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 exists[1]. 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.

[1]However, 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 way 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) Relative Risk (RR)	
		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).

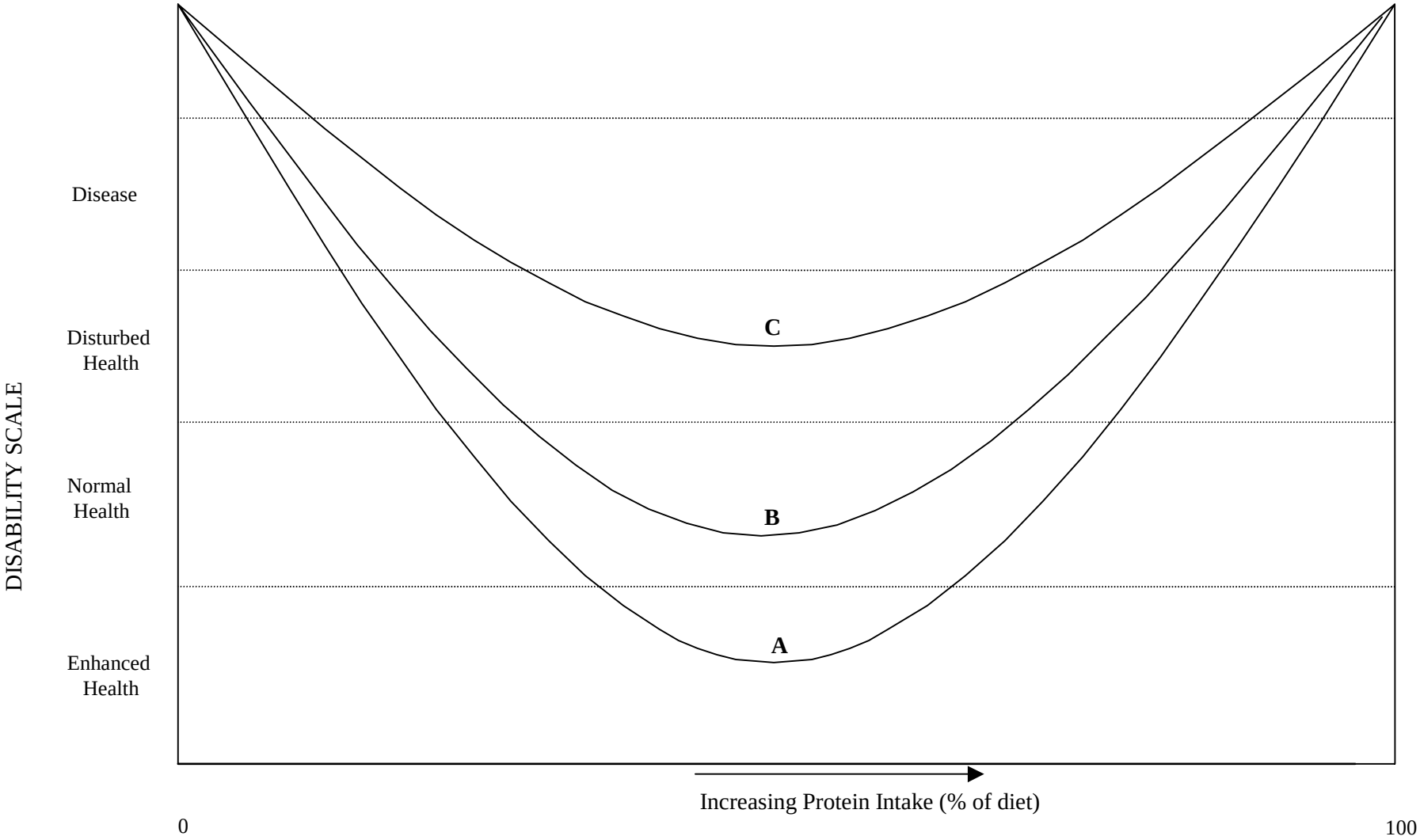


Figure 6-1. Hypothetical curve: No data are presented nor is the scale likely to be correct. Disability scale as a function of amount and quality of protein intake as a percent of diet. Curve A is protein intake that is low in fat & salt, and high in nutrients. Curve B is mixed protein intake (perhaps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

