin B ₃	13 280 mg	2 513 mg	7 123 mg	2.179 mg	4.632 mg	10.667mg	3 654 mg	2 436 mg	5 245 mg	3.300 mg	1 070 mg
Vitamin B ₆	0 350 mg	0 283 mg	0.397 mg	0 240 mg	0.346 mg	0 381 mg	0 346 mg	0 270 mg	0 167 mg	0 180 mg	0 077 mg
Vitamin B ₁₂	2 990 ug	1.048 ug	1 366 ug	2.509 ug	1.387 ug	4 230 ug	2 310 ug	1 154 ug	8 940 ug	7 300 ug	3 110 ug
Chordane	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DDT	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chlorpyrifos	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dioxins	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lindane	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PCBs (Total)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mercury	<0.10-0.75 ppm ³	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

¹Protein Efficiency Ratio - gain in weight divided by weight of protein consumed

²Biological Value - the percentage of absorbed nitrogen retained

³Dellinger, J. A. et al 1996 The Ojibwa Health Study: fish residue comparisons for Lakes Superior, Michigan, and Huron Tox. Ind. Health 12 393-402

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Table 3-2 Nutrition Values and Contaminant Levels in Other Protein Sources - values for 100 g edible portion

	Chicken (brst, roast)	Lamb (shank & sirloin)	Beef (tenderloin)	Pork (loin)	Pork (shoulder)	Ham (sliced)	Sausage (turkey)	Sausage (pork link)	Bacon	Fish Sticks
Protein	31.0 g	28.3 g	28.3 g	28.6 g	25.6 g	17.6 g	14.4 g	16.3 g	30.5 g	15.7 g
Protein Efficiency Ratio ¹	NA	NA	2.30	NA	NA	NA	NA	NA	NA	NA
Biological Value ²	74.3	NA	74.3	74.0	74.0	74.0	NA	74.0	74.0	NA
Calories	165 kcal	191 kcal	222 kcal	210 kcal	259 kcal	182 kcal	160 kcal	343 kcal	576 kcal	272 kcal
Total fat	3.6 g	7.7 g	11.2 g	9.8 g	16.6 g	10.6 g	9.6 g	30.5 g	49.2 g	12.2 g
Saturated fat	1.01 g	2.8 g	4.2 g	3.6 g	6.0 g	3.4 g	2.7 g	10.7 g	17.4 g	3.1 g
MUFA=s	1.2 g	3.4 g	4.2 g	4.5 g	7.4 g	5.0 g	3.6 g	14.8 g	23.7 g	5.1 g
PUFA=s	0.8 g	0.5 g	0.4 g	0.8 g	1.5 g	1.2 g	2.7 g	3.7 g	5.8 g	3.2 g
18:2 Linoleic	0.590 g	0.410 g	0.340 g	0.680 g	1.260 g	1.040 g	2.420 g	3.130 g	4.890 g	2.738 g
18:3 Linolenic	0.030 g	0.050 g	0.040 g	0.020 g	0.050 g	0.170 g	0.260 g	0.550 g	0.790 g	0.172 g
20:4 AA	0.060 g	0.050 g	0.050 g	0.040 g	0.070 g	0	NA	NA	0.130 g	0.018 g
20:5 EPA	0.010 g	0	NA	0	0	0	NA	NA	0	0.086 g
22:6 DHA	0.020 g	0	NA	0	0	0	NA	NA	0	0.128 g
Cholesterol	85 mg	89 mg	84 mg	79 mg	95 mg	57 mg	64 mg	77 mg	85 mg	112 mg
Zinc	1.00 mg	4.94 mg	5.59 mg	2.48 mg	4.51 mg	2.14 mg	2.15 mg	2.60 mg	3.26 mg	0.66 mg

Cooperative Agreement with U.S. EPA on Comparative Dietary Risk

Iron	1 04 mg	2 12 mg	3 58 mg	0 91 mg	1 40 mg	0 99 mg	1.38 mg	1 72 mg	1 61 mg	0.74 mg
Calcium	15 mg	8 mg	7 mg	17 mg	36 mg	7 mg	26 mg	16 mg	12 mg	20 mg
Vitamin A	6 RE	0	0	2 RE	3 RE	0	0	0	0	31 RE
Vitamin B ₃	13.712 mg	6 340 mg	3 920 mg	5 243 mg	4.070 mg	5 251 mg	NA	NA	7 322 mg	2 129 mg
Vitamin B ₆	0 600 mg	0 170 mg	0.440 mg	0 492 mg	0 277 mg	0 340 mg	NA	NA	0 270 mg	0 060 mg
Vitamin B ₁₂	0 340 ug	2.640 ug	2 570 ug	0 720 ug	1.060 ug	0 830 mg	NA	NA	1 750 ug	1 797 ug
Chordane	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DDT	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chlorpyrifos	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dioxins	NA	NA	0.6 ppt, wet wt ₃	59.3 ppt wet wt ₃	NA	59 3 ppt wet wt ₃	NA	NA	NA	NA
Lindane	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PCBs (Total)	416 pg/g wet wt ₄		528 pg/g wet wt ₄	672 pg/g wet wt ₄	NA	NA	NA	NA	NA	N
Mercury	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

¹Protein Efficiency Ratio - gain in weight divided by weight of protein consumed

²Biological Value - the percentage of absorbed nitrogen retained

³Research Triangle Institute. 1997 Toxicological profile for Chlorinated Dibenzo-p-dioxins (Draft) p 384

⁴Newsome, W H et al 1998 Residues of polychlorinated biphenyls (PCB) in fatty foods of the Canadian diet Food Addit & Contam 15(1) 19-29

NA indicates Not Available

Table 3-2 Nutrition Values and Contaminant Levels in Other Protein Sources - values for 100 g edible portion

	Hot Dog (plain)	Burger (double)	Chicken (fast food)	Fish Sandwich (fast food)	Kidney Beans	Refried beans	Pasta	Rice	Tofu (firm)	Yogurt (plain)	Cheddar Cheese	Egg (boiled)
Protein	10.6 g	17.0 g	21.9 g	10.7 g	5.2 g	5.5 g	4.8 g	2.7 g	15.8 g	3.5 g	24.9 g	12.6 g
Protein Efficiency Ratio ¹	NA	2.30	NA	NA	NA	NA	NA	NA	NA	NA	NA	3.92
Biological Value ²	NA	74.3	74.3	NA	NA	NA	NA	NA	NA	NA	NA	93.7
Calories	247 kcal	309 kcal	303 kcal	273 kcal	81 kcal	94 kcal	141 kcal	130 kcal	145 kcal	61 kcal	403 kcal	155 kcal
Total fat	14.8 g	15.9 g	18.1 g	14.4 g	0.3 g	1.3 g	0.7 g	0.3 g	8.7 g	3.3 g	33.1 g	10.6 g
Saturated fat	5.2 g	5.9 g	4.8 g	3.3 g	0.05 g	0.5 g	0.1 g	0.1 g	1.3 g	2.1 g	21.1 g	3.3 g
MUFA=s	7.0 g	6.9 g	7.5 g	4.9 g	0.02 g	0.6 g	0.1 g	0.1 g	1.9 g	0.9 g	9.4 g	4.1 g
PUFA=s	1.7 g	1.3 g	4.2 g	5.2 g	0.2 g	0.2 g	0.3 g	0.1 g	4.9 g	0.1 g	0.9 g	1.4 g
18:2 Linoleic	1.310 g	NA	3.840 g	4.821 g	0.067 g	0.132 g	0.249 g	0.062 g	4.339 g	0.065 g	0.577 g	1.188 g
18:3 Linolenic	0.432 g	NA	0.214 g	0.399 g	0.105 g	0.021 g	0.024 g	0.013 g	0.582 g	0.027 g	0.365 g	0.035 g
20:4 AA	NA	NA	0.083 g	NA	NA	0	0	0	NA	0	0	0.149 g
20:5 EPA	NA	NA	0.001 g	NA	NA	0	0	0	NA	0	0	0.005 g
22:6 DHA	NA	NA	0.023 g	NA	NA	0	0	0	NA	0	0	0.038 g
Cholesterol	45 mg	56 mg	91 mg	35 mg	0	8 mg	0	0	0	13 mg	105 mg	424 mg
Zinc	2.02 mg	3.25 mg	0.95 mg	0.63 mg	0.55 mg	1.17 mg	0.53 mg	0.49 mg	1.57 mg	0.59 mg	3.11 mg	1.05 mg

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Iron	2 36 mg	2 59 mg	0 91 mg	1 65 mg	1 23 mg	1 66 mg	1 40 mg	1 2 mg	10 47 mg	0 05 mg	0 68 mg	1 19 mg
Calcium	24 mg	49 mg	37 mg	53 mg	27 mg	35 mg	7 mg	10 mg	205 mg	121 mg	721 mg	50 mg
Vitamin A	0	0	36 RE	19 RE	0	0	0	0	17 RE	30 RE	278 RE	168 RE
Vitamin B ₃	3 720 mg	4 690 mg	7.35 mg	2 15 mg	0 502 mg	0.315 mg	1 672 mg	1.476 mg	0 381 mg	0 075 mg	0 080 mg	0 064 mg
Vitamin B ₆	0 050 mg	0 180 mg	0.350 mg	0 070 mg	0 069 mg	0.143 mg	0 035 mg	0 093 mg	0.092 mg	0 032 mg	0 074 mg	0 121 mg
Vitamin B ₁₂	0 520 ug	1.660 ug	0 410 ug	0 680 ug	0	0	0	0	0	0.372 ug	0 827 ug	1 10 ug
Chlordane	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DDT	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chlorpyrifos	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Dioxins	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Lindane	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PCBs (Total)	678 pg/g wet wt.	428 pg/g wet wt.	454 pg/g wet wt.	NA	NA	NA	NA	NA	NA	NA	NA	867 pg/g wet wt.
Mercury	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

¹Protein Efficiency Ratio - gain in weight divided by weight of protein consumed

²Biological Value - the percentage of absorbed nitrogen retained

³Newsome, W H et al 1998 Residues of polychlorinated biphenyls (PCB) in fatty foods of the Canadian diet Food Addit. & Contam 15(1).19-29.

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4 Health Risks from Eating Contaminated Fish

4.1 Introduction

Assessing and quantifying the potential risks to human health from eating contaminated fish is essential to evaluating both the target risks from consuming contaminated fish and the countervailing risks that may result from consumers following fish advisory advice. Adverse health effects from contaminants in fish range widely and may include cancer, developmental and reproductive toxicity, and other systemic effects. The occurrence and severity of the effects will depend upon the amount to which a person is exposed, and characteristics of the individual, including genetic makeup and life stage.

Traditionally, risk assessors have calculated estimates of an individual or population's risk for getting cancer from exposure to chemicals, while for non-cancer endpoints, a reference dose or concentration (for contaminants in air) is identified at which one would not expect to see adverse effects in a population (including sensitive subgroups). Cancer slope factors are estimates of risk that are derived from dose-response data from laboratory animal or human epidemiology studies. Traditionally, a linearized multi-stage model has been used to extrapolate from what is observed at high experimental concentrations to lower environmental exposure levels. This cancer potency is estimated as the 95% upper confidence limit of the slope of the dose-response curve in the low dose region. This is an upper estimate of risk and the actual risk may be much lower or even approach zero. EPA proposed revised cancer guidelines in 1996 (U.S. EPA 1996) and additional proposed guidance in 1998 (U.S. EPA, 1998), which recommend that the mode of action be considered. The guidance recommends that a linear extrapolation should be used if the chemical is believed to act via a genotoxic mode of action, if the mode of action is expected to be linear at low doses, or (as a default) if no mode of action data are available. The guidance also recommends that a non-linear approach to extrapolation to low doses should be used when sufficient information on mode of action warrants. For non-cancer effects, a single estimate of a "safe" dose is identified from animal or human data, using the No Observed Adverse Effect Level (NOAEL) divided by uncertainty factors to account for extrapolation from animals to humans, variability in the human population, and deficiencies in the database of studies on the substance. The resulting 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 1999).

These cancer risk estimates and reference doses have been used to estimate consumption rates of contaminated fish which would be without appreciable risk to humans following exposure over a lifetime (U.S. EPA, 1997b). However, in order to compare risks to risks and risks to benefits for both cancer and non-cancer endpoints, we thought it necessary to express both types as a risk estimate. A method to determine how likely it is that adverse effects will occur above the RfD (or with a hazard index (HI) greater than 1 for a mixture of chemicals) is needed. In this document we use a method for estimating non-cancer risk above the reference dose (RfD) developed by the U.S. EPA and the ChemRisk Division of McLaren/Hart (Price *et al.*, 1997). This is an evolving area of research, however, which needs further development.

To assist in illustrating the framework, six target substances were chosen to develop estimates of risk above the RfD (see Table 4-1). The six were selected based upon the frequency of detection in a national study of chemical residues in fish (U.S. EPA 1992), and the number of states that have issued advisories for that substance. Of these six substances appropriate data for developing these non-cancer estimates were available for methylmercury and chlordane.

Table 4-1. Frequency of residue presence in fish, and the number of states that have issued advisories for the chosen chemicals.¹

Chemical Name	Number of states with advisories	Percent of sites sampled where compound was detected in fish ²
DDT and Metabolites	9	99%
Methylmercury	27	92%
Dioxin (TCDD)	22	70%
PCBs	31	91%
Chlordane	24	61%
Chlorpyrifos	--	26%

¹ Source: U.S. EPA (1992).

² Fish were collected from 388 sites throughout the United States. Sites included target areas near point and nonpoint sources, sites representative of background levels, and USGS NASQAN sites. A subset of 103 sites were sampled during the National Dioxin Study (U.S. EPA, 1987) that had been analyzed only for 2,3,7,8 TCDD, but were reanalyzed for all dioxin/furan congeners and other xenobiotic compounds.

This chapter briefly explains the available methods for estimating risk above the RfD and resulting risk information for the six selected chemicals. More information on traditional risk assessment methods and calculating risks from contaminants in fish is found in EPA's *Guidance for Assessing Chemical Contaminant Data for use in Fish Advisories: Volume 2* (U.S. EPA 1997b).

4.2 Calculating Risk above the Reference Dose for Noncancer Endpoints

The RfD approach and measures of hazard such as the Margin of Exposure (MOE) and Hazard Index (HI) are useful to determine unsafe doses or aid in the evaluation of mixtures and comparison of chemicals; however, these approaches provide no guidance on risk. The framework developed in this document looks at both the noncancer and carcinogenic risks from chemicals together to balance these with the health benefits of consuming fish. This necessitates using a method to estimate health risk for noncancer endpoints when the RfD or "safe" level is exceeded.

Unlike for carcinogenicity, there is no noncancer dose-response model commonly accepted for estimating risks above the RfD. For the purposes of illustrating this framework, we estimated risk using the approach developed by the U.S. EPA and ChemRisk (Price *et al.*, 1997). This approach was selected because of its ease of use and fidelity to existing EPA sources of information. Two other possible approaches are briefly presented below. Estimating noncancer risk is an area that needs further research and development.

4.2.1 EPA/ChemRisk Model

This approach is the result of a four-year collaboration between the ChemRisk division of McLaren/Hart and the U.S. EPA (Price *et al.*, 1998; Swartout *et al.*, 1998b). It builds on the existing RfD framework requires minimal new information, and quantitatively deals with uncertainty and variation in response. The basic premise is that there is generally more information available than is used to derive the RfD and that the same method that estimates the RfD can be applied to other points on the dose-response curve for humans. This method postulates a conservative linear threshold model for the dose-response relationship of noncarcinogenic agents. The approach uses Monte Carlo simulation of uncertainty factor distributions to develop a family of potential dose-response curves reflecting the uncertainty in interspecies extrapolation, interindividual variability, extrapolation from subchronic to chronic responses, extrapolation from LOAEL to NOAEL, and database uncertainty.

The approach is based on three concepts:

- Use the RfD as a model of a zero (or minimal) risk (ED_0 - effective dose zero) in humans.
- Use the current system of uncertainty factors to predict the dose that causes an effect in a typical human (ED_{50}).
- Use a linear model as an upper bound to the actual dose response for doses between the ED_{50} and ED_0 .

To model the ED_0 , one can use the definition of the RfD where ED_0 is equal to the NOAEL, or Benchmark Dose, divided by the uncertainty factors for various extrapolations (e.g., intra- and interspecies extrapolation). These uncertainty factors are defined as distributions

The concept of estimating the dose that causes an effect in a "typical individual" is not usually considered in noncancer risk assessment; in this approach the dose causing a response in a typical individual is conceptually similar to a chronic ED_{50} . To calculate the ED_{50} for humans one could take the ED_{50} in animals (ED_{50a}) and divide by the uncertainty factor for interspecies extrapolation (UF_A). In this case the intraspecies uncertainty factor (UF_H) is not applied. This UF_A is traditionally viewed as representing interspecies differences in the NOAEL, not in the ED_{50s} . The ED_{50a} should be based on all adverse effects in the test animals, not just the critical effect.

The third concept -- use of a linear model -- assumes that the fraction of the population that responds at doses between ED_{0h} and ED_{50h} is a linear function of dose in excess of the ED_{0h} . This assumption will be conservative for compounds with sublinear dose-response curves.

In this model the uncertainties in factors such as UF_A and UF_H are expressed as distributions. The model predicts the dose response by randomly selecting values for UF_A and UF_H and calculating a response to the dose. The process is repeated several thousand times and a range of response values is produced for each dose. There is a limitation to this approach in that the

assumption that a linear response is conservative only holds for doses below the ED₅₀. The proposed model cannot be used, therefore, to predict the dose that causes responses greater than 50 percent.

The predicted response should be viewed as a conservative (health protective) estimate of the probability of one or more adverse effects occurring in an exposed individual. Due to limited evidence of concordance between effects in animals and humans, however, the effect in humans should not be assumed to be the same. The linear response will result in an overestimate of risk. This approach has several strengths: it can produce quantitative estimates of risk; the analysis is independent of the actual dose-response curve, and the analysis is conservative (linear model assumption).

Because of the uncertainty in the level of risk at the RfD, this model should be used to estimate doses associated with low risk above the RfD with some caution. An estimate of a dose causing a 5% response (ED₀₅), however, would not be expected to change much. The assumptions upon which this approach is based are not without controversy. Many toxicologists and risk assessors are not comfortable with the assumption that the RfD is a measure of the ED₀, while others believe that the RfD is a subthreshold dose. For certain uses, this model is insensitive to whether the RfD compares to zero risk or merely very low risk (ED_{0.0001}). This proposed method produces a constant measure of risk, is consistent with the RfD, and differentiates between uncertainty and variability.

To illustrate this framework, calculation of risks above the RfD were attempted for the six selected chemicals (DDT, methylmercury, dioxin, PCBs, chlordane, and chlorpyrifos). The risks are based on the critical effect given in EPA's Integrated Risk Information System (IRIS). Dose response modeling was used to estimate the dose causing a 50% response (ED₅₀). Probability distributions were employed for each uncertainty factor (UF) used by EPA in setting the RfD. Where an uncertainty factor of ten was used in the RfD derivation, the reference distribution developed by Swartout *et al.* (1998b) to represent the uncertainty factor was used. Where a value of three was used, the square root of the values from the Swartout *et al.* (1998b) distribution was used. In cases where another factor was used, an alternative distribution was used (e.g., methylmercury). The specific distributions used are detailed in the sections on individual chemicals below.

The results of this analysis is an estimate of the dose response for a substance between the threshold (or minimal risk level, such as the ED₀₁) and the ED₅₀. The model assumes that the dose response is linear over this range, and where a compound has a sub-linear response this approach will over-estimate the risk. The approach also characterizes the uncertainty in the dose response that occurs because of the uncertainty in the estimates of the threshold and the ED₅₀. In this analysis, this uncertainty is presented in terms of the median estimate of a response for a given dose (i.e., the response that has a good chance of being above or below the true risk) and the 90 percent confidence limits for the response.

Analyses of risks above the RfD for chlordane and methylmercury were completed. The critical studies and UFs for chlorpyrifos are also presented below; however, the analysis could not be

completed due to unavailability of necessary data from the critical studies. Risks above the RfD could not be estimated for dioxin, DDT, and PCBs due to limitations in the available data. Details regarding the limitations of the critical study/effect data are provided below.

4.2.2 Other Approaches to Calculate Risk above the RfD

Another method to potentially estimate risk above the RfD is to adapt the use of a benchmark dose (BMD). EPA (1995) has defined the BMD as a statistical lower confidence limit for a dose that produces a predetermined change in response rate of an adverse effect compared to background. The BMD method attempts to use more of the available dose-response information by fitting a mathematical model to the data and then determining the dose associated with a specified response rate of an adverse effect. The resulting BMD value is used as a substitute for the no effect level and divided by appropriate uncertainty factors to estimate a RfD.

A number of decisions need to be made in applying the BMD method to estimate RfDs and likewise apply to estimating risks above the RfD. For example, for risk above the RfD decisions must be made on which mathematical model to use, what confidence limit to use, and what effect to model. Furthermore, the choice of uncertainty factor must also be incorporated into the estimation of risk and the model should have some way to approximate the RfD as zero risk.

A third method that has been proposed for quantitative dose-response analysis for noncancer toxicity data is that of categorical regression. This involves statistical regression on severity categories of overall toxicity (Hertzberg and Miller 1985; Hertzberg and Wymer 1991; Hertzberg 1991). By assigning severity categories, all adverse effects may be taken into account rather than focusing on the critical effect only, as in the previous two approaches. In addition, toxicity data from multiple studies can be used in this approach. [Categorical regression also has the added advantage of incorporating a severity ranking into its determination, thereby avoiding unnecessary criticism of the scale severity that we highlight in Chapter 6.]

The results of the regression can then be used to estimate risk above the RfD, by providing information about increasing toxicity with increasing dose rate. Categorical regression may be a preferred approach for calculating risk above the RfD because it uses more data than the other approaches. However, the approach is data and resource intensive and has not been done for the most significant fish contaminants. We recommend that the categorical regression approach be used for common pollutants found in fish in order to better estimate risks and allow consideration of benefits.

Confidence in this approach was enhanced by the close proximity of the data to the RfD. Confidence in using categorical regression or BMD modeling to estimate the risk above the RfD is increased when the RfD is based on human data (and thus a small uncertainty factor was used). Greater caution would be needed in the estimation of risks further from doses at which data exist.

BMD and categorical regression are newer dose response modeling techniques for use with noncancer toxicity data. One can with caution extend the modeling below the data to regions above the RfD – and the closer the extrapolation is to the data, the more confidence one has in the results.

4.3 Dose Response Information for the Six Selected Target Substances

The framework relies upon estimates of risk for both cancer and non-cancer endpoints. For illustration in this document, EPA risk estimates from the IRIS have been used (along with the estimates of risk above the RfD calculated for this project, which were based on IRIS RfDs and their corresponding principal studies).

Volume 2 of U.S. EPA's series on *Guidance for Assessing Contaminant Data for Use in Fish Advisories* provides guidance on chemical contaminant data for use in fish advisories and on the development of risk-based meal consumption limits for 25 high-priority chemical contaminants, referred to as target analytes (U.S. EPA, 1997b). These 25 target analytes were identified by EPA's Office of Water as significant based on documented occurrence in fish and shellfish, persistence in the environment, potential for bioaccumulation, and oral toxicity to humans. Volume 2 contains a toxicological profile summary for each of the target analytes is provided and consumption limit tables for adults and children are presented. Instructions for modifying the consumption limit tables to reflect local site-specific conditions for populations of concern are given. Separate tables are provided for women of reproductive age for methylmercury and polychlorinated biphenyls (PCBs). Additional information on risk assessment methods, population exposure, fish consumption patterns consumption surveys, risk reduction through use of various preparation and cooking procedures, and risk characterization is presented. Unless otherwise noted the toxicity data in this chapter are summarized from Volume 2.

In the development of the following framework, a hypothetical example was used which included estimates for risks above the RfD for methylmercury and chlordane. The details of these estimations are found below, and were derived using methods summarized below. In addition, cancer risk was estimated for chlordane since an EPA slope factor is available. Several of the other chemicals have cancer slope factors, but for none of the others have risk above the RfD calculations been developed.

4.3.1 DDT and Metabolites (DDE and DDD)

DDT is an organochlorine pesticide that in experimental animals causes cancer, liver damage, and to a lesser extent leukocytosis and decreased hemoglobin levels. Adverse developmental and immunological effects have been shown as well as estrogen-like effects on the developing reproductive system with chronic exposure. Prenatal exposure in experimental animals also evokes latent effects such as altered learning ability and permanent structural changes in the brain. Immunological effects have been also observed after short exposures. Some groups of people may be at greater risk, including children, those with cardiac disease, diseases of the nervous system or liver, and nursing infants (due to increased exposures).

EPA's IRIS classifies DDT (and its metabolites DDE and DDD) as B2, probable human carcinogens by the U.S. EPA. This classification is based upon studies in various mouse strains and studies in rats. IRIS reports a medium confidence RfD of 0.0005 mg/kg-day for liver lesions based upon a 1950 dietary study with rats. For cancer, the slope factor for oral exposure to DDT is 0.34 per (mg/kg)/day. This corresponds to a risk specific dose (RSD) of 0.00003 mg/kg-day at

the 1 in 100,000 risk level. These values should be used for the sum of the 4,4', and 2, 4' isomers of DDT, DDE, and DDD.

To estimate risk from exposures above the RfD, the IRIS RfD was examined. This RfD was derived from a dietary study in weanling rats in which animals (25/sex/group) were fed commercial DDT at levels of 0, 1, 5, 10, or 50 ppm for 15-27 weeks (Laug *et al.*, 1950). The critical effect was defined by EPA as liver lesions described as hepatocellular hypertrophy, especially centrilobularly, increased cytoplasmic oxyphilia, and peripheral basophilic cytoplasmic granules (based on H and E paraffin sections). The NOAEL and LOAEL were defined as 0.05 mg/kg-day (1 ppm) and 0.25 mg/kg-day (5 ppm), respectively. A total UF of 100 was used representing values of 10 each for interspecies extrapolation and interindividual variation.

Unfortunately, dose response modeling for noncancer endpoints could not be performed and risks above the RfD for DDT could not be quantified because sufficient data were not available from the critical study (Laug *et al.*, 1950) regarding the incidence of animals with liver lesions in each dose group. It is also important to note that the liver changes observed in this study were subsequently suggested to be adaptive in nature and not representative of actual liver toxicity (Ortega, 1966). The noncancer risks for DDT may be overestimated by using a RfD based on this study.

4.3.2 Methylmercury

Chronic exposure to methylmercury (MeHg) produces impairment of nervous system development in human fetuses, with exposure at sufficient levels evoking cerebral palsy-like symptoms. Prenatal exposure to lower doses shows more subtle retardation of infant development. In postnatal chronic exposure from fish consumption, neurological effects are also exhibited. Symptoms include visual and aural impairment, numbness in the extremities and around the mouth, impairment of fine motor functions such as writing, speaking, and walking, and mental disturbances. Chronic oral risk values have been developed by EPA (1999), ICF Kaiser (ITER, 1999) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1999). Mice exposed to methylmercury developed kidney tumors in males but not females. However, carcinogenic effects in mice were observed in the presence of extensive tissue damage.

For methylmercury, the U.S. EPA's IRIS reports a medium confidence oral RfD for chronic exposure of 0.0001 mg/kg-day based upon neurological effects on 81 Iraqi children who had been exposed in utero. The mothers had consumed methylmercury-contaminated grain. The RfD is based on a level of exposure estimated by determining the mercury level in hair associated with the 95% lower confidence limit on a benchmark dose (BMDL) of 10%. The BMDL of 11 ppm maternal hair is adjusted by a dose conversion equation used to relate exposure level to the concentration of methylmercury in blood and hair, and an uncertainty factor of 10. The U.S. EPA has not evaluated the risk of carcinogenic effects because of insufficient data.

A site-specific RfD distribution (1-99 percentiles) of 0.0003 to 0.001 mg/kg-day, based upon a cohort study of mother-infant pairs in the Seychelles Islands has been developed by ICF Kaiser

and peer reviewed by an independent group of scientists (*ITER*, 1999). The RfD is based on a distribution of intakes associated with a BMDL of 10% of 21 ppm maternal hair, a physiologically-based pharmacokinetic (PBPK) model, and an uncertainty factor of 3.

The Agency for Toxic Substances and Disease Registry (ATSDR, 1999) updated its earlier Toxicological Profile on Mercury and developed a minimal risk level (MRL) of 0.0003 mg/kg-day based upon a cohort study of mother-infant pairs in the Seychelles Islands, a NOAEL of 0.0013 mg/kg-day, an uncertainty factor of 3, and a modifying factor of 1.5. ATSDR noted high confidence that the MRL of 0.0003 mg/kg-day "is protective of the health of all potentially exposed human populations" (ATSDR, 1999; p. 258). In its announcement of this new MRL, ATSDR advises fish consumers, states and other agencies not to revise their existing fish advisories based on the ATSDR updated profile.

Developing fetuses and individuals with impaired central nervous system (CNS), kidney, or liver function are particularly susceptible to adverse effects from exposure to methylmercury. Individuals with inadequate levels of zinc, glutathione, antioxidants and/or selenium are also at a higher risk.

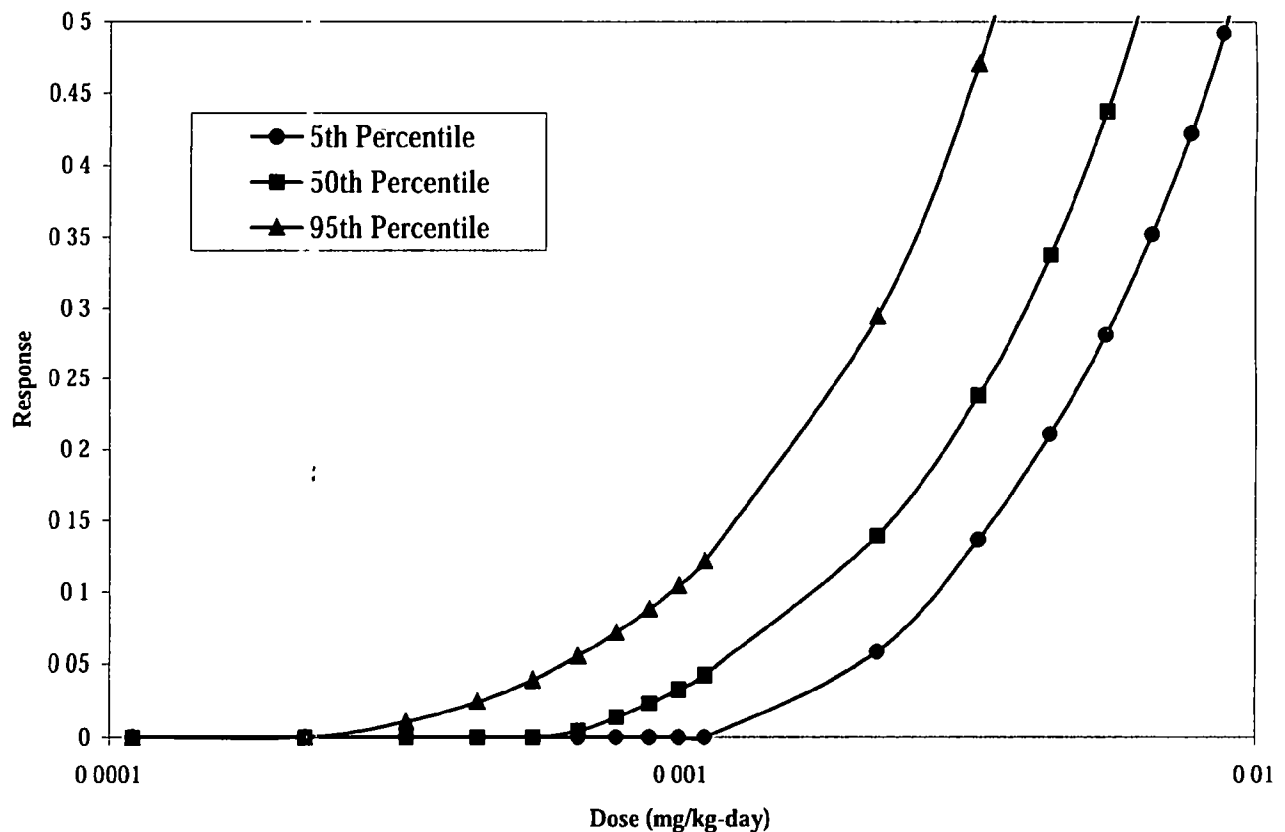
EPA issued interim guidance in April 1999 to EPA managers directing them to continue to use the RfD on IRIS until the National Academy of Sciences completes its report in 2000. Therefore, to calculate the risk above the RfD, the data behind the RfD on IRIS were examined. The methylmercury RfD is based on an evaluation of mother-child pairs from Iraq who were exposed to methylmercury in grains and bread (Marsh *et al.*, 1987; Seafood Safety, 1991). The critical effect used by EPA to derive the RfD were developmental effects in infants, including delayed onset of walking, delayed onset of talking, mental symptoms, seizures, and neurological scores based on clinical evaluations. Continuous data from this study were placed in 5 different dose groups and incidence rates were determined. The RfD (0.0001 mg/kg-day) was based on a benchmark dose of 11 ppm methylmercury in maternal hair. A pharmacokinetic algorithm was used to transform the concentration in maternal hair to the daily intake of 1.1 ug/kg-day. The following quantal data were used to calculate the benchmark dose and the ED₅₀:

<u>Dose (ppm in hair)</u>	<u>Incidence of Developmental Effects</u>
1.37	5/27
10.0	3/14
52.5	6/13
163	8/12
437	14/15

The MLE (maximum likelihood estimate) of the ED₅₀ for this data is 117 ppm MeHg in maternal hair or 0.0011 mg/kg-day. This value was derived using a Weibull model with the threshold set as zero (Swartout, 1998a).

A total UF of 10 was used for the IRIS RfD, which represents values of 3 each for human variability and database uncertainty, respectively. The UF of 3 for human variability represents the uncertainty in the ratio of daily intake to hair levels due to human variability in

Figure 4-1. Dose-Response Curves for Methylmercury



methylmercury pharmacokinetics. This uncertainty was characterized by EPA using a one-compartment pharmacokinetic model and data on interindividual variation in the model inputs (EPA, 1997a). Therefore, the distribution used to characterize this UF was based on specific data on methylmercury pharmacokinetics (Swartout, 1998a). The square root of the reference distribution was used to establish the distribution of the database UF.

Figure 4-1 shows the 5th, 50th, and 95th percentile dose-response curves for methylmercury. Responses at these percentiles for given multiples of the methylmercury RfD are also presented in Table 4-2. Figure 4-1 and Table 4-2 suggest a much steeper dose-response curve for methylmercury than for chlordane (see below). As the table shows, at a dose only five times higher than the RfD, the 90% confidence limit suggests that as many as 4% of the population might respond. At 50 times the RfD, there is 50% probability that 44% of the population would respond, with 90% certainty that the response would range from 28% to greater than 50%.

Table 4-2: Methylmercury Responses at Multiples of the Reference Dose¹

Multiple of Reference Dose	Dose (mg/kg-day)	Response		
		5th Percentile	50th Percentile	95th Percentile
1	0.00011	0.0%	0.0%	0.0%
5	0.00055	0.0%	0.0%	3.9%
10	0.0011	0.0%	4.3%	12.1%
50	0.0055	28.2%	43.7%	>50%
100	0.011	>50%	>50%	>50%

¹ Based on the RfD and underlying data as on EPA's IRIS (U.S. EPA, 1999). The use of other, more recent, data is also possible which may lead to a different estimation of the risk above the RfD

4.3.3 Dioxin

Dioxin is a generic term that is used for 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD). However, seventeen 2,3,7,8-substituted dibenzo-*p*-dioxin compounds are grouped together in the interest of simplicity (U.S. EPA 1987). Dioxin is extremely toxic and targets multiple organ systems in experimental animals. Some of these effects have also been seen in humans. Effects observed in animal studies include teratogenicity, fetotoxicity, reproductive dysfunction, carcinogenicity, and immunotoxicity. Wide differences in the toxic responses to dioxin are seen among species. There is a great deal of concern over the health effects of TCDD because of its persistence in the environment, its potency as a carcinogen, and its potential for bioaccumulation (U.S. EPA 1987). Dioxin is currently under reassessment by the U.S. EPA; for the purposes of this report information from U.S. EPA (1987) is summarized below.

Dioxins have the highest cancer potency in animals of any chemicals evaluated by the U.S. EPA. U.S. EPA (1987) reports a cancer slope factor of 1.56×10^5 per (mg/kg)/day, based on experimental animal results. This corresponds to an RSD of 6.4×10^{-11} mg/kg-day or 2×10^{-9} mg/L drinking water at the 1 in 100,000 risk level. EPA at one time calculated a RfD of 0.000001 mg/kg-day. EPA is in the process of revising its assessment of the risk from dioxin exposure. This reassessment may likely change both the cancer and noncancer risk values for this chemical.

To calculate the risk above the reference dose, the acceptable daily intake (ADI) of 0.000000001 mg/kg/day from EPA's Ambient Water Quality Criteria Document for 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (EPA, 1984) was examined. This ADI was based on a reproductive effects reported in a 3-generation rat study (Murray *et al.*, 1979). A LOAEL of 0.001 ug/kg-day was determined for a reduction in the gestation index, decreased fetal weight, increased liver to body weight ratio, and increased incidence of dilated renal pelvis. This was based on a re-evaluation of the data from the original study (Nisbet and Paxton, 1982). A total uncertainty factor of 1000 was used, consisting of interspecies, interindividual, and LOAEL to NOAEL UFs of 10 each.

The gestation survival index was the only critical effect data available from the Murray *et al.*, (1979) for which dose response modeling could be performed to generate an ED₅₀. Gestation survival data for the f1a and f1b generations (offspring of two separate matings of exposed parents) were combined prior to dose response modeling. Dose response modeling was performed for this data using the THRESH multistage model (ICF Kaiser, 1997). The gestation survival data failed the goodness of fit criteria for the model and the ED₅₀ could not be estimated. Risks above this ADI could therefore not be determined for TCDD using this data.

4.3.4 Polychlorinated Biphenyls (PCBs)

Polychlorinated biphenyls (PCBs) are mixtures of chlorinated biphenyl compounds manufactured by under the trade name Aroclor with a numeric designation indicating the chlorine content of the mixture. Manufacture and use of PCBs was banned 1979, however, PCBs are extremely persistent in the environment and biomagnify *via* the food chain (U.S. EPA, 1997b).

The majority of mutagenicity assays for PCBs have been negative, but positive cancer responses are seen with the higher chlorinated congeners (ATSDR, 1997). EPA classifies PCBs as Group B2, probable human carcinogens, based liver tumors seen in studies in rats exposed to various Aroclor mixtures.