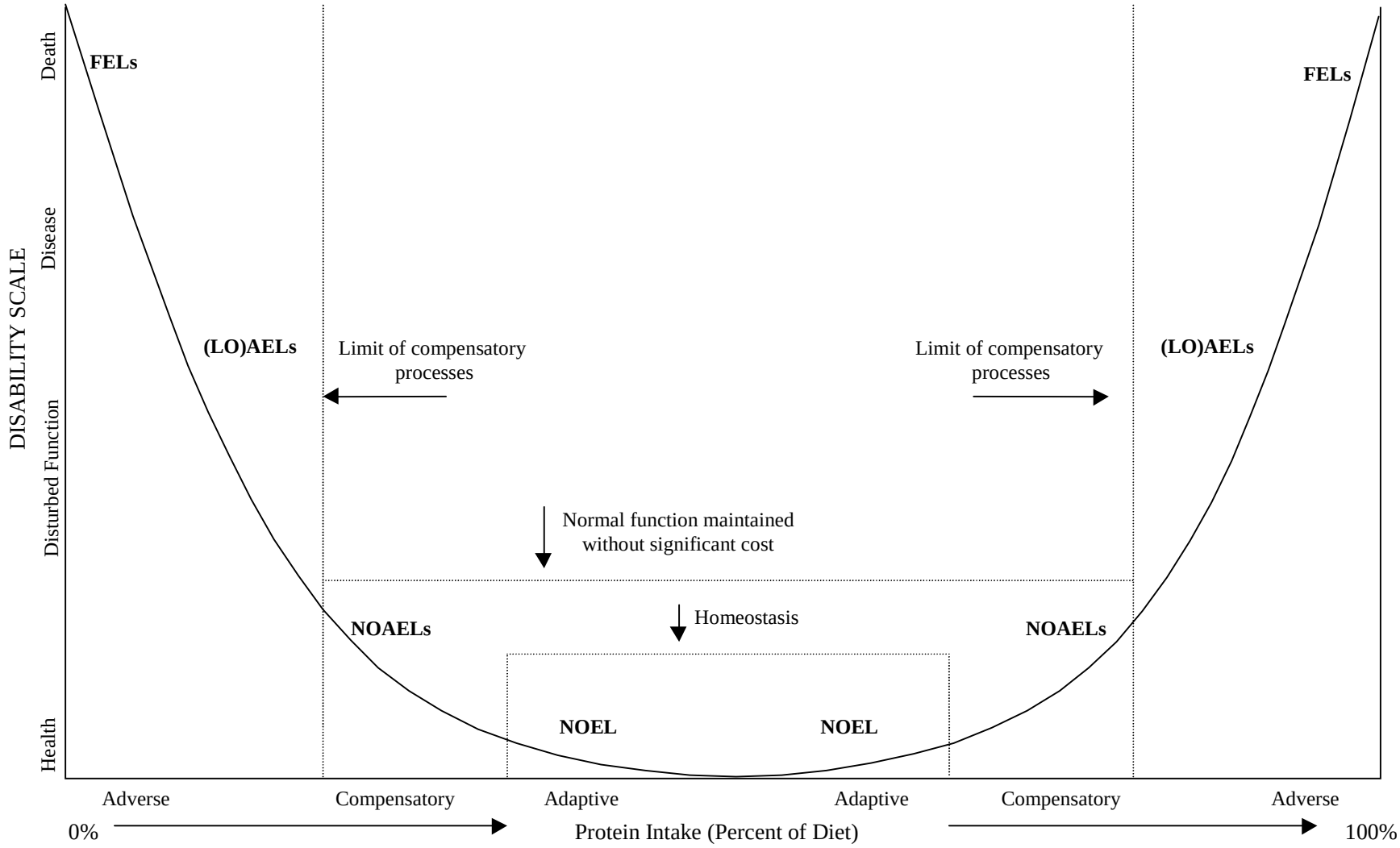


Figure 6-2. Hypothetical curve: No data are presented nor is the scale likely to be correct. Organism disability as a function of target organ impairment. A uniform scale of NOELs, NOAELs, (LO)AELs and FELs is proposed. Figure adapted from DeRosa et al. (1989).

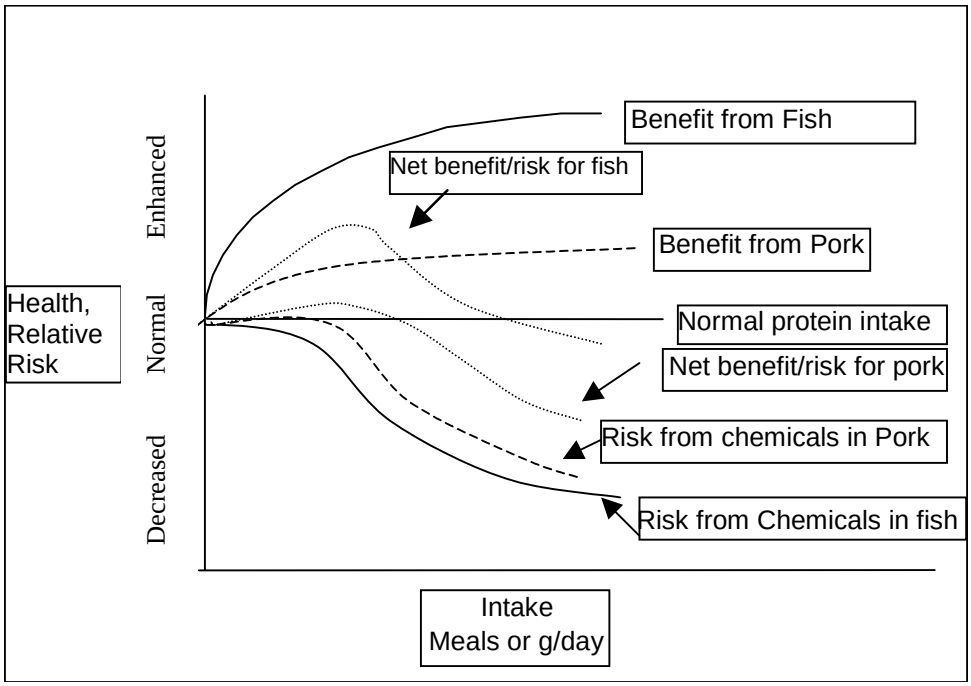


Figure 6-3. Relative risk as a function of intake rate and source of protein. Hypothetical curves: no data are presented nor is the scale likely to be correct.