Because environmental processes such as degradation and transportation alter the composition of environmental PCB mixtures compared with commercial mixtures, EPA has used a tiered approach for assessing cancer potency of PCB mixtures and developed several ranges of risk values. For the "high risk and persistence" tier, EPA calculated a central-estimate slope factor of 1.0 per (mg/kg)/day and an upper-bound slope factor of 2.0 per (mg/kg)/day, based on several studies of Aroclor 1254. This corresponds to Risk Specific Doses of 0.00001 and 0.000005 mg/kg-day at the 1 in 100,000 level. This range of risk values should be used when exposure is likely to be through the food chain, soil ingestion, dust or aerosol inhalation, or whenever there is potential for exposure in early life (U.S. EPA, 1999). Evaluating exposure and risk from contaminated fish would use this range of slope factors.

The U.S. EPA has established a chronic oral RfD for both Aroclor 1254 and Aroclor 1016. The medium confidence RfD for Aroclor 1254 is 0.00002 mg/kg-day based upon a LOAEL of 0.005 mg/kg-day for ocular and immunological effects in monkeys. The medium confidence RfD for Aroclor 1016 is 0.00007 mg/kg-day based on reduced birth weights in a monkey reproductive bioassay. The ATSDR also has established a minimal risk level (MRL) for Aroclor 1254 of 0.00002 mg/kg-day based upon a LOAEL of 0.005 mg/kg-day for an immunological endpoint (ATSDR, 1999).

To estimate risk above the RfD, the Aroclor 1254 RfD was examined (it is more toxic and the 1016 data did not appear adequate for modeling). This RfD is based on dermal/ocular and immunological changes in rhesus monkeys exposed to dietary concentrations of 5, 20, 40, or 80 ug/kg-day Aroclor 1254 for over 5 years (Tryphonas *et al.*, 1989, 1991a,b; Arnold *et al.*, 1993a,b). The lowest dose was designated as a LOAEL for these effects. A total uncertainty

factor of 300 was used based on an interindividual UF of 10, an interspecies UF of 3, a subchronic to chronic UF of 3, and a NOAEL to LOAEL UF of 3.

The incidence data for the dermal/ocular effects in each dose group is not available from the critical studies. Group mean data are available for some of the immune system parameters measured (i.e., decrease in antibody response to sheep erythrocytes). However, the data from each individual monkey was needed for conversion of the data to a quantal form that could be used in standard dose response modeling to generate the ED₅₀. Individual clinical records for each monkey could be reviewed to generate incidence data for the clinical health findings; however, this was beyond the scope of the current project. Thus, risk above the RfD was not estimated for aroclor 1254.

To date, U.S. EPA has not evaluated data on Aroclors 1242 or 1260; nor has EPA developed RfCs for any of the Aroclors. The Great Lakes Task Force has developed an interim position on the noncancer toxicity of PCBs in fish using an average of the RfDs for Aroclors 1016 and 1254. This value is 0.00005 mg/kg-day. As mentioned above, the U.S. EPA has also published a revised position on PCB cancer risk assessment on IRIS (EPA, 1999).

A problem with the available risk values is that they are based on the toxicity of commercial mixtures, and the environmentally-relevant mixtures have not been tested. While use of a sufficiently similar mixture may be appropriate, the question of what constitutes "sufficiently similar" for environmental mixtures of PCBs when compared to commercial mixtures needs to be answered at each individual site or situation. Toxicity equivalency factors have been discussed for different PCB congeners and some limited conclusions reached (EPA, 1997b). For the purposes of this report, however, we assume that the toxicity data on PCBs found on EPA's IRIS is relevant for the estimation of potential risks from PCB mixtures found in fish.

The results of human epidemiology studies differ somewhat from the non-human primate toxicity studies in critical effect. PCB mixtures passed to neonates from *in utero* exposure and breast milk have been shown to cause developmental defects including cognitive deficits that persisted at least until 4 years of age in human infants (ATSDR and U.S. EPA, 1997).

A number of epidemiological studies relating fish consumption with deleterious effects have been conducted over the past two decades. Several cohort studies in the Great Lakes Basin have been conducted (the New York State Angler Cohort, the Michigan Sports Fisherman Cohort, the Michigan Maternal/Infant Cohort, and the Wisconsin Maternal/Infant Cohort). These studies have focused upon possible adverse effects due to fetal PCB exposure from mothers who consume fish from the Great Lakes. There have been indications of alterations in birth size, gestational age, and neurological development in these studies. ATSDR and EPA recently reviewed studies of exposure to PCBs through fish consumption, particularly for fish from the Great Lakes. The two agencies prepared a paper entitled "Public Health Implications of Exposure to Polychlorinated Biphenyls (PCBs)" (ATSDR and U.S. EPA, 1999) which concluded that the "weight of evidence clearly indicates that populations continue to eat fish containing PCBs and that significant health consequences are associated with consumption of large amounts of some fish" (ATSDR and U.S. EPA, 1999, p. 2). Health effects include possible reproductive

function may be disrupted, neurobehavioral and development deficits in newborns and school-aged children exposed in utero, other systemic effects that are associated with elevated serum levels of PCBs, and increased cancer risks.

Swain (1991) compared all four of the cohorts and concluded that PCB exposure from fish could be correlated with alterations in neonatal health and health in early infancy with reasonable certainty (Swain, 1991). Swain (1991) found that effects in infant birth weight, maternal health condition, gestational age, composite activity ranking and McCarthy memory scale deficits had to be classified as indeterminate, but could not be negated. Swain (1991) also stated that the relationship between adverse effects on the health status of neonates and infants and PCB exposure in the Michigan cohort could be causally affirmed and that data from other geographic locals only tends to support this hypothesis. The available human data could not be used to estimate a risk above the RfD.

Contrary to the findings of most other studies, Dar *et al.* (1992) found increasing birth weight with increased fish consumption for women who gained less than 34 pounds during pregnancy. Dar *et al.* (1992) showed a positive correlation between maternal serum PCB levels, and fish consumption. However, PCB exposures were lower than those in the other studies (Dar *et al.*, 1992).

In a recent study (Lonky et al. 1996), 395 infant-mother pairs that consumed Lake Ontario fish were compared to 164 pairs who did not. The exposed pairs were divided into high and low exposure groups and examined using the NBAS (Neonatal Behavioral Assessment Scale). The neonates from the high exposure group scored more poorly on the reflex, autonomic, and habituation clusters of the NBAS. These results confirm the findings of the Michigan maternal/infant Cohort.

It may be useful to look at these human data to estimate an RfD for PCB mixtures in fish. If possible, risk above this new RfD might be very useful in future evaluations of the framework.

4.3.5 Chlordane

Chlordane exposure affects the liver, nervous system, and immune system. Liver effects include hepatocellular hypertrophy (swelling), hepatic fatty degeneration, hepatocellular adenomas, and hepatic necrosis. Neurological effects include *grand mal* seizures and altered EEG results. Prenatal and postnatal chlordane exposure may have permanent effects on the immune system such as a reduction in the number of stem cells. Early childhood exposure to chlordane has been associated with prenatal and early childhood neuroblastoma and acute leukemia.

Chlordane is classified as a probable human carcinogen (B2) by the U.S. EPA based on oral studies in animals. IRIS reports an oral slope factor of 0.35 per (mg/kg)/day, which corresponds to a RSD of 0.00003 mg/kg-day at the 1 in 100,000 risk level. U.S. EPA's IRIS (1999) reports a medium confidence oral RfD of 0.0005 mg/kg-day for chlordane based on a 2-year mouse NOAEL of 0.15 mg/kg-day for hepatic necrosis.

To calculate risk above the RfD the IRIS RfD was examined. A chronic feeding study in mice was used to define the RfD for chlordane (Khasawinah and Grutsch, 1989). ICR mice (80/sex/group) were fed 0, 1, 5, or 12.5 ppm technical grade chlordane in the diet for 104 weeks. The critical effect is defined in IRIS as liver necrosis in male mice. Other cited effects include increased liver weight, liver cell hypertrophy and fatty degeneration of the liver. Hepatocellular adenomas were also observed at the high dose group. Hepatic necrosis was observed in male mice only at the following incidence rates:

<u>Dose (mg/kg-day)</u>	<u>Incidence of Hepatic Necrosis in Male Mice</u>
0	7/80
0.15	8/80
0.75	25/80
1.88	27/80

EPA has defined the NOAEL and LOAEL doses as 0.15 mg/kg-day and 0.75 mg/kg-day, respectively. A total uncertainty factor of 300 was used, which includes factors of 10 for interspecies extrapolation, 10 for interindividual variation, and 3 for lack of reproductive studies (database uncertainty).

The ED₅₀ was calculated using the THRESH multistage model (ICF Kaiser, 1997). To estimate risks above the RfD, reference distributions were used for the interspecies and interindividual UFs. The square root of the reference distribution was used to establish a distribution for the database UF.

Figure 4-2 shows the 5th, 50th, and 95th percentile dose-response curves for chlordane. The 50th percentile curve can be viewed as the estimate of dose response that is equally likely to over estimate or under estimate response if the substance followed a linear response between the RfD and the ED₅₀. The remaining two curves can be viewed as the 90 percent confidence limits for the dose response. That is the true response has a 90 percent certainty of falling between the values. Responses at these percentiles for given multiples of the chlordane RfD are also presented in Table 4-3. As the figure and table show, at a dose of 0.005 mg/kg-day, or ten times the chlordane RfD, the median estimate is 0% with 90% certainty that less than one percent of the population would respond. Likewise, at 50 times the RfD, the median estimate is less than 2% with 90% certainty that less than 10% of the population would respond.

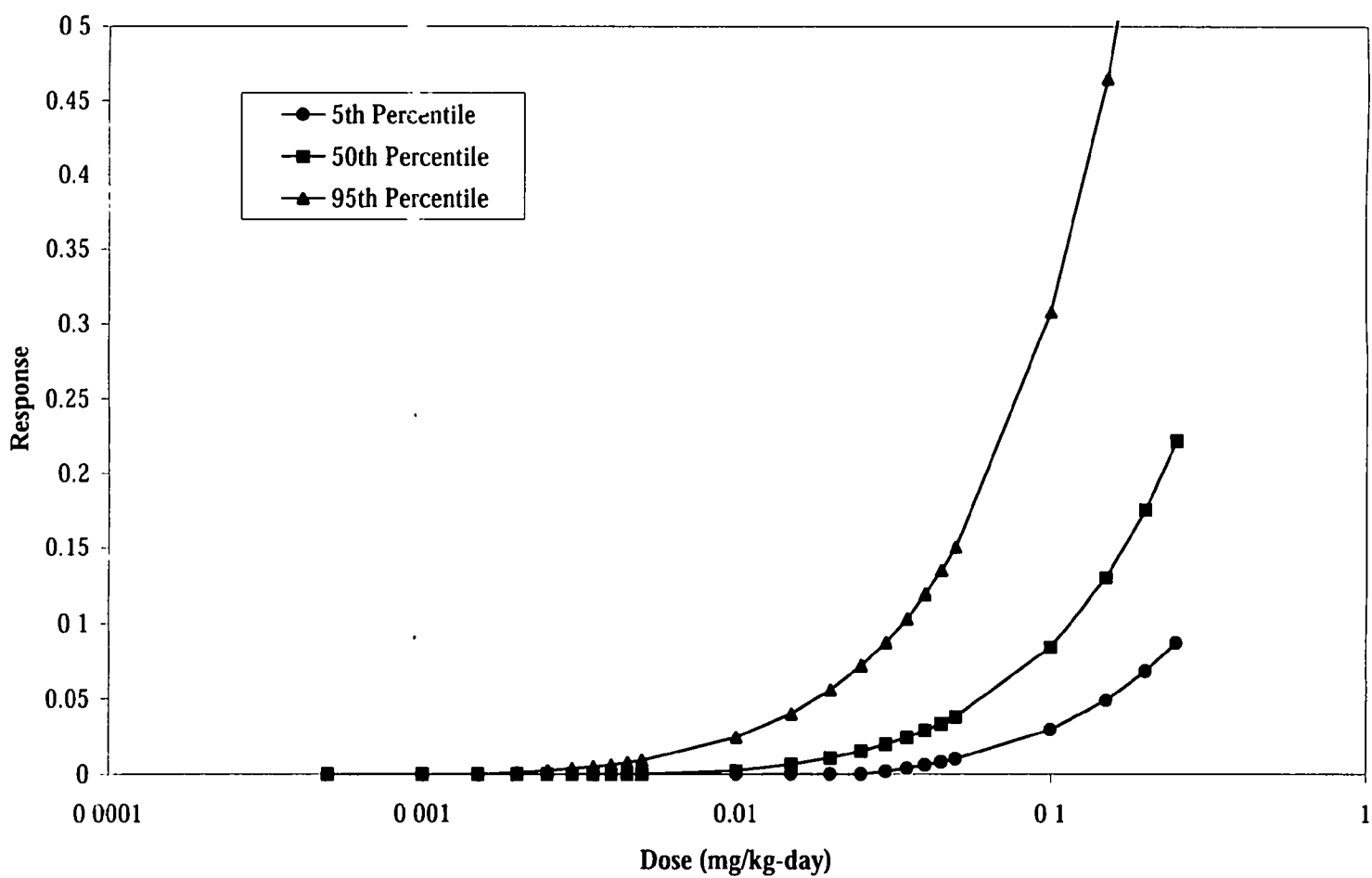
Figure 4-2. Dose-Response Curves for Chlordane

Table 4-3: Chlordane Responses at Multiples of the Reference Dose

Multiple of Reference Dose	Dose (mg/kg-day)	Response		
		5th Percentile	50th Percentile	95th Percentile
1	0.0005	0.0%	0.0%	0.0%
5	0.0025	0.0%	0.0%	0.2%
10	0.005	0.0%	0.0%	0.9%
50	0.025	0.0%	1.5%	7.2%
100	0.05	1.0%	3.8%	15.0%
500	0.25	8.7%	22.2%	>50%

4.3.6 Chlorpyrifos

Chlorpyrifos is known to cause cholinesterase inhibition in human blood serum. Other CNS effects do not occur at similar or lower doses than that causing cholinesterase inhibition. For this reason, some controversy exists as to whether cholinesterase inhibition in and of itself should be considered an adverse effect. In experimental animals, cholinesterase inhibition is seen at low doses and more severe neurotoxicity is seen at higher doses. It is also thought to be fetotoxic.

For chlorpyrifos, IRIS provides a medium confidence oral RfD of 0.003 mg/kg-day based on a NOEL of 0.03 from a 20-day human study reported in 1972 for plasma cholinesterase inhibition in adult males after 9 days of exposure. The U.S. EPA has not developed a risk value for the carcinogenicity of chlorpyrifos.

To estimate risk above the RfD, the IRIS RfD was examined. The critical study for the RfD was conducted in human volunteers that were treated with chlorpyrifos (4/dose group) at doses of 0, 0.014, 0.03, or 0.1 mg/kg-day (Dow Chemical Company, 1972). Doses were administered in a capsule for 20 days at the low and mid dose and 9 days at the high dose. Treatment at the high dose was discontinued after 9 days due to runny nose and blurred vision in one individual. Mean plasma cholinesterase (ChE) in the high dose group was 65% of control. No effect on RBC ChE was observed at any dose. Decreased plasma ChE after 9 days was considered the critical effect and EPA defined the NOAEL and LOAEL as 0.03 mg/kg-day and 0.1 mg/kg-day, respectively. A UF of 10 was used as the standard factor for the range of human sensitivity to ChE inhibition.

The detailed dose response data for the critical study is not available from IRIS. The Dow Chemical Company report (1972) presumably contains the pretreatment and 9-day plasma ChE level for each individual subject, but it was not available at the time our analysis was performed. Incidence data could be generated from this study by assuming that individuals with a greater than 20% decrease in the plasma ChE level at 9 days are adversely impacted (Dourson *et al.*, 1997). The quantal incidence data derived from this study could be used to calculate the ED₅₀.

The reference distribution for interindividual uncertainty would be used to estimate risks above the RfD.

It should be noted that the time scale of the effects of chlorpyrifos is much shorter than chlordane and methylmercury. Both of those compounds must accumulate in the body and reach a critical level in order to produce adverse effects in individuals or their offspring. In contrast, chlorpyrifos is rapidly metabolized and does not accumulate in humans to any great extent. The adverse effects on which the RfD is based are from short term (9-20 days) toxicity studies in humans. As a result, it may be appropriate to evaluate the risks based on acute exposures (the day the fish was consumed) rather than annual average doses.

4.4 Multigenerational Study of Great Lakes Salmon Fed to Rats

The vast majority of studies on health effects of contaminants involve single compounds due to the complexities of testing mixtures of chemicals. However, many human exposures, including exposure to contaminated fish, involve combinations of chemicals. To help address this issue, Health Canada initiated a multigenerational study of the health effects in rodents consuming diets containing Lake Ontario or Lake Huron chinook salmon (*Oncorhynchus tsawytscha*) (Arnold *et al.*, 1998a; Arnold *et al.*, 1998b; Feely and Jordan, 1998; Tryphonas *et al.*, 1998a; Tryphonas *et al.*, 1998b; Pappas *et al.*, 1998; Seegal *et al.*, 1998; Iverson *et al.*, 1998). Contaminant levels exceeded existing standards for commercial fish and seafood for PCBs, dioxins, mirex, chlordane, and mercury (Feely *et al.*, 1998). Results of this study are summarized here. It is the only experimental dose-response study with environmentally relevant exposures to mixtures of chemicals of interest in fish.

The chinook salmon fillets used in the dietary formulations for this study were lyophilized and analyzed for concentrations of the following contaminants: polychlorinated biphenyls (PCBs), dibenzodioxins (PCDDs), dibenzofurans (PCDFs), polycyclic aromatic hydrocarbons (PAHs), organochlorine pesticides, metals, volatile organics, chlorinated phenols, and benzenes (Feely and Jordan, 1998). Levels of contaminants were obtained before and after lyophilizing. Lyophilized salmon fillets were then incorporated into the normal rat diet in varying proportions (control, 5% salmon, 10% salmon, 15% salmon, 20% salmon for five different dose groups including one control. After 70 days on the diet males and females (F₀) were mated on a one-to-one basis within each group (Arnold *et al.*, 1998b). The (F₁) pups were weaned from the dam after 21 days and then fed the diets for 13 weeks. Seventy days after weaning, one (F₁) male and one (F₁) female within each dose group were mated. The (F₂) pups were then treated similarly to the (F₁) pups. Randomly selected (F₀), (F₁), and (F₂) adults and neonates were necropsied (Arnold *et al.* 1998b). The study included a reversibility group (F₁-R) in which the rats were switched to the control diet after 13 weeks of exposure for 13 weeks (Tryphonas *et al.*, 1998a). Increased relative liver and kidney weights were observed in both generations and both sexes fed diets containing 20% Lake Huron or Lake Ontario salmon (Arnold *et al.*, 1998b). Tryphonas *et al.* (1998a) reported on additional effects. Reduced thymus weights were observed in the Lake Ontario (20%) female (F₁-R) reversibility group. Increased growth rates in the (F₁) male rats were observed in those consuming the Lake Huron diets compared with those consuming the Lake Ontario diets. Reduced, reversible, decreases in counts of red blood cells, white blood

cells, neutrophil, lymphocytes, and monocytes in the fish-fed (F₁) females were seen. This reduction in counts was greater in the Lake Ontario salmon fed females than the Lake Huron fed females. Red blood cell, white blood cells, and lymphocyte counts were decreased in the (F₂) male rats fed the Lake Ontario (20%) diets compared to the Lake Huron (20%) diets.

Although quantitative aspects of the immune system were affected by the treatments, no significant effect on its function was observed (Tryphonas *et al.*, 1998b). No significant behavioral effects were observed in any of the treatments except for one effect observed in the 20% (F₁) Lake Ontario and the (F₂) Lake Huron males (Pappas *et al.*, 1998). These males showed reduced performance in the reference/working memory version of the radial arm maze. Frontal cortex dopamine concentrations were significantly reduced in all of the fish fed rats (Seegal *et al.*, 1998). Caudate nucleus dopamine levels were also reduced in all fish fed groups (Seegal *et al.*, 1998). However, decreases in dopamine levels in the *substantia nigra* were only observed in the Lake Ontario (20%) fed rats (Seegal *et al.*, 1998). Significant effects on all of the fish fed groups except the Lake Ontario 5% group in levels of norepinephrine concentrations were observed in the *substantia nigra* (Seegal, 1998). The same was true for 3,4-dihydroxyphenylacetic acid (Seegal, 1998).

Overall, the authors concluded that the consumption of the fish diets by rats of two consecutive generations resulted in a variety of effects that can be described as adaptive responses or of limited biological significance (Feeley *et al.*, 1998). Exceptions to their general statement include potential modification of working and reference memory, an effect on thymus weights noted in the first generation and an effect of lymphocyte numbers in the second generation. All of these exceptions occurred at the highest dose. The authors concluded that the risk presented by the complex mixture of contaminants in salmon collected from two locations in the Great Lakes could be considered minimal, especially if sport fish consumption advisories are followed.

4.5 Breast Milk as a Source of Contaminants

Breast milk is the ideal source of nutrients for newborns. However, breast milk is also a route of excretion for some toxic substances and an extremely important route of exposure for the nursing child. Substances are secreted into the milk by simple diffusion (Klaassen, 1991). Several factors influence excretion of substances in breast milk.

- (1) Three to four percent of human milk consists of lipids. Lipid soluble compounds diffuse into the mammary gland along with fats from the plasma.
- (2) Milk is more acidic than plasma. Therefore, basic compounds are concentrated in the milk, while acidic compounds have lower concentrations in the milk than in the plasma (Findlay, 1983; Wilson, 1983).
- (3) Compounds that are chemically similar to calcium such as lead and substances that form complexes with calcium are excreted into the milk (Klaassen, 1991).
- (4) Differences in excretion between mammalian species depends upon the amount of lipid secreted into the mammary gland from the plasma vs. the amount of lipid synthesized *de novo* in the mammary gland.

Mercury is an example of an environmental contaminant that transfers to mother's milk. In mice, the transfer of inorganic mercury from plasma to milk is greater than the transfer of methylmercury to the milk. However, neonate uptake of methylmercury is greater than uptake of inorganic mercury. In humans exposed to mercury via dental amalgam and contaminated fish in Sweden, milk levels of mercury were approximately 30% of plasma levels. Exposure to methylmercury from recent consumption of fish was reflected in the plasma but not in the milk (Oskarsson *et al.*, 1996)

4.6 Conclusions and Research Needs

For the framework to be most useful, noncancer risks above the RfD must be estimated for all significant critical effects of chemicals that contaminate fish, in particular, for the contaminant PCBs. For example, the case study of the Vietnamese immigrant women consuming Lake Ontario sportfish (discussed later) was severely hampered by our inability to estimate the risks above the RfD for PCBs; this was critical because some exceedances of the RfD were as much as 40-fold. Other chemicals need similar investigation.

RfDs are designed to be protective of the critical effect. This means that as long as doses remain below the RfD, neither the critical effect, nor any other adverse effect associated with the chemical is expected to manifest itself in the population. When doses exceed the RfD, as the framework assumes they could, then the critical effect may begin to manifest itself in the exposed population. The framework uses dose-response information on the critical effect to predict the increased incidence of the critical effect. But in addition to the critical effect, other effects may also be seen at higher doses. Some of these may be more severe than the critical effect. At present, EPA has not developed dose-response relationships for non-critical effects in humans. For the framework to fully characterize potential risks, and the net possible health benefit of eating contaminated fish, dose-response relationships for non-critical effects should also be developed.

Moreover, the method that we chose for determining these risks above the RfD (Price *et al.*, 1997) should be more closely examined. This method has the advantages that it is more generally applicable than categorical regression and is less resource intensive. It can be used directly from the existing data as on EPA's IRIS. However, it is not the only approach to the problem of risk above the RfD, and as demonstrated, the method does not work for all chemicals.

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5 Socio-Cultural Considerations of Fish Consumption

5.1 Introduction

This chapter discusses several different ethnic and other groups of people who either consume more fish than others, consume different parts of fish, or who may fish more contaminated waters. Included below are discussions on Asian-Americans, Native Americans, subsistence anglers, and low-income, urban anglers (including African-American and Latino anglers)¹. These groups have special behaviors in regard to fish consumption that should be considered in evaluating risks and benefits of fish consumption. Fish advisories can impact social, cultural, religious, and/or economic aspects of life that may affect an individual or group's health and well being. A framework for evaluating risks and benefits of fish consumption needs to consider these impacts.

Food, as an important part of a culture, serves economic, social, aesthetic, ceremonial, and religious functions. Food is used to solidify social ties. Specific foods are often seen as having special nutritional or medicinal qualities, such as the belief that the consumption of oysters improves libido. Foods often serve as social class or status markers. Foods are important gift items. Specific foods, and methods of food preparation, are frequently part of one's cultural identity.

Patterns of food consumption are often very resistant to change. When new immigrants arrive in the U.S. (or elsewhere), many aspects of cultural identity change rather quickly. It is common for country-of-origin language fluency to be lost by the second or third generation in immigrant families, for example. However, along with religious practices, food habits are among the most resistant to change. They often act in a powerful way to build and/or maintain cultural identity. The use of food to maintain cultural identity is of particular importance for ethnic groups for whom the consumption of fish is a long-standing tradition.

Fish, as an important cultural resource, may contribute to community well being and cohesiveness. Fish may hold a prominent place in religious and social ceremonies and rituals. Fishing activity often involves the intergenerational transfer of knowledge, and may contribute to sharing and social bonding within the family and community. For some, the consumption of self-caught fish is an important means of augmenting family food supplies; it has important economic impacts. In isolated, rural communities, alternate food sources may not be readily available. In poorer communities, families may lack sufficient income to purchase alternate foods. For some ethnic groups, especially certain Native American communities, fish hold

¹ These group designations are not mutually exclusive, but rather refer to dominant cultural identity (in the case of the first two) or socioeconomic and residence status (in the case of the last two). "Asian-American/Pacific Islander," as used here, also includes individuals who trace their ancestry to the indigenous peoples of Australia and New Zealand. "Native American," as used here, includes all indigenous peoples of the Americas, including the Inuit. Subsistence anglers are considered to be those who fish primarily to meet or supplement household food needs. Low-income, urban anglers are included because these form a special at-risk population. The small amount of research data discovered regarding Latino and African-American fishing and consumption behavior is included in the section on low income, urban anglers. "Latino," as used here, refers to individuals whose primary language is Spanish or Portuguese and/or to those individuals who trace their ancestry to predominantly Spanish or Portuguese-speaking populations.

important cultural meaning and are inextricably linked to traditional religious and cosmological concepts regarding the place of humans within local ecosystems and the health of the environment. If fish foods are culturally revered, it may be difficult to conceive of these foods as "hazardous," particularly if immediate negative health effects are not perceived to occur. Certain ethnic groups may also have special concern with the preservation of fishery resources for future generations and with questions of social inequality (environmental justice) in regard to these.

Fish advisories, especially if they result in rapid culture change, or loss of cultural identity, in a community, can have numerous catastrophic effects. These may include loss of self-esteem, loss of social solidarity (sense of community), loss of culturally meaningful social activities, a switch to less healthy foods, worsened economic conditions, and increases in violence and substance abuse. Consequently, it is not uncommon for individuals in such communities to resist changing their consumption habits. Some, especially those living in isolated locations with limited incomes, may have few if any viable options to consuming locally procured fish.

Certain ethnic groups are also subject to special health concerns. Many individuals of Asian, African, and Native American ancestry are lactose intolerant, so dairy products are not viable alternate protein sources. African-Americans have a higher rate of heart disease than the general population. Switching from fish to meats with a high-fat content would be deleterious for many of these people. Many Native American communities suffer from exceptionally high rates of diabetes and obesity. Reduced fish consumption could exacerbate these problems. Chapter 2 discusses possible health benefits of consuming fish, although most studies have not been conducted to determine differences between sub-populations of the U.S., or other groups.

Because foods, and fish in particular, are incorporated into a complex of socio-cultural phenomena, changes in eating habits often have multiple, complex (and sometimes unforeseen) consequences within a particular family, community, or ethnic group. For this reason, special consideration should be given to subcultural groups known to have special behaviors in regard to fish consumption. In the U.S., these include Asian-Americans, Native Americans, subsistence anglers, and low-income, urban anglers (including African-American and Latino anglers).

5.2 Asian-Americans and Fish

While the designation, "Asian-American," encompasses a diverse range of particular ethnic populations, several studies have delineated general fish consumption characteristics that distinguish this group from the majority U.S. population. Allen *et al.* (1996), as part of a general study of fishing behavior and fish consumption in the Santa Monica Bay area of California, found that Asian-Americans (including Pacific Islanders) exhibited higher rates of fish consumption, and were more likely than other ethnic groups to eat whole (gutted) fish. Rockfishes and chub mackerel were the most preferred finfish. Asian-Americans were also found to consume a greater variety of species and to consume more fish body parts than other groups.

In a recent study of San Francisco Bay fishing for food activities (Wong, 1997), the majority of anglers (70%) were persons of color. Asian-American males were most numerous. The average rate of fishing activity increased with age. An estimated 90% of respondents consumed more

than the recommended amounts of fish from the Bay. Commonly consumed species included perch, striped bass, white croaker, salmon, and smelt, often cooked whole with the skin on. Crab was the most common shellfish consumed. Many respondents were unaware of current fish advisories. On average, Asian-Americans consumed approximately three times the recommended quantities of fish recommended by the current advisories.

A similar study focused upon Asian-Americans and Pacific Islanders in the Puget Sound area of Washington State (Nakano, 1996). Recent immigrants (first or second generation) were found to be most at risk because they are most likely to practice seafood collection, preparation, and consumption habits closely resembling those in their native countries. The majority of these individuals do not speak English well, experience high levels of trauma or stress (many came to the U.S. as refugees), and cannot compete well in the U.S. job market. They are limited in obtaining adequate access to environmental health-related educational materials and environmental protection. Many new immigrants identify fishing and self-collection of seafood as ways to maintain activities familiar to them from their native lands. These activities provide a sense of cultural continuity. Seafood harvesting may be regarded as a coping mechanism to ease the oftentimes painful and difficult transition into U.S. society and culture.

Nakano (1996) found that the Asian-Americans and Pacific Islanders they studied had a preference for a wide range of seafood, including species likely to experience higher levels of contamination, especially shellfish, bottom feeders like catfish and sole, and sea cucumber. The consumption of fish heads, internal organs, skin, and cooking water is common among some Asian-Americans. There is also a clear cultural preference for some body parts that are known to have higher contaminant concentrations, such as crab hepatopancreas.

Hutchison and Kraft (1994), studying Hmong consumers in the Midwest, found that fishing was predominantly a male activity. Hmong tend to consume the more easily caught species, and those that do not require expensive tackle to catch, especially white bass, perch, and, to a lesser extent, trout. They did not, however, fish for carp or catfish, species otherwise commonly caught by other lower income anglers. While the researchers state that Hmong fishing (in the Midwest) is primarily "recreational," 90% of fish caught were consumed, and consumption rates were above the norm for this part of the country.

In Laos, fishing is a common, learned activity used to supplement the family diet. This conception of fishing is, according to Hutchison and Kraft (1994), carried over to the U.S. Hmong and consumption probably exceeds state guidelines. White bass may be preferred because they are most analogous to species common in Laos, unlike walleye and other spiny-rayed fish.

Story and Harris (1989), studying Cambodian and Hmong residents in the U.S., observed that fish foods serve as a link with the past, ease the shock of entering a new culture, and provide a means to maintain ethnic identity. Consumption of fish, however, was much less than in respondents' Asian home lands, with red meats (especially beefsteak) being the preferred substitute foods.

5.3 Native Americans and Fish

In Native American communities, tribal (ethnic) identity includes culture, religion, and place. Traditional tribal cultural practices have evolved over long periods of time in tandem with sustainable associations between humans and other species and their environment. Breaking the links between an indigenous people and their environment negatively impacts the culture and religion of these people. Tribal identity is often inseparable from place. Full and safe access to places and their resources is often necessary to preserve cultural values (Harper, 1997).

In many Native American communities, the perceived sacredness or purity of a place and its resources is extremely important. Environmental contaminants and the existence of health advisories may harm this sacredness or purity, making a place and its resources impure. This negatively impacts cultural, religious, and aesthetic beliefs, sentiments, and values. In many Native American cultures, personal identity or sense of self is derived more from group identification than may be true for European-Americans. Native American group identity is generally very strongly associated with place. Negative impacts upon the resource base of an indigenous community are likely to have considerable negative impact upon individual identity and self-worth.

The use of traditional foods can help "boost a lagging cultural morale" (Kuhnlein, 1989, p. 102). Traditional foods can provide nutrients otherwise lacking in the diet of impoverished peoples. In general, Native Americans are the poorest ethnic group in U.S. society. They may not have the means to acquire healthy alternative foods. Many Native Americans have only seasonal employment; the off-season procurement of traditional foods (like fish) can help families and communities economically (Kuhnlein, 1989).

Taste, availability, and harvest time help to determine the particular fish species preferred in Native American communities. Peoples of the Northwest Coast, for example, make considerable use of ooligan or candlefish (*Thaleichthys pacificus*). Coastal inhabitants relish this oily food. It is especially rich in retinol and tocopherol. The fish seasonally migrates up particular coastal streams in large numbers, making it a very efficient food source. Large quantities can be caught with relatively little effort. The same is true of the many salmon species native to this region. In fact, the native peoples of the Northwest are among the most fish-dependent populations in North America.

According to Berkes (1990), in those Native American communities highly dependent on fish as a food source, there often exists extensive local traditional knowledge regarding the distributions and life cycles of particular fish species. A reduction in fishing activities may endanger such valuable bodies of knowledge. For many indigenous communities, fishing is "a critical economic activity, not an incidental cultural remnant from the past" (Berkes, 1990, p. 41).

Even when fishing for subsistence purposes is no longer the norm, fish may still serve important, beneficial social functions. Among the Chippewa of Wisconsin, for example, spring spearfishing for walleye is an important communal activity. The fishing is done primarily by men. The season is short (2-3 weeks), but highly productive. Traditional feasts are held, and the

widespread sharing of the catch is an important social activity during this time of the year, helping to increase social cohesion and cooperation (Peterson *et al.*, 1994).

In several Canadian Native communities, especially among the Cree people, advisories to suspend the consumption of fish from certain bodies of water (due to high methylmercury levels) resulted in serious negative sociocultural and health-related impacts. Increased levels of diabetes, obesity, community and family violence, alcoholism, drug abuse, and suicide have been reported. The social and cultural disruption that followed the advisories seems to have had more deleterious impacts than would the continued consumption of locally-procured fish (Wheatley and Paradis, 1996).

5.4 Subsistence Fishing

In some rural areas of the country, and especially in a large portion of Alaska, fishing for subsistence purposes is quite common. What has been termed the "mixed subsistence-market economy" is important in many rural communities. Subsistence fishing and other subsistence activities may be important domestic (family-based) economic activities. This style of life, in which part of a household's needs is met via subsistence activities, is highly valued in rural Alaska (Wolfe and Walker, 1987). A subsistence-based lifestyle has positive impacts upon an individual's self-definition, and sense of self-determination (Egeland *et al.*, 1998)

In Alaska, fish is a primary food staple throughout the state. Salmon species constitute the majority of fish caught and consumed, but others, including arctic grayling, herring, flounder, pike, smelt, whitefish, and cod, make substantial contributions to local diets as well (Egeland *et al.*, 1998). In a survey of Alaskan Native American communities, it was found that 30-45% of calories consumed came from local, self-procured food sources. In Alaska, fish consumption is six times the national average; the majority of protein consumed is derived from local fish sources. Social aspects of sharing the fish harvest are very important. Traditional harvesting activities provide meaningful work, promote self-reliance, help maintain social bonds, provide economic benefits, enhance cultural identity, and help to sustain the intergenerational transfer of local knowledge (Egeland *et al.*, 1998).

5.5 Low-Income, Urban Anglers

A number of recent studies have focused attention upon the fishing and consumption behavior of low-income, urban anglers because this group may be at higher risk of exposure to fish-borne contaminants. West (1992), studying fishing along the Detroit River, found that "non-white" anglers (in this case, mostly African-American anglers) were more likely to view fishing as a food source than were "white" anglers. They were also more likely to eat species with higher contaminant levels, such as white bass and sheepshead.

Belton *et al.*, (1986) observed finfishing and crabbing activities in the New York City area. Most anglers were older (over 50), employed in blue-collar jobs or service occupations, and "white." One-third were retired. The most common species sought by these anglers were snapper (juvenile bluefish) and blue crab. These were both among those species contaminated above FDA tolerance levels. Other species caught included fluke, bluefish, striped bass, and

flounder. Most anglers, nearly 60%, reported eating some of their catch, and many shared with families, friends, and neighbors. Most often consumed species included blue crab, flounder, fluke, and snapper, followed by striped bass and bluefish. Most respondents had consumed fish from these (polluted) waters for 10 years or more. Crabs were most often boiled, finfish mostly fried. No respondents reported eating the crab hepatopancreas and crab cooking water was always discarded.

In terms of local risk perception, two-thirds of the anglers interviewed thought that their catch was totally safe. About one-fifth saw their catch as slightly polluted but not harmful. Those who considered their catch fairly polluted said that the fish would, nonetheless, not hurt them, or that they rarely ate the fish. Most acknowledged that the local waters are polluted. However, some thought that crabs could rid themselves of pollutants. Others said that the finfish had moved in from cleaner waters. Thus, most anglers were able to explain away the risk (Belton *et al.*, 1986).

Belton *et al.* (1986) also found that there seemed to be much misunderstanding and/or ignorance of local fish advisories. One-quarter of the anglers felt that they could effectively assess the safety of consuming particular animals based upon visual inspection, observation of the animal's behavior, smell, and taste. Many felt that washing, cleaning, and/or cooking could make the fish safe to consume. Approximately one-half said that if you eat fish and one or two days later are not sick, then the fish was safe to consume.

Burger *et al.* (1993) reported results of surveys in the New York City area. They found that most anglers equated unsafe fish with lesions, discoloration, or odor, not with undetected chemical contaminants. A majority of subjects in the study were African-American or Latino. Most believed that designated contaminated sites were actually safe, and that the fish caught in these places were safe to eat. Possible reasons cited for the widespread ignoring (or ignorance) of health advisories include a low literacy rate among the subject population, language problems (for Latino anglers), and the inadequate dissemination of health advisory information. Burger *et al.* (1993) posited that people underestimate risks associated with voluntary, necessary, and/or familiar hazards, and overestimate risks from involuntary, unusual, and/or unexpected hazards.

In a similar study, also in the greater New York City area, May and Burger (1996) found that anglers underestimated the risks of consuming self-caught fish because this was an enjoyable, voluntary, familiar activity. They observed a common optimistic bias. While an individual angler might acknowledge that a hazard existed, she or he would feel that she or he had a less than average chance of experiencing the hazard. There was a common mistrust of government sources of information, and, faced with uncertain risks, many chose to ignore the risks.

The May and Burger (1996) study involved more African-American respondents. Most respondents consumed fish fried, and frequently whole. Crabs were generally boiled. There was a common belief that fish are less contaminated than the waters in which they live. Crabs were also believed to be able to filter out pollutants. Most anglers admitted that they fished even though they were aware of the local health warnings. Many preferred self-caught fish because they were fresher than those purchased in stores.

Burger and Gochfeld (1991) examined fishing at a lagoon with high methylmercury levels near San Juan, Puerto Rico. They discovered that only one person had reported sickness from eating locally caught fish. Almost all of the anglers questioned were aware of the mercury problem. Most felt, however, that there was not any serious pollution in the particular places on the lagoon where they fished. Crab, tarpon (*Megalops atlanticus*), and *Tilapia mossambica* were most commonly caught. In general, Puerto Ricans fish more, for more of the year, and consume more fish than U.S. mainland residents. Fish heads and crab hepatopancreas are more often consumed. Fish and crab are frequently prepared in stews and soups, so essentially all body parts are consumed.

In Michigan, Smith and Thompson (1989) witnessed persistent angling occurring in the face of strong warnings to avoid a contaminated portion of the Tittibawassee River. Most anglers were low-income, blue-collar, and unemployed or underemployed. Just over two-thirds had completed high school. Most were aware of health concerns, but fished and consumed fish from the river regardless. Some respondents cited no adverse health impacts from past consumption of locally caught fish. Others expressed fatalistic sentiments. According to Smith and Thompson, reasons for noncompliance with the posted advisories include possible denial of recognized truths, fatalism, and alienation. Information overload, in the form of so much negative news in the mass media, may also have resulted in anglers ignoring one more piece of "bad" news about their river. For these anglers, fishing in the local river constituted one of the few recreational outlets that they had and that they could afford. A general distrust of government authorities may also contribute to noncompliance with fish consumption advisories.

5.6 Conclusions and Research Needs

In using the framework outlined in this report, it is important to consider how socio-cultural factors impact the relative risks and benefits of fish consumption. This should include not only consideration of health-related risks and benefits, but also those related to the economic, social, and cultural well being of particular communities. Among isolated and/or lower-income groups, fish may represent an important economic resource, and a source of needed high-quality protein, that is not easily replaced. For others, especially certain Native American and Asian-American communities, fish may have special cultural and/or religious significance. In such communities, advisories designed to limit consumption of fish may have unforeseen detrimental socio-cultural impacts. These potential consequences need to be considered when assessing the risk and benefits of fish consumption.

A participatory approach to incorporating socio-cultural factors into frameworks for assessing the risks and benefits of fish consumption in local communities or among specific target populations needs to be adopted by risk managers. Socio-cultural risks and benefits are ultimately based upon shared community values, and these can be best understood by actively including members of affected groups in the planning process.

For example, Harper and Harris (Harper, 1999) are developing a process to estimate cultural consequences of contamination to specific locations or resources. In addition, they are also working on a universal harm scale, which could be used to help normalize the severity of

disparate risks. This work has not yet been published, but ultimately might be very useful in conjunction with the framework we propose in the next chapter.

While considerable scientific attention has focused on the biological health risks and benefits of fish consumption, a relative paucity of concomitant research has been conducted examining concurrent sociocultural risks and benefits. As delineated in this chapter, for a number of specific human populations, fish serve important social, cultural, religious, economic, and aesthetic functions. Fish are integrally positioned within a matrix of shared beliefs, norms, and behaviors. The more central the position of fish within the social fabric of a community, the greater the number of these social interconnections.

As the relative importance of fish, fishing, and fish consumption behaviors varies markedly among the many ethnic and socioeconomic groups comprising the larger U.S. population, there is a clear need for more comprehensive, comparative analysis of the sociocultural risks and benefits of fish consumption. More quantitative information needs to be amassed on specific consumption behaviors, with the aim of more productively combining sociocultural data with biological data in developing risk assessments and consequent risk management strategies.

There is a need for more detailed empirical data differentiating specific ethnic populations within larger culture groups, for example, data on the consumption behaviors of Japanese-Americans as compared to Chinese-Americans, in contrast to data only on Asian Americans in general. The development of measurement tools (typologies, scales, indices) that will allow for better comparisons of various sociocultural groups should be a high priority in future research. These might lead to the eventual development of a theoretical model for better predicting the outcomes of advisories on specific human populations. There is also a definite need for more research on environmental justice issues in regard to fish consumption, and on the relationship between fish consumption and group sovereignty issues, especially in regard to Native American communities. A related concern that has received only limited attention to date is the influence of past government relations on the current acceptance of advisories, and other risk management communication, by specific ethnic and socioeconomic groups.

5.7 References

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6 Framework and Case Studies

6.1 Introduction

This chapter presents an initial comparative dietary risk framework (referred to as the framework) that combines and compares the potential benefits and potential risks associated with eating contaminated fish. The results of this framework are imprecise, due to the multi-factorial analysis involved. Thus, while the framework is a quantitative representation of the net risk (or benefit) associated with eating contaminated fish, it should be used to investigate and compare various alternative fish protein sources, including perhaps other non-fish proteins. The framework should not be used in its present form for decisions regarding the merit of specific fish consumption advisories.

The output of the framework is referred to as the fish consumption index (FCI). The FCI is an estimate of relative risk. It is not an estimate of absolute risk. In other words, it does not provide users of the framework with an estimate of their increased or decreased incidence of a particular health outcome. It simply provides a mechanism by which users can weigh the health risks versus the health benefits of eating contaminated fish. Alternate net health risks or benefits of various food alternatives can then be compared. Cultural benefits of catching and eating fish (or detriments of not being able to fish or consume fish) may also be considered, however this framework does not attempt to quantify these benefits.

The framework provides information for a range of fish consumption rates. This allows a user to determine the range of consumption rates at which he or she may have the largest benefit, the largest risk, a “net” benefit, or a “net” risk. The user can also determine the fish consumption rate at which benefits are first affected by the health risks, or the consumption rate at which there is no net change in the health index. The user can also compare an FCI from one type of contaminated fish to another.

The framework was designed to be flexible. It can account for multiple health benefits for which dose response information is available and for as many different health endpoints as information exists¹. When estimating the potential risk associated with chemicals in fish, the framework considers both cancer and non-cancer effects and is able to consider the presence of multiple chemicals in fish. Because some health endpoints are considered less severe than others (e.g., developing arthritis versus dying of coronary heart disease), a method of incorporating a modifier to account for the biological differences in the severity of different health endpoints is needed. The framework also can accommodate a factor to account for personal perceived differences in severity, and for culture-related benefits of fish consumption, if desired. However, we did not develop a method for estimating cultural benefits or personal perception of severity in this project.

The remainder of this chapter describes the goals of the framework and its inputs, and demonstrates how it could be used with both hypothetical examples and two case studies.

¹However, there are limited quantitative data available on health benefits of consuming fish. See Chapter 2 for a discussion of available data.

6.2 Goals of the Comparative Dietary Risk Framework

This section presents the goals of the framework. As described in Chapter 2, substantial data exist suggesting that consumption of fish leads to a reduction in the relative risk of several adverse health endpoints. At the same time, analyses of fish in water bodies throughout the United States have confirmed the presence of environmental chemicals in fish (AFS, 1997; U.S. EPA, 1995). In many cases the concentrations of chemicals have been high enough to warrant the posting of fish consumption advisories by state governments. Although some effort is made in some of these advisories to describe the benefits of eating fish, the actual advisory is usually based solely on the potential adverse effects posed by the chemicals in fish, and not on a consideration of any potential nutritional or health benefit.

Weighing the benefits of fish consumption in setting of advisories is not straightforward. Prior to having knowledge about the benefits, all one needed to do was estimate the potential risk at various consumption rates and then select a maximum allowable consumption rate that corresponded to an allowable risk level. Since consumption of fish also confers health benefits to people, incorporating information about potential health benefits might be helpful for fish consumers. One of the goals of this framework is to provide an approach to quantitatively compare the potential risks and benefits of eating contaminated fish.

The publications to date that have quantified the risks and benefits of eating contaminated fish have focussed primarily on the increased incidence of cancer and not on other adverse health effects (e.g., Anderson and Wiener, 1995). Including adverse effects other than cancer will likely increase the estimates of health risk from eating contaminated fish. Thus, another goal of the framework is to include adverse health outcomes in addition to cancer to more accurately represent the overall risk. This is especially important because some chemicals for which advisories exist are judged not to be carcinogenic (e.g., methylmercury). A framework that is not able to weigh non-cancer risks versus benefits would be of little help to someone evaluating risks and benefits of fish consumption for such a chemical.

Anderson and Wiener (1995) compared the risks and benefits to adults of eating contaminated fish. Because they focussed on cancer (for which average daily dose over a lifetime is assumed to be relevant) as the adverse health effect, estimating risk for adults was appropriate. However, exposure periods considerably shorter than lifetime and exposures of children, infants and fetuses (via the mother) are also relevant. Doses received by children (or breast-fed infants whose mothers are eating contaminated fish) over a short period of time are important to consider when setting fish consumption advisories for non-cancer health endpoints. Some existing advisories differentiate between adults, women of childbearing age, and children to reflect this differences in risk relative to consumption (e.g., Minnesota, 1998). Similarly, the net benefit of eating fish may differ among these groups (e.g., differences in genetic susceptibility to cardiovascular disease) and this should be taken into consideration.

Once more than one health endpoint is included in the comparison (whether two or more risk endpoints, two or more benefit endpoints or different risk and benefit endpoints), a mechanism must be developed to account for differences in the biological severity and perceived severity of the different health endpoints. For example, it may be appropriate to treat mortality from cancer

and coronary heart disease as being equally severe biologically, but the perceived severity by individuals or subpopulations of these two outcomes might differ. Thus, another goal of the framework is to incorporate measures of biological and perceived severity of different health outcomes in the weighing of risks and benefits. We discuss several ways to incorporate biological severity, and show where a scale for personal perceived severity may fit.

The issuance of fish advisories may pose a risk to the livelihood of certain cultures and subpopulations whose existence or cultural wellbeing depend upon catching and eating certain species of fish (see Chapter 5). Ideally the framework would be able to quantitatively account for the cultural benefits associated with catching and eating fish, in order to weigh these against the risks.

The final goal of the framework is that it be flexible so that it can be used in a variety of situations. It should be able to compare the risks and benefits of fish consumption over a wide range of fish consumption rates, different fish species, different bodies of water, and different mixtures of chemicals. People using the framework should be able to apply it to a variety of contaminants and contaminant concentrations within a species. The framework should be able to easily incorporate new data on either health benefits of eating fish or adverse health outcomes associated with chemicals in fish.

6.3 Inputs for the Comparative Dietary Risk Framework

6.3.1 Potential Health Benefits of Fish Consumption

Researchers have identified numerous potential health benefits associated with eating fish that are discussed in Chapter 2. Evidence of benefits can be thought of as arising from two sources. The first source consists of studies that look at how the change in the incidence of a particular health outcome is related to fish consumption rate. The results of these studies can be used to derive a dose-response relationship between fish consumption rate and the health outcome being investigated, within the limits imposed by the research results. The second source results from investigation of how general nutritional status changes as fish is substituted for some other source of protein or removed from the diet as discussed in Chapter 3. Often, the change in the incidence of a particular health outcome cannot be quantified from these latter investigations. This is because the studies conclude that a particular nutritional component (i.e. high density cholesterol) either increases or decreases with the change in dietary pattern, but they do not tie the change in the nutritional parameter to a change in a specific health outcome (i.e. incidence of coronary heart disease). The absence of a quantitative relationship among fish consumption, changes in nutritional parameters, and changes in specific health outcomes makes it more difficult to incorporate information from these latter types of studies into the framework.

When incorporating fish consumption benefits information, the framework relies primarily upon results from the first type of study (i.e., Chapter 2). Because change in fish consumption rate affects many measures of general nutritional health, this report also presents a summary of nutritional content of numerous protein sources (i.e., Chapter 3). These data are presented to provide additional perspective about how to interpret the results of the framework. For example, the framework may indicate that a net health benefit exists when eating contaminated fish at a

particular rate; however, additional nutritional information may suggest that skinless chicken confers many of the same nutritional benefits as eating fish, but with perhaps a lower level of contaminants. Such information may be especially useful to segments of the population that are monitoring one or more nutritional parameters (e.g., cholesterol intake).

For several health endpoints quantitative dose-response data are available. These allow development of dose-response curves for benefits that relate the change in relative risk of the health outcome to change in fish consumption rate. These are the data the framework relies upon to develop an estimate of the net benefit (or risk) of eating contaminated fish. These data are more fully discussed in Chapter 2.

Because the framework is concerned with the decrease or increase in risk that can be attributed to consumption of fish, it is the attributable risk, not the relative risk that is desired. The attributable risk (AR) estimates the excess rate of disease among the exposed and non-exposed individuals that is attributable to the exposure, while the relative risk (RR) estimates the magnitude of an association between exposure and disease. The RR also indicates the likelihood of developing the disease in the exposed group relative to those who are not exposed. Another way to look at these differences is that RR is the ratio between two incidence rates (exposed and non-exposed) while AR is the difference between these two incidence rates.

Unfortunately, most of the published data report results as relative risk ratios. Therefore, relative risk ratios were used in the analysis of the framework in this report. For the purposes of developing the framework, we chose the relative risk ratios as shown in Table 6-1.

Please note that other values could have been selected. Further study to determine the relative risks of eating specific types of fish is needed.

Table 6-1. Relative Risks for Various Endpoints listed in Table 2-1.

Health Endpoint	Background Incidence (B)	Consumption Rates (grams/day)	
		6.5 grams/day	60 grams/day
Coronary Heart Disease	0.32	0.6	0.45
Stroke	0.07	0.85	0.55
Arthritis	0.13	0.92	0.57

6.3.2 Measuring Severity of Health Outcomes and Magnitude of Health Benefits

6.3.2.1 Introduction

The biological severity of a toxic response, based on pathological staging of a disease or collection of symptoms, must be considered in any framework that attempts to compare the responses of often disparate effects. However, no one approach can be expected to account for the totality of the observed effect and the results are only crude approximations of the underlying biology, subject to change with additional data and judgment.

In addition, the concept of severity also has a societal or personal perception component. Quite simply, some individuals might rather suffer one type of health effect than another---heart disease versus cancer, for example -- despite the fact that when judged from the biological perspective of overall impact on the organism, these effects might be considered similar. This personal perception of severity is important in any comparison of health effects, but is not considered further in this text other than to show where it can be used as a possible modifier of the framework results.

In the development of this framework, biological severity is considered directly in the development of a health index. Several approaches to address the biological severity of toxic effects have been published and are actively used in several environmental assessment programs, although not without controversy. For example,

- Within the Superfund office of the U.S. EPA, a 10-value scheme for severity of toxic effect is used to determine Reportable Quantities (RQs) for noncancer health effects (e.g., DeRosa *et al.*, 1985). This scheme has been used since 1983 to determine RQs that are used to determine the responses to environmental spills in the U. S. Hartung and Durkin (1986) have also published on the merits of this approach, and suggest ways to make it more general and usable. Some scientists believe, however, that this scheme incorporates both pathological staging of severity (the biological component) and personal perception of severity.
- In the development of RfDs and RfCs by EPA and MRLs by ATSDR, a simpler severity scheme is employed whereby no observed adverse effect levels (NOAELs), lowest observed adverse effect levels (LOAELs), less serious and serious LOAELs, or Frank Effect Levels (FELs) are identified (Dourson *et al.*, 1985; Jarabek, 1994; Pohl and Abadin, 1995). The identification of these levels is not often recognized as a severity approach *per se*, but it does reflect a crude tool to gauge pathological staging of different environmental effects. One advantage of this approach is that NOAELs, LOAELs and FELs have been identified for hundreds of chemicals in the supporting documentation of risk assessment values for these U.S. agencies. In addition, similar schemes are used by other world health organizations (e.g., Health Canada; Meek *et al.*, 1994), and similar lists of NOAELs, LOAELs and FELs have also been compiled.
- An approach has also been proposed for the effects caused by drugs (Tallarida *et al.*, 1979). These investigators assign relative weights to adverse effects of increasing severity based on physicians' judgments. This judgment in turn is based on the acceptability that the adverse effect is likely to be associated with a dose that has a specified probability of curing a disease of a different severity. This scheme has been considered for use with environmental agents by Durkin (1999).
- An approach for the development of fish consumption advisories has also been proposed which incorporates the severity of the effect and the years of life affected, while also considering the beneficial effects of eating fish (Ponce *et al.*, 1998). Here investigators use the benchmark dose to define a risk curve and a logit model for defining the benefits curve. A judgment is made as to the "severity" of both risk and benefit on a scale of 0 to 1 (where 0 indicates no significance and 1 indicates loss of life). This severity score is then multiplied by the number of years of life through which the individual must suffer the risk or enjoy the

benefit. This latter multiplication, often referred to as Quality-Adjusted Life Years (QALYs), is also being considered by the U.S. Environmental Protection Agency in its deliberations of comparative risk for disinfectant byproducts (U.S. EPA, 1998). The result of this approach is similar to the framework proposed in this text.

6.3.2.2 Incorporation of Severity into the Framework

For this framework, we use the severity approach of EPA and ATSDR for estimating RfDs/RfCs and MRLs. This approach has the advantages of simplicity, familiarity and consistency with the use of information from EPA's IRIS, and of ATSDR information found in its toxicology profiles. The adaptation of this approach into a multiplier factor for use in the framework is shown in Table 6-2.

A shortcoming to this approach is the implied equal spacing between levels. There is no scientific or mathematical justification proposed for a FEL being considered thrice as "severe" as a less serious LOAEL. This is a disadvantage of the Ponce *et al* (1998) and DeRosa *et al.* (1985) severity schemes as well. Tallarida *et al.* (1979) addresses this concern somewhat through the use of physicians' judgments. Other caveats associated with this choice of severity scale are shown in Table 6-3.

In like fashion, some modifier to the magnitude of benefits accrued from eating fish needs to be used in order to roughly compare to the risk of different health endpoints. Such an approach has been developed for risk/benefit tradeoffs in clinical medicine (Tallarida *et al.*, 1979), and the scheme by Ponce *et al.* (1998) uses such a modifier to the magnitude of benefits. For this framework, we chose to use a simple, scheme that matches the choice of severity ranking for health risks. Thus, we also rank severity of health outcome avoided (e.g., coronary heart disease) as none, minimal, moderate or severe, as shown in Table 6-2. As with health risks, we are using these qualitative labels that are being used in a quantitative fashion in the framework. This is not an ideal situation.

However, none of the proposed comparative risk schemes solve this problem directly. This is because the effects of concern in overt clinical disease are not easily comparable with the effects of concern from widespread environmental exposures. For example, Durkin (1999), has studied the similarities and differences of effects between clinical disease and environmental exposures and states that all of the clinical effects covered in the Tallarida *et al.* (1979) scheme are by definition, effects associated with signs or symptoms of toxicity. Thus, these effects would be classified as FELs or serious LOAELs in environmental parlance. In environmental exposures, however, anticipated effects are generally not overt (e.g., minimal fatty infiltration of the liver), or are less severe, adaptive or compensatory. These effects would be classified as less serious LOAELs or NOAELs.

Table 6-2. Severity Ranking of Effects and Benefits and Resulting Multipliers for the Framework^a

EPA Severity Ranking of Effects	Multiplier to the Incidence of Effect/Benefit
NOEL or NOAEL	0
Less serious LOAEL	1
More serious LOAEL	2
FEL	3
"Severity" Ranking of Benefits	
None	0
Minimal	1
Moderate	2
Maximum	3

^a Please note the intended association of the term "severity" with "benefits." In order to balance risks with benefits within a framework that was easy to implement, a comparable scaling and terminology was chosen.

The scores in Table 6-2 are multiplied by the available quantitative information on risks and benefits to yield a modified risk or benefit curve. These modified curves are only expected to be crude approximations of reality. A number of caveats must be considered before such modifiers could be used in making final judgments (see Table 6-3). However, this approach was a starting point that allowed us to develop the framework.

The resulting health scores from use of these multipliers in Table 6-2 have not been further modified with QALYs. The decision to withhold the use of QALYs was based on practicality. Quite simply, we chose to see if a framework could be developed using the simplest information available. If appropriate, the use of QALYs can be added later. The anticipated effect of adding QALYs on the modified risk or benefit curve is expected to be minimal, however, because the typical effect or benefit used in the framework is expected to generally occur over a large portion of an individual's lifespan. If the comparable risk and benefits occur over significantly different portions of lifespan, then the lack of use of QALYs becomes more important, and the results of the framework would need additional study.

Other severity schemes could be used -- and in fact are proposed for comparing the health risks and benefits of fish consumption. For example, Ponce *et al.* (1998) uses further distinctions among effects and benefits of different severity than shown in Table 6-2, which necessitates additional judgment regarding the appropriate severity level of both the critical effect and benefit. Ponce *et al.* (1998) also incorporates the concept of duration of the effect or benefit through the use of QALYs. However, we do not perceive a great difference between the results of Ponce *et al.* (1998) and what is proposed here. If benefits and risks were matched in these other schemes similarly to what we propose here, the resulting health scores would also be similar. Moreover, the framework can encompass other severity schemes as appropriate.

Table 6-3. Caveats with the Use of Severity Schemes Shown in Table 6-2 for Adjusting Quantitative Information on Risks and Benefits.

Caveat	Description
Scheme is too simple	The suggested severity scheme is so simple that distinctions are not possible among, for example, survival of an individual versus survival of the species through reproduction; such a scheme should enfold additional complexity ^a .
Multipliers cannot address severity	The use of multipliers implies that effects of a given severity are simple multiples (or divisors) of other severities; with a limited severity scale, this lead to comparisons that do not always make biological sense.
Scheme cannot use error bars	Error bars around the "net" health score are not possible because of the arbitrary value of the multiplier; this makes interpretation of the appropriate "net" score difficult.
Health scales do not match	Health benefits and risks are equally matched through the use of the same "severity" ranking; this may not be appropriate for effects or benefits that occur over different durations ^b .
Benefits data lack contamination history	Benefits of fish consumption have been observed in populations consuming fish with an unknown contamination level; thus, the net benefit score may be inappropriately low if all other items are equal.

^a See for example the severity scheme for reportable quantities (DeRosa *et al.*, 1985) which gives specific values for developmental and reproductive toxicity

^b Note the method of Ponce *et al.* (1998) specifically addresses the duration issue through the use of number of years affected by the health endpoint.

6.3.3 Estimates of Human Health Risk

Chapter 4 provides details on estimates of cancer risk, reference doses for non-cancer endpoints, and calculation of risk above the RfD. These are the inputs needed for the framework. Dose response information for six common contaminants found in fish (DDT and metabolites, methylmercury, dioxin, PCBs, chlordane and chlorpyrifos) is provided. EPA's Integrated Risk Information System (IRIS) (U.S. EPA, 1999) is the source of RfDs and cancer estimates. Estimates of risk above the RfD were calculated specifically for this project using data from IRIS.

6.3.4 Dietary Considerations

In order to assess changes in risk to an individual or population with varying consumption of chemically contaminated fish, a common measure of health is needed. For this framework a "disability," or health, scale is the measure against which relative comparisons are made with regard to chemical contamination and health benefits of fish consumption.

Figure 6-1 shows a hypothetical plot of health status with varying protein intake as a percent of diet. The expected U-shaped dose response curve is presented for protein intake as a percent of diet, spanning disease on both the high and low ends of protein intake, and normal health status in between (see curve B).

For a number of reasons, it is difficult to quantify the specific values of the health status scale. The primary reason is the lack of a good single indicator of health status. However, the lack of a good measurement does not preclude the use of judgment to distinguish the likely effects of how this function would change if different types and quality of protein were consumed. For example, if total protein were to come from a source high in saturated fats and salt, and low in other nutrients, it would be easy to envision a curve similar to C as shown in Figure 6-1. Alternatively, if the total protein were to come from a source low in unsaturated fats and salt, and high in other nutrients, it would be easy to envision a curve similar to A as shown in Figure 6-1. In fact, such curves might be very representative of sole protein sources such as hot dogs (curve C) or fish (curve A) when compared to an average mixed diet (curve B).

The contamination of these same protein sources with chemicals adds another layer of complexity to this analysis, but one that can be investigated at least theoretically. For example, if chemical contamination of hot dogs was low, but of fish was high, then the expected curves of health status would move towards one another, that is, curves A and C would move closer together. Although the direction of movement is known, the degree of movement and the determination of whether the resulting health curves overlap, would necessitate a uniform scale for health effects.

Such a uniform scale for health effects has been proposed, where organism disability is shown as a function of target organ impairment (DeRosa *et al.*, 1989). An adaptation of this curve is shown in Figure 6-2, where organism disability as a function of target organ impairment is shown for both insufficient and excess protein intake. Curves for different protein sources (as in Figure 6-1) could also be drawn here. This single curve given in Figure 6-2 might represent a balanced (as to source) protein intake. This uniform scale ties in nicely with the proposed severity modifiers that we discussed in sections 6.3.2.2 (Table 6-2).

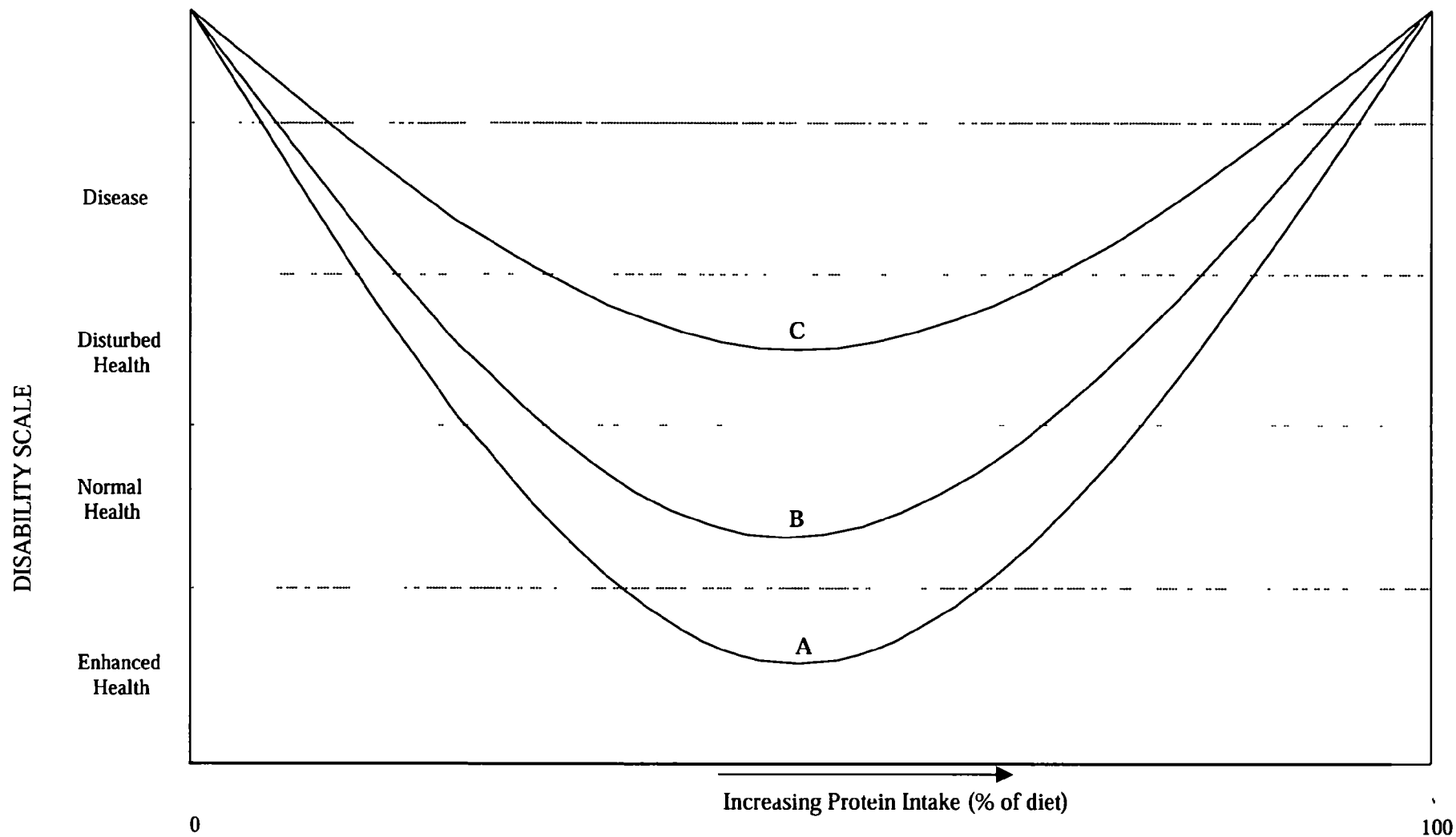


Figure 6-1. Hypothetical curve: No data are presented nor is the scale likely to be correct. Disability scale as a function of amount and quality of protein intake as a percent of diet. Curve A is protein intake that is low in fat & salt, and high in nutrients. Curve B is mixed protein intake (perhaps a normal average diet). Curve C reflects protein intake that is high in fat & salt, and low in nutrients.

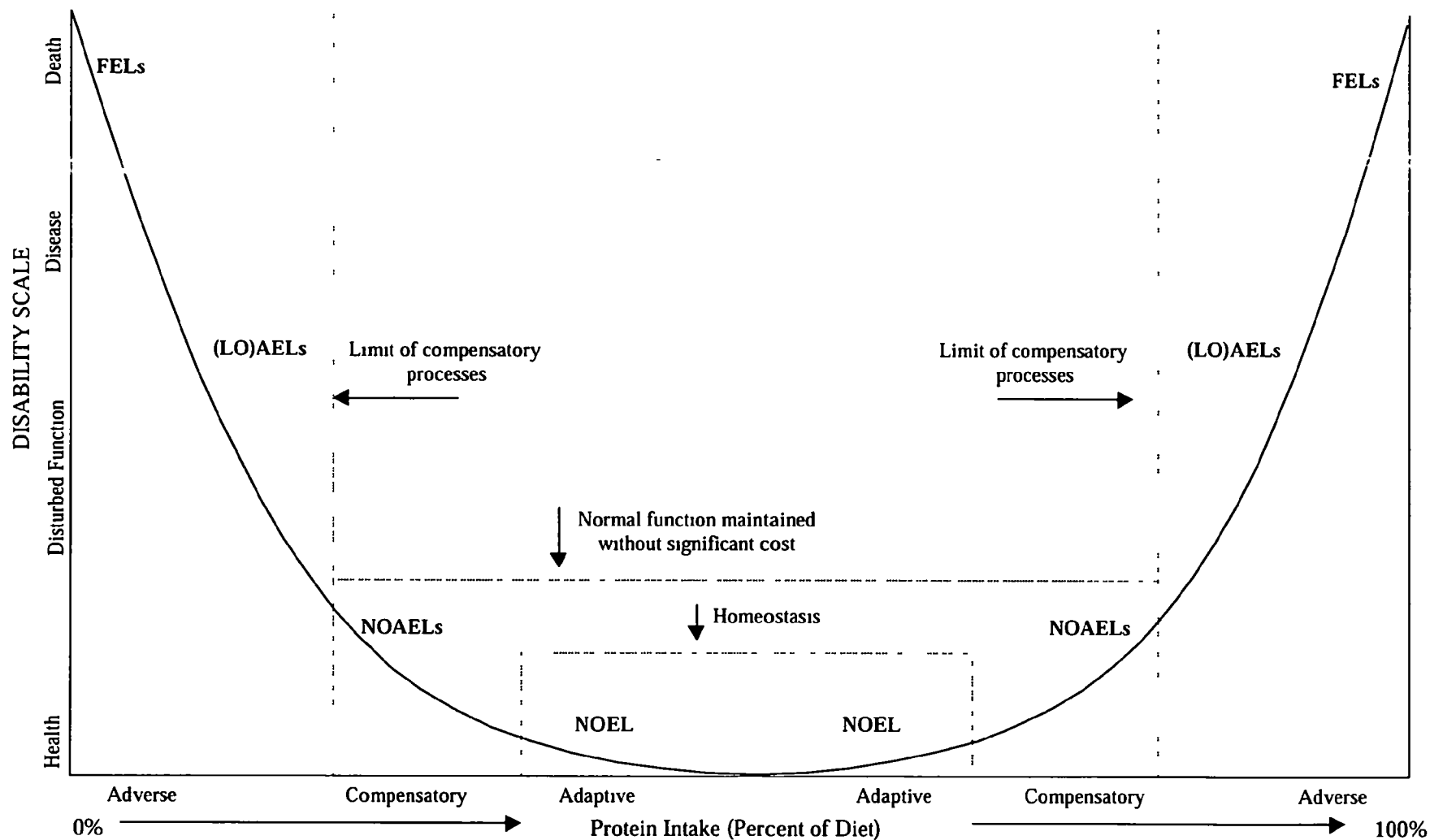


Figure 6-2. Hypothetical curve: No data are presented nor is the scale likely to be correct. Organism disability as a function of target organ impairment. A uniform scale of NOELs, NOAELs, (LO)AELs and FELs is proposed. Figure adapted from DeRosa et al (1989).

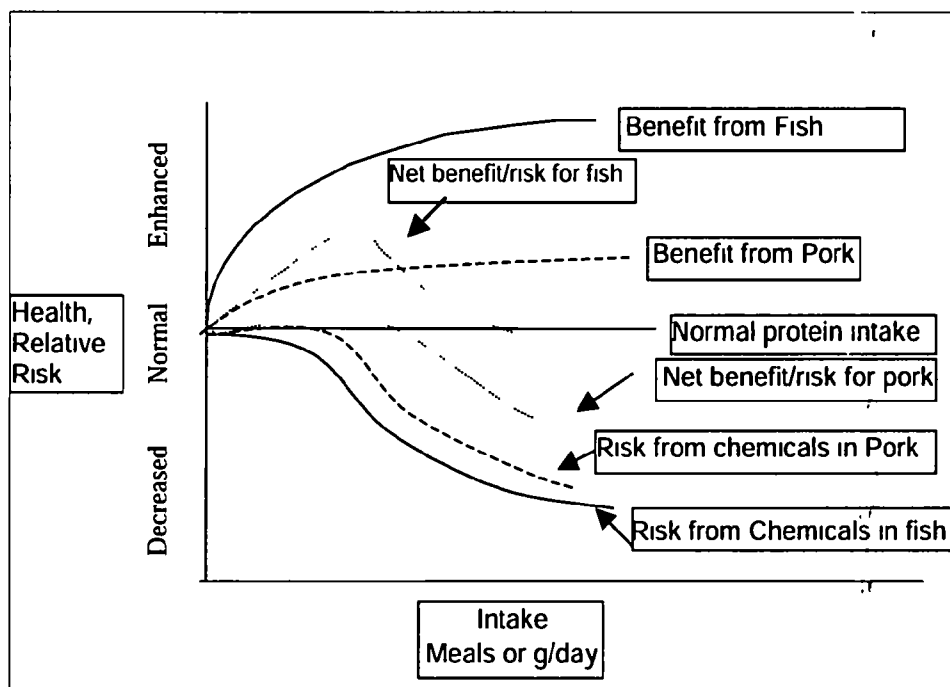


Figure 6-3 Relative risk as a function of intake rate and source of protein. Hypothetical curves; no data are presented nor is the scale likely to be correct.

Figure 6-3 presents yet another idea for a uniform scale with relative risk on the y-axis and intake on the x-axis. The solid line on top indicates "enhanced" health from consuming fish. A "normal" health status is the solid line in the middle from normal protein intake, and the risk curve from the chemical in fish is the lowest solid line indicating "decreased" health. The broken lines in between indicate a hypothetical benefit and risk for pork as an alternative protein source to fish. Net changes in benefits and risks (shown as dotted lines) might then be compared amongst protein sources.

Such comparison of net benefits from different protein sources as shown hypothetically in Figures 6-1 and 6-3 might be considered ideal, because trade-offs among protein sources are quantifiable. Unfortunately, chemical contamination of different protein sources is generally not known for many chemicals (Chapter 3). Nor are quantifiable benefits data readily available for protein sources other than fish (Chapter 2). Because of this, further use of either of these adapted scales to compare chemical contamination was not further investigated. This remains a viable area for future study.

6.3.5 Cultural Considerations

In developing the framework, it is important to consider that social and cultural factors may also impact the relative risks and benefits of fish consumption. One must consider not only health-related risks and benefits, but also aspects related to the economic, social, religious, and cultural well being of particular communities. For example, among isolated and/or lower-income groups, fish may represent an important economic resource, and a source of needed high-quality protein,

that is not easily replaced. For others, particularly Native American tribes or Asian American communities, fish may have special cultural significance. In such communities, advisories designed to limit consumption of fish may have unforeseen detrimental socio-cultural impacts. These potential consequences or countervailing risks need to be considered when assessing the risks and benefits of fish consumption. Socio-cultural considerations were discussed further in Chapter 5.

A modifying factor for considerations could be incorporated into the framework below. However, the magnitude of this factor and how much impact these considerations have on a community or individual must be assessed on a case-by-case basis and ideally by the community members themselves. A process and scales for assessing socio-cultural impacts and weighing them against other health risks and benefits is not available, and developing one was beyond the scope of this project. In particular, if a cultural modifying factor is employed and a more refined derivation methodology developed, explicitly including the perspectives and concerns of the culture in question is strongly recommended. The cultural modifying factor should not be imposed upon a culture without their consent or involvement. It is expected that the population will agree with the use of such a factor. Harper and Harris (1999) are developing a cultural impact scale that normalizes disparate kinds of risk, but this has not yet been published.

6.4 The Benefit/Risk Framework

The simplest representation of health risks and benefits associated with eating contaminated fish is shown in Figure 6-4. This figure presents the change in several health benefits in the top part of the figure and the change in health risk as a function of fish consumption rate for several endpoints in the lower part of the figure. Several measures of benefit and risk are plotted on the y-axis and fish consumption rate (shown as grams/day) is plotted on the x-axis.