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

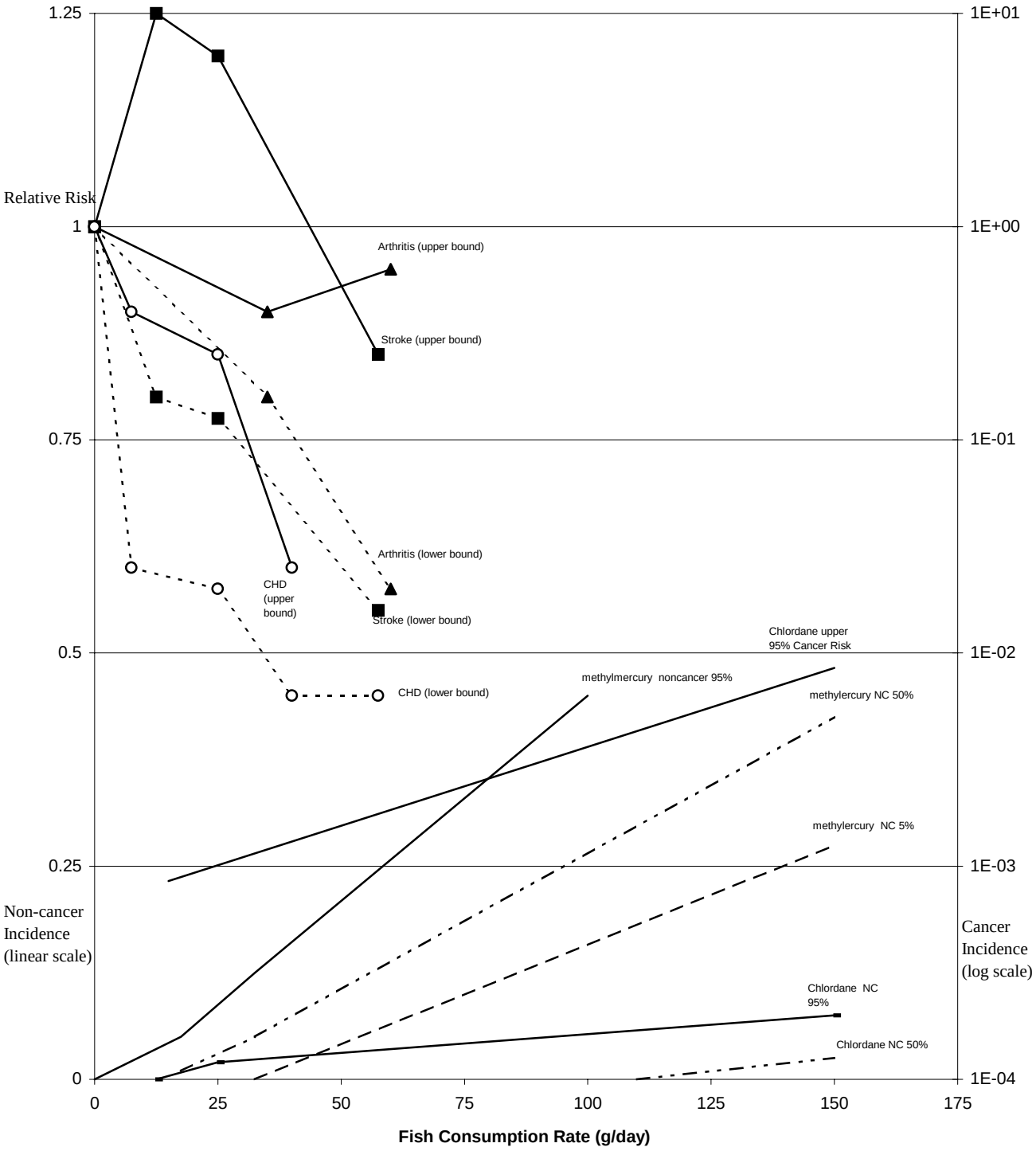


Figure 6-4. Relative risk of benefits and toxicity as a function of different amounts of fish consumed assuming contamination with 2.1 ppm methylmercury and 12 ppm chlordane. Note different scales for non-cancer and cancer toxicity.

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 $1x10^{-3}$ and the increased risk approaches $1x10^{-2}$ 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 ($1x10^{-3}$) 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:

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

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:

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

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

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

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:

$$(R_i \times S_i) \times (-1) = Risk_i$$

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:

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

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:

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

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]

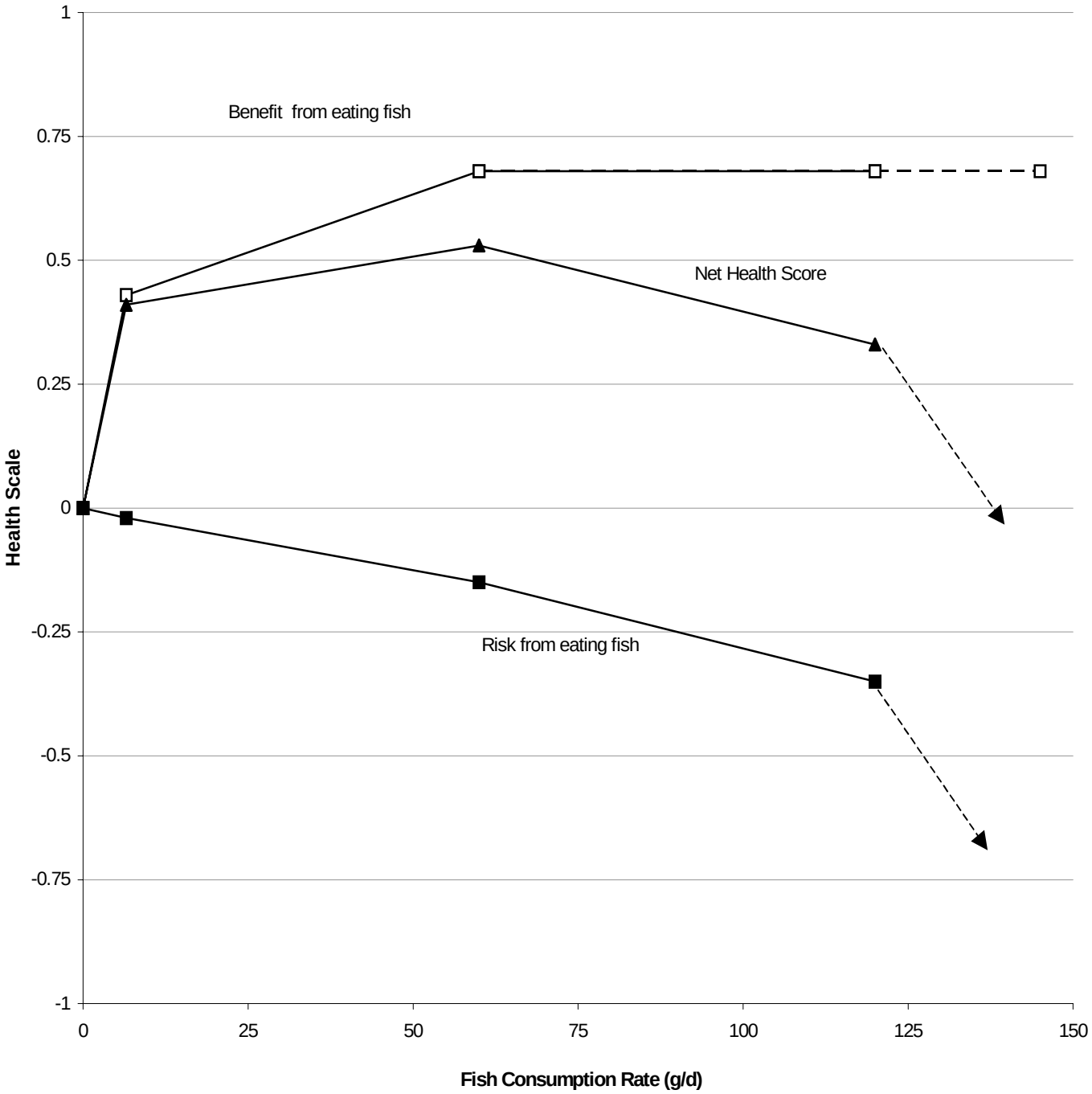
Note that if cultural benefits or personal perception of severity are included in the framework, the FCI is not strictly a health index, but rather represents a combination of health risks and benefits, personal perception, and cultural benefits and risks.