The top part of the figure presents the change in benefit, specifically the decrease in risk for coronary heart disease, arthritis, and stroke with increasing fish consumption. Thus, the curve (labeled "CHD (Upper Bound)") indicates that people eating about 20, about 35 and about 60 grams of fish per day had a 12% lower, 16% lower and 38% lower (relative risks of 0.88, 0.84 and 0.62, respectively) incidence of CHD than people consuming 0 grams of fish per day. The dose response curves shown for these endpoints are based upon results from human epidemiological studies. These endpoints have been selected because quantitative epidemiological data are available that relate changes in these endpoints to changes in fish consumption rate. Because the incidence of many of these effects is assumed to decrease with increasing fish consumption, reductions in incidence can be viewed as examples of the benefits of eating fish. For each endpoint, an upper bound and lower bound curve are presented to provide a sense of the range of a particular health benefit. These are not statistical upper and lower bounds (i.e., they are *not* the upper and lower 95% confidence interval of a relative risk ratio). Rather they represent the range of best-estimate responses reported by different studies or of different populations of people within a single study. In the case of coronary heart disease (CHD), the upper bound represents the best-estimate change in the adjusted relative risk of death from all causes of CHD reported by Daviglus *et al.* (1997). The lower bound represents the best-estimate change in the crude risk ratio

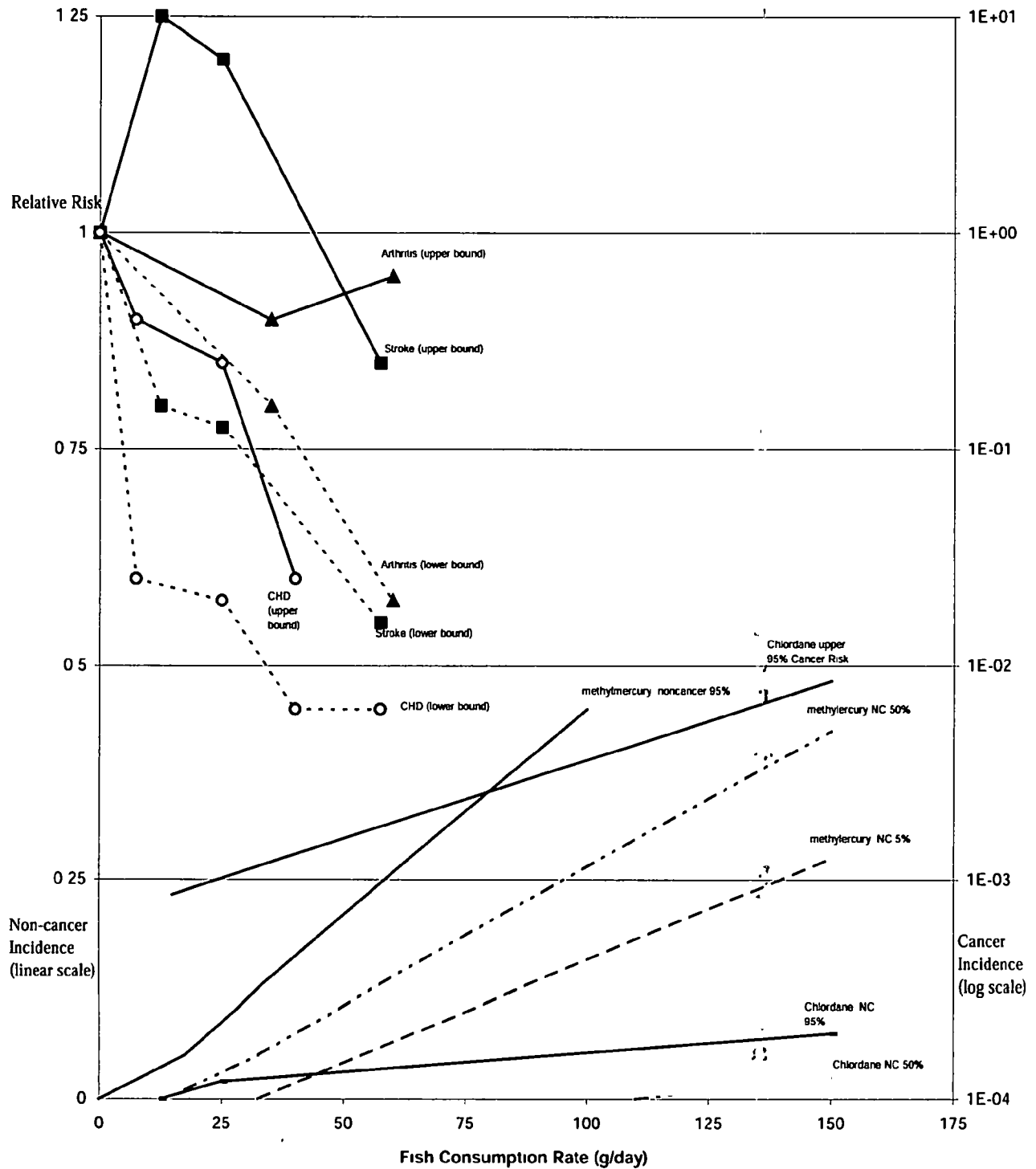


Figure 6-4. Relative risk of benefits and toxicity as a function of different amounts of fish consumed assuming contamination with 2.1 ppm methylmercury and 12 ppm chlordane. Note different scales for non-cancer and cancer toxicity.

of death due to CHD during a 20 year-long follow-up period reported by Kromhout *et al.* (1985)². The upper and lower bound changes in incidence of stroke represent the best-estimate adjusted relative risk of acute stroke in men and women, respectively, between the ages of 45 and 74 (Gillum *et al.*, 1996). For rheumatoid arthritis, the upper bound is the change in the best-estimate adjusted odds ratio for all types of fish consumed by the subject population while the lower bound is the best estimate change in the adjusted odds ratio when considering only broiled or baked fish (Shapiro *et al.*, 1996). Chapter 2 provides further details about these studies.

It is important to recognize that the benefit curves shown in Figure 6-4 are based upon a selection of the available quantitative data. They do not represent the conclusions of an in-depth review of all available quantitative health benefit data. Use of data from other studies would have produced alternative benefits curves (and some studies may not show a benefit at all [e.g., Siscovick *et al.*, 1995]). Because the studies used to develop the benefits curves shown in Figure 6-4 are for illustrative purposes only, the results shown in this report should also be considered illustrative and not definitive.

The framework examples in this report and the case studies use the best estimates (i.e. 50th percentile of population response) of potential non-cancer risk and health benefit to predict the net change in health associated with eating contaminated fish. To estimate excess lifetime cancer risk, the framework uses the EPA cancer slope factor (CSF) that represents a 95% upper bound of the distribution of CSFs calculated by the linearized multistage model. Use of the upper bound CSF will cause an underestimate of the net benefit (or overestimate of risk) because an upper bound estimate of risk (derived using the standard conservative toxicity assumptions employed by EPA) is being compared to a best estimate of benefit. This is recognized as a conservative bias. However, the framework uses the upper bound because it is what EPA has available for the majority of chemicals. In the future, use of the best estimate of the CSF to calculate cancer risk is preferred in order to derive a more reasonable comparison of health risk and health benefit data.

Other comparisons are possible to address this bias. For example, the upper bound of potential risk could be compared to the greatest estimate of potential benefit to derive an alternative estimate of potential benefit.

The five curves in the lower portion of Figure 6-4 (originating from the x-axis) present the change in noncancer risk associated with methylmercury (assumed to be present in fish at 2.1 ppm) and chlordane (assumed to be present in fish at 12 ppm). Noncancer risk is expressed as the change in incidence of a particular effect in the exposed population. Thus, the upper 95% confidence bound of the mercury dose-response curve of Figure 6-4 (labeled "Mercury 95%"), indicates that at a consumption rate of about 60 grams of fish per day, twenty-five percent (0.25) of the exposed population would be expected to experience the critical effect associated with methylmercury.

² Note that if the adjusted risk ratios (instead of crude ratios) from the Kromhout *et al.* study had been used, the reduction in death due to CHD would have been slightly less than shown in Figure 6-4 at low fish consumption rates and greater than that shown at high fish consumption rates (Kromhout *et al.*, 1985)

Unlike most non-cancer risk assessments, which simply assume that exceedence of the RfD is unacceptable and do not estimate the incidence of non-cancer effects above the RfD, the five lower curves on the this graph estimate the incidence of adverse non-cancer effects caused by both methylmercury and chlordane. The method for calculating risks above the RfD is described in Chapter 4, which also presents the actual calculations for several chemicals of interest. For methylmercury, three curves are shown: the upper 95% bound of population response (labeled "Mercury 95%"); the best estimate of population response (labeled "Mercury 50%"); and, the lower 5% bound (labeled "Mercury 5%"). For chlordane, the upper 95% bound (labeled "Chlordane 95%") and best estimates (labeled "Chlordane 50%") are shown. The bounds refer to the lower 5%, best estimate (i.e., 50%) and upper 95% bound of the dose response curve for the critical noncancer effect associated with methylmercury and chlordane. It is important to recognize that, with the exception of the noncancer risks curves discussed above, uncertainty in health benefits and risks is not dealt with explicitly by this initial version of the framework. An important future refinement of the framework would be explicit consideration and quantification of uncertainty surrounding estimates of potential health risk and benefit. These uncertainties could be addressed by considering different benefit curves than the ones we chose or varying the chemical concentrations or mixtures of chemicals in fish. Some of this variations are shown later in this chapter.

The potential cancer risk associated with chlordane is also presented in Figure 6-4. It is shown as the straight line in the middle of the graph labeled "Chlordane Upper 95% Cancer Risk". Note that the scale for increased cancer risk is shown on the right-hand side of Figure 6-4. Thus, at a consumption rate of about 20 grams per day of fish, the increased cancer risk is about 1×10^{-3} and the increased risk approaches 1×10^{-2} as the consumption rate approaches 200 grams per day. The change in cancer risk is shown on a separate scale because it would not have been visible on the scale used for the other non-cancer endpoints. Changes in non-cancer effects represent an percent level increase in a person's risk of manifesting the critical effect associated with a chemical, while an excess cancer risk of even as high as one in one thousand (1×10^{-3}) represents an increase in risk of only a tenth of a percent.

Figure 6-4 illustrates the complexity of capturing the relative changes in risk or benefit as a function of fish consumption. Note that the six benefit curves on the top portion of the figure are independent of the concentrations and types of chemicals in fish, to the extent that the chemical contamination of the fish in these studies was generally not known. Thus, they are assumed to represent fixed health benefits associated with eating fish.³ The five noncancer risk curves and one cancer risk curve on the lower portion of the graph will change as the types and concentrations of chemicals change. The illustration presented in Figure 6-4 estimates potential risk from just two chemicals (methylmercury and chlordane) at fixed concentrations in the fish of 2.1 mg/kg and 12 mg/kg, respectively. The chemicals and concentrations do not represent any particular site. They were chosen simply to provide an example of how the framework can be

³ Actually, they include any potential adverse effect associated with chemicals in the fish, though information about chemical concentration in fish is not available for most benefit studies. To the extent such chemicals are present and that they directly impact the change in benefit incidence, these benefits curves might represent net benefit already; fish with less chemical contamination might be associated with even greater benefits

used. The shape and slope of the cancer and noncancer risk curves is a direct result of the types and concentrations of chemicals in fish.

Figure 6-4 is already quite complicated and yet it only presents the benefits and risks associated with consuming fish containing a specific set of chemicals at specific concentrations over a range of fish consumption rates. Figure 6-4 also does not capture all of the possible health benefits information available (see Chapter 2). Nor does it capture situations where the identity of chemicals and their concentrations vary. Indeed, it is very difficult to combine all this information to determine whether a net benefit exists. This problem becomes more complex when fish of different chemical concentrations are considered, because multiple versions of Figure 6-4 could then be drawn. In other words, a public health official modifying an existing risk-based advisory might have difficulty deciding whether to modify the advisory and if so, by how much, based on Figure 6-4, or its many versions. Nonetheless, for the framework to be of greatest use, the multiple benefits and risks need to be combined and a net health outcome needs to be derived. We approach this problem by developing separate algorithms of benefit, risk and their combination.

6.4.1 Algorithm for Health Benefits

For each health endpoint where fish consumption has been shown to improve health, we develop a quantitative algorithm for estimating the benefit. The benefit is a function of the background incidence of that health endpoint in the U.S. population, the relative reduction in risk of that endpoint caused by eating fish, the biological severity of that health endpoint, and the amount of fish eaten. The equation used to calculate the benefit for any particular endpoint at a given fish consumption rate is:

$$[B_i \times (1-RR_i)] \times S_i = \text{Benefit}_i$$

Where:

B_i	is the background incidence of health endpoint i (see Chapter 2);
RR_i	is the relative risk of health endpoint i at the given consumption rate (see Table 6-1);
S_i	is the biological "severity" of health benefit endpoint i (see Table 6-2);
	and,
Benefit_i	Is the possible benefit for health endpoint i associated with eating a given amount of fish.

Background incidences of various health endpoints are available from a variety of sources. Relative risks associated with fish consumption are summarized above (Table 6-1) and all readily available quantitative data are presented in Chapter 2. As described above, the benefits from fish consumption for different health endpoints will vary in their biological and perceived "severity" (health risks that were the basis for the calculation of risk above the RfD vary in severity in a like manner). For the purposes of illustrating this framework, we assigned a score to the biological "severity", or magnitude of the disease avoided using the values presented in Table 6-2 and discussed earlier. Severity of benefits (and risks) must be included in the

calculation of the FCI in order to add benefits and risks of disparate effects and diseases. For the presentation of the framework here, we did not attempt to incorporate personal or societal perception of severity. The biological “severity” scores used for the benefits in the framework range from 0 to 3, with a higher score being assigned to reduction of more severe disease.

The health benefit associated with eating fish is expressed as a unitless positive number and is plotted on a health scale. The number is positive because a reduction in an adverse effect is assumed to represent an improvement, as opposed to a decrement, in health. As described below, risk from consuming chemicals in fish is expressed as a negative number to connote an anticipated decrement in health.

When a benefit associated with fish consumption exists for more than one health endpoint the framework calculates a total benefit by summing the benefits associated with each individual health endpoint using the equation shown below:

$$\sum_{i=1}^n \{ [B_i \times (1-RR_i)] \times S_i \} = \Sigma \text{ Benefit}$$

The framework can also be modified to account for the cultural benefits of eating fish as described below.

$$\sum_{i=1}^n \{ [B_i \times (1-RR_i)] \times S_i \} \times C = \Sigma \text{ Benefit}_c$$

All the parameters are the same except for the addition of a cultural factor “C”. The cultural factor represents the cultural value associated with fish consumption (this could also represent religious or social benefits). For use in the framework, the cultural value is expressed relative to the health benefits because it modifies the predicted total health benefit. Thus, if a particular subpopulation decides that the cultural benefits of eating fish are equal to the health benefits, then the total benefit of eating fish would be twice the health benefit alone and “C” in the above equation would be assigned a value of 2. Other ways to incorporate the cultural benefits of eating fish are also possible. For example, instead of multiplying the total benefit by “C”, the constant “C” could be added to the health benefits. Addition of “C” suggests that the cultural value of fish consumption is constant across all fish consumption rates while multiplication (as shown in the above equation) connotes that cultural benefit follows health benefit and increases with increasing fish consumption rate. A third alternative is to have cultural value be very high at low consumption rates but decrease with increasing fish consumption rate. Such a relationship may represent a situation where fish are essential in ceremonies that mark a subpopulation's continued existence but do not have to be a large fraction of that particular culture's daily diet.

An “objective” scale that can be applied to measure cultural benefits has not been developed for this framework. This must be determined on a case-by-case basis, ideally by the individuals and populations themselves. Obstacles to developing such a quantitative factor include measurement of physical, emotional and mental well being with the disruption or enhancement of a “cultural”

practice such as catching or consuming fish. Quantitative data are not available, but the population itself may have a qualitative judgment about the negative or positive consequences of a cultural practice. For example, a tribe that relies heavily on locally caught fish, could examine the consequences to the population's health (e.g., effects of use of replacement foods), or to the continuation of its traditional lifestyle. From the perspective of the cultural value of fish, the key aspect of the framework is that it contains the flexibility to incorporate the cultural importance of fish and to weigh that importance against potential health risks. There are many possible ways this important parameter could be included. A specific approach for estimating "C" has not been developed for this project, although others are investigating ways to estimate cultural consequences (Harper, 1999).

6.4.2 Algorithm for Health Risk

The process used to derive a single estimate of risk from chemicals in fish parallels that used to derive a single estimate of the benefit associated with eating fish. For each chemical and single adverse effect it causes, the increased risk associated with contaminated fish is calculated using the following equation:

$$(R_i \times S_i) \times (-1) = \text{Risk}_i$$

where:

R_i	is the increased risk of health endpoint i associated with a particular fish consumption rate,
S_i	is the biological severity of health endpoint i ; and,
Risk_i	is the decrease in health (because of the increase in risk of health endpoint i) associated with eating a given amount of fish.

Risk (R_i) is the increased risk of health endpoint "i", above the background incidence, which is assumed to be caused by exposure to chemicals in fish (see Chapter 4). The severity score (S_i) is the same as described above (see Table 6-2). Risk_i is the change in health associated with eating fish containing a chemical that causes an increase in endpoint i and is expressed as a unitless negative number. The number is negative because an increase in an adverse effect leads to a decrement in health.

When a risk associated with fish consumption exists for more than one chemical, or a chemical causes more than one adverse effect, the framework calculates a total risk by summing the risks associated with each individual chemical (or for each endpoint caused by a single chemical) using the equation shown below:

$$\sum_{i=1}^n [(R_i \times S_i) \times (-1)] = \sum \text{Risk}$$

Note that both cancer and noncancer risks are added after adjustment by the biological severity index S_i . For example, the increased incidence of the critical (noncancer) effect associated with

methylmercury is added to the increased risk of cancer and noncancer effects from chlordane. Once severity is considered, the resulting risk curve cannot be viewed as the possible increased incidence of a specific effect in the exposed population or an individual's increased risk of manifesting a specific effect.

6.4.3 Algorithm for the Fish Consumption Index (FCI)

To estimate the net health effect of eating contaminated fish, the framework sums the total benefit and total risk to derive the Fish Consumption Index (FCI) using the following equation:

$$\Sigma \text{ Benefit} + \Sigma \text{ Risk} = \text{FCI}$$

The FCI is plotted over a range of fish consumption rates to establish the relationship between change in health and fish consumption (Figure 6-5). As described above, the FCI is an estimate of relative risk. It is not an estimate of absolute risk. Nor does it provide users of the framework with an estimate of their increased or decreased incidence of a particular health outcome.

However, the FCI does provide a simple mechanism by which users can weigh the health risks versus the health benefits of eating contaminated fish. It also accounts for differences in severity of the different endpoints. Because the framework provides this information for a range of fish consumption rates, users will be able to determine the range of consumption rates at which they may have the largest benefit, and the largest risk. Consumers will also know the possible net risk or net benefit across consumption rates, or the consumption rate at which the benefits of fish consumption are first affected by the health risk.⁴

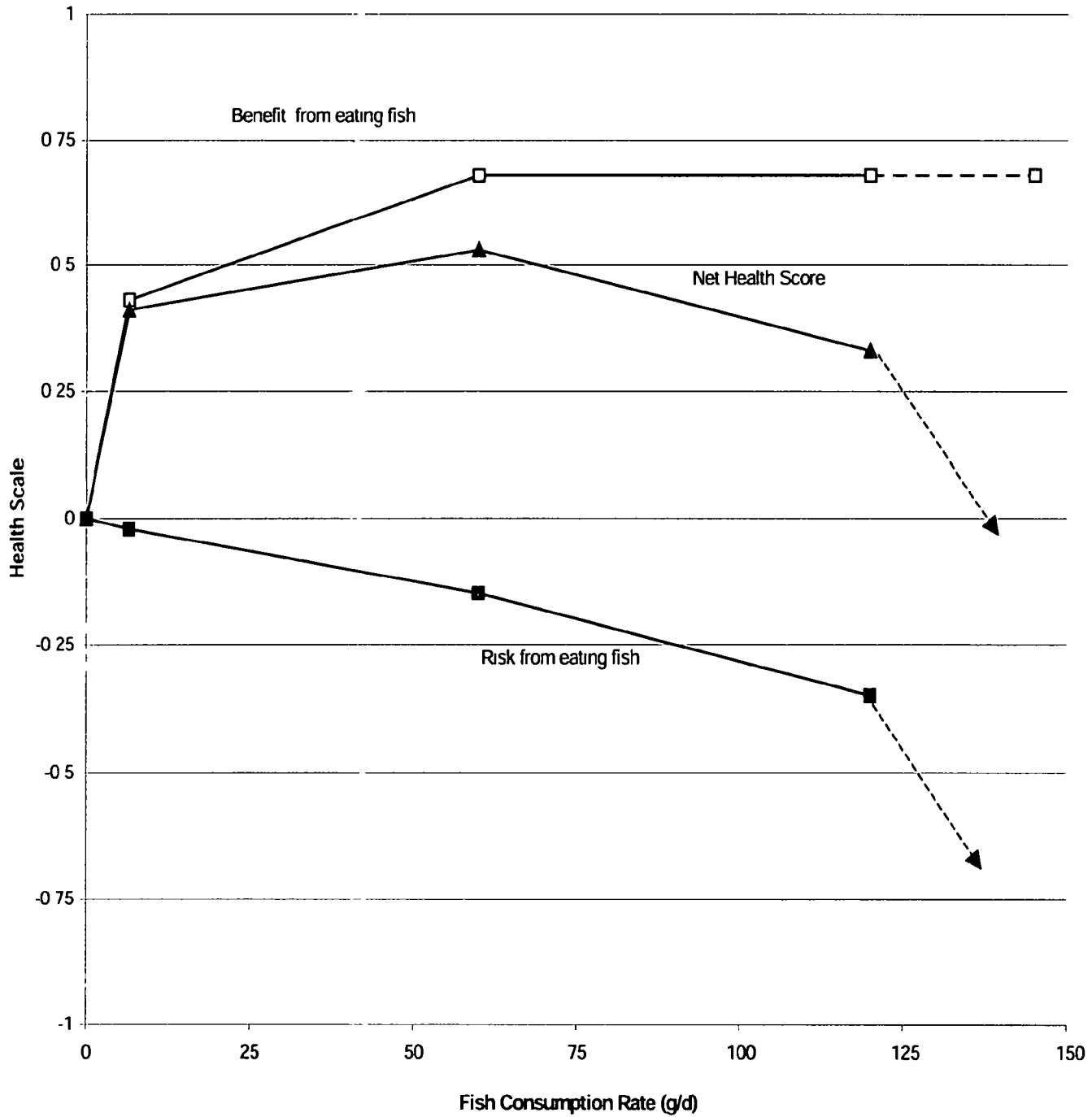
Note that if cultural benefits or personal perception of severity are included in the framework, the FCI is not strictly a health index, but rather represents a combination of health risks and benefits, personal perception, and cultural benefits and risks.

6.5 Demonstrating the Framework

This section presents a quantitative hypothetical example of how the framework can be applied. The example is hypothetical and is selected to illustrate particular aspects of the framework that may be useful. Other hypothetical examples are presented to illustrate various aspects of the framework, including impacts of changing levels in contaminant concentrations, evaluation of different subgroups, consideration of mixtures of chemicals and multiple endpoints, and inclusion of cultural benefits. Detailed examples of applying the framework to real world situations are presented in section 6.6.

⁴ In addition, it provides the user with the tool for comparing risks from different diet options; however, lack of contaminant data in other foods currently limits one's ability to do this

Figure 6-5. Health Scale as a Function of Fish Consumption Rate. Data are Derived from Figure 6-4 as Explained in the Text. Dashed lines are Extrapolated Values.



6.5.1 Quantitative Example of the Framework

As described above, the hypothetical example used in this document assumes fish contain 2.1 ppm (mg/kg) of methylmercury and 12 ppm (mg/kg) of chlordane.⁵ Consumption of fish is assumed to decrease the incidence of three health endpoints: coronary heart disease, arthritis, and stroke. The magnitude of the reduction (i.e., of the relative risk) depends upon the rate of fish consumption and is based upon data discussed in Chapter 2. As described above, the health benefits assumed by the framework to be associated with increased fish consumption are based upon a somewhat arbitrary choice of studies from the literature. They do not represent the conclusion of an in-depth evaluation of all the available data. Arthritis is judged to be the least severe of the three endpoints and is assigned a severity score of 1. Coronary heart disease and stroke are judged to be the most severe and are assigned a severity score of 3. Cultural benefits are not included in this example. The calculations used to develop this example are shown below in Table 6-4.

Table 6-4. Input Parameters To Estimate Benefits

Health Endpoint	Background Incidence (B)	"Severity" Score (S)	Consumption Rates (grams /day)/Relative Risk (RR)
Coronary Heart Disease	0.32	3	6.5/0.6 and 60/0.45
Stroke	0.07	3	6.5/0.85 and 60/0.55
Arthritis	0.13	1	6.5/0.92 and 60/0.57

Risk also depends upon the rate of fish consumption. Increased lifetime cancer risk is estimated using standard EPA exposure and toxicity assumptions (e.g. a CSF of 0.35 per mg/kg-day for chlordane, a body weight of 70 kg, and a 70-year exposure duration). Increased risk of the non-cancer effects of chlordane and methylmercury are estimated using exposure assumptions identical to those used to estimate increased cancer risk combined with the "risk above reference dose" technique described in Chapter 4. Table 6-5 below summarizes the inputs used to estimate risks for this hypothetical example.

Note that the benefit curve shown in Figure 6-5 becomes flat at a fish consumption rate of about 60 grams per day and is drawn as a dashed line for higher consumption rates. This is because few studies have quantified the benefits of fish consumption at specific consumption rates of greater than about 60 grams per day. Most studies report the maximum consumption rate as greater than some specific rate (i.e., more than two meals per week). The benefit curves assumed the highest consumption rate to be equal to the "greater than" consumption rate reported by a particular study. Based upon the absence of specific data on high consumption rates and some minimal evidence that some benefits appear to be leveling off (Figure 6-4) at the higher

⁵ We chose these values for no particular reason. Other values could be used in the development of this hypothetical example.

Table 6-5. Inputs Parameters To Estimate Risks

Chemical/Health Endpoint	Severity Score (S)	Consumption Rate (grams/day)/Increased Risk (R)
Chlordane/cancer	3	6.5/1x10 ⁻³ and 60/0.01 and 120/0.02
Methylmercury/non-cancer: neurological abnormalities	1	6.5/0.02 and 60/0.12 and 120/0.30
Chlordane/non-cancer: hepatic necrosis	3	6.5/0 and 60/0.001 and 120/0.01

consumption rates, it is assumed that the possible benefits remain constant at higher consumption rates. This is recognized as a conservative assumption, and it is important to recognize that possible benefits at high consumption rates may be underestimated by the framework.

Conversely, by ascribing the benefits reported for consumption rates of “greater than 60 grams per day” to a consumption rate of 60 grams per day (see Figure 6-5), the framework may be overestimating benefits at an actual consumption rate of 60 grams per day. The increased benefits reported by a study for the population of people eating “greater than 60 grams per day” may be occurring in people who are actually eating 90 or 100 grams per day.

Note that unlike the benefits curve, the slope of the risk curve becomes steeper at higher consumption rates. This is based on the slope of the non-cancer dose response curves that become steeper with increasing dose. The FCI, therefore, generally decreases after about 60 grams of fish per day in this hypothetical example.

The benefits and risks from each chemical can then be summed to derive the FCI and the result plotted against fish consumption rate (Figure 6-5). In this hypothetical example, the FCI increases from 0 at a consumption rate of 0 grams per day, reaches its maximum at a consumption rate of about 60 grams per day and then begins decreasing at higher consumption rates. The FCI becomes 0 at about 140 grams per day and is negative at higher fish consumption rates.

Different users of the framework may be interested in different portions of the FCI curve. For example, someone may decide to select a consumption rate where benefits equal risks (i.e., the point at which fish does not pose an increased risk above background). Alternatively, someone else may decide to focus on the consumption rate at which the FCI (overall health) is maximized. In the case of the hypothetical example used here, no net change in health outcome occurs at about 140 grams per day, while maximum benefit is realized at about 60 grams per day.

Yet another use of the FCI curve is to compare it to the benefit curve. The benefit curve can be viewed as the best representation of an ideal health benefit associated with eating fish. The FCI represents the possible health benefit when potential risks from chemicals are included. The difference between the two curves is the reduction in benefit caused by the chemical contamination. Note too, that the FCI can be used in a similar way to estimate the effect of very restrictive fish consumption advisories, in terms of unrealized health benefits. For example, when the FCI associated with setting an advisory at 5 grams per day is compared to the benefits

associated with setting an advisory at 60 grams per day. The FCI curve could also be used to compare different fish of the same species to find out the quantitative benefit of eating smaller, less contaminated fish.

A number of assumptions and estimates have been folded together to create this FCI and the resulting net health risk curves. However, the sometimes disparate information used in the development of the FCI does not lend itself to an easy estimation of error. One approach to seeing how such potential error might affect the use of the framework is to suppose that a set of FCI values, for example that of 0.25 to -0.25, defines a range of reasonable error. Thus, someone for this example might consider 140 grams per day as the consumption limit for adults because that is the consumption rate at which risks and benefits are equal. However, someone else might consider a value of 125 grams per day as the consumption limit for adults because that is the approximate rate at which the risks and benefits are at a value of 0.25.

It is notable that in this example, typical risk assessment techniques indicate that the upper bound cancer risk from chlordane alone equals one in one thousand (1×10^{-3}) at a consumption rate of about 25 grams per day and contamination of 12 ppm (mg/kg) (Figure 6-4). In the absence of the benefit information and based upon the results of a typical risk assessment, it might be that an advisory for the fish used in this example would restrict consumption to rates much lower than the either of the choices given above.

6.5.1.1 Calculations for Estimating Benefits

In the hypothetical example given above, benefits are predicted using the following equation (described in Section 6.4.1 of the framework):

$$[B_i \times (1-RR_i)] \times S_i = \text{Benefit}_i$$

Where:

B_i	is the background incidence of health endpoint i (see Table 6-4 and Chapter 2);
RR_i	is the relative risk of health endpoint i at the given consumption rate (see Table 6-4 and Chapter 2);
S_i	is the biological "severity" of health benefit endpoint i (see Table 6-2);
	and,
Benefit_i	is the benefit for health endpoint i associated with eating a given amount of fish.

The hypothetical example calculates benefits at two unique consumption rates (6.5 grams per day and 60 grams per day). Because data about benefits do not exist beyond a consumption rate of 60 grams per day, benefits are assumed to remain constant at higher consumption rates. Of course, this assumption breaks down as the percent of protein in diet approaches 100 (see Figure 6-1). However, for purposes of this framework example, the assumption is very reasonable because of the amount of fish consumed is a smaller part of the total daily food consumption (for example, 10 to 200 grams of fish is only approximately 1 to 20% of a daily food intake of 1 kg).

Table 6-4 gives values for background incidence, severity ratings and relative risks, and are shown below. Please note that the severity ratings reflect our judgments. Other judgments may be appropriate.

Using the above equations, at 6.5 grams per day:

CHD benefit: $(0.32 \times (1-0.6)) \times 3 = 0.38$;
 Stroke benefit: $(0.07 \times (1-0.85)) \times 3 = 0.03$; and,
 Arthritis benefit: $(0.13 \times (1-0.92)) \times 1 = 0.01$.

The total benefit is derived by summing the benefit for each health endpoint using the following equation (described in Section 6.4.1 of the framework):

$$\sum_{i=1}^n \{ [B_i \times (1-RR_i)] \times S_i \} = \sum \text{Benefit}$$

Thus, the total benefit at 6.5 grams per day of fish consumption is 0.42.

At 60 grams per day:

CHD benefit: $(0.32 \times (1-0.45)) \times 3 = 0.53$;
 Stroke benefit: $(0.07 \times (1-0.55)) \times 3 = 0.09$;
 Arthritis benefit: $(0.13 \times (1-0.57)) \times 1 = 0.06$; and,
 the total benefit is: 0.68.

6.5.1.2 Calculations for Estimating Risks

In the hypothetical example given above, risks from fish consumption are estimated using standard risk assessment equations (EPA 1989). As indicated before, fish in this hypothetical example are assumed to contain 2.1 mg/kg of methylmercury and 12 mg/kg of chlordane. People are assumed to weigh 70 kilograms and eat fish at a specified rate for their entire lifetime.

6.5.1.2.1 Excess Lifetime Cancer Risk

The equation used to estimate increase in excess lifetime cancer risk is:

$$R = a \times b \times c \times d \div e:$$

Where:

R = excess lifetime cancer risk;
 a = concentration of chemical in fish (mg/kg);
 b = consumption rate of fish (g/person-day);
 c = cancer slope factor (per mg/kg-day);

d = conversion factor (kg/1000 g); and,
e = body weight (kg/person).

Using the above assumptions and equation and assuming chlordane has a CSF of 3.5×10^{-1} results in an upper bound excess lifetime cancer risk of:

4×10^{-4} at 6.5 grams per day;
 4×10^{-3} at 60 grams per day; and,
 7×10^{-3} at 120 grams per day.

6.5.1.2.2 Excess Lifetime Non-Cancer Risk

Non-cancer risk is estimated by first calculating the daily exposure and then comparing that exposure to the dose response data for non-cancer effects presented in Chapter 4. The comparison requires determining how many times greater than the RfD the estimated dose is, and then estimating the response for that exceedence of the RfD (from the risk above RfD dose-response data).

Daily dose is estimated using the following equation:

$$D = a \times b \times c \div d:$$

Where:

D = daily dose;
a = concentration of chemical in fish (mg/kg);
b = consumption rate of fish (g/person-day);
c = conversion factor (kg/1000 g); and,
d = body weight (kg/person).

Using the above assumptions and equation, the daily doses of chlordane at three different consumption rates are:

1.1×10^{-3} mg/kg-day at 6.5 grams per day;
 1.0×10^{-2} mg/kg-day at 60 grams per day; and,
 2.1×10^{-2} mg/kg-day at 120 grams per day.

Similarly, the daily doses for methylmercury are:

2.0×10^{-4} mg/kg-day at 6.5 grams per day;
 1.8×10^{-3} mg/kg-day at 60 grams per day; and,
 3.6×10^{-3} mg/kg-day at 120 grams per day.

Using the dose-response information for chlordane for the percentage of the population predicted to manifest an effect, the best estimate (50th percentile) of the increased incidence of the critical effect is:

0 at 1.1×10^{-3} mg/kg-day;
 0.005 at 1.0×10^{-2} mg/kg-day; and,
 0.01 at 2.1×10^{-2} mg/kg-day.

For mercury the best estimate (50th percentile) of the increased incidence of the critical effect is:

0 at 2.0×10^{-4} mg/kg-day;
 0.12 at 1.8×10^{-3} mg/kg-day; and,
 0.30 at 3.6×10^{-3} mg/kg-day.

Risk (R), as used in the framework, is then calculated using the following equation (described in Section 6.4.2 of the framework):

$$(R_i \times S_i) \times (-1) = \text{Risk}_i$$

At 6.5 grams per day:

Chlordane cancer risk:	$-(4 \times 10^{-4} \times 3) = -1 \times 10^{-3}$;
Chlordane non-cancer risk:	$-(0 \times 3) = 0$; and,
Methylmercury non-cancer risk:	$-(0 \times 1) = 0$.

The risk for each health endpoint and chemical is summed using the equation shown below (described in Section 6.4.2) to arrive a total risk of -0.001 at 6.5 grams per day:

$$\sum_{i=1}^n -1 \times (R_i \times S_i) = \sum \text{Risk}$$

At 60 grams per day:

Chlordane cancer risk:	$-(4 \times 10^{-3} \times 3) = -1 \times 10^{-2}$;
Chlordane non-cancer risk:	$-(0.005 \times 3) = -0.015$;
Methylmercury non-cancer risk:	$-(0.12 \times 1) = -0.12$; and
the total risk is:	-0.15.

At 120 grams per day:

Chlordane cancer risk:	$-(7 \times 10^{-3} \times 3) = -2 \times 10^{-2}$;
Chlordane non-cancer risk:	$-(0.01 \times 3) = -0.03$;
Methylmercury non-cancer risk:	$-(0.3 \times 1) = -0.30$; and,
the total risk is:	-0.35

6.5.1.3 Estimating the FCI

The FCI is derived by combining the total benefit (B) and the total risk (R) for each consumption rate using the equation shown below (described in Section 6.4.3 of the framework):

$$\Sigma \text{ Benefit} + \Sigma \text{ Risk} = \text{FCI}$$

Thus:

at 6.5 grams per day the FCI is equal to 0.42
(the total benefit of 0.42 plus the total risk of -0.001);

at 60 grams per day the FCI is equal to 0.53
(the total benefit of 0.68 plus the total risk of -0.15); and,

at 120 grams per day the FCI is equal to 0.33
(the total benefit of 0.68 plus the total risk of -0.35).

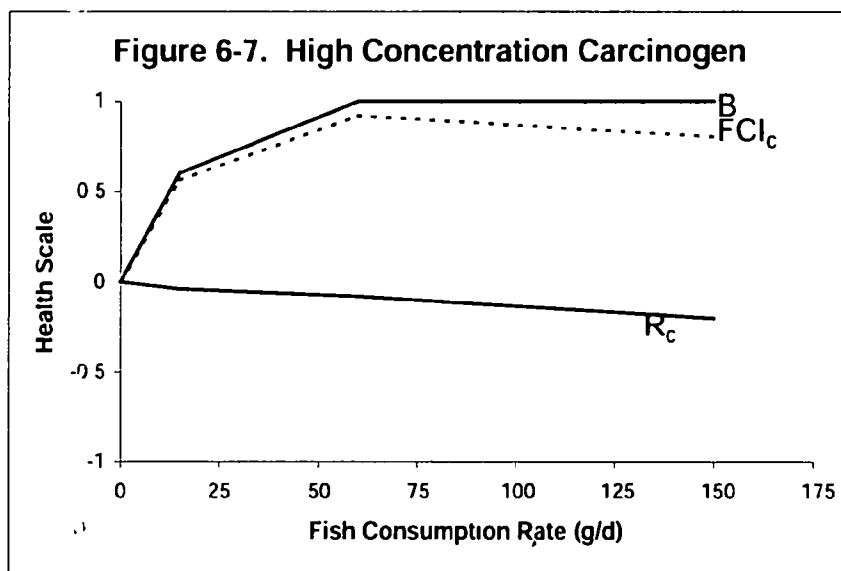
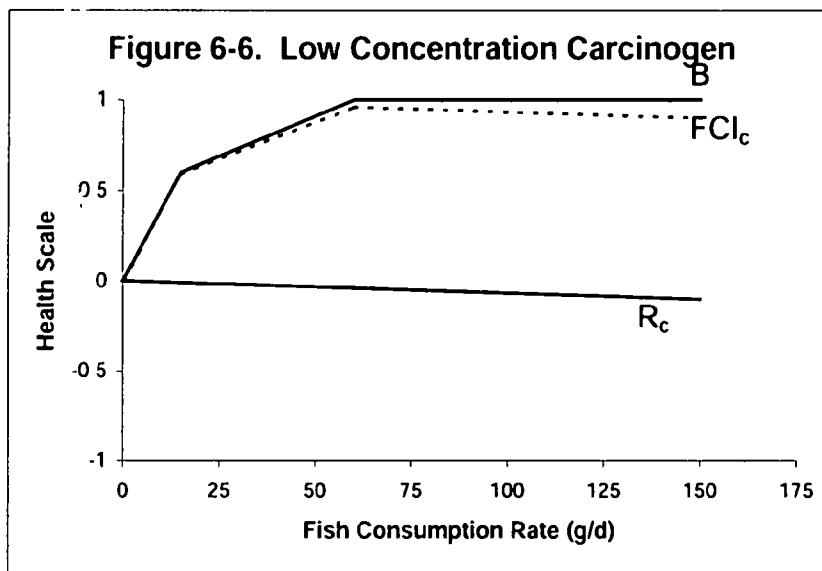
The benefit (B), risk (R) and FCI are plotted in Figure 6-5.

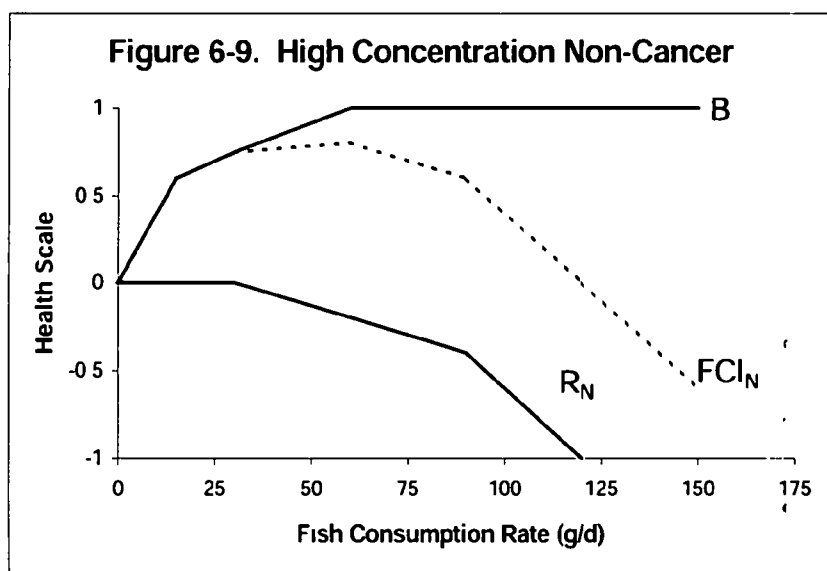
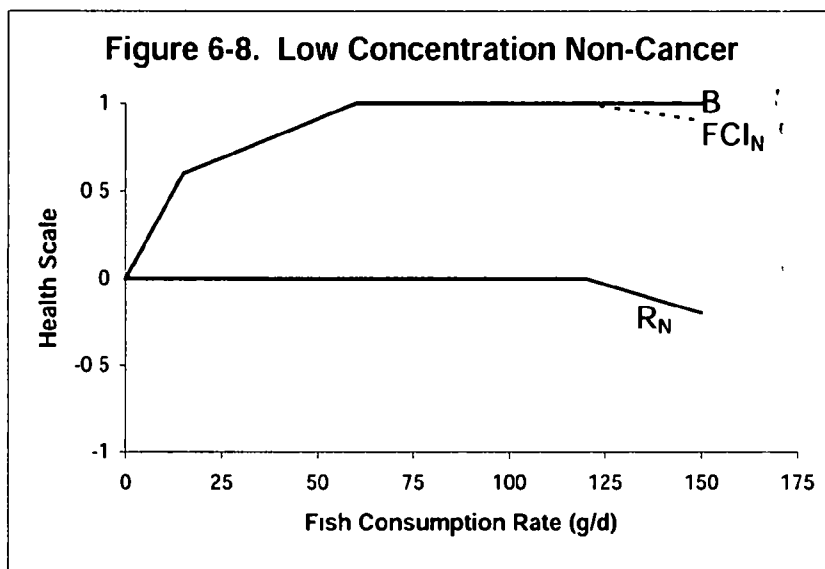
6.5.2 Impacts from Changes in Contaminant Concentrations

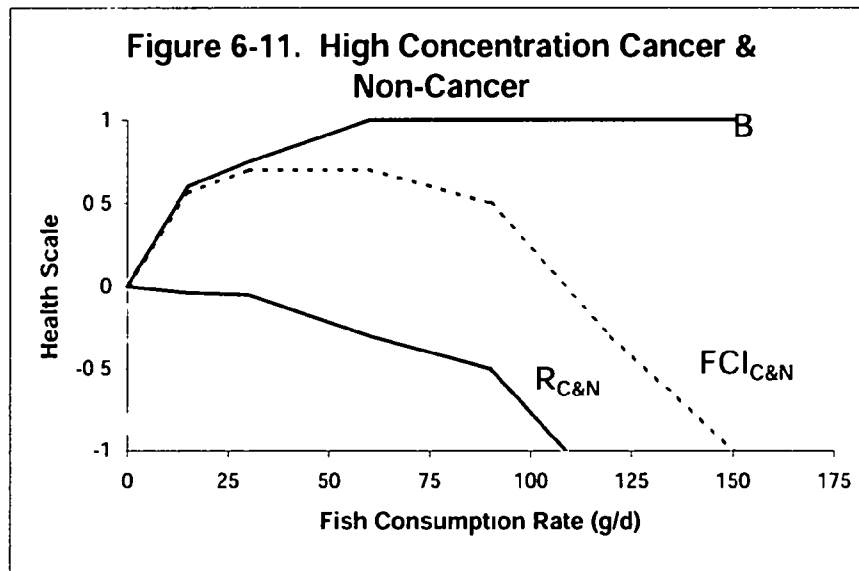
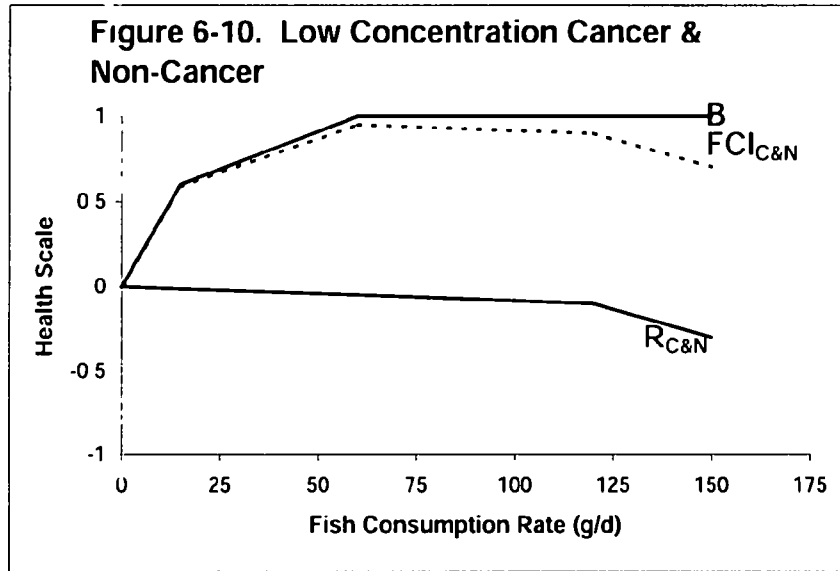
Changes in chemical concentration in fish and the type of health endpoint (i.e., cancer or non-cancer) a chemical causes will have a substantial effect on the FCI. Three observations about the interaction of chemical concentration and type of effect are important to recognize.

First, as evident from the quantitative example presented above (Section 6.5.1) even relatively large increases in excess lifetime cancer risk (large when evaluated using typical allowable risk levels of 1×10^{-6} to 1×10^{-4}) have a relatively small effect on the FCI. This is consistent with the results of Anderson and Wiener (1995) and is shown in Figure 6-6. As concentration of a chemical increases, the excess lifetime cancer risk also increases, but because increase in cancer risk is assumed to be linear for environmental exposures, the change in FCI remains relatively small. A comparison of Figure 6-6 (low concentration of a carcinogenic chemical) to Figure 6-7 (a four-fold increase in chemical concentration) reveals that the general shape of the risk (R) and FCI curves is not dramatically different. (Note that the benefit curve (B) remains the same because benefits depend only upon the amount of fish eaten and not the concentration of chemicals in fish.) In general, it appears that only in those instances where either people eat extraordinarily high amounts of fish or where the fish have very high levels of many carcinogenic chemicals, will the potential cancer risk associated with contaminated fish be greater than the potential benefits as identified for this example.

A second observation is that accounting for non-cancer effects can have a substantial effect on the shape of the risk curve (R) and the FCI. This difference occurs because the estimated risk from noncancer effects for these chemicals is on the order of a few percent compared to 10^{-3} to 10^{-4} risk from cancer at the doses of interest. At low concentrations of a chemical in fish, non-cancer effects may not manifest themselves until large amounts of fish are eaten (see Figure 6-8)







and the FCI may remain positive even at high consumption rates. When the concentration of a chemical in fish increases (in the case of this hypothetical example, by four-fold), the risk curve (R) shifts to the left and causes the FCI curve to do the same (compare Figures 6-8 and 6-9). Contrary to the observations made regarding concentrations of chemicals assumed to cause cancer, changes in the concentration of chemicals assumed to cause non-cancer effects could lead to substantial changes in the FCI.

In this hypothetical example, the combined cancer and non-cancer risk (R) and the FCI are dominated and largely determined by non-cancer effects (see Figures 6-10 and 6-11). This appears to be the case at both low (Figure 6-10) and high concentrations (Figure 6-11) of a chemical in fish. This hypothetical example may or may not apply to real situations, but it emphasizes the importance of evaluating noncancer effects for chemicals that cause cancer. Exceptions to this finding would be a chemical that is a highly potent carcinogen and causes no, or very minimal, non-cancer effects. None of the six chemicals currently included in the framework has this set of characteristics.

Part of this behavior can be explained by the use of a severity scheme that only allows differences of 1, 2, or 3 to effects of different biological severity. If a different quantitative scale is used, for example 1, 3, and 10, a different outcome might be expected. The suggested framework can use different severity scales if needed.

6.5.3 Evaluation of Different Subgroups

The framework has been designed to allow evaluation of the benefits and risks to multiple subgroups exposed to chemicals in fish. For example, children, teenagers, and adults may be exposed to chemicals in fish via direct consumption while a breast-fed infant may be exposed to chemicals in its mother's milk. If the chemicals in fish bioaccumulate in mother's milk, a breast-fed infant's exposure may be greater than an adult's for any given concentration of a chemical in fish (for a brief discussion of this issue, please see Chapter 4). In addition, differences in body weight among people who eat fish will result in differences in exposure. Dividing a population into subgroups allows one to estimate the exposure for each subgroup and the framework can calculate a unique FCI for each subgroup.

Figures 6-12 through 6-15 show how the potential risk and resulting FCI change for adults and infants with different concentrations of non-bioaccumulative or bioaccumulative chemicals in fish. Fish consumption rate is shown on the horizontal axis and the health scale is shown on the vertical axis. Several curves are shown on each figure. Curve "B" represents the benefit associated with eating fish and remains constant for all subgroups and in all figures. Curve "R" represents the potential risk associated with eating fish. Separate risk curves are shown for adults (R_A) and infants (R_I). Figures 6-12- and 6-13 show two infant curves, one for low concentration in breast milk ($R_{I, low}$) and one for high concentration ($R_{I, high}$). The curves labeled FCI_A and FCI_I show the FCI for adults and infants, respectively.

These four hypothetical examples present FCIs for an adult and breast-fed infant. One example each is presented for fish with a low (Figure 6-12) and high (Figure 6-13) concentration of a non-bioaccumulative chemical and for fish with a low (Figure 6-14) and high (Figure 6-15)

concentration of a bioaccumulative chemical. The framework assumes that the same toxicity benchmarks (CSFs and risk above the RfDs) can be used to estimate risk and calculate FCIs for different individuals. Given this assumption, the differences in risk and FCI are solely a function of differences in estimated dose.

Non-bioaccumulative Chemicals. For a chemical that does not bioaccumulate in breast milk (such as methylmercury) the differences in the infant and adult FCI may not be large (see Figures 6-12 and 6-13) regardless of the chemical concentration in fish. Any differences in FCI between these two subgroups arise from differences in dose. If a chemical is not readily transferred to breast milk or in situations where breast milk comprises a small fraction of an infant's diet, the infant FCI may be higher than the adult FCI (curve $FCI_{I, low}$ on Figures 6-12 and 6-13). This would mainly be due to the fact that the infant is exposed to less chemical on a per kilogram body weight basis. In such a scenario the adult is the more exposed individual.

Alternatively, if a chemical is readily transferred (but not bioaccumulated) to breast milk and if the majority of an infant's diet is comprised of breast milk, then the infant's FCI may be lower (i.e., more negative) than the adults (Figures 6-12 and 6-13). This would be mainly due to the fact that the infant is exposed to more chemical on a per kilogram body weight basis. When this occurs, a fish consumption advisory could be set to protect the infant and adult separately. This could be accomplished by selecting two sets of consumption rate limits, one for breast-feeding (or soon to be breast-feeding) mothers and another for other fish consumers. As an example, for the scenario shown in Figure 6-13, the FCI_A and FCI_I curves could be used to guide a decision-maker in setting appropriate levels.⁶

Bioaccumulative Chemicals. For chemicals that bioaccumulate in breast milk (chlorinated pesticides for example), the infant FCI may be much lower (i.e., more negative) than the adult regardless of the concentration of the chemical in fish (Figures 6-14 and 6-15). At low concentrations the adult FCI may remain positive (i.e., fish consumption leads to a net health benefit) and perhaps even at very high consumption rates, while the breast-fed infant FCI may become negative when the mother eats even moderate amounts of fish (Figure 6-14). At high concentrations, the infant's FCI may become negative when the breast-feeding mother eats low amounts of fish (Figure 6-15).

Thus, for bioaccumulative chemicals the FCI may differ substantially between adults and breast-fed infants. It is important to note that the consumption limits derived using the framework apply to the people eating the fish (i.e., older children, teenagers, and adults eating a particular amount of fish per day): Calculating a breast-feeding infant FCI depends upon estimating the infant's exposure through breast milk, which in turn requires conversion of the breast-feeding mother's fish consumption exposure into a breast milk concentration. This can be done using empirical data that relates an infant's exposure (consumption and breast milk concentration) to a mother's exposure or by using pharmacokinetic models that predict breast milk concentrations

⁶ Note that the framework does not consider how many months prior to beginning breast-feeding a mother should restrict her consumption of fish. This issue arises whenever setting advisories to protect breast-fed infants and depends upon the pharmacokinetics of the chemicals being evaluated. The same methods used to derive traditional fish consumption advisories can be used in the framework

based upon maternal exposure. The Everglades case study presented later in this chapter illustrates the latter approach.

6.5.4 Mixtures of Chemicals and Multiple Endpoints

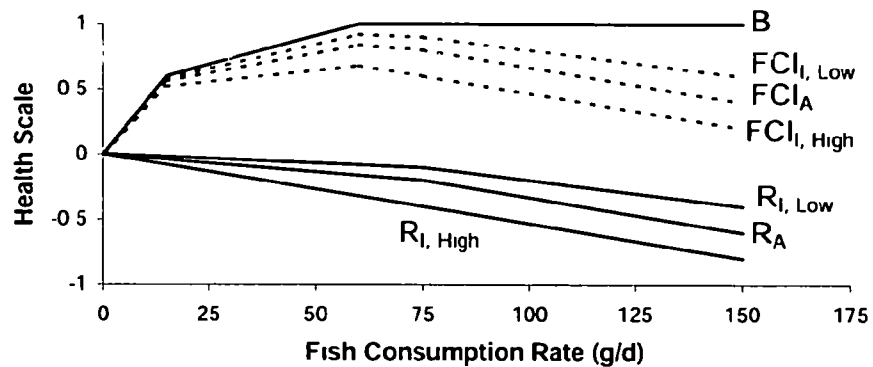
Fish can, and often do, contain more than one chemical. The framework has been designed to consider this. In addition, more than one non-cancer effect could be possible after exposure to chemicals. Many uncertainties and complexities arise when assessing exposures to mixtures or evaluating multiple endpoints.

Data on the toxicity of a specific mixture of chemicals in fish will generally not be available. In the absence of such toxicity data, the framework, like most other mixture risk assessments, defaults to an additivity approach, as per EPA guidelines (U.S. EPA, 1986; 1988). Cancer risk is estimated for each chemical individually and the risk from each chemical is then added together to derive a total risk associated with the mixture of chemicals. For non-cancer endpoints (with similar mechanism of action or at least target organ) the daily dose is divided by the RfD and the resulting fractions are summed for all chemicals to calculate a Hazard Index (HI). As long as the HI is at or below one, no hazard is assumed; a HI above one may be cause for concern, but cannot be interpreted in a quantitative fashion.

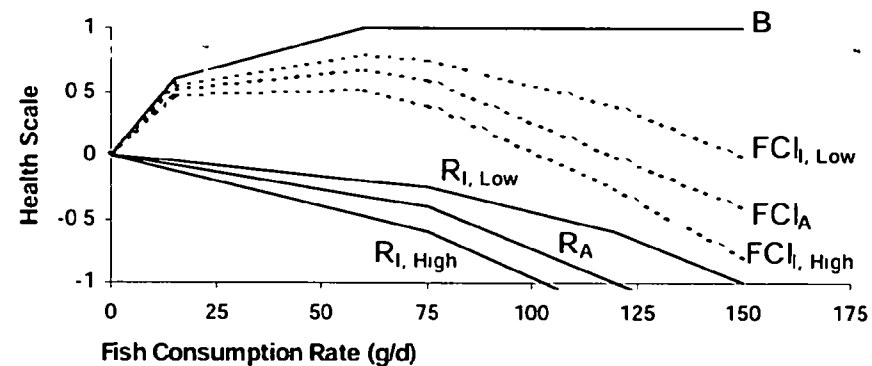
In this framework, as the potential risk from each successive chemical is combined, the total risk increases and the FCI decreases (Figure 6-16). However, the benefit curve remains the same whether there is one chemical or multiple chemicals present. Here fish consumption rate is shown on the horizontal axis and the Health Scale is shown on the vertical axis. Curve "B" represents the benefit associated with eating fish and remains constant regardless of how many chemicals are included in the analysis. Curves "R" and "FCI" represent the risk and FCI, respectively, associated with eating fish. Separate risk and FCI curves are shown for chemical A (R_A , FCI_A), chemicals A and B combined (R_{AB} , FCI_{AB}), and chemicals A, B and C combined (R_{ABC} , FCI_{ABC}). As discussed above, a parallel but opposite change in the FCI might occur if new or greater benefits associated with fish consumption (e.g., cultural benefits) are included in the framework.

Figures 6-17, 6-18, and 6-19 show how risk and FCI might change as risks from additional endpoints, which were not the basis for the RfD, are added to the framework. The top part of each figure shows the hypothetically dose response data for the critical effects and effects A & B. The low part of each figure shows fish consumption rate on the horizontal axis and the Health Scale on the vertical axis. Curve "B" represents the benefit associated with eating fish and remains constant regardless the number of adverse effects that are included in the analysis. Curves "R" and "FCI" represent the risk and FCI, respectively, associated with eating fish. Separate risk and FCI curves are shown for the critical effect only (R_{CE} , FCI_{CE}) and all endpoints (R_{all} , FCI_{all}). Figure 6-17 shows an example where the non-critical effects begin to manifest themselves at doses much greater than the critical effect. Figure 6-18 shows an example where the non-critical effects manifest themselves at doses similar to the critical effect but their dose response curve has a much smaller slope than that of the critical effect. Figure 6-19 shows an

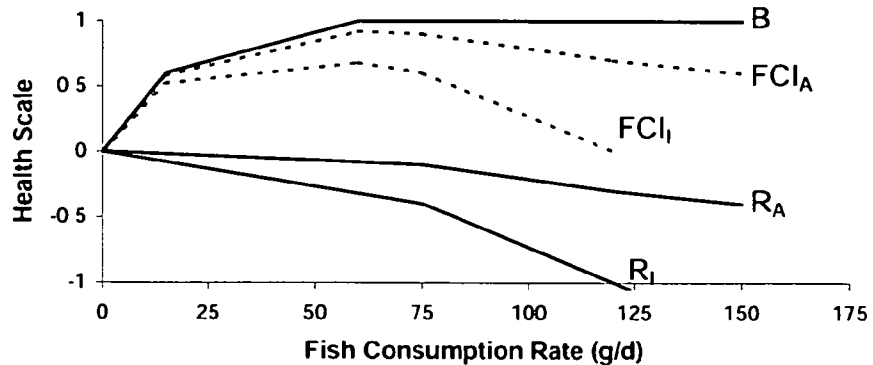
**Figure 6-12. Low Concentration
Non-Bioaccumulative**



**Figure 6-13. High Concentration
Non-Bioaccumulative**



**Figure 6-14. Low Concentration
Bioaccumulative**



**Figure 6-15. High Concentration
Bioaccumulative**

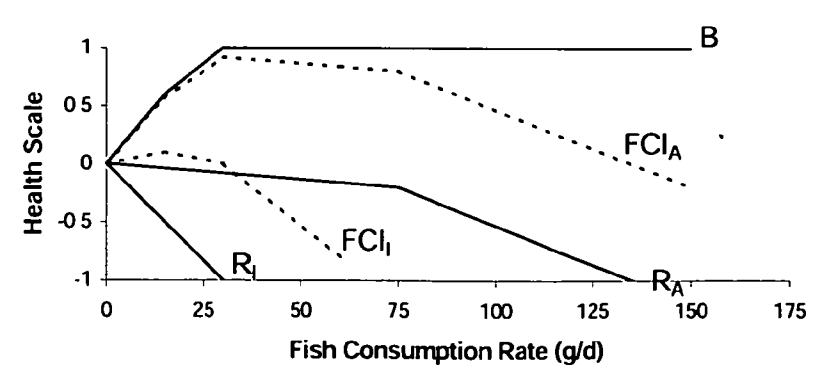


Figure 6-16. Change in FCI as more chemicals are evaluated for health risk in fish Figure 6-16.

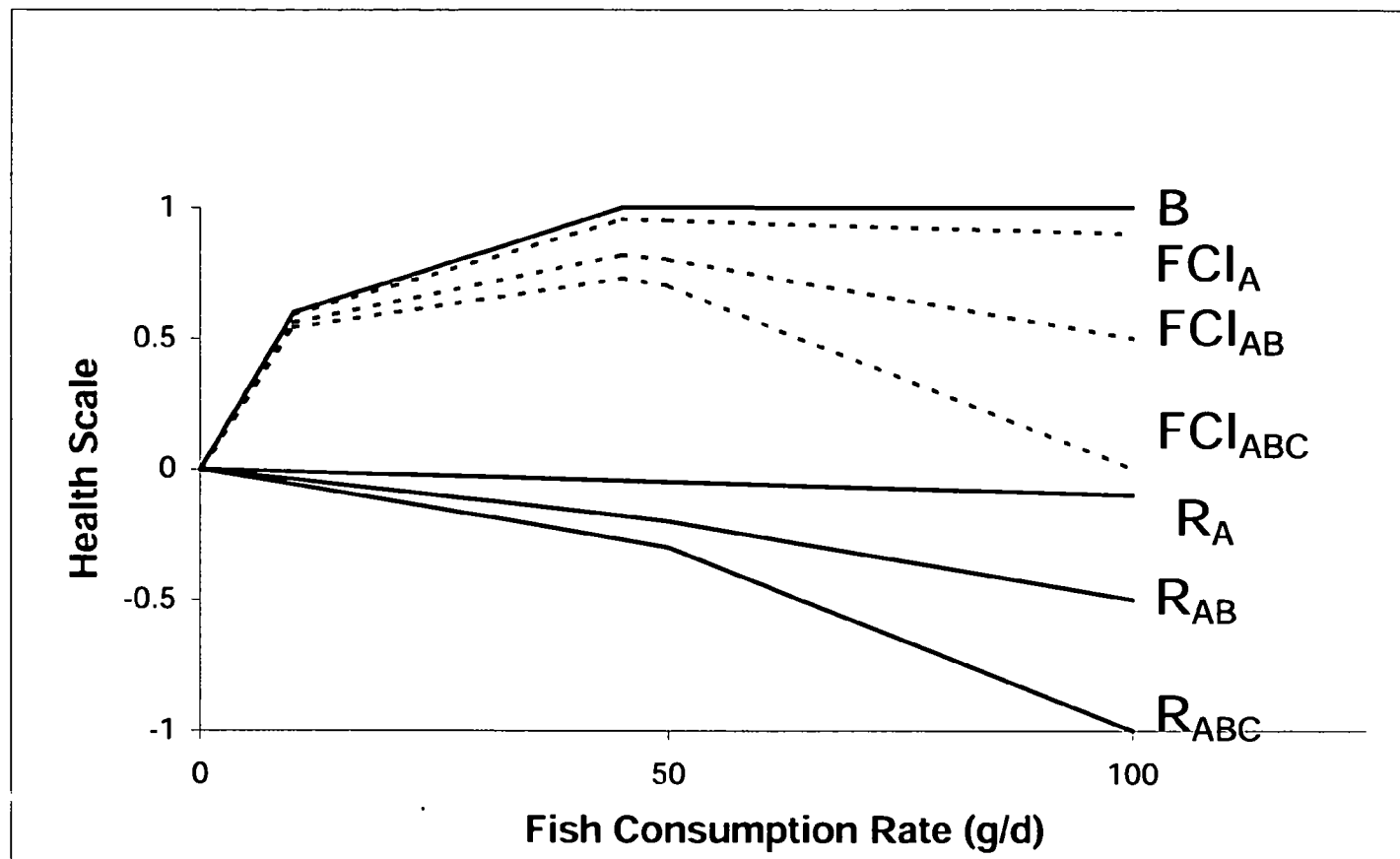


Figure 6-17. Non-critical effects begin to manifest themselves at doses much greater than the critical effect.

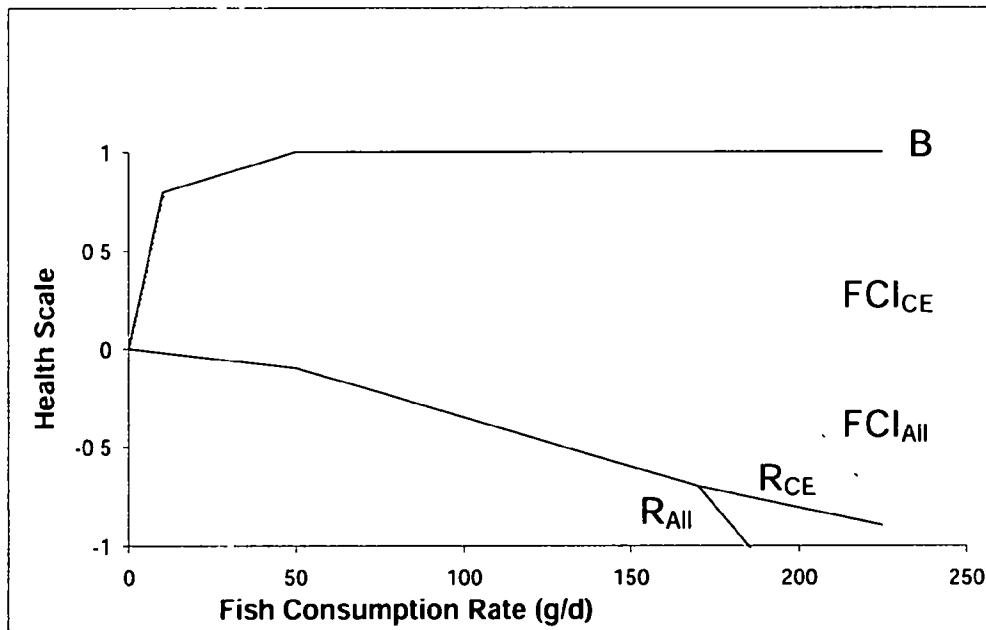
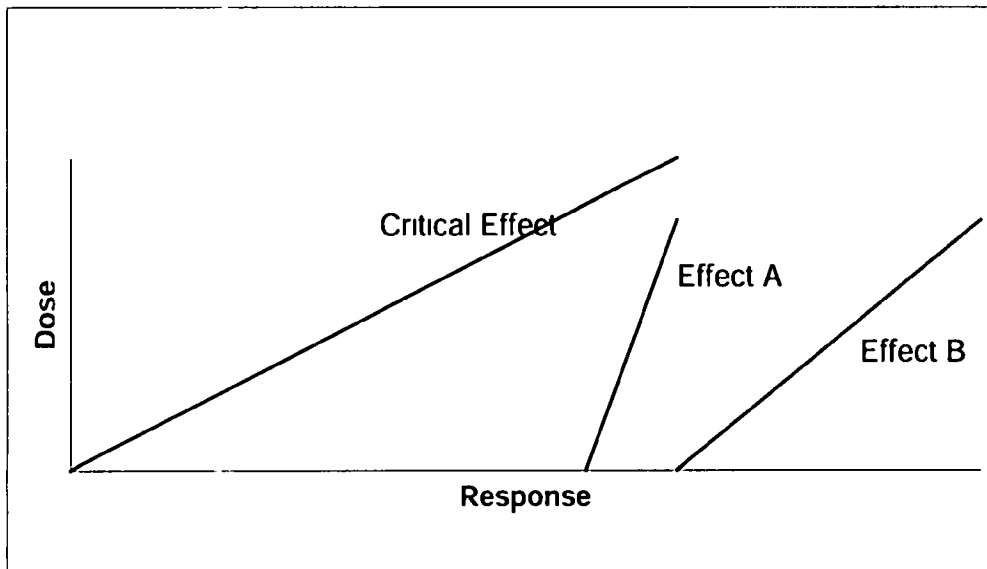


Figure 6-18. Non-critical effects manifested at doses similar to critical effect but dose response curves are shallower.

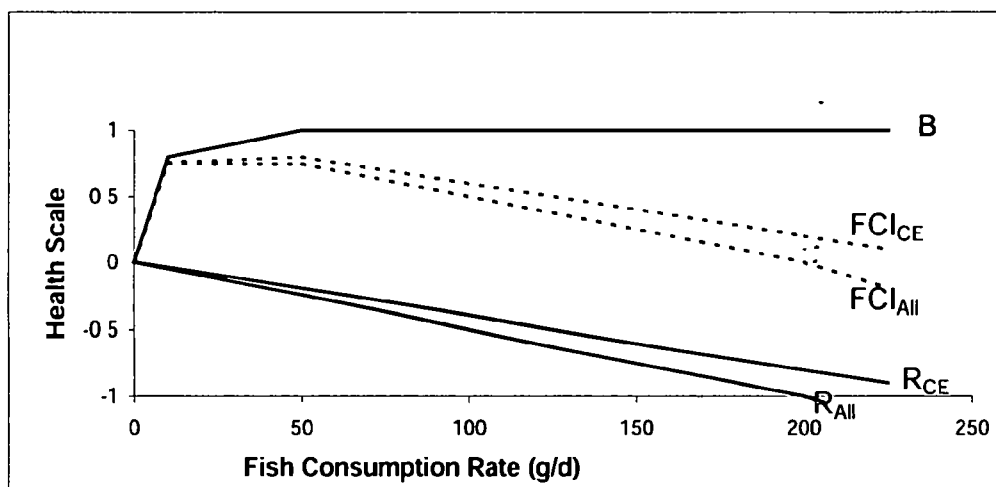
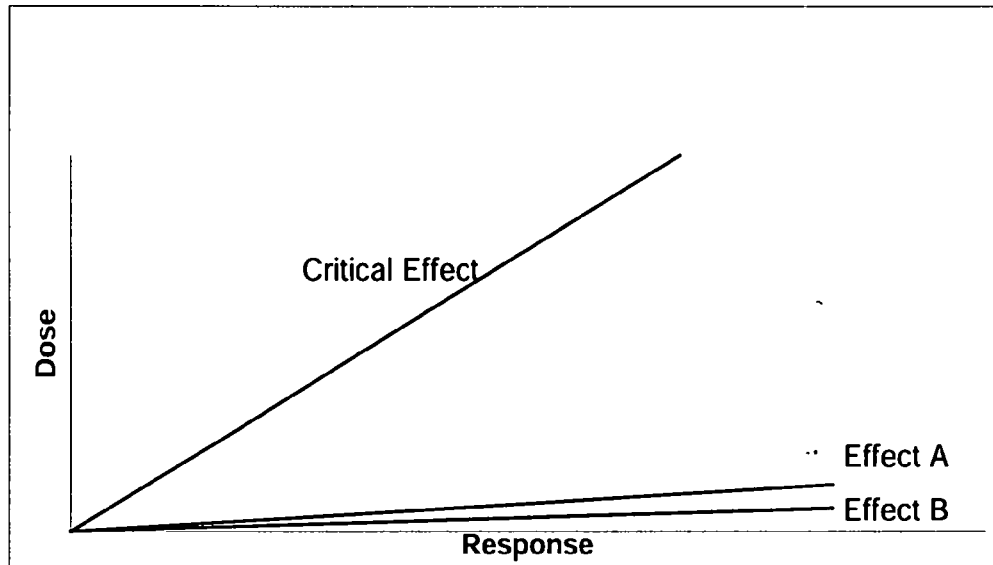
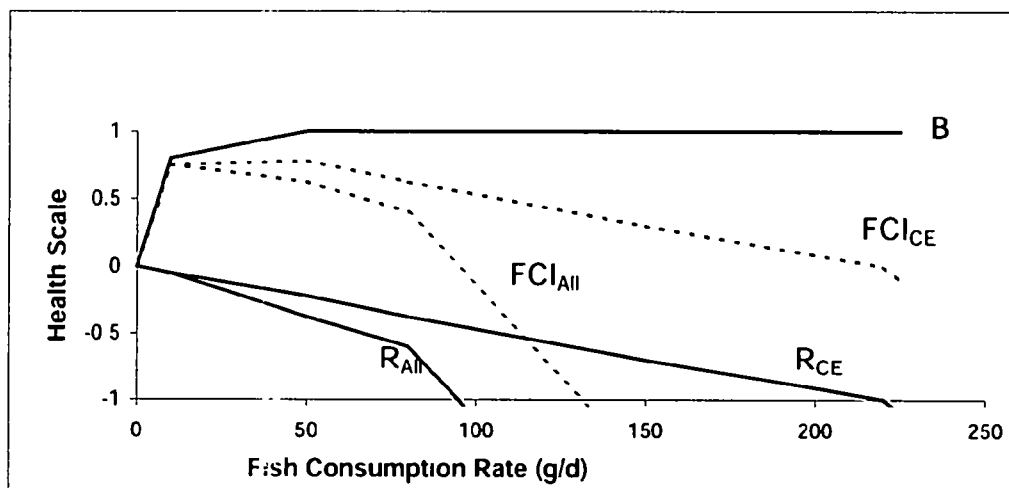
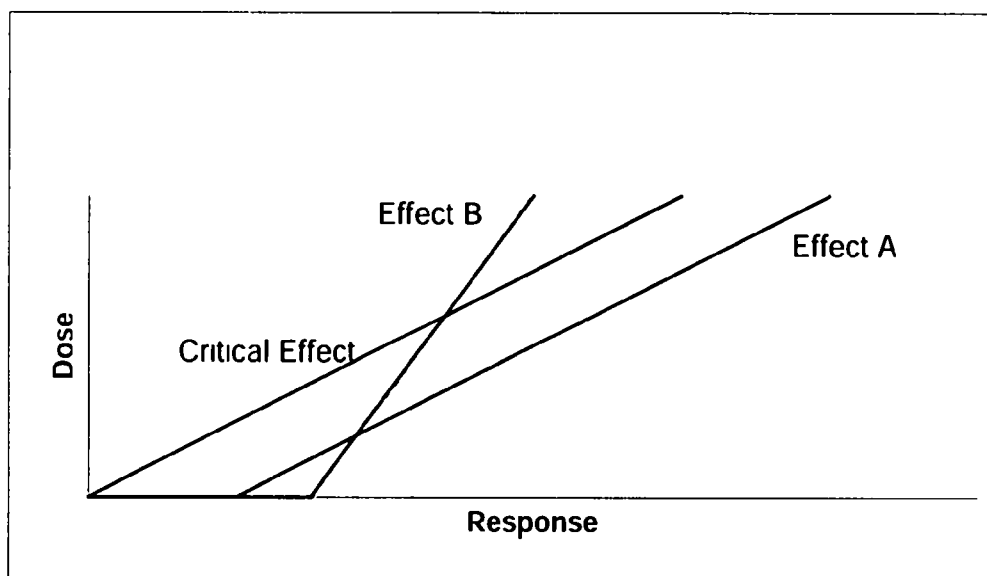


Figure 6-19. Non-critical effects begin at doses similar to the critical effect and their dose response curves are ~ similar.



example where the non-critical effects begin to manifest themselves at doses similar to the critical effect and their dose response curve has a slope that is similar to or larger than the slope of the critical effect.

The framework discussed here differs from most risk assessments in how it estimates risk from a mixture of chemicals in two important ways. First, most mixture risk assessments estimate non-cancer risk by combining the hazard quotients only for those chemicals that adversely effect the same health endpoint. This approach can lead to the estimation of several hazard indices (one for each health endpoint) for a mixture of chemicals, which are then combined into the overall Hazard Index (HI). The current framework described in this text combines the potential risks for all noncancer endpoints (regardless of endpoint) and thus, may predict a greater noncancer risk from a mixture of chemicals than a traditional risk assessment following U.S. EPA (1986) mixture guidelines.

Second, traditional mixture risk assessments separate the evaluation of cancer and non-cancer endpoints. However, because this framework uses a biological severity score, the cancer and non-cancer risks can be added to estimate the total risk and the FCI. Thus, as with mixtures of chemicals causing non-cancer effects only, the framework estimates different risks than traditional risk assessment might, for chemicals and chemical mixtures that cause both cancer and non-cancer effects.

The current version of the framework highlights another phenomenon that is similar to, but not related to, the effects of mixtures of chemicals. Namely, chemicals can cause more than one non-cancer effect. Because of the approach used by the framework in plotting risk above the RfD relates to only one effect (i.e., the critical effect caused by each chemical), consideration of non-critical effects has the potential to change the outcome of the framework. This can lead to an underestimation of adverse effects associated with chemicals in fish.

RfDs are derived to be protective of the critical endpoint (i.e., the first adverse effect or its known precursor as dose increases). It is assumed that if exposure remains at or below the RfD, then the critical effect will not be manifested, and neither will any other adverse endpoints. Once exposures exceed the RfD, however, the critical endpoint may be manifested, and if the exceedance is large enough, other endpoints would be expected.