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 the 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 ($1x10^{-3}$) 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):

$$[B_i \times (1-RR_i)] \times S_i = Benefit_i$$

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 x (1-0.6)) x 3 = 0.38;
Stroke benefit:	(0.07 x (1-0.85)) x 3 = 0.03; and,
Arthritis benefit:	(0.13 x (1-0.92)) x 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 x (1-0.45)) x 3 = 0.53;
Stroke benefit:	(0.07 x (1-0.55)) x 3 = 0.09;
Arthritis benefit:	(0.13 x (1-0.57)) x 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 (50^{th} percentile) of the increased incidence of the critical effect is:

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

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

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

$$(R_i \times S_i) \times (-1) = Risk_i$$

At 6.5 grams per day:

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

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

At 60 grams per day:

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

At 120 grams per day:

Chlordane cancer risk:	-(7 x 10^{-3} x 3) = -2 x 10^{-2};
Chlordane non-cancer risk:	-(0.01 x 3) = -0.03;
Methylmercury non-cancer risk:	-(0.3 x 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):

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

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 $1x10^{-6}$ to $1x10^{-4}$) 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} to10^{-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)

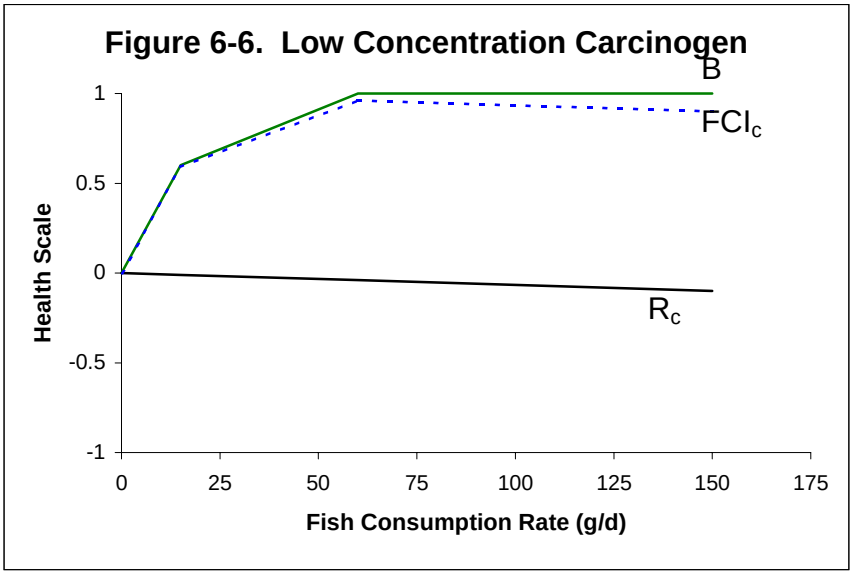


Figure 6-6. Low Concentration Carcinogen
B
FCIc
Rc
Health Scale
1
0.5
0
-0.5
-1
0
25
50
75
100
125
150
175
Fish Consumption Rate (g/d)

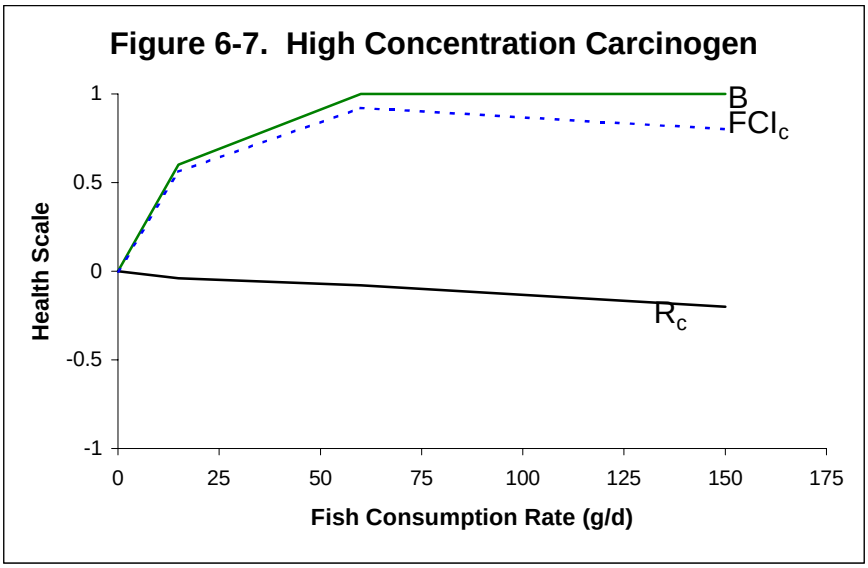


Figure 6-7. High Concentration Carcinogen
B
FCIc
Rc
Health Scale
1
0.5
0
-0.5
-1
0
25
50
75
100
125
150
175
Fish Consumption Rate (g/d)

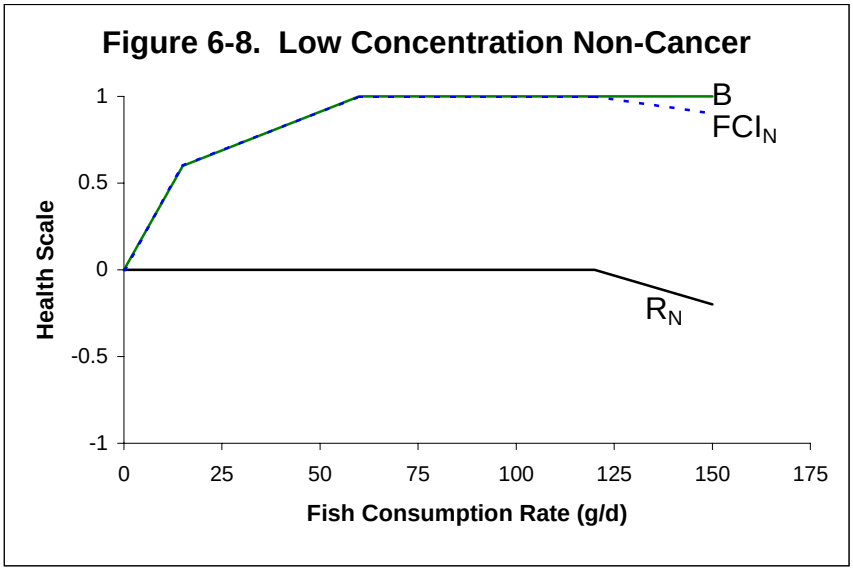


Figure 6-8. Low Concentration Non-Cancer
B
FCI_N
R_N
Health Scale
1
0.5
0
-0.5
-1
0
25
50
75
100
125
150
175
Fish Consumption Rate (g/d)