For the most part, risk management decisions based upon the results of typical risk assessments consider exposures above the RfD to be unacceptable. Such a paradigm makes the other adverse effects associated with exposure above the RfD moot. It is essential to appreciate that the framework described in this text explicitly uses estimates of risks above the RfD for the critical effect of several chemicals. Estimates of the risks from other endpoints that may occur at doses above the RfD are not used here, as the data were not available. Other approaches to estimating risk above the RfD could take multiple possible endpoints into consideration (e.g., categorical regression). As a result, non-cancer risks associated with doses above the RfD may be underestimated.

The magnitude of this underestimate is unknown. It depends in part on the number of adverse effects caused by the chemical other than the critical effect and the dose response curves for these other effects. For example, if dose response curves for these other effects either begin at doses much greater than the RfD (Figure 6-17), or have a small slope compared to the critical effect (Figure 6-18), then the current omission of non-critical effects is likely to have little effect on the results of the framework (i.e., the FCI) – and little effect on conclusions resulting from its use. Alternatively, if these other non-critical effects begin to manifest themselves at doses similar to those at which the critical effect is observed, and have dose response curves with slopes similar to or greater than that for the critical effect, then the risk could be substantially underestimated.⁷ Of course, RfDs are established to be protective, and methods to estimate risks at exposures above the RfD assume that adverse effects occur immediately. This immediacy may not be correct, but it is in the direction of countering the concern expressed with the lack of modeling effects other than the critical effect.

Although these concerns would tend to cancel each other out, the resulting uncertainty in the value of the FCI is increased. This is one reason why risk assessors and managers may wish to use FCI values in a range, such as 0.25 to -0.25, rather than a single FCI value when making decisions.

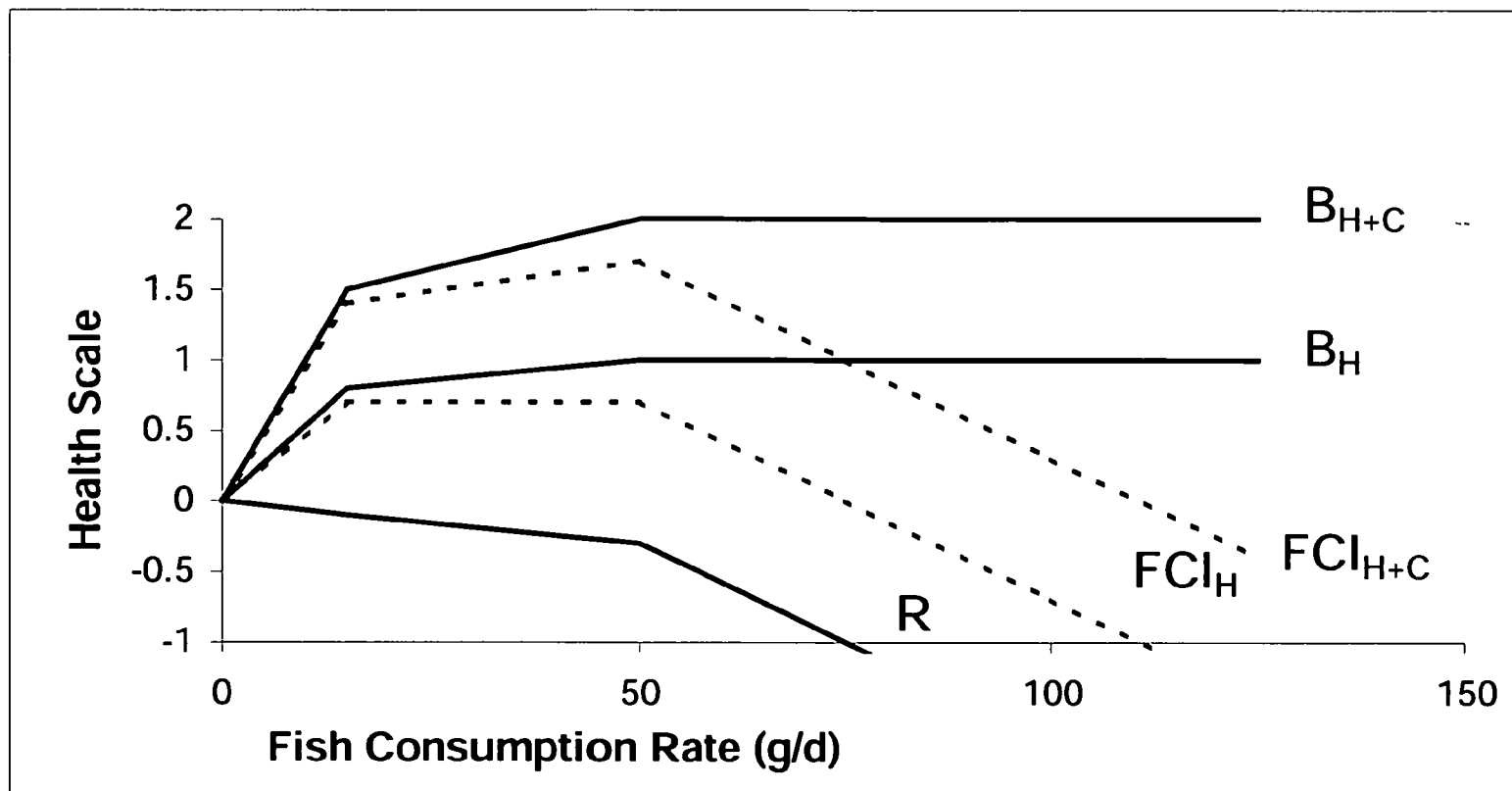
6.5.5 Cultural Benefits

All of the examples presented in the above sections derived FCIs by comparing health risks to health benefits. For some subgroups, fish are of great cultural importance and their value cannot be measured as simply a source of protein or a source of important health benefits (see Chapter 5). As described above, the framework has built into it the flexibility to adjust the FCI (the net benefit of consuming fish) based upon cultural impacts or some other factor not explicitly accounted for by the risk and benefit equations.

The framework allows for a factor or modifier to adjust the FCI for culture-based impacts. The value of this factor can be based upon the cultural value of fish and/or fishing-related activities to the population. As the cultural importance increases, the factor can increase. This leads to an increase in the benefits associated with fish consumption, which in turn leads to an increase in FCI (Figure 6-20). However, as described above, the cultural factor may not be a multiple of health benefits. It could be a constant added to the FCI or some other consumption rate-related adjustment of the FCI. The current framework does not contain a methodology to derive the

⁷ At the present time, existing data have not been used to estimate the dose response curve for each of the non-cancer effects that may be caused by a particular chemical. As resources permit, the framework allows the incorporation of such information.

Figure 6-20. FCI changes when cultural benefits of fish consumption are added.



cultural factor. It is assumed that this factor would be developed by public health regulators and the population for whom fish is of great cultural importance. Such a methodology would need to evaluate and ideally quantify the physical, emotional and mental well-being aspects along with the disruption or enhancement of a “cultural” practice such as catching or consuming fish. Quantitative data are not available, but the population itself may have a qualitative judgement about the negative or positive consequences of a cultural practice, which they would want to incorporate.

An important attribute of the framework is that by including cultural importance in the derivation of the FCI, it provides a basis for responding to the needs of the subpopulation. For example, both the general population and a subpopulation may be eating the same species of fish from the same water body. If the subpopulation places great cultural value on fish consumption, the framework can reflect this. Figure 6-20 illustrates hypothetically how the FCI could change when cultural benefits of fish consumption are added. Fish consumption rate is shown on the horizontal axis and the Health Scale is shown on the vertical axis. Curves “B_H” and “B_{H+C}” represent, respectively, the health benefits only and the health and cultural benefits combined. Curves “R” and “FCI” represent the risk and FCI, respectively, associated with eating fish. Separate FCI curves are shown for health benefits only (FCI_H) and health and cultural benefits combined (FCI_{H+C}).

The outcome of making this adjustment is that the framework can identify one consumption rate for the general population and in this hypothetical example, a higher consumption rate for the subpopulation. In this example, the C factor is equal to the other health benefits combined and therefore nearly doubles the FCI.

6.5.6 Personal Perception of Severity

As for cultural benefits, a scaler for the personal perception of the severity of an effect or benefit could be added to the framework. Like for the cultural scaler, the resulting FCI could not be consider a strictly health-based score. We do not attempt to provide a quantitative handle on the value of this potential personal perception of severity. If it was used, however, it would appear to be best placed at the development of the risk scale as shown below:

$$(R_i \times S_i) \times (-1) \times PPS = \text{Risk}_{iPPS}$$

Where:

R _i	is the increased risk of health endpoint i associated with a particular fish consumption rate,
S _i	is the severity of health endpoint i,
PPS	personal perception of severity, and,
Risk _i	is the decrease in health (because of the increase in risk of health endpoint i) associated with eating a given amount of fish.

6.6 Case Studies

6.6.1 Case Study: The Florida Everglades

6.6.1.1 Background

In 1989, a Florida panther was found dead in the Everglades with extremely high mercury levels in the liver (>100 ppm) (Fleming *et al.*, 1995). As the apex carnivore in the Everglades ecosystem, the panther is a good indicator of the potential for biomagnification of methylmercury. This incident, along with elevated levels of mercury in other wildlife (raccoons, otters, and alligators) has sparked concern over the potential health effects on humans who eat fish from the Everglades. Factors such as wetland morphology, hydroperiod, water chemistry, dissolved organic carbon, and bacterial processes in the Everglades have resulted in increased the methylation and subsequent biomagnification of mercury, although the mechanisms behind these associations are not fully understood (Choi and Bartha, 1994).

Analyses of freshwater fish from the Everglades revealed the presence of methylmercury at concentrations up to 7 ppm (Science Subgroup, 1994). The average concentration ranged from 2 to 3 ppm in freshwater fish, and other wildlife (Fleming *et al.*, 1995). Florida's advisory level for methylmercury is 1.5 ppm (Krabbenhoft, 1996). As a result, the state of Florida issued a Health Advisory in March 1989 recommending limits on consumption of several fish species that are caught in the Everglades. No cases of human poisoning due to Everglades fish consumption have been reported; however, clinical diagnosis of mercury poisoning is difficult.

6.6.1.2 Summary of Existing Data

Fleming *et al.* (1995) recruited and questioned 1794 people who had consumed Everglades fish (sport anglers, subsistence fishers, Native Americans and other Everglades residents). Of the 1794 individuals, 405 had eaten fish and/or wildlife from the Everglades. Of these 405 individuals, 55 refused to participate, leaving 350 subjects. No data were collected from those that refused, so it is not known if their consumption differs from the study population. Fleming *et al.* (1995) reported a weekly fish consumption of 1.79 meals per week for all subjects who consumed fish over the 6-month sampling period.

The subjects completed a questionnaire and provided a hair sample. The hair samples were analyzed by atomic absorption for total mercury. The detection limit (DL) for total hair Hg was 1.26 ppm. Out of 330 subjects sampled, 119 (36%) subjects had total hair mercury concentrations above the detection limit. For samples with concentrations above the DL, the mean level of total Hg in the hair was 3.48 ± 3.01 ppm (Fleming *et al.* 1995). The highest total hair mercury concentration measured was 15.57 ppm. Because the mercury concentrations in the 211 hair samples with values below the detection limit were not known, a default value of one-half detection limit (0.63 ppm) will be used for the purposes of this case study. The resulting mean for all 330 samples is 1.66 ppm, using 0.63 ppm as the default value for all samples below the detection limit.

This study found that the most exposed groups were men and African-Americans. Within these groups, those with highest hair Hg levels were mostly subsistence anglers with a small income and a low level of education (Fleming *et al.*, 1995).

6.6.1.3 Exposure Assessment

In estimating the risk to the fetus from methylmercury exposure, maternal mercury exposure is used as a dose surrogate for fetal exposure. U.S. EPA (1999) provides one method for extrapolating an estimated daily dose of mercury from hair mercury levels. Fleming *et al.* (1995) provides a distribution of total Hg in the hair, as well as an estimated mean fish consumption rate. The estimated dose based upon self-reported consumption can be verified by extrapolating daily dose from total hair mercury. Please see Section 6.6.1.6 for a detailed description of this procedure.

Fleming *et al.* (1995) did not report the size of meal that corresponded to the reported mean consumption of 1.79 meals/week. For the purposes of this case study, we assumed that a meal consists of 4 oz. of fish; however, the true average portion size may differ from this assumption. It is important to have an accurate estimate of meal size in order to estimate the average number of grams of fish consumed per day. An accurate estimate of fish tissue methylmercury concentrations is also crucial in the resulting estimate of daily methylmercury dose at a given level of consumption.

Since maternal hair total mercury is used as a dose surrogate for fetal methylmercury, the average weight for a pregnant woman is used (60 kg) (U.S. EPA, 1998). The dose extrapolated from maximum reported hair concentration is 1E-3 mg/kg-day (see Table 6-6). We can also use the range of daily methylmercury dose estimated from consumption of fish at 28 g/day containing 2-3 ppm mercury. For a 60-kg pregnant woman consuming 28 g/day of fish containing 3 ppm the estimated dose is 1E-3 mg/kg-day. This dose is consistent with the dose (1E-3 mg/kg-day) extrapolated using the maximum reported hair concentration (15 ppm). This consistency tends to validate the approaches and assumptions used here.

Table 6-6. Calculation of estimated daily doses using total hair Hg data from Fleming *et al.* (1995).

Components in the Equation	C_h (ug/g) ÷ 250 =	C_b (mg/L) x	b x	V (L) ÷	A x	f =	I (mg/day) ÷ 60kg=	D (mg/ kg-day)
Adjusted mean (0.63 ppm substituted for values below the DL)	1.66	0.0066	0.014	4.9	0.95	0.05	1 E-2	2 E-4
Maximum	15.6	0.062	0.014	4.9	0.95	0.05	9 E-2	1 E-3
Mean of data above DL	3.48	0.014	0.014	4.9	0.95	0.05	2 E-2	3 E-4

6.6.1.4 Calculation of FCI

The critical effects of methylmercury poisoning, on which the RfD is based, occur in the fetus exposed *in utero* (See Chapter 4). Risk above this RfD is estimated and compared to benefits for the general population (See Figure 4.1 in Chapter 4). Benefits data are available for the fetus/children of women who consumed methylmercury contaminated fish in the Seychelles Islands (Davidson *et al.*, 1998). The incorporation of these data into a benefits curve for fetuses/infants of mothers who consumed fish has not been attempted; however, because of the preliminary nature of these data.

The estimate of risk to the adult population (See Figure 4.1 in Chapter 4) may be conservative, because the critical effect is in the fetus; however, it is also likely that not all of the contaminants present in the fish have been included here. Adding additional chemicals would reduce the FCI because additional risk would be added, but the benefits remain constant.

U.S. EPA (1999) reports a RfD of $1\text{E-}4$ for methylmercury (see Chapter 4 for details). The estimated methylmercury dose extrapolated from the adjusted mean mercury hair concentration is $2\text{E-}4$ mg/kg-day. This exceeds the EPA's RfD for methylmercury by 2-fold. The dose extrapolated from the maximum hair mercury concentration, and the dose estimated based upon consumption of fish containing 3 ppm methylmercury ($1\text{E-}3$ mg/kg-day) both exceed the EPA's RfD by 10-fold. Therefore, a risk of adverse health effects may exist for this population.

In order to apply the framework, risk above the RfD must be calculated for various levels of fish consumption. Table 6-7 is a summary of calculations of risk above the RfD (as more fully described in Chapter 4).

Table 6-7. Dose-response estimates for methylmercury (Price *et al.* 1997).

Multiple of RfD ($1\text{E-}4$ mg/kg-day)	Dose (mg/kg-day)	Response		
		5th percentile	50th percentile	95th percentile
1	0.0001	0.0%	0.0%	0.0%
5	0.0005	0.0%	0.0%	3.9%
10	0.001	0.0%	4.3%	12%
50	0.005	28%	44%	>50%
100	0.01	>50%	>50%	>50%

For example, according to this dose response model, a mean risk of 4.3% and an upper 95% limit risk of 12% exist at a dose $1\text{E-}3$ mg/kg-day. This value which is 10-fold greater than the RfD, corresponds to the consumption of 28 g/day of fish containing 3 ppm mercury.

For the purposes of this case study the FCI will be calculated for 6.5, 60 and 120 g of fish per day. Benefits from other consumption rates can be determined, if needed, from Figure 6-5. Daily dose is estimated using the following equation.

$$D = a \times b \times c - d$$

Where:

D = daily dose;
a = concentration of chemical in fish (mg/kg),
b = consumption rate of fish (g/person-day),
c = conversion factor (kg/1000 g); and,
d = body weight (kg/person).

For a consumption rate of 6.5 g/day at 3 mg Hg/kg fish tissue the dose is approximately 3E-4 mg/kg-day.

$$D = 3 \text{ mg Hg/kg fish} \times 6.5 \text{ g/day consumed} + 60 \text{ kg body weight} \times 1 \text{ kg/1000 mg} = 3\text{E-4 mg/kg-day.}$$

These calculations are repeated for several consumption rates.

This dose (3E-4 mg/kg-day) corresponds to a best estimate of relative risk (50th percentile) of 0.0. The severity factor used in the framework for subtle neurodevelopmental defects is judged to be 1 (other judgments and severity scales are possible). The risk is adjusted by multiplying by -1 and the severity factor (1). The resulting adjusted risk is 0.0. For the upper bound of risk (95th percentile) the relative risk is about 0.02, and resulting adjusted risk is -0.02.

For a consumption rate of 60 g/day at the same mercury concentration the dose is approximately 3E-3 mg/kg-day. This corresponds to a best estimate of relative risk of approximately -0.23. Since the severity factor for the target endpoint is 1, the adjusted risk is -0.23. The upper bound of risk is -0.45, and resulting adjusted risk is -0.45.

For consumption of 120 g/day, the dose is approximately 6E-3 mg/kg-day. This corresponds to a best estimate of relative risk of -0.50 mg/kg-day. The upper bound of risk is greater than -0.50.

The best estimate (50th percentile) of the benefits in adults for fish consumption at 6.5, 60 and 120 g were calculated above to be 0.42, 0.68 and 0.68 respectively. There are no data for benefits at consumption levels greater than 60 g/day. The Price *et al.* (1997) model only predicts to the estimated ED₅₀ in humans. Again the working assumption is that these benefits remain constant until the percent protein in the diet approaches 100% at which time the expected benefits will decrease as shown hypothetically in Figure 6-1. These resulting FCIs are 0.42, 0.45, and 0.18 for 6.5, 60 and 120 g/day, respectively, when mean values (best estimates) are compared. See Figure 6-21a for comparison of benefits and risk for the general population, and Figure 6-21b for the fetus.

6.6.1.5 Discussion

Figure 6-21a illustrates the relationship between relative risk, benefit, and the resulting FCI for the general population. The results show that the loss of benefits first occurs near 10 g of fish/day, but that for the entire range of 6.5 to 120 g, the general FCI based on the average values is positive. However, it should be remembered that fetal endpoints were the critical effect for development of the RfD and risk above the RfD. For a man, or a woman who is not of child bearing age, the FCI values may actually be higher.

Deleterious effects of fish consumption predicted by the Price *et al.* (1997) model used in this framework are based upon higher exposures to methylmercury from contaminated bread in the Marsh *et al.* (1987) Iraqi cohort (See Chapter 4). Recent results from the Seychelles Islands cohort consists of mothers and infants exposed to methylmercury from fish (Davidson *et al.* 1998). These results show increased cognitive performance for four of six measures in children from mothers with the highest hair mercury levels at 66 months of age after pre- and postnatal methylmercury exposure (Davidson *et al.* 1998). It is unlikely that the methylmercury is the cause of this increased cognitive performance. However, it might be that the higher levels of maternal methylmercury are an indicator of more fish consumption, and that it is the increased consumption of fish is the cause of enhanced performance in the most exposed children.

A quantitative dose-response treatment of this benefit is not attempted here, however, because of the preliminary nature of the findings. The Faroe Islands cohort studied by Grandjean and colleagues shows contrasting results in cognitive performance; however pilot whales were the primary source of methylmercury in the Faroe Islands, from which the mothers were also exposed to high levels of PCBs (30 ppm in blubber) (Grandjean *et al.* 1997; Weihe *et al.* 1996). Exposure to PCBs is a potential serious confounder in the Faroe Islands cohort that may also explain the decreased cognitive performance. In the Seychelles PCBs were not detected (DL 0.2 ng/ml) in the blood of 49 of the children tested at 66 months of age (Davidson *et al.*, 1998). Alternatively, the Faroe Islands data may serve as a very good case study for combined exposures.

Since benefits data for the fetus are either preliminary (Davidson *et al.*, 1998) or not quantifiable (Chapter 2), only risk can be input into the framework. For the fetus, the FCI is negative for the entire consumption range (Figure 6-21b). A dose-response relationship for fetal benefits of maternal fish consumption can be established when the data from Davidson *et al.* (1998) are verified or if quantitative benefits can be derived from the information provided in Chapter 2. This illustrates an important aspect of this case study. In order to derive a FCI, **benefits and risks should be compared for the same populations.** In the case of fetotoxicants more data on the pre- and postnatal benefits of maternal fish consumption are needed in order to apply the framework correctly.

Consumption of these fish by women of childbearing age should also be carefully considered. This is because the benefit that these women may accrue from consumption of fish may also result in a risk to their offspring (although the preliminary data from the Seychelles Islands suggest otherwise). Perceived risk may be greater when the risks accrue to the next generation as opposed to the current generation.

Figure 6-21a Estimated Risk, Benefit, and FCI for Mercury Contaminated Fish from the Everglades for the General Population.

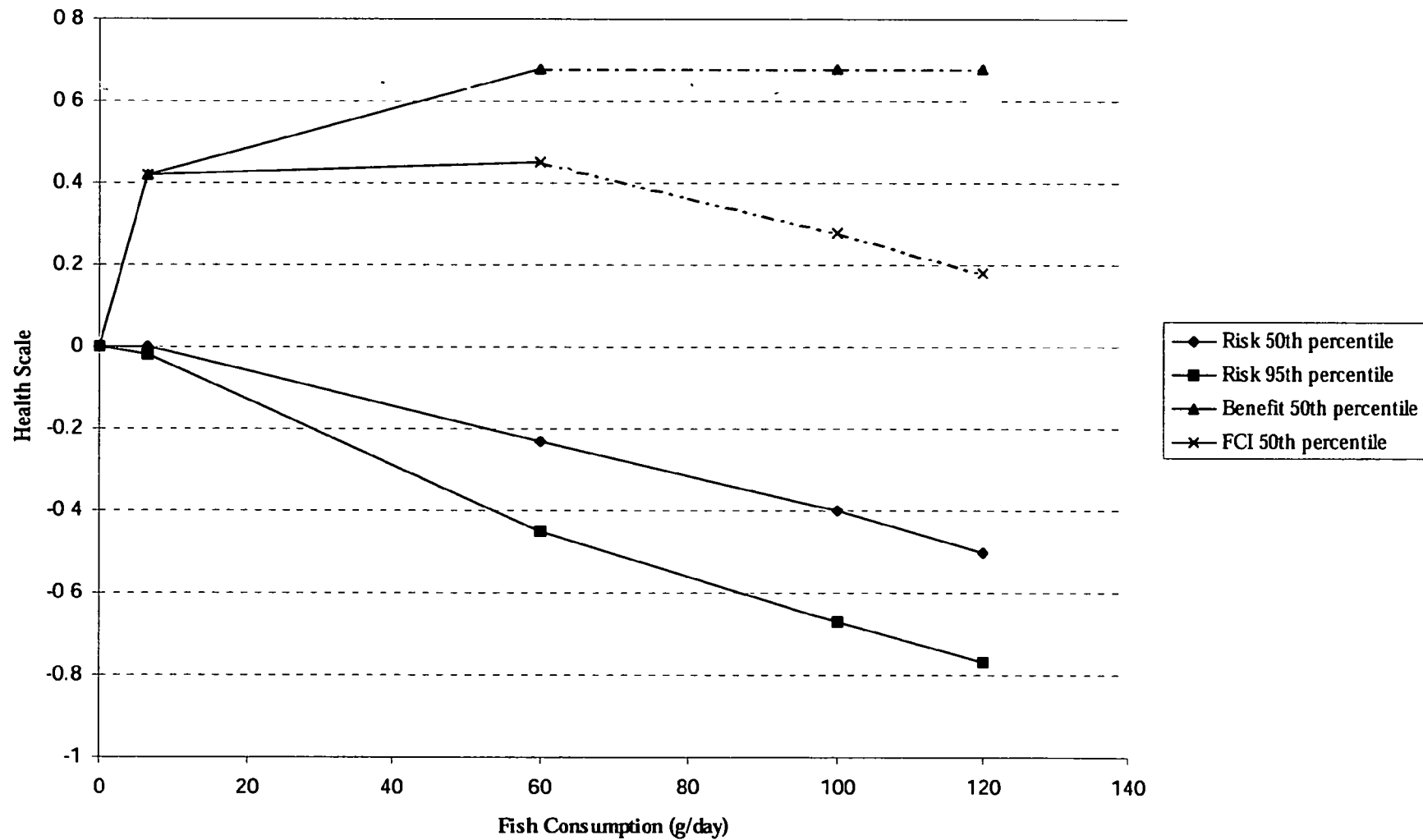
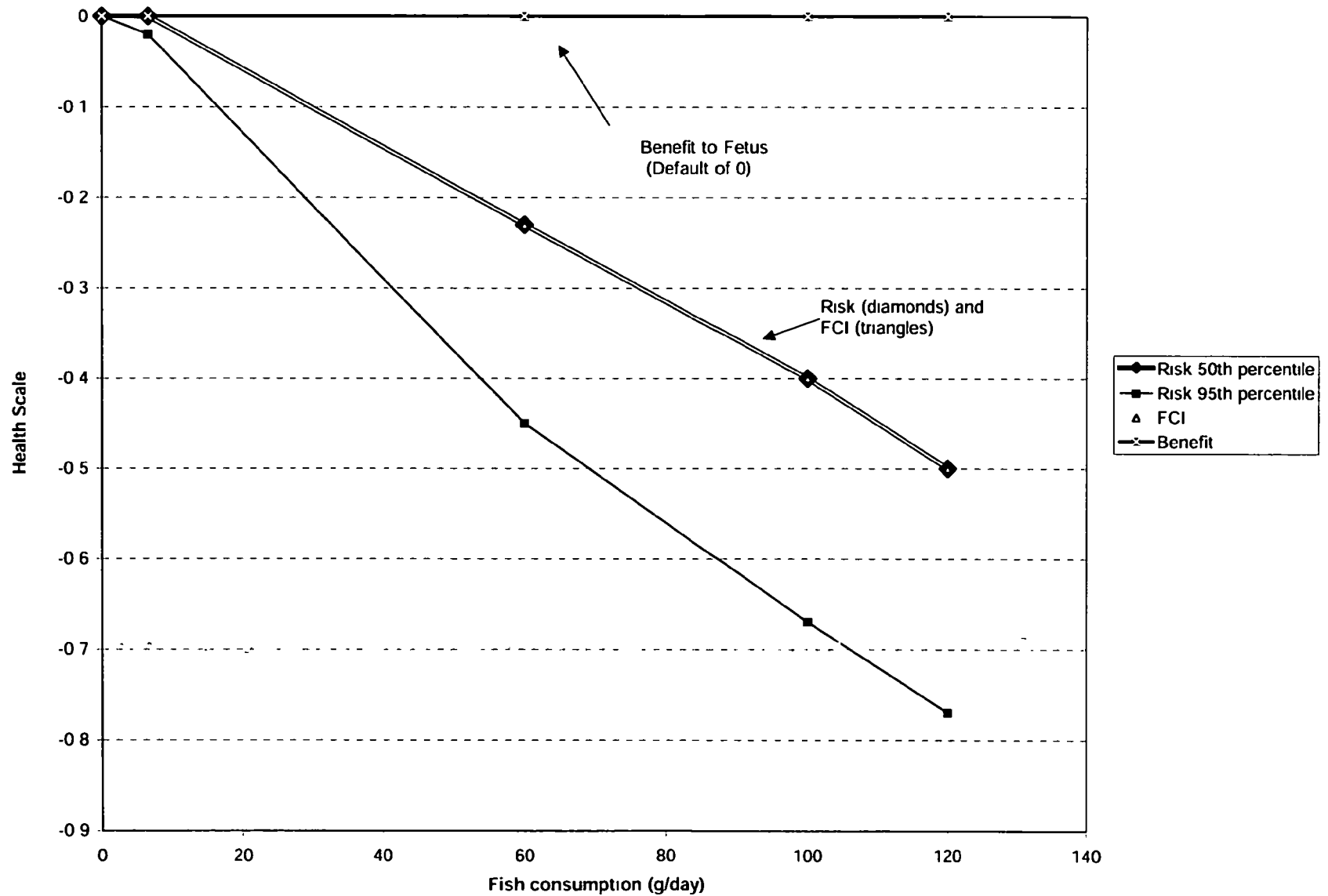


Figure 6.21b Estimated Risk to the Fetus As a Function of Everglades Fish Consumption.



It is important to communicate to the fishers in the Everglades these potential risks and benefits. The highest mercury levels in hair correlated with impoverished men, with little or no access to health education. For this group, the necessity, and benefits of consuming the fish may outweigh the risks. It is also important that health effects information reach these individuals, especially if fish are being taken to pregnant family members, since the risk is greatest for the fetus. An additional difficulty is the lack of knowledge of the nutritional background of the study population. Specifically, it is not known whether the RR of coronary heart disease in this population is representative of the national values used in the calculation of benefits. It should also be noted that only data concerning methylmercury contamination were available for this case study. A more complete analysis of the risks to the populations consuming fish in this area would necessitate a more complete picture of the contamination profiles of the fish being consumed. With the addition of these contaminants, the FCI at a given consumption rate may be reduced.

6.6.1.6 A Method for Verifying Fish Consumption Estimates

When using fish concentration data coupled with consumption estimates, it is useful to verify the daily intake by extrapolating daily mercury dose from total hair mercury and compare to a dose based upon consumption rate. The first step in this extrapolation is to relate the mercury concentration in the hair to serum mercury levels. The hair to serum concentration ratio for Hg varies seasonally, peaking after fishing season in late fall to early winter. This ratio also depends upon from what part of the body the hair is sampled (Phelps, *et al.*, 1980). U.S. EPA's IRIS uses the ratio 250:1, based upon the results of several studies (Phelps *et al.*, 1980; Suzuki *et al.*, 1993; Tsubaki and Irukayama, 1977).

U.S. EPA (1999) uses the following equation to estimate daily dose of mercury from serum mercury concentration based upon assumptions that steady state conditions exists, and that first order kinetics for Hg are being followed.

$$I = (C_b \times b \times V) / (A \times f)$$

Where:

I = daily intake of mercury,
 C_b = serum mercury concentration,
 b = elimination constant,
 V = blood volume,
 A = absorption factor, and
 f = fraction of tissue uptake from the serum.

U.S. EPA (1999) reports the elimination constant (b) for Hg to be approximately 0.014 day^{-1} based upon two studies (Cox *et al.*, 1989; Sherlock *et al.*, 1982). The volume of blood (V) is approximately 7% of the body mass. Assuming an average mass of 60 kg (U.S. EPA, 1999), the average blood volume is approximately 4.9L. The absorption factor (A), is 0.95 assuming dietary intake of MeHg from fish (U.S. EPA, 1999; Miettinen *et al.*, 1971; Aberg *et al.*, 1969).

The fraction of daily uptake of mercury from the blood was derived experimentally (WHO, 1990; Sherlock *et al.*, 1982) to be 0.05. The results of this calculation are shown in Table 6-7.

In order to verify this estimate, reported fish consumption levels from Fleming *et al.* (1995) can be used in conjunction with fish tissue Hg concentrations to estimate a daily dose for comparison. Fleming *et al.* (1995) reported mean fish consumption of 1.79 meals/week. Assuming that an average meal consists of about 4 ounces (≈ 0.11 kg) of fish, this is about 0.028 kg of fish per day. Fish fillet concentrations in the area fished were about 2 or 3 ppm (or mg of chemical per kg of fish). Therefore, the estimated daily Hg intake based upon the given range concentrations in fish, and the estimated amount of fish consumption, would range from $6\text{E-}2$ mg/day or $8\text{E-}2$ mg/day (i.e., 0.028×2 or $3 = 6\text{E-}2$ or $8\text{E-}2$). Assuming a body weight of 60 kg this corresponds to a dose of $1\text{E-}3$ mg/kg-day.

This range of daily Hg doses based on fish consumption falls within the range of the daily doses determined from hair concentration found in Table 6-7. Both methods resulted in a similar estimation of daily dose. Therefore, Hg levels found in hair are not inconsistent with the hypothesis that this Hg is due to the consumption of contaminated fish, at the rate reported by Fleming *et al.* (1995). This validates the risk, and FCI estimates at a given consumption rate, since these estimates are related to fish consumption rate, but rely upon known contaminant intake at a given fish consumption rate. For example, if average meal size was 8 ounces as opposed to 4 ounces in this case, then by using 4 ounces, and 3 ppm mercury in fish, daily dose would be underestimated by half. But by verifying meal size as shown above, this error can be identified before calculating risk.

6.6.2 Vietnamese Immigrant Women Consuming Lake Ontario Sportfish

6.6.2.1 Background

Along the accessible shorelines of western Lake Ontario and the Niagara River, Vietnamese families can be observed fishing together, filling buckets with fish to take home, and occasionally cooking a meal of fresh fish near the water's edge. This study of Vietnamese women arose from concerns about the potential health risks associated with eating fishing from Great Lakes Areas of Concern (AOCs), designated by the International Joint Commission as such because of unacceptable levels of persistent toxic substances. Immigrants from Southeast Asia appear to eat more sportfish than the average consumer in North America (Hutchison and Kraft, 1994). This would make them potentially at risk of adverse health effects associated with chemical contaminants, because of their greater exposures. The focus is on women of reproductive age because of the possible risks associated with eating contaminated fish during pregnancy; pregnant and nursing women, and unborn babies, are at risk groups because their physiological and developmental stages may confer greater sensitivity to chemical contaminants frequently found in fish.

Studies of wildlife show that organochlorines (such as polychlorinated biphenyls) in the Great Lakes basin interfere with normal reproduction and development, but few studies have investigated the effects of mixtures specific to Great Lakes fish on humans. Women participating in the New York State Angler Study were found to have shorter menstrual cycles if they had

been consuming contaminated fish for seven or more years, or had more than one fish meal monthly (Mendola *et al.*, 1997). However, fish consumption did not appear to interfere with time-to-pregnancy (Buck *et al.*, 1997). Jacobson and Jacobson (1996) have shown that women who ate Great Lakes fish contaminated with PCBs during their pregnancies, gave birth to children who had poorer growth and memory in infancy and at 4 years of age, and below average IQ scores at 11 years. Several studies have investigated the levels of PCBs and DDE in human breastmilk, attempting to determine the toxicity to infants (Dewailly *et al.*, 1991; Dewailly *et al.*, 1996; Mes and Weber, 1989).

This case study uses data collected from 1996 to 1998 and not yet published. It is hoped that the following scenario may be typical of others in states and provinces where multi-cultural populations eat fish from contaminated 'hot spots'. It may also have relevance for other groups who consider themselves 'subsistence' fishers, such as Native Americans or Canadian Aboriginal populations.

6.6.2.2 Summary of Existing Data

6.6.2.2.1 Descriptive Data

The sample for this case study consists of 27 Vietnamese women of reproductive age (17-47 years; mean $\pm$ SD = 35.0 $\pm$ 7.3) who consume sportfish caught from Lake Ontario AOCs. These women have spent 2-16 years in Canada (mean $\pm$ SD = 6.9 years $\pm$ 3.4), and have been eating Great Lakes fish from 2 to 8 years (mean $\pm$ SD = 3.7 years $\pm$ 1.7). There was a wide range in years of schooling: from 4 to 16 years (mean & median = 11 years).

Households ranged in size from 2 persons to 7 (mean = 4.1), and 82% of the reported household incomes fell below the Statistics Canada Low Income Poverty cut-off (based on income, household size, size of city/town in urban or rural area). Poverty is linked to "food insecurity", a condition roughly defined as having insufficient nutritious and culturally-appropriate food or the need to rely on emergency sources of food. Not surprisingly, only 31% (n=8) of these women reported that their households were food secure. The remaining 69% (n=19) indicated they experienced some degree of food insecurity; 42% of the sample (n=11) reported that their children sometimes were hungry because of a lack of food.

However, fishing was not viewed as an inexpensive means of gathering food, but instead was considered an activity that promoted good health; one could ease stress, enjoy fresh air, and spend time with families and friends. Catching fish and giving it to others was an important act of sharing, and to catch fish but not eat it (particularly if the fish would not survive when thrown back) was considered a waste of the resource and unethical.

Some of these women fished themselves; others prepared and ate fish that their partners or friends caught. Most tended to rely heavily on their partners' judgments about the safety of the fish, and generally were uninformed about the fish advisories. Thirty-five percent said they could tell a fish was safe to eat by looking at its skin surface and color; 46% agreed that "I can tell if a fish is contaminated (not safe to eat) by the way it smells." Fifty percent agreed with the statement, "I feel confident that the Great Lakes fish I eat are safe because I catch them myself."

Burger *et al.* (1998) have reported similar confidence in self-caught fish among individuals fishing and crabbing in New Jersey.

Women were asked their perceptions of the risks to their health from eating Great Lakes fish. Fifty percent felt that any risks were minor compared to other risks to which they were exposed. Eighty-one percent said they would eat more Great Lakes fish if health risks from chemical contaminants did not exist. And 73% agreed with the statement, "For me personally, there are more benefits to my health from eating Great Lakes fish than risks to my health".

Body weights averaged 53.9 kg (range was 42.2 - 72.2 kg), and body fatness, assessed using the Body Mass Index, was in the desired 20-25 range for 67% (n=18). Seven women (26%) had less body fat than generally considered healthy, and two (7%) were considered "overfat".

The average of individuals' macronutrient dietary profiles was excellent: protein averaged 19% of energy (calories), fat was 22%, carbohydrates 59%, and saturated fats were only 6% of energy. Only one person had usual dietary intakes of saturated fat and total fat above the current dietary recommendations. On average, this group consumed 45 g of dietary fat and 85 g of protein daily, and met current recommendations for calories for their gender and age group (mean $\pm$ SD = 1846 $\pm$ 775 kcal). However, many had low intakes of nutrients considered important for women of reproductive age: calcium (n=18, 67%), vitamin A (n=11, 41%), iron (n=10, 37%), folate (n=7, 26%) and zinc (n=7, 26%).

6.6.2.2.2 Biochemical Data

Although these women had diets low in saturated fat and total fat, and healthy body weights, several had already been diagnosed with high cholesterol. Blood analyses revealed there were 2 women at high risk, 8 at moderate risk, and 17 had normal blood cholesterol levels. Two subjects had low HDL (high density lipoprotein)-cholesterol values, 7 had high LDL (low density protein)-cholesterol values, and 4 had high triglycerides. These biochemical data suggest that up to 10 women had abnormal blood lipids, which put them at higher risk for heart disease. Two women had low hemoglobin values, indicating iron-deficiency anemia, likely a result of the low iron intakes noted above.

Blood plasma values for the omega-3 fatty acid DHA (C22:6N3) ranged from 2.71 to 9.94 (expressed as percent of total plasma lipids) (mean $\pm$ SD = 5.80 $\pm$ 1.63), and values for EPA (C20:5N3) ranged from .29 to 3.70 (mean $\pm$ SD = 1.13 $\pm$.77). The ratios of omega-3 fatty acids to the omega-6 fatty acid, arachidonic acid were:

DHA/AA ratio was from .27 to .98 (mean = .56 $\pm$.55)
 EPA/AA ratio was from .04 to .35 (mean = .11 $\pm$.07)
 EPA+DHA/AA ratio was from .32 to 1.15 (mean = .67 $\pm$.21)

Organochlorine residues with higher-than-usually-observed levels were PCBs (n=11, 41% of sample) and beta-BHC (beta-1,2,3,4,5,6-hexachlorocyclohexane)- (n=2 in the highest 10%). It is possible that the latter is due to residues in foods eaten or imported from Vietnam (see Kannan *et al.*, 1992) and Hong Kong (see Ip, 1990). One individual was in the highest 10% for Mirex, and

this may be related to eating fish from the Niagara River. Eight subjects (30%) had high mercury values.

6.6.2.3 Exposure Assessment

The total number of all meals of Great Lakes fish during the previous 12 months ranged from 31 to 277 meals (mean $\pm$ SD = 99 ± 52.7), averaging 2 meals per week. These women were high consumers of other types of fish as well; they ate from 5 to 312 meals (mean $\pm$ SD = 118 ± 89.9) of fish from inland locations, and 3 to 306 meals (mean $\pm$ SD = 111 ± 80.4) of purchased or processed fish. Their total fish consumption over 12 months was 83 to 751 meals (mean $\pm$ SD = 322 ± 169 ; median = 306), an average of 6.2 meals of any kind of fish per week.

The percentage of total fish meals that were Great Lakes fish ranged from 9% to 90%; on average, 39% of all fish meals for this group were sportfish from the Great Lakes (mostly Lake Ontario). Women were asked to list the top 3 species they consumed most often. They were rock bass (n=12, 44% of sample), crappie and smallmouth bass (both mentioned by 10 women or 30% of sample), largemouth bass (n=7, 26%), white bass (n=6, 22%), and channel catfish and freshwater drum (n=5 each, 19% each).

For the 3 species listed, the subject was asked which parts of the fish were consumed and how the fish were cooked. Only 3 women (11%) stated that they discard the belly fat, but 14 (55%) discard fat from around organs and 19 women (70%) will puncture or cut the skin. Four women said they eat the fish eggs. The most common ways to prepare the 3 most frequently consumed species were stir-frying/frying (93%), and using in soups and stews (82%) where the liquid/sauce would also be consumed. None reported baking, boiling or smoking fish.

Portion sizes depended upon the species and the way the fish were prepared--i.e., as fillets, pieces, or used whole. None of the women reported eating their top 3 species as fish steaks, only 3 ate any as fillets and 3 ate some as pieces. Every subject reported eating the whole fish, many for all 3 of their top species. The average portion size when the whole fish was used in a dish, was 268 grams. At two meals per week, this is approximately 38.3 grams per day.

For estimates of contaminant levels in freshwater fish, values from salmon caught during the spawning run of fall 1991 in the Credit River near Toronto published by Feely and Jordan (1998) were used. These data were chosen to estimate contaminant concentration because of the location of the Credit River on the northwestern shore of Lake Ontario, and the large number of contaminants analyzed. Contaminant data for small mouth bass and rock bass in the Niagara River below Niagara Falls were obtained from the New York State Department of Environmental Conservation, Bureau of Habitat (N.Y. DEC, 1994). There are data for both rockbass and smallmouth bass for 1993-1994. The fish were not analyzed for a comprehensive number of contaminants, but they allow for the incorporation of species and geographic variation in FCI. Table 6-8 lists concentrations from the Feely and Jordan (1998) values for salmon. Table 6-9 compares hazard indices for each contaminant and mixtures H.I.s for the total mixture and by target organ. Table 6-10 shows cancer risk, benefit and FCI based solely on cancer risk. Risk estimates for PCBs were not available, however dose exceeded the RfD at every consumption level. Tables 6-11 and 6-12 present dose, RfD, HI, cancer risk, methylmercury

risk, total risk, and FCI for smallmouth bass (6-11) and rockbass (6-12). The results in these tables are further explained in the next section.

6.6.2.4 Calculation of FCI

6.6.2.4.1 Salmon from Credit River

Table 6-8 shows the dose of several contaminants as a function of fish consumption. Note that the doses for PCBs exceed the RfD at every consumption level shown, if the value of the Aroclor 1254 RfD of EPA is used. At the average consumption for the study population (38g/day), exposure to PCBs is 25-fold the RfD. Currently risk estimates for exposure to PCBs above the RfD are not available (See Chapter 4). Table 6-9 shows hazard indices for individual compounds, all compounds, and by critical organ/effect. A hazard index is calculated by dividing the exposure level by the RfD. A hazard index greater than one indicates the possibility of adverse effects. The total hazard index at 38 g/day fish consumption approaches 30. This indicates that there is a strong possibility that adverse health effects due to the contaminants present might be observed in the study population. The hazard index for the liver begins to exceed a value of one around 60 g/day of consumption. The hazard index for PCBs, the only chemicals with an immunological effect is 25.

Table 6-10 shows the estimated (95th percentile) risk of increased cancer incidence. These estimations use the cancer slope factors (CSFs) published in EPA's IRIS (U.S. EPA, 1999). Risk in terms of the framework incorporates a severity factor of three. The severity factor used to describe coronary heart disease is also three. Figure 6-22 illustrates the relationship between benefit, risk, and FCI. In general, increases in cancer risk only marginally affect the increase in benefits due to fish consumption. This general behavior would change if different severity scores were used for cancer and CHD, but the change would not be dramatic. Figure 6-23 shows the relative contribution of each contaminant to total cancer risk.

Dose (mg/kg-day) as a Function of Fish Consumption Rate and RfDs for Contaminants from EPA (1999).

	[Total TCDD]*	Total PCB	Biphenyl	Phen-anthrene	DDE	DDT	Aldrin	Dieldrin	Heptachlor epoxide	Mirex	Trans-nonachlor	Cadmium	Lead	Mercur
ion*	45.08	834.58	64	13	200	23	1.8	2.4	6.7	110	27	0.043	1	0.5
	5E-9	9E-5	7E-6	1E-6	2E-5	2E-6	2E-7	3E-7	7E-7	1E-5	3E-6	5E-9	1E-07	4
	3E-8	5E-4	4E-5	8E-6	1E-4	1E-5	1E-6	2E-6	4E-6	7E-5	2E-5	3E-8	6E-07	2
	5E-8	8E-4	6E-5	1E-5	2E-4	2E-5	2E-6	2E-6	7E-6	1E-4	3E-5	4E-7	1E-06	3
	9E-8	2E-3	1E-4	2E-5	4E-4	5E-5	4E-6	5E-6	1E-5	2E-4	5E-5	9E-7	2E-6	7
	NA	2E-5†	5E-2	NA	NA	5E-4	3E-5	5E-5	1E-5	2E-4	NA	5E-4	NA	1
	NA	Immune	Kidney	NA	Liver	Liver	Liver	Liver	Liver	Liver	NA	Kidney	CNS	CNS
e at ay	NA	25 fold	No	NA	NA	No	No	No	No	No	NA	No	NA	No

Concentrations of contaminants are taken from Feely and Jordan (1998) based upon salmon from the Credit River in Ontario.

Concentrations in ppb except TCDD (ppt)

The RfD for PCBs shown here is for Aroclor 1254 for which the critical effect is immunosuppression. The critical effect for Aroclor 1016 is a developmental effect. EPA does not currently have an RfD for PCBs found in fish. The RfD for Aroclor 1254 is used as a surrogate for the mixture found in fish

Hazard Indices Assuming Additive Toxicity for Salmon taken from the Credit River. Calculations for Individual, all Compounds, and by Target Organ or Critical Effect. Possibility of Toxic Effect.

n	Total PCB	Biphenyl	DDT	Aldrin	Dieldrin	Heptachlor epoxide	Mirex	Cadmium	Mercury	Arsenic	Total HI	Liver HI	CNS HI	Immune HI
6.5	5E+00	1E-4	5E-3	7E-3	6E-3	6E-2	6E-2	9E-6	4E-4	2E-5	5	0.1	4E-4	5
38	3E+01	8E-4	3E-2	3E-2	3E-2	3E-1	3E-1	5E-5	2E-3	1E-4	30	0.8	2E-3	30
60	4E+01	1E-3	4E-2	7E-2	4E-2	5E-1	5E-1	9E-5	3E-3	2E-4	40	1	3E-3	40
120	5E+01	2E-3	8E-2	1E-1	1E-1	1	1	2E-4	7E-3	4E-4	50	2	6E-3	50
1	Immune	Kidney	Liver	Liver	Liver	Liver	Liver	Kidney	CNS	Skin	Total	Liver	CNS	Immune

Table 6-10. Cancer Incidence, Cancer Risk (Including Severity Factor), Benefit (Including Magnitude) and FCI for Salmon Taken from the Credit River.

Cancer Incidence	Total PCB	DDE	DDT	Aldrin	Dieldrin	Heptachlor Epoxide	Arsenic	Total Risk	Total Benefit	FCI
Cancer Slope Factor	2.00E+00	3.40E-01	3.40E-01	1.70E+01	1.60E+01	9.10E+00	1.50E+00			
6.5 g/day	1.8E-04	7.3E-06	8.4E-07	3.3E-06	4.1E-06	6.6E-06	9.8E-09	2.0E-04		
38 g/day	1.1E-03	4.3E-05	5.0E-06	1.9E-05	2.4E-05	3.9E-05	5.7E-08	1.2E-03		
60 g/day	1.7E-03	6.8E-05	7.8E-06	3.1E-05	3.8E-05	6.1E-05	9.0E-08	1.9E-03		
120 g/day	3.3E-03	1.4E-04	1.6E-05	6.1E-05	7.7E-05	1.2E-04	1.8E-07	3.8E-03		
Risk x Severity	R_{pcb}	R_{DDE}	R_{DDT}	R_{aldrrn}	$R_{dieldrrn}$	R_{hepta}	R_{Ar}	ΣR_i	ΣB_i	FCI
6.5 g/day	-5.4E-04	-2.2E-05	-2.5E-06	-1.0E-05	-1.3E-05	-2.0E-05	-2.9E-08	-6.1E-04	0.42	0.42
38 g/day	-3.2E-03	-1.3E-04	-1.5E-05	-5.8E-05	-7.3E-05	-1.2E-04	-1.7E-07	-3.6E-03	0.68	0.68
60 g/day	-5.0E-03	-2.0E-04	-2.4E-05	-9.2E-05	-1.2E-04	-1.8E-04	-2.7E-07	-5.6E-03	0.68	0.67
120 g/day	-1.0E-02	-4.1E-04	-4.7E-05	-1.8E-04	-2.3E-04	-3.7E-04	-5.4E-07	-0.01	0.68	0.67

Table 6-11. Dose (mg/kg-day) of chemicals detected in smallmouth bass taken from the Niagara River as a function of fish consumption (g/day).

Consumption	PCB dose	DDT dose	DDE dose	Mirex dose	Hexachloro benzene dose	mercury dose	Cancer incidence	Cancer risk*	Mercury risk**	Total risk	Total benefit	FCI
6.5 g/day	1.E-04	1.E-06	2.E-05	7.E-06	2.E-07	4.E-05	3.E-04	-8.E-04	0	-8.E-04	0.42	0.42
38 g/day	8.E-04	7.E-06	1.E-04	4.E-05	1.E-06	2.E-04	2.E-03	-5.E-03	0	-5.E-03	0.68	0.68
60 g/day	1.E-03	1.E-05	2.E-04	6.E-05	2.E-06	3.E-04	3.E-03	-8.E-03	-0.01	-0.02	0.68	0.66
120 g/day	2.E-03	2.E-05	3.E-04	1.E-04	4.E-06	7.E-04	5.E-03	-2.E-02	-0.08	-0.09	0.68	0.59
RfD	2.E-05	5.E-04	NA	2.E-04	8.E-04	1.E-04						
Exceedence ?	YES	NO	NA	NO	NO	YES						
Hazard Index Range	40 to 100					2 to 7						

Cancer incidence calculated using EPA slope factors (U.S. EPA, 1999) Mercury risk estimated using Price *et al.* (1997)

* severity factor of 1 incorporated.

** Severity factor of 3 incorporated.

Table 6-12 Dose (mg/kg-day) of chemicals detected in rockbass taken from the Niagara River as a function of fish consumption (g/day).

Consumption	PCB dose	DDT dose	DDE dose	Mirex dose	Hexa Chloro Benzene dose	Mercury dose	Cancer incidence	Cancer risk*	Mercury risk**	Total risk	Total benefit	FCI
6.5 g/day	3.E-05	3.E-06	6.E-06	2.E-06	2.E-07	4.E-05	7.E-05	-2.E-04	0	-2.E-04	0.42	0.42
38 g/day	2.E-04	2.E-05	4.E-05	1.E-05	1.E-06	2.E-04	4.E-04	-1.E-03	0	-1.E-03	0.68	0.68
60 g/day	3.E-04	3.E-05	6.E-05	2.E-05	2.E-06	4.E-04	7.E-04	-2.E-03	-0.01	-0.01	0.68	0.67
120 g/day	6.E-04	5.E-05	1.E-04	4.E-05	4.E-06	7.E-04	1.E-03	-4.E-03	-0.03	-0.03	0.68	0.65
RfD	2.E-05	5.E-04	NA	2.E-04	8.E-04	1.E-04						
Exceedence ?	YES	NO	NA	NO	NO	YES						
Hazard Index range	1.5 to 30					2 to 7						

Cancer incidence calculated using EPA slope factors (U.S. EPA, 1999) Mercury risk estimated using Price *et al.* (1997)

* severity factor of 1 incorporated.

** Severity factor of 3 incorporated.

6.6.2.4.2 Rockbass and Smallmouth Bass from the Niagara River

Tables 6-11 and 6-12 show doses, risk, benefit, and FCI for smallmouth bass (6-11) and rockbass (6-12). The FCI for rockbass and smallmouth bass at 38 g/day (the study population average consumption) is $7E-1$. PCB intake exceeds the RfD by 10-fold for rockbass; however, the RfD was exceeded by 40-fold at the same consumption rate for smallmouth bass. If risk above the RfD estimates were available for PCBs, there would be a difference in FCI between species. As for the Credit River Salmon FCI, risk estimates as a function of PCB consumption are needed.

Unlike the estimated intake of salmon from the Credit River, methylmercury intake exceeded the RfD at the two highest consumption levels. Methylmercury risk was estimated using the Price *et al.* (1997) model as discussed in Chapter 4. At 38 g/day the best estimate (50th percentile) methylmercury risk was approximately zero for rockbass and smallmouth bass. Methylmercury risk for Niagara River fish consumption begins to appear at 60 g/day. The best estimate (50th percentile) of risk at 60 g/day is 1% for both species (See Figures 6-25 and 6-26).

6.6.2.5 Discussion

Cancer risk is far outweighed by health benefits from eating Lake Ontario and Niagara River fish; however, non-cancer risks from PCB mixtures, and to a lesser extent methylmercury are the primary hazard in this instance. Unfortunately, since the noncancer risks from PCBs could not be determined (at least during this present effort), the calculation of an FCI as shown in Figure 6-22 is misleading, in fact hypothetical Figure 6-24 gives an idea of just how misleading Figure 6-22 can be. Without calculations of risk above the RfD for PCBs it is difficult to calculate an FCI for the study population. Please note that neither Figures 6-25 nor 6-26 include risks above the RfD for PCBs. Until such information is developed, the risks from these case studies cannot be fully appreciated; however, the exposure levels here fall within the range of exposure at which lower scores in reflex, autonomic and habituation were observed in infants from the Lonkey *et al.* (1996) study (see Chapter 4).

However, this case study illustrates the versatility of the framework. The framework can incorporate as many chemicals and effects as necessary. Although at 38 g/day there was no risk of subtle neurological effects due to methylmercury intake from Niagara River fish, at 60 g/day risks begin to appear. This case is also instructive, because it shows how cancer and noncancer risks are combined. Especially in the case of smallmouth bass, it is apparent that when intake levels exceed oral RfDs, the noncancer endpoints will rapidly overtake any benefit from eating fish. For cancer, there is a steady, but small, increase in the risks incurred and decrease in benefits.

This case study is far more comprehensive than the simple example presented in the Everglades. It incorporates both cancer and noncancer risks, and compares FCIs for different species and different bodies of water. The estimated FCI was approximately equal for all three analyses (See Table 6-13). However, a large difference in PCB exposure exists for which the noncancer risk could not be quantified.

Table 6-13. FCI at 38 g/day for Salmon Rockbass and Smallmouth Bass.

	Salmon	Rockbass	Smallmouth bass
Niagara River		6.8E-1	6.8E-1
Credit River	6.8E-1		

Table 6-14. Hazard Index for PCBs at 38 g/day.

	Salmon	Rockbass	Smallmouth bass
Niagara River		10	40
Credit River	25		

Overall, given the available information, equal FCIs (See Table 6-13) for each species and location, and the disparity in total PCB hazard index (See Table 6-14), rockbass from the Niagara River are probably a better source of fish of the three species analyzed here in terms of minimizing risk. PCB tissue concentrations are the most important factor in the determination of the FCI, yet as explained in Chapter 4, the data were insufficient to model risk above the RfD for this case study. This is, and will continue to be, a critical data gap in any application of the framework in PCB contaminated waters and should be a priority research need. The framework illustrates the importance of dose response modeling of noncancer health endpoints in comparative dietary risk assessment

6.7 Overall Conclusions and Research Needs

This chapter has outlined an approach to evaluate the potential health benefits of consuming fish against the potential health risks of eating contaminated fish. Consuming uncontaminated fish (or at least fish that are smaller, younger, or in general less contaminated) may provide health benefits, but without the potential health risks associated with contamination. The eating of such "cleaner" fish rather than more contaminated fish would maximize the net benefit of fish consumption. This is shown specifically in Figures 6-6 to 6-16 for low versus high concentrations of chemicals in fish, those chemicals that either bioaccumulate or not, or for fish contaminated with more than one chemical.

Figure 6-22. Risk, Benefit, and FCI as a Function of Consumption of Salmon from the Credit River.

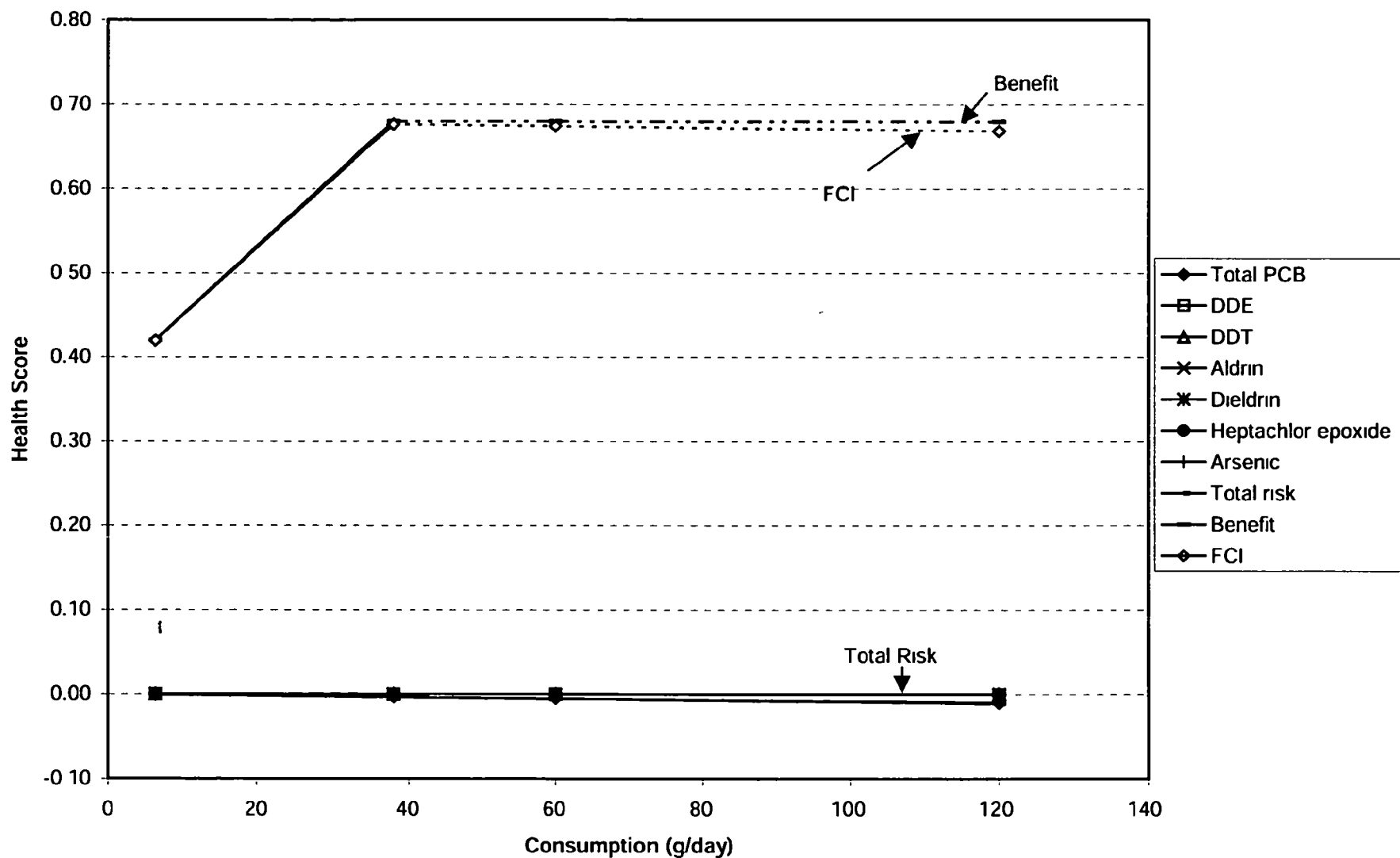


Figure 6-23. Total Cancer Risk and Individual Components for Salmon Taken from the Credit River.

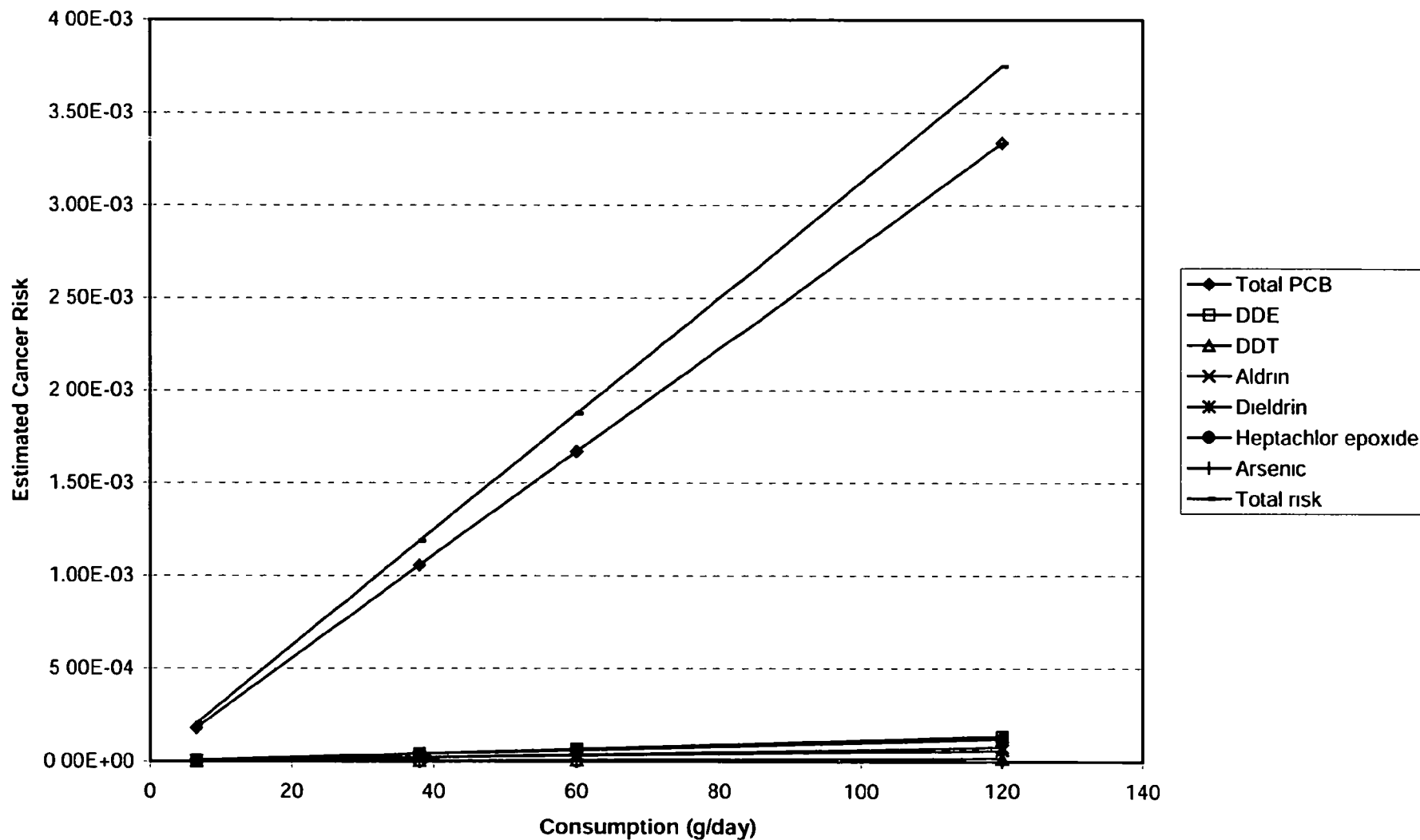


Figure 6-24 Hypothetical Risk, Benefit, and FCI Assuming that the Shape of the Noncancer Dose-Response Curve for PCBs is the Same as that for Methylmercury for Salmon from the Credit River.

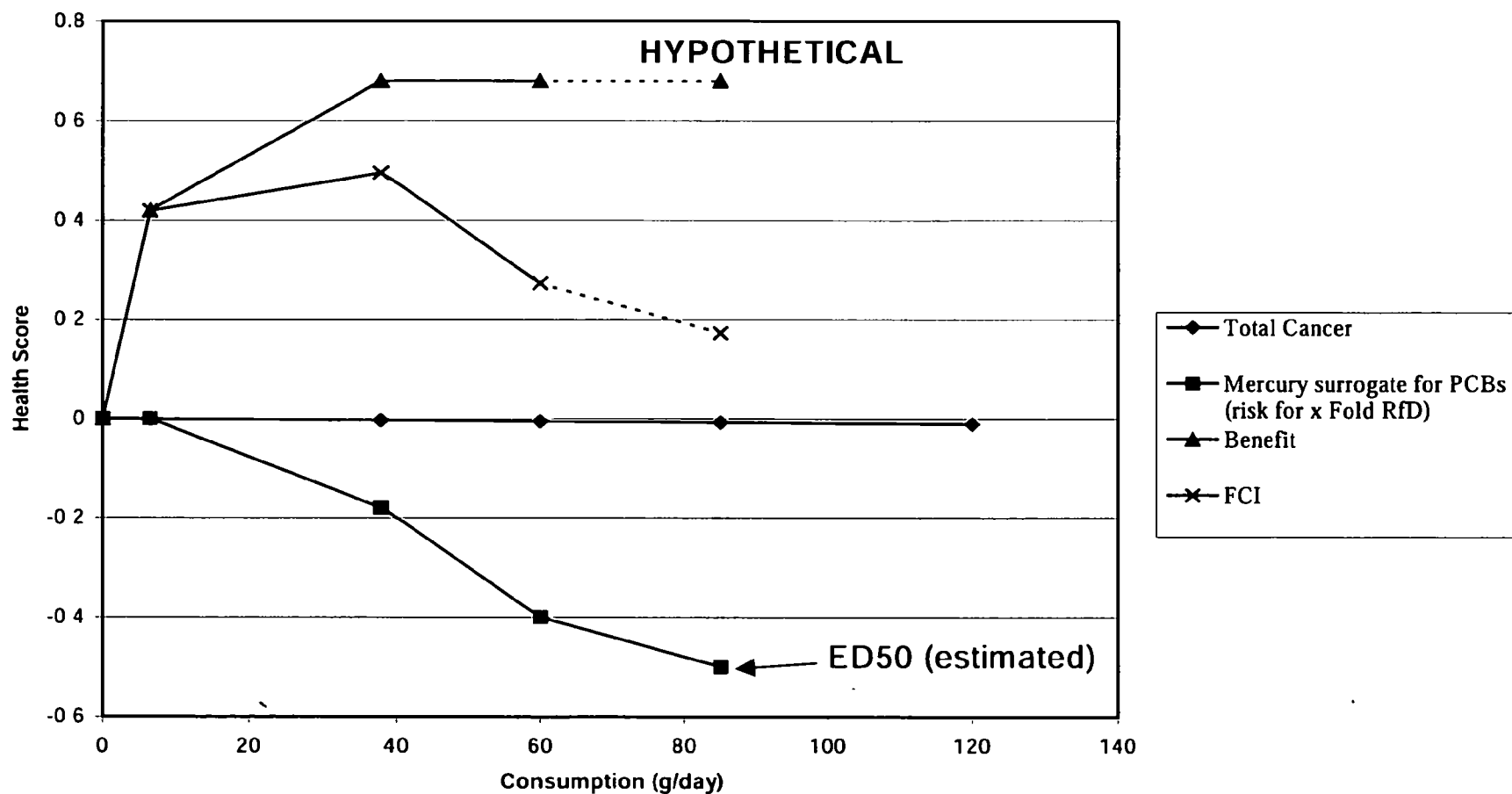
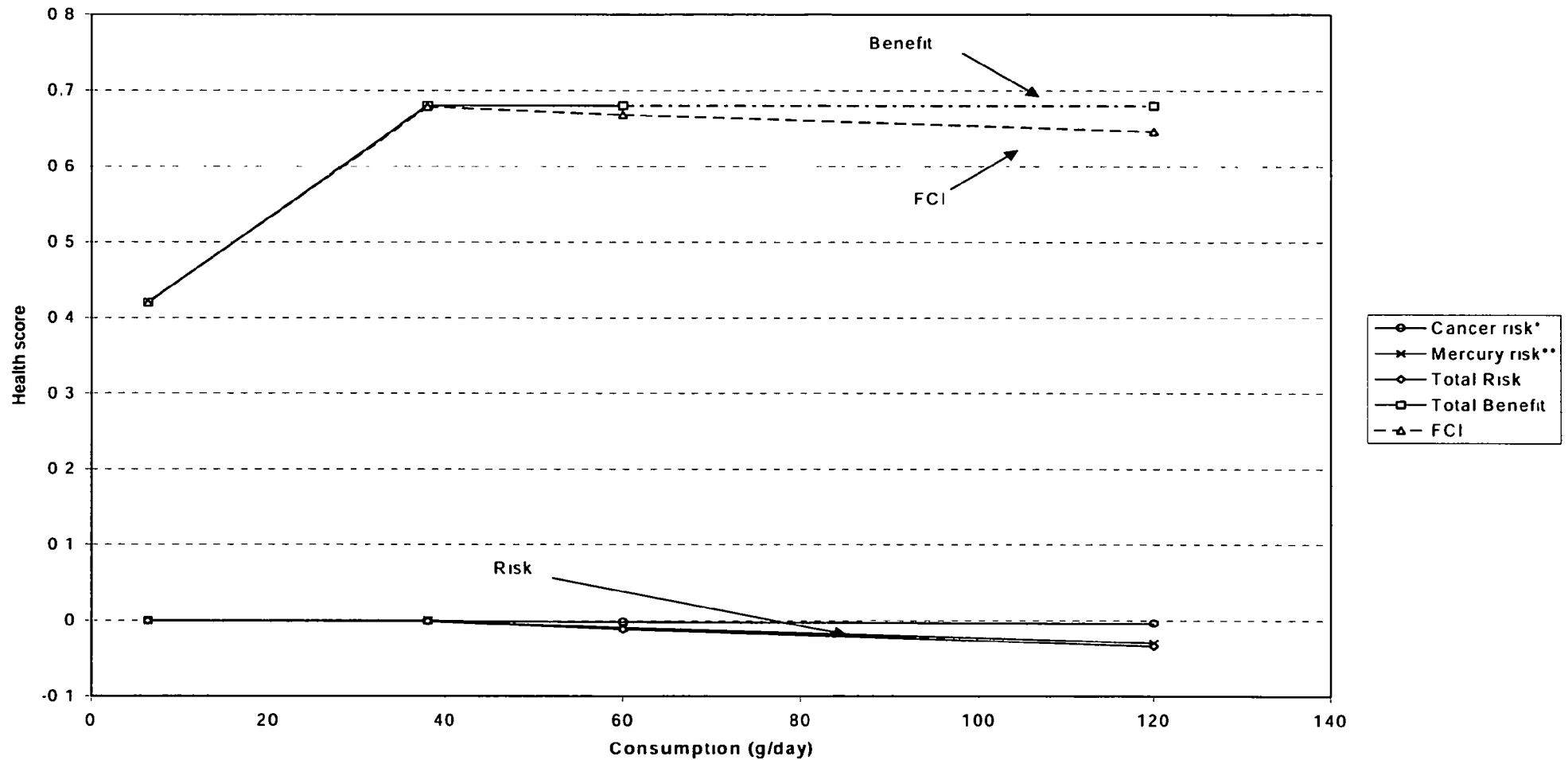


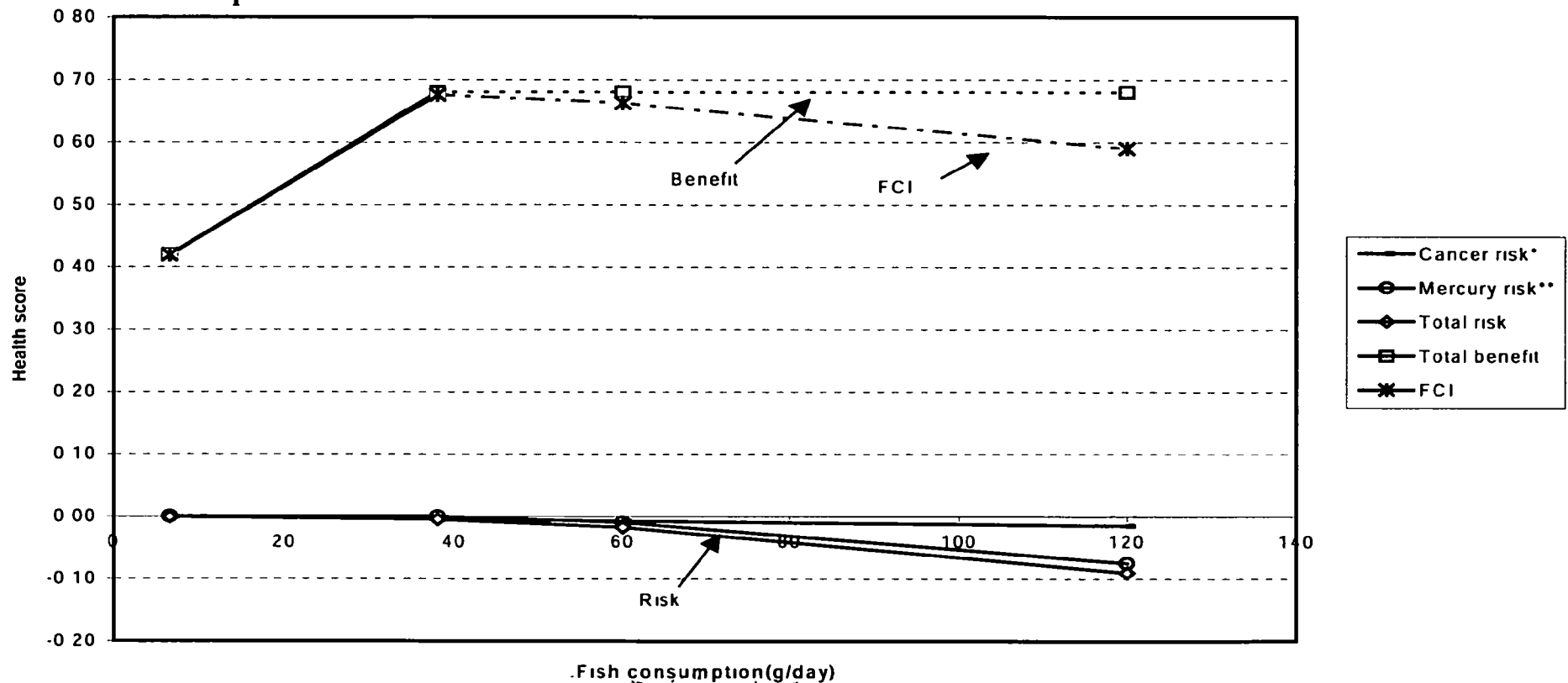
Figure 6-25. Risk, Benefit, and FCI as a Function of Niagara River Rockbass Consumption.



* 95th Percentile

** 50th Percentile

Figure 6-26. Risk, Benefit, and FCI as a Function of Niagara River Smallmouth Bass Consumption.



* 95th Percentile

** 50th Percentile

When alternatives to the eating of contaminated fish are not available, it may be appropriate to weigh the risks of eating less of these contaminated fish with the benefits gained from eating more of these same fish. The framework developed here can crudely compare these risks and benefits. However, this framework has a number of significant data gaps. These gaps are sufficiently large so as to prevent any definitive conclusions from this study or any overall recommendations regarding existing fish consumption advisory programs of the U.S. or other countries. Further study is needed to confirm and extend these preliminary findings.

This framework is an initial attempt to evaluate risks and benefits (both qualitatively and quantitatively) on a common scale. Constructing this framework has identified numerous areas that need further research and development. Two needs seem paramount. First, better estimations of benefits are needed for the general population and its sensitive subgroups. Although information in this text is highly suggestive of the protective effects of eating fish and allows some quantification, more definitive work is needed to support the quantitative values shown in Table 6-1. Second, better risk information is needed on the chemicals that commonly contaminate fish. Indeed, we have sufficient knowledge on the toxicity of most of these pollutants that quantifying risks above the RfD should be done. This information is essential for this framework, or any other construct, to be effective.

Specific conclusions and research needs are summarized below.