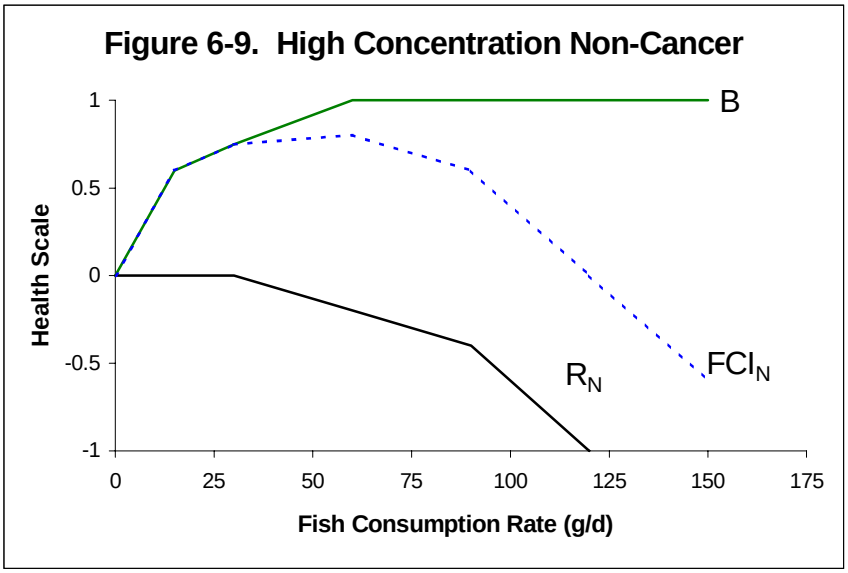


Figure 6-9. High Concentration Non-Cancer
B
FCI_N
R_N
Health Scale
1
0.5
0
-0.5
-1
0
25
50
75
100
125
150
175
Fish Consumption Rate (g/d)

Figure 6-10. Low Concentration Cancer & Non-Cancer

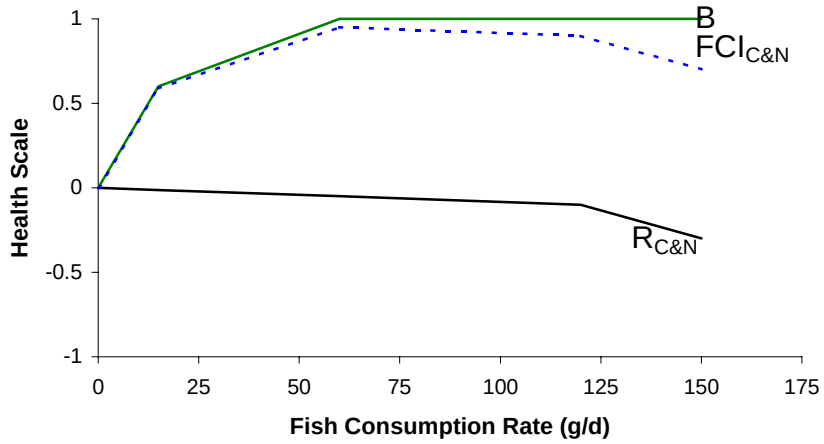
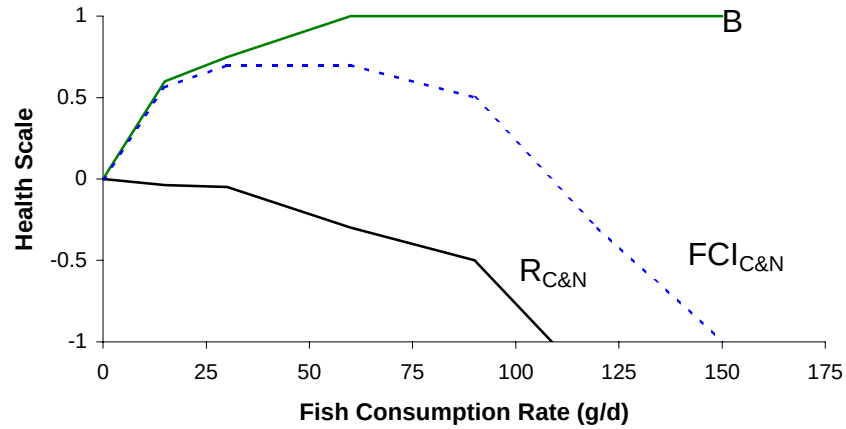


Figure 6-11. High Concentration Cancer & Non-Cancer



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 show 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 shows 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