- Incorporate full range of benefits data: The examples of benefits that are presented in the framework are representative based on the available data. However, they do not incorporate the entire quantitative benefits data (see Table 2-1). At a minimum, all the data sets supporting, or contradicting, the existence of a particular health benefit should be further summarized and discussed, and data should be presented for any endpoint having quantitative benefits information. A meta-analysis might be considered for each endpoint supported by more than one data set. This might allow the development of a single dose-response curve for each health endpoint. Such single dose-response benefit curves would make the framework easier to use.
- Reconsider severity schemes: For this framework, the severity approach of EPA and ATSDR for estimating RfDs/RfCs and MRLs (Table 6-2) was used to modify the health risks associated with chemical exposure. This approach has the advantages of simplicity, familiarity and consistency with the use of information from EPA's IRIS, and of ATSDR information found in its toxicological profiles. One shortcoming of this approach is the implied equal spacing between levels. There is no scientific or mathematical justification proposed for a FEL being considered three times as "severe" as a less serious LOAEL. Other caveats were discussed in Chapter 6 (see Table 6-3).

In like fashion, a modifier to the magnitude of health benefits accrued from eating fish was used to roughly compare with the risk of different health endpoints. This modifier of health benefits (e.g., coronary heart disease avoided) was ranked as none, minimal, moderate or maximum. This modifier has the advantages of simplicity and consistency with the use of information for health risks. As for health risks, however, the scheme for health benefits is being used in a quantitative fashion in the framework, and this results in several shortcomings which were discussed in Chapter 6 (see Table 6-3).

Other severity schemes should be explored for comparing the health risks and benefits of fish consumption. The results are likely to be more complex, however. Several of these schemes will necessitate additional judgment regarding the appropriate severity level of both the critical effect and benefit. At least one of these schemes (i.e., Ponce *et al.*, 1998) also incorporates the concept of duration of the effect or benefit through the use of QALYs. Every attempt should be made to see if these more complex severity schemes add value when compared to the simpler one, which was used here.

- **Explicitly incorporate uncertainty:** It is important to recognize that with the exception of noncancer risks (see Figures 4-1 and 4-2), uncertainty in health benefits and risks is not dealt with explicitly by the framework in its current version. Moreover, the uncertainty surrounding the estimates of the different benefits and risks associated with eating fish are unlikely to be the same. For example, the uncertainty surrounding estimated cancer risks based on animal toxicity data is likely much greater than the uncertainty surrounding estimated coronary heart disease benefits based on human data.

An important future refinement of the framework would be explicit consideration and quantification of uncertainty surrounding estimates of potential health risk and benefit, because both have the potential to alter the interpretation of the framework and the resulting FCI. Future efforts should be devoted to this area.

- **Conduct a sensitivity analysis:** The current version of the framework uses fixed inputs for most of the variables that determine potential risk, potential benefits and the FCI. Such fixed information helped develop the framework and also allowed for exploration of a number of issues associated with its use. However, many of these fixed parameters can and do vary, and additional work is needed to investigate how the FCI changes when these parameters are changed. Such a sensitivity analysis would greatly improve interpretation of the framework results and perhaps help focus future work on the input variables that have the greatest potential to affect the FCI.
- **Evaluate additional mixtures of chemicals:** The framework and case studies used only a few chemicals and concentrations to examine the relationship between potential risks and benefits of eating contaminated fish. While the choice of these chemicals reflected the frequency of residues and number of fish consumption advisories (Table 4-1), other chemicals are also found in fish. While the analysis of a limited number of chemicals is useful for the development of the framework and its application, the choice of concentrations could perhaps better reflect those typically observed in waters of the U.S (the example concentrations presented here were much higher than average). Based upon comments from the Advisory Committee, methylmercury, PCBs and dioxin are the chemicals for which advisories are most commonly needed and typical high concentrations might vary between 0.2 and 1 mg/kg for methylmercury and PCBs, and be around 1 ng/kg for dioxin toxic equivalents.
- **Develop risk curves for non-sensitive groups:** For health risks, specific risk curves for non-sensitive members of the population could also be developed. This would avoid

matching the health risk for the sensitive individual with the health benefit to the average individual. For example, with methylmercury the risk curve is based on risk to the infant and fetus, whereas the benefit curve was for the adult. Use of an adult risk curve would have changed the conclusions of the Florida Everglades case study.

- Develop risk curves for doses above the RfD for selected pollutants, in particular for PCBs: It comes as no surprise that PCBs are a common pollutant in fish and one that needs to be better studied. As amply demonstrated by the Vietnamese case study, however, the need for determining the risk above the PCB RfD is paramount. Quite simply, this case study is woefully deficient without this determination, as demonstrated by reference to the differences between Figures 6-22 and 6-24.

6.8 References

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7 Using and Communicating the Comparative Dietary Risk Framework

This framework and approach could be used by state, tribal, and local risk managers who set fish advisories to provide additional information on possible health benefits to those who fish and eat fish. Because of the data intense process and results of the FCI, a solid risk communication program is necessary to insure successful usage of the information generated. The risk communication process associated with fish consumption health advisories has been described in depth in U.S. EPA's *Guidance for Assessing Chemical Contaminant Data for Use in Fish Advisories, Volume 4* (U.S. EPA 1995). This chapter summarizes key elements of that process applied to the comparative dietary risk framework, emphasizing that risk communication is a process of information exchange between the target audience and the risk communicator.

Two cautions about communicating information from the framework should be reiterated. First, instituting a risk communication program assumes the existence of quality information to communicate. Developing a risk communication approach at this stage of evolution in the Comparative Dietary Risk Framework is appropriate; however, implementing a risk communication program is not appropriate until the data are available for calculating the actual values that would be used in the framework and the FCI.

Second, although the framework provides a mechanism for comparing risks and benefits associated with fish consumption, it is not a justification for accepting fish consumption risks as long as there is a net benefit. Decisions about acceptable risks and distribution of risks and benefits throughout society is a social decision, to be made collectively by the communities affected (Shrader-Frechette, 1990; Knuth, 1995). That the FCI may demonstrate cases in which fish consumption benefits appear to outweigh the risks is not a license to pollute. Rather, society must determine policy about long-term goals for minimizing environmental pollution based on a range of ethical, economic, and social criteria. Further, environmental justice and equity issues are raised when certain communities are forced to assume more health risks than others. For example, some communities consuming large amounts of fish may score high on the "benefits" side of the equation. If those fish are chemically contaminated, however, the same communities also score high on the "risks" side. Use of the framework and FCI does not imply the proper choice is simply achieving a situation in which the net risks and benefits are zero. Rather, the framework helps make the tradeoffs between risks and benefits transparent, and should be used to foster discussion on environmental equity and justice issues, and questions of who should bear the costs of pollution vs. derive the benefits from the fisheries resource.

7.1 Overview of Risk Communication as a Process

Risk communication includes several stages: problem analysis; audience needs assessment; communication strategy design; communication strategy implementation, and evaluation (Fig. 7-1). Problem analysis includes examination of both external and internal factors that may or should influence the risk communication program. This first phase also involves identifying the specific objectives to be achieved through the risk communication process.

The second phase, audience identification and needs assessment, begins with target audience identification. The risk communication objectives established in the problem analysis phase

provide insights about potential types of target audiences. In this phase, those audiences are characterized in terms of demographics; awareness and knowledge about advisories, contaminants, and fish consumption; beliefs and attitudes about related topics; and behaviors related to fishing and fish consumption. Based on this information about target audiences, health advisory information needs are identified.

Strategy design and implementation, phase three, reflects the communication objectives and the target audience information needs identified earlier. Strategy design includes considerations about the style of communication (e.g., format, tone, text vs. graphics, reading level), the content (e.g., comparisons of sites, health effects, health benefits), and means for disseminating the information (e.g., mass media, interpersonal contacts, specialized media). Strategy implementation includes pre-testing the message, modifying the design as needed, creating a timetable, and finalizing and disseminating the message(s).

Evaluation as a component of the risk communication process occurs at three stages of the process. Formative evaluation occurs during problem analysis, audience needs assessment, and the initial stage of communication strategy design. Process evaluation occurs during the communication strategy implementation period. Summative evaluation occurs after the communication strategy has been implemented, but refers back to information identified in the problem analysis and audience needs assessment phases.

7.2 Designing, Implementing, and Evaluating a Communication Program for the Comparative Dietary Risk Framework

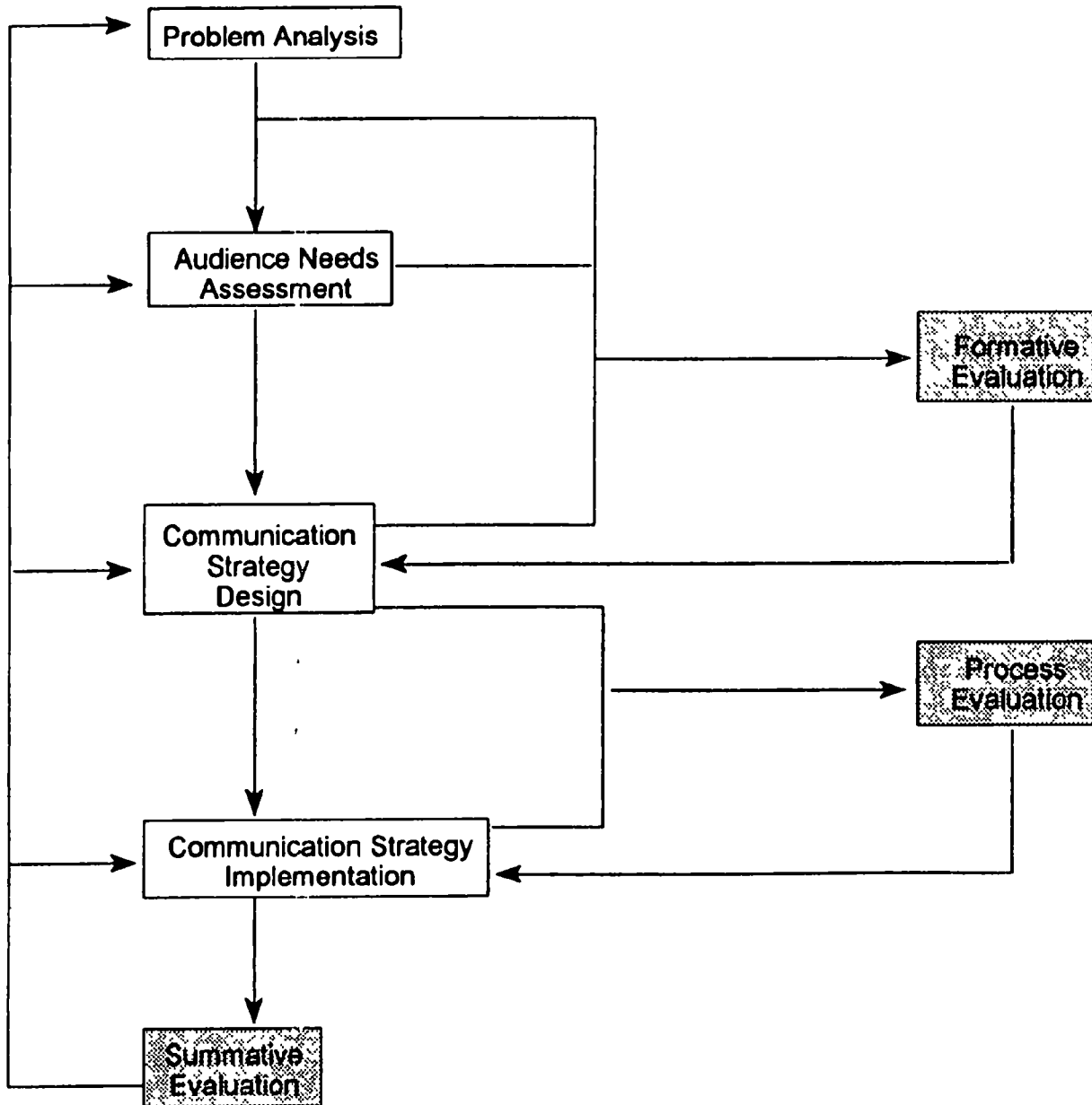
This section examines each stage of the risk communication process in relation to using the Comparative Dietary Risk Framework, indicating both strengths and challenges. The Comparative Dietary Risk Framework responds to several risk communication needs identified for fish consumption health advisory programs. Recent studies of angler and fish consumer response to advisory communications suggest that potential fish consumers desire particular types of information, although these information needs may differ among target audiences.

Information about how risks change with different levels of fish consumption has been identified by anglers, fishery experts, and health care experts as very important for health advisory communication programs (Velicer and Knuth, 1994). Studies of licensed anglers have indicated the perceived importance of health advisory information about topics such as potential health benefits and risks associated with fish consumption, how risks change as more or less fish is eaten, and comparing the health risks of eating fish with the risks from other protein sources (e.g., Connelly *et al.*, 1992; Connelly and Knuth, 1993).

Other studies have demonstrated that anglers do respond to health risk information by changing their fishing-related behavior. Changes include eating less sport-caught fish, changing fish-cleaning methods, changing fishing locations, changing species eaten, changing the size of fish eaten, and changing cooking methods (Connelly *et al.* 1992). Connelly *et al.* (1996) provided

Figure 7-1. The risk communication process, adapted from Velicer and Knuth (1994).

RISK COMMUNICATION PROCESS



evidence that fish consumption suppression (anglers eating less fish than they would in the absence of health advisories) was prevalent among Lake Ontario anglers. Montgomery and Needelman (1997) outlined a method to quantify the economic impacts of fishing behavior related to chemical contamination of fisheries.

Key among information needs identified is the desire of many potential fish consumers to understand the impacts of the advisory, and of fish consumption, for them individually. The framework enables risk communicators to facilitate this understanding, providing a mechanism to better meet many risk communication goals.

The FCI is the key communication element of the framework. The FCI may be conveyed graphically across a range of fish consumption rates (see Figure 6-5 Health Scale as a Function of Fish Consumption Rate), or as a single value. The latter approach is similar to many current health advisory communication programs, in which a determined level of fish consumption is recommended for a particular group (e.g., eat no more than 1 fish meal a month). The graphical presentation of FCI, however, conveys a greater degree of information than does a single fish consumption rate. The reader is able to visualize how benefits and risks, and hence net benefits, change with changes in the fish consumption rate. Ideally, it would be possible to convey this comparative information for different species of fish, because many fish consumers face the question of "substitution" rather than "abstinence;" i.e., changing species, sizes, or locations of fish caught and eaten, rather than reducing or eliminating overall fish consumption.

In theory, this graphical presentation increases the information available to the decision-maker (a government agency or the potential fish consumer) and is thus more individualized. Used in this way, however, the framework focuses on individual diets, increasing the risk communication challenge particularly for agencies used to developing and disseminating a "one size fits all" type of health advisory. Limited resources for health advisory and associated communication programs, coupled with a mandate to address large, diverse groups in society, constrain the abilities of agencies to target very specific audiences.

From a risk communication standpoint, the framework's greatest strengths (i.e., use of the FCI across varying fish consumption rates to estimate changes in net benefits) lie in application to local areas, to situations in which individual consumer concerns can be identified, and to internally homogenous groups with particular cultural or dietary concerns. On larger (e.g., statewide, region wide) scales, using a single FCI value on which to base fish consumption recommendations may be the best option. Statewide, portraying all the possible combinations of exposure and benefits would be infeasible, but presenting summary information would be possible to help anglers decide on appropriate "substitutions" - i.e., switching species, sizes, or fishing locations to target those that have, on balance, greater benefits than risks. In local or special audience cases, however, it may be feasible to present a range of figures (FCI graphs) demonstrating a limited number of exposure and benefit scenarios to enhance local understanding of the options and tradeoffs available.

7.2.1 Problem Analysis

The first stage in risk communication is problem analysis, a careful consideration of external and internal factors that influence the selection of risk communication objectives and the likelihood of meeting those objectives. Objectives indicate the outcomes that reflect the mandate of the agency and the impact to be achieved through the risk communication program.

Analyzing external and internal factors improves understanding of the context in which the health advisory risk communication program will occur. Without an understanding of the context, it is difficult to establish realistic objectives. Contextual factors external to the health advisory program include the characteristics of the community(ies) to be affected by the health advisory, and the degree of certainty and completeness of information used to establish the health advisory. Data needs for calculating the FCI within the framework have been discussed earlier. Internal factors include staff, budget, and other resources available to or required by the health advisory program.

A variety of objectives are often associated with health advisory programs. The involvement of more than one agency in the development and dissemination of health advisories (Reinert *et al.* 1991) often complicate such programs. For example, environmental quality agencies may conduct the chemical and fish tissue monitoring programs. Health agencies may conduct the risk assessment (or calculate the FCI). Health agencies in cooperation with fishery management agencies may be charged with communicating the health advice. Because these agencies have differing mandates, they may have differing objectives they hope to accomplish through health advisory programs.

In a study of Great Lakes agencies involved in health advisory programs, one of the most frequently cited objectives (by all types of agencies) for health advisory communication programs was to enable consumers to "make their own, informed decision" about fish consumption (Knuth and Connelly 1991). Other objectives focused on reducing human health risks, educating people about risk-reducing fish preparation methods, encouraging public support for fisheries and facilitating positive fishery resource use, and following agency mandates.

Value-based risk management judgments are inherent in risk communication, particularly using the FCI-based approach. Because the framework (through the graphic presentation of FCI) compares potential health risks and benefits of eating fish affected by contaminants, risk communicators have an increased ability to help individual fish consumers be informed in their decision making, addressing the first objective noted above. Including a graph such as Fig. 4 in health advisory communication programs would improve a potential fish consumer's ability to make an informed decision based on his or her own choice about balancing fish consumption benefits with risks. However, objectives focused on reducing human health risks might prompt agencies to choose the FCI represented by zero or near-zero risk, the FCI represented by maximum net benefits, or some other value. Objectives focused on encouraging public support for and use of fishery resources might support choosing the FCI represented by zero net benefits (i.e., that level at which net risks are offset by net benefits so that maximum fish consumption opportunities at zero net risk are promoted) or some other value.

Thus, the communication resources available to an agency, the context in which the communication will occur, and the objectives inherent in the health advisory program will influence the way in which the framework and FCI are implemented. As noted, the FCI may be communicated graphically as a range of values across differing fish consumption levels, or as a point value recommending one set fish consumption rate as a maximum allowable level. The single point value selected would differ depending on the program objectives, reflecting an agency's decision about the appropriate manner in which to balance risks and benefits associated with fish consumption.

7.2.2 Audience Identification and Needs Assessment

The second stage in the risk communication process is audience identification and needs assessment. A combination of "expert" input from those within the health advisory agency(ies) and those knowledgeable about the potential target audiences, and direct input from the potential audiences is usually required. "Expert" viewpoints about target audience information needs may not agree with needs identified by the target audiences themselves (Velicer and Knuth 1994). Judgments about factors such as the relative importance of risks and benefits to community members, and about cultural importance of fish consumption in the diet or as part of local tradition, are needed. Risk communication experts may not be informed enough or aware enough to make such judgments without considerable local input.

Identifying potential target audiences is the first step in this phase. Ideally, selection of target audiences would have been completed during development of the FCI. Calculations within the framework require a variety of data about health status and impacts, dietary tradeoffs, etc., which should be collected for the target audiences of concern. From a communication standpoint, target audience segmentation should be based on identifying groups that are relatively homogenous from the perspective of information content needs, and who can be reached through similar information dissemination mechanisms.

Characterizing the information needs of target audiences includes assessing a variety of factors, such as audience demographics (age, gender, education, language ability, income, residence, race, family status); typical information sources used; fishing and fish consumption experience; and prior awareness, knowledge, beliefs, and behaviors related to fishing and fish consumption, including cultural forces. These information needs are similar to those in the risk communication components of existing health advisory programs. Using the framework, however, these information needs are relevant not only to the risk communication process, but also to the preceding process of developing the basic health advisory recommendations.

The information requirements for an audience needs assessment using the framework occur earlier in the health advisory development process than in traditional health advisory approaches. The framework can consider different subgroups (e.g., adults, children, breast-feeding mothers and infants), health benefits, cancer and non-cancer health endpoints, biological and perceived severity of health endpoints, and cultural values. Because of this, more information about target audience characteristics, behaviors, values, and information needs is required at the time the fish consumption recommendations are generated - not just at the risk communication stage.

Emphasis must be placed on incorporating information about target audiences early in the process of developing data to insert in the framework.

Applying the framework to a particular audience requires knowledge of how the target community (or individuals within the community) perceives the severity associated with different health outcomes, what health outcomes are most important in the community given its demographics, and the cultural values the community assigns to fish consumption. Other important information includes understanding how dietary behavior changes in response to reduced fish consumption (e.g., what alternative food sources would replace fish) so the appropriate comparisons of health risks/benefits between current and modified (less fish consumption) dietary patterns can be factored into the framework.

Early and in-depth assessment of target audience information needs is particularly important for applications of the framework in which cultural risk factors will be incorporated. Rarely (if ever) will a group of risk-management or risk-assessment experts be able to characterize adequately the cultural risks associated with fish consumption and/or potential loss of fish consumption. If fish consumption and associated activities are a key element of the local culture (e.g., see Chapter 5 *Socio-cultural Considerations of Fish Consumption*) decision-making methods are needed that will allow the local community to help quantify or characterize the perceived severity and cultural risk factors that will be incorporated into the calculations of the framework.

Techniques for determining target audience information needs, based on input from both audience members and experts, are detailed in U.S. EPA (1995). These include personal interviews and group discussions, mail and telephone surveys, and document review.

7.2.3 Communication Program Strategy Design and Implementation

The flexibility of the framework for designing and implementing risk communication programs is both appealing and challenging. Because of the types of information used in operating the framework, very specific risk communication messages can be developed that are responsive to the special concerns of a given subpopulation, community, or individual. The converse, however, is the challenge of providing all of the information needed for the framework to be applied to its fullest - detailed descriptions of perceptions, cultural values, and behaviors within the community of concern. Thus, this approach can be particularly cost-intensive in terms of information and the staff resources needed to acquire it.

In many cases, decisions will have to be made about which set of perceptions and values to apply, treating a known heterogeneous community as if it was homogenous, to simplify calculation and communication of the FCI. In large, heterogeneous communities, therefore, the full benefits of the framework may not be realized because of the number of assumptions (of homogeneity) that will be necessary. However, in small communities that are homogeneous on several parameters important in the framework (e.g., perceived severity of health outcomes, cultural importance of fish in the diet), the FCI should improve the ability of individuals to make their own "informed decisions" about an appropriate fish consumption rate, particularly if the FCI is presented graphically relative to differing fish consumption levels and species or locations.

8 Conclusions and Research Needs

8.1 Overall Conclusions and Research Needs

This document has outlined an approach to evaluate the potential health benefits of consuming fish against the potential health risks of eating contaminated fish. Some evidence exists for an association between decreased risk of CHD or MI, and consumption of small amounts of fish, including mainly lean (non-fatty) fish. Additional studies have seen some association between eating fish and reduced risk of stroke and arthritis, and enhanced immunological and nervous system development. These data, along with the superior nutritional value of fish, are strong enough that public health officials routinely encourage the public to eat more fish.

Consuming uncontaminated fish (or at least fish that are smaller, younger, or in general less contaminated) may provide health benefits as mentioned above, but without the potential health risks associated with contamination. Before eating any contaminated fish, consumers should consider fish supplies from cleaner water bodies, eating smaller, less contaminated fish, and cooking and cleaning methods that reduce contaminants. The eating of such "cleaner" fish rather than more contaminated fish would maximize the net benefit of fish consumption. This is shown specifically in Figures 6-6 to 6-16 for low versus high concentrations of chemicals in fish, for those chemicals that bioaccumulate, or for fish contaminated with more than one chemical.

When alternatives to the eating of contaminated fish are not available or desired, it may be appropriate to weigh the risks of eating less of these contaminated fish with the benefits gained from eating more of these same fish. The framework developed here can crudely compare these risks and benefits. However, this framework has a number of significant data gaps. These gaps are sufficiently large so as to prevent any definitive conclusions from this study or any overall recommendations regarding existing fish consumption advisory programs of the U.S. or other countries. Further study is needed to confirm and extend these preliminary findings.

This framework is an initial attempt to evaluate risks and benefits (both qualitatively and quantitatively) on a common scale. Constructing this framework has identified numerous areas that need further research and development. Two needs seem paramount. First, better estimations of benefits are needed for the general population and its sensitive subgroups. Although information in this text is highly suggestive of the protective effects of eating fish and allows some quantification, more definitive work is needed to support the quantitative values shown in Table 6-1. Second, better risk information is needed on the chemicals that commonly contaminate fish. Indeed, we already have sufficient knowledge on the toxicity of most of these pollutants that quantifying risks above the RfD can be done. This information is essential for this framework, or any other construct, to be effective.

Specific conclusions and research needs on each technical chapter are summarized below.

8.2 Chapter 2

Some evidence exists for an association between decreased risk of CHD or MI, reduced risk of stroke and arthritis, enhanced immunological and nervous system development, and consumption

of small amounts of fish, including mainly lean (non-fatty) fish. However, it seems unlikely that decades-long intake of small amounts of fish protect, if fish is indeed etiologically protective, via the very small amounts of omega-3 long-chain polyunsaturated fatty acids so ingested. The resolution of this issue has important implications for public health and nutritional recommendations. Thus, further studies -- observational and interventions, particularly clinical trials -- are needed to resolve whether there is an etiologically significant protection against CHD or MI afforded by regular ingestion of modest amounts of fish. Similarly, more research is needed on the relationship of fish intake and health endpoints other than CHD or MI.

Data gaps and research needed on the benefits of fish consumption include:

- More understanding is needed on the benefits of consuming fish and why consuming fish provides these benefits. For example, is it the n-3 FAs? Selenium or some other mineral? Substitution for other less healthful foods? Or another mechanism or combination of factors yet to be determined?
- Numerous epidemiological studies have been conducted which provide some evidence for an association between consuming fish and reduced risk of coronary heart disease, stroke and arthritis. More research is needed in this area and on the other possible beneficial effects of fish consumption. More long-term studies and randomized controlled clinical trials are needed.
- Studies are needed on groups of people who consume more fish than the national average. These people are at most risk due to their high consumption, but the existing epidemiology studies have not included groups with high rates of consumption. Do the potential benefits increase with increases in consumption, or is there a point at which benefits plateau at some consumption rate? Are there health detriments to even higher consumption of fish?
- The information used in this report on the change in specific health effects with consuming fish was limited to studies primarily in adults and for only three health endpoints. Additional studies on the benefits of fish consumption should be encouraged. Every effort should be made to ascertain quantitative information on the benefits of fish consumption to pregnant women, infants and young children, as well as health impacts of larger consumption rates.

8.3 Chapter 3

Fish is high-quality protein that the public should be encouraged to eat. There are many nutritional benefits associated with eating fish, regardless of the species type. Unlike red meats, eggs and dairy products, fish provides very high quality protein *and* a "heart healthy" combination of fatty acids. Further, fish (both lean and fatty) is one of the few foods that contain n-3 (omega-3) fatty acids, a class of fatty acids that are essential for the development of the nervous system and that may have other beneficial health effects. Calcium, iron, zinc, vitamin A, niacin, vitamin B6, and vitamin D tend to be low in U.S. diets; fish supplies all of these vitamins and minerals, in addition to others.

Data gaps and research needed on the nutritional aspects of fish consumption include:

- Fish is known to be a good dietary source of selenium, but few reference data are published; more research into the role of selenium in human health is also needed.
- Nutrient databases contain a wide range of fish species, but samples used to obtain nutrient values are composites of cooked fish from various unknown locations.
- Nutrient values are generally expressed on the basis of a 100 gram cooked fish portion. This limits the extent to which comparisons can be made with contaminant data, which are usually based on raw tissue samples of wild fish gathered from specific geographic areas, and expressed as concentrations rather than on a weight basis.
- Different methods of preparing and cooking fish will alter some of the organochlorine contaminant levels. Ideally, the same samples of prepared and cooked fish would be sent for both contaminant and nutrient analysis, and weighed records of amounts of the fish consumed would be kept to enable researchers to better assess the physiological risks and benefits to humans.
- A comparison of the nutritional and contaminant contents of protein sources other than fish would be ideal, since it would give information on the benefits and risks of other protein sources. This would allow one to make risk to risk comparisons with fish substitutions. See Figure 6-3 for a hypothetical discussion of this issue.

8.4 Chapter 4

The risks of consuming fish with chemical contaminants are not completely understood. However, information for the six chemicals selected for this document was available on EPA's IRIS (U.S. EPA, 1999). The majority of this information was of medium confidence, which means that additional toxicity data may change the resulting risk values somewhat. For most compounds, this risk information was based on data from laboratory animal studies (methylmercury and chlorpyrifos were the exceptions). These results must be extrapolated to humans with considerable uncertainties involved, but the methods used for this extrapolation are widely accepted as health protective.

This framework requires an understanding of potential health risks at doses above those that are considered "safe" or at a threshold for toxicity. Traditional cancer risk methods have provided risk assessors with extrapolation to levels of environmental concern. While these estimates are uncertain, they are generally regarded as falling on the side of being health protective. The method that was chosen to estimate risks above the RfD is more recently developed and while is designed to also be health protective, it has not been widely tested. It has the advantage of ease of use with existing EPA information from IRIS.

Concordance of effects between laboratory animals and humans is not generally known. Therefore, the critical effects driving the risk estimates derived from laboratory animal data may not necessarily be the effects one would see in humans. However, the framework is flexible and

could be used with information on the non-critical effects of these same chemicals to further refine the overall risk estimates.

Data gaps and research needed on the potential risks from fish consumption include:

- One of EPA's methods for calculating risk above the RfD was used here (Price et al., 1997). This method is new and needs further exploration. It has the advantages of being more generally applicable than categorical regression or benchmark dose, and is less resource intensive. It can be used directly from the existing data as on EPA's IRIS. However, it is not the only approach to the problem of risk above the RfD, and as demonstrated, the method does not work for all chemicals.
- For the framework to be most useful, noncancer risks above the RfD must be estimated for all significant critical effects of chemicals that contaminate fish, in particular, for the contaminant PCBs. For example, the case study of the Vietnamese immigrant women consuming Lake Ontario sportfish was severely hampered by the inability to estimate the risks above the RfD for PCBs (Figure 6-24). Some exceedances of the PCB RfD were as much as 40-fold. Other chemicals need similar investigation.
- RfDs are designed to be protective for all adverse effects based on the data for the critical effect. When doses exceed the RfD, as the framework assumes they could, then the critical effect may begin to manifest itself in the exposed population. The framework uses dose-response information on the critical effect to predict the increased incidence of the critical effect. But in addition to the critical effect, other effects may also be seen at higher doses. Some of these *non-critical effects* may be more severe than the critical effect (e.g., reduced body weight versus liver toxicity). At present, EPA has not developed dose-response relationships for non-critical effects in humans. For the framework to fully characterize potential risks, and the net health benefit of eating contaminated fish, dose-response relationships for non-critical effects should also be developed.

8.5 Chapter 5

The benefits of catching and eating fish can go beyond the nutritional value and potential reduced risk of certain diseases. For some subgroups such as tribes it may be important to consider the social, religious and cultural importance of fish to that society. Economic impacts might also be considered for this and other groups. Among isolated and/or lower-income groups, fish may represent an important economic resource, and a source of needed high-quality protein, that is not easily replaced. In such communities, advisories designed to limit consumption of fish may have unforeseen detrimental socio-cultural impacts. These potential consequences need to be considered when assessing the risk and benefits of fish consumption.

Data gaps and research needed on the cultural aspects of fish consumption include:

- A scale to measure these impacts and benefits should be developed which can be directly compared to those used to measure health risk and benefits. Several approaches might be considered, including normalized scales being developed for use with tribal communities

(e.g., Harper, 1999). The affected individual or group should determine the magnitude of the modification.

- More quantitative information needs to be amassed on specific consumption behaviors of population groups for whom fish is important, with the aim of more productively combining socio-cultural data with biological data in developing risk assessments and consequent risk management strategies.
- More research is needed on environmental justice with fish consumption, and on the relationship between fish consumption and group sovereignty, especially in regard to Native American communities.

8.6 Chapter 6

The current version of the framework represents a significant step forward over the way risks and benefits of eating fish have been addressed in the past. However, future work should further explore several important aspects of the framework. A number of conclusions and recommendations for additional work are listed below.

- Incorporate full range of benefits data. The examples of benefits that are presented in the framework are representative based on the available data. However, they do not incorporate the entire quantitative benefits data (see Table 2-1). At a minimum, all the data sets supporting, or contradicting, the existence of a particular health benefit should be further summarized and discussed, and data should be presented for any endpoint having quantitative benefits information. A meta-analysis might be considered for each endpoint supported by more than one data set. This might allow the development of a single dose-response curve for each health endpoint. Such single dose-response benefit curves would make the framework easier to use.
- Severity Schemes. For this framework, the severity approach of EPA and ATSDR for estimating RfDs/RfCs and MRLs (Table 6-2) was used to modify the health risks associated with chemical exposure. This approach has the advantages of simplicity, familiarity and consistency with the use of information from EPA's IRIS, and of ATSDR information found in its toxicological profiles. One shortcoming of this approach is the implied equal spacing between levels. There is no scientific or mathematical justification proposed for a FEL being considered three times as "severe" as a less serious LOAEL. Other caveats were discussed in chapter 6 (see Table 6-3).

In like fashion, a modifier to the magnitude of health benefits accrued from eating fish was used to roughly compare with the risk of different health endpoints. This modifier of health benefits (e.g., coronary heart disease avoided) was ranked as none, minimal, moderate or maximum. This modifier has the advantages of simplicity and consistency with the use of information for health risks. As for health risks, however, the scheme for health benefits is being used in a quantitative fashion in the framework, and this results in several shortcomings which were discussed in Chapter 6 (see Table 6-3).

Other severity schemes should be explored for comparing the health risks and benefits of fish consumption. The results are likely to be more complex, however. Several of these schemes will necessitate additional judgment regarding the appropriate severity level of both the critical effect and benefit. At least one of these schemes (i.e., Ponce et al., 1998) also incorporates the concept of duration of the effect or benefit through the use of QALYs. Every attempt should be made to see if these more complex severity schemes add value when compared to the simpler one, which was used here.

- Explicitly incorporate uncertainty. It is important to recognize that with the exception of noncancer risks (see Figures 4-1 and 4-2), uncertainty in health benefits and risks is not dealt with explicitly by the framework in its current version. Moreover, the uncertainty surrounding the estimates of the different benefits and risks associated with eating fish are unlikely to be the same. For example, the uncertainty surrounding estimated cancer risks based on animal toxicity data is likely much greater than the uncertainty surrounding estimated coronary heart disease benefits based on human data.

An important future refinement of the framework would be explicit consideration and quantification of uncertainty surrounding estimates of potential health risk and benefit, because both have the potential to alter the interpretation of the framework and the resulting FCI.

- Conduct a sensitivity analysis. The current version of the framework uses fixed inputs for most of the variables that determine potential risk, potential benefits and the FCI. Such fixed information helped develop the framework and also allowed for exploration of a number of issues associated with its use. However, many of these fixed parameters can and do vary, and additional work is needed to investigate how the FCI changes when these parameters are changed. Such a sensitivity analysis would greatly improve interpretation of the framework results and perhaps help focus future work on the input variables that have the greatest potential to affect the FCI.
- Evaluation of additional mixtures of chemicals. The framework and case studies used only a few chemicals and concentrations to examine the relationship between potential risks and benefits of eating contaminated fish. While the choice of these chemicals reflected the frequency of residues and number of fish consumption advisories (Table 4-1), other chemicals are also found in fish. While the analysis of a limited number of chemicals is useful for the development of the framework and its application, the choice of concentrations could perhaps better reflect those typically observed in waters of the U.S (the example concentrations presented here were much higher than average). Based upon comments from the Advisory Committee, methylmercury, PCBs and dioxin are the chemicals for which advisories are most commonly needed and typical high concentrations might vary between 0.2 and 1 mg/kg for methylmercury and PCBs, and be around 1 ng/kg for dioxin toxic equivalents.
- Risk curves for non-sensitive groups. For health risks, specific risk curves for non-sensitive members of the population could also be developed. This would avoid matching the health risk for the sensitive individual with the health benefit to the average individual. For

example, with methylmercury the risk curve is based on risk to the infant and fetus, whereas the benefit curve was for the adult. Use of an adult risk curve would have changed the conclusions of the Florida Everglades case study.

8.7 Chapter 7

A strong communication program is needed to best implement use of the framework and approach outlined in this document. This approach can provide individuals and groups (communities, states or tribes) the ability to describe and analyze tradeoffs between benefits and risks. Ultimately, however, no approach will be successful if it cannot be understood and applied by the audiences for which it is intended. Therefore research is needed with at-risk populations (e.g., tribes with potentially heavy fish consumption, women of childbearing age, fish-eating families with children), to identify their information needs. This is an iterative development of communication approaches and content, with communicators and target audiences working in partnership.

A key to the approach proposed in this document is research-based evaluation. Since no approach will be successful if it cannot be understood and applied by the audiences for which it is intended, both formative and summative evaluation research efforts are needed.

- Formative evaluation research would include working with the target audiences to identify their information needs. Ideally, formative evaluation begins with in-depth, qualitative analysis of information needs and the range of potential responses to and concerns about various types of information. Focus groups and other interactive forums often provide the best mechanism for this stage of research. Formative evaluation continues with iterative development of communication approaches and content, with communicators and target audiences working in partnership.
- Summative evaluation, an empirical assessment of the impact of the communication process, is a critical research need to assess the efficacy of the FCI approach. Summative evaluation is often hypothesis-based. For example, possible hypotheses related to use of the FCI include:

H₁: Availability of health benefit/risk comparison information via the FCI will be related to increased confidence of fish consumers that they are making an informed decision about fish consumption;

H₂: Increased information provided to fish consumers through the FCI will lead to improved compliance with health advisory recommendations.

Summative evaluation assesses the extent to which program objectives were achieved. Thus, achievement of the objectives of health advisory programs using the FCI should be evaluated systematically, both before implementing FCI, and after. Collecting baseline data is critical to evaluating the impact of new risk management and communication programs.

8.8 Final Comment

The need to consider the health and nutritional benefits of fish consumption has long been recognized when crafting public policy regarding people eating fish contaminated with low levels of chemicals. Due in part to this well-defined need, the purpose of this research was to develop an understanding and framework by which to evaluate the comparative risks posed by dietary changes as a result of fish consumption advisories. We have been partially successful in this endeavor. This research should lead to a better understanding of the health benefits and health risks of fish consumption, although further work is needed before the framework that we suggest can be generally useful. We anticipate that public health officials and consumers will use this increased understanding to evaluate a broader range of dietary information before making decisions about this important resource.

8.9 References

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