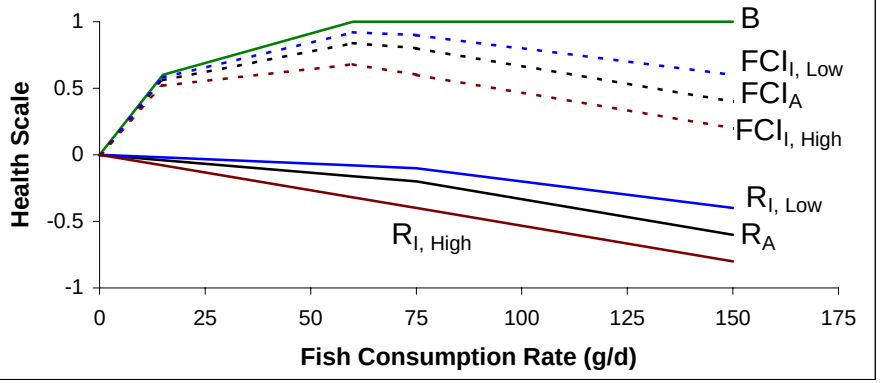


Figure 6-13. High Concentration Non-Bioaccumulative

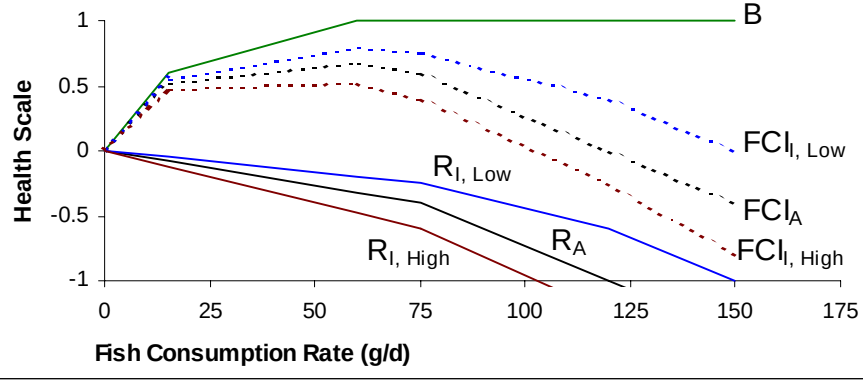


Figure 6-14. Low Concentration Bioaccumulative

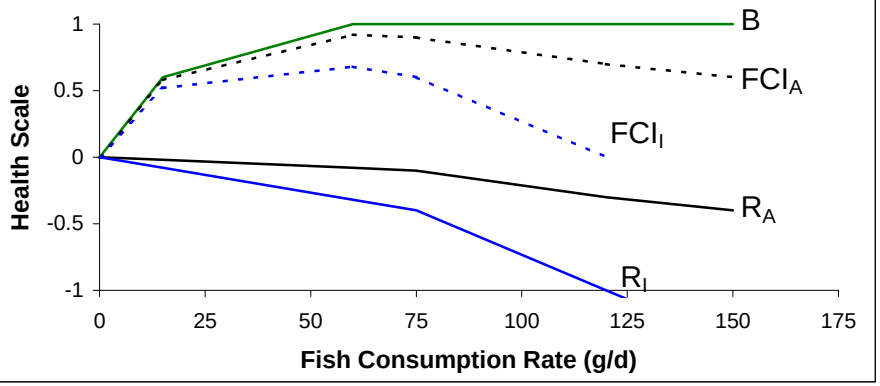


Figure 6-15. High Concentration Bioaccumulative

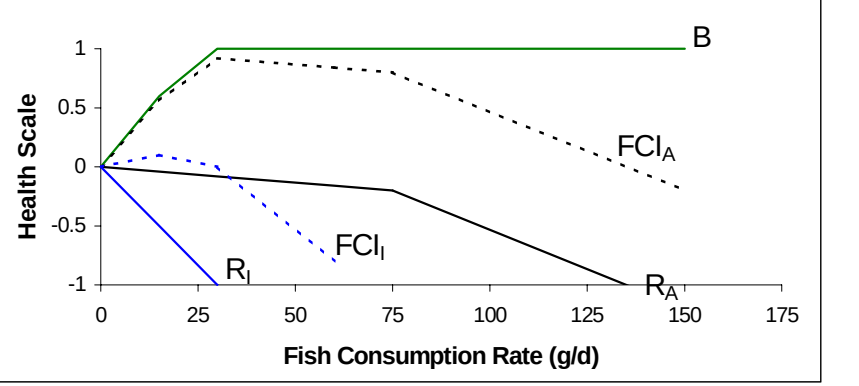


Figure 6-16. Change in FCI as more chemicals are evaluated for health risk in fish Figure 6-16.

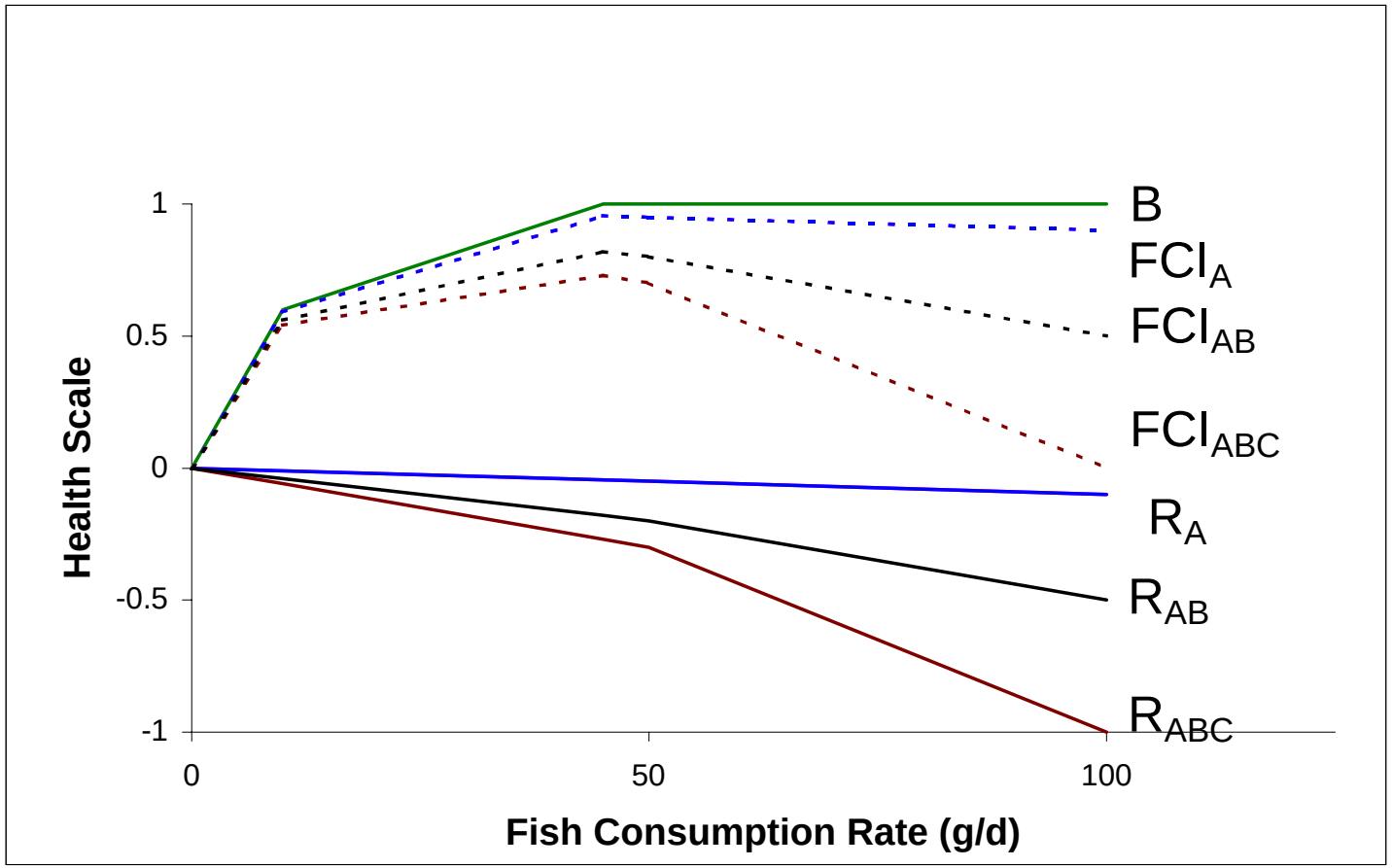
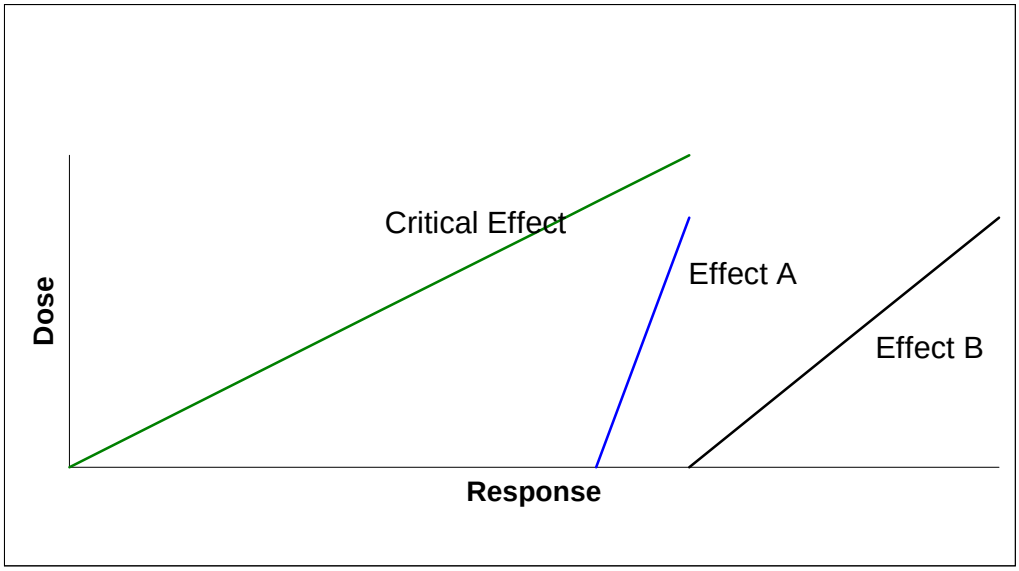


Figure 6-17. Non-critical effects begin to manifest themselves at doses much greater than the critical effect.



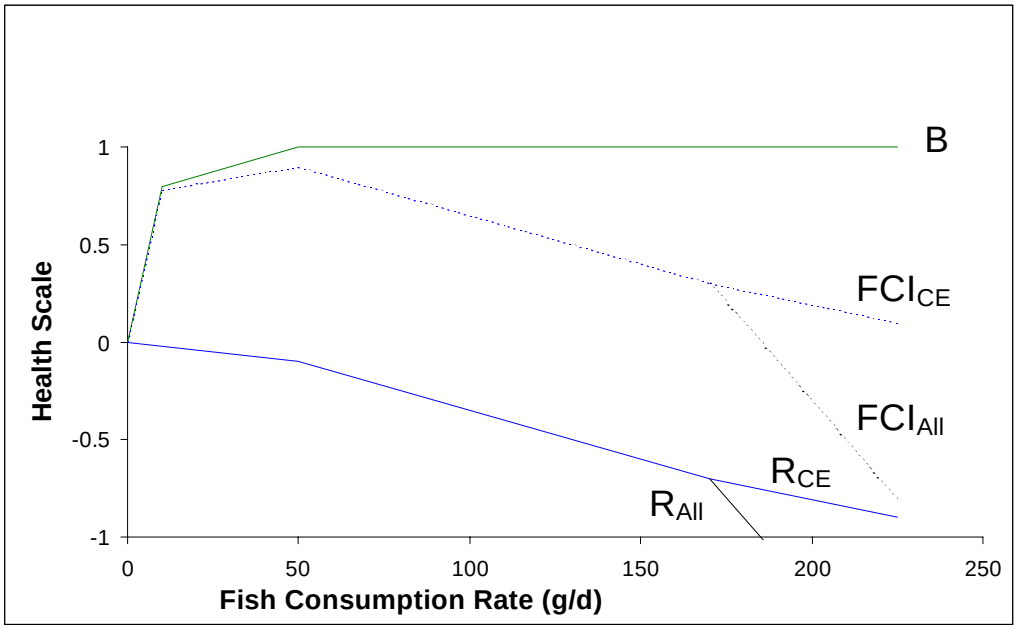
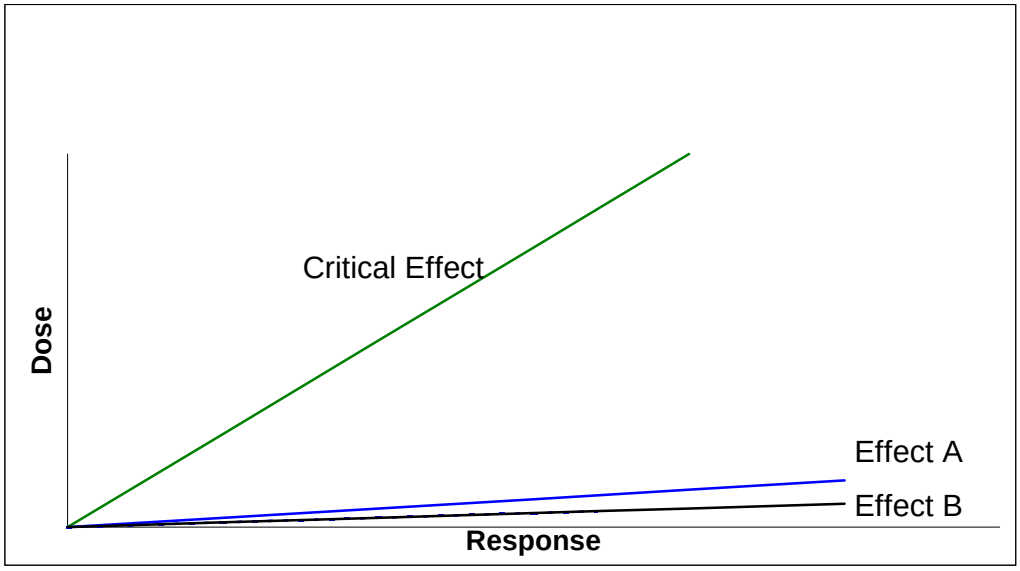


Figure 6-18. Non-critical effects manifested at doses similar to critical effect but dose response curves are shallower.



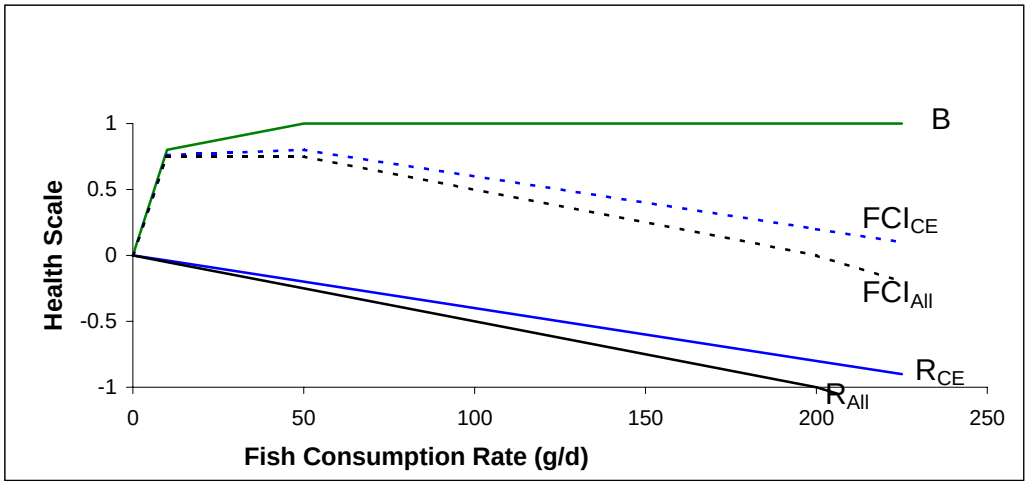
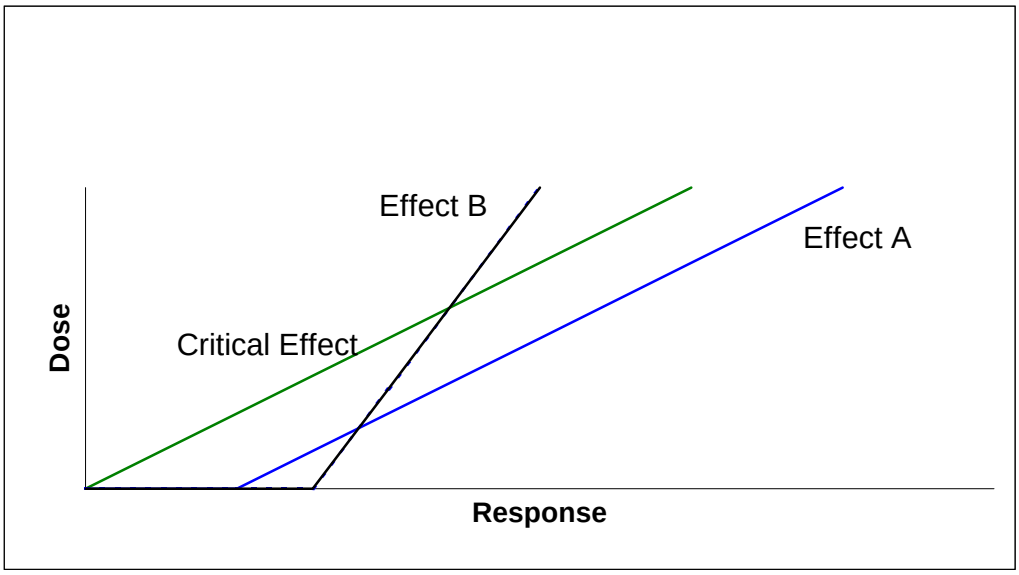
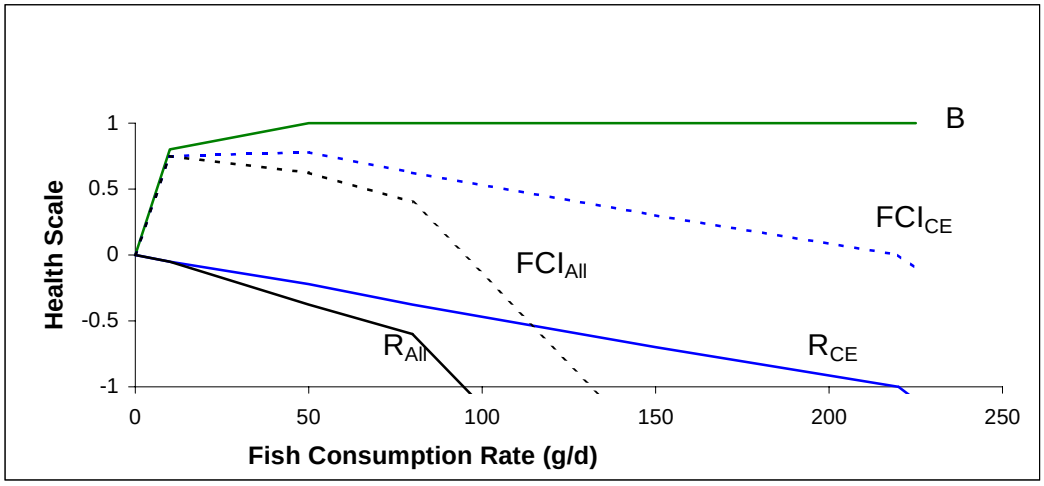


Figure 6-19. Non-critical effects begin at doses similar to the critical effect and their dose response curves are ~ similar.





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.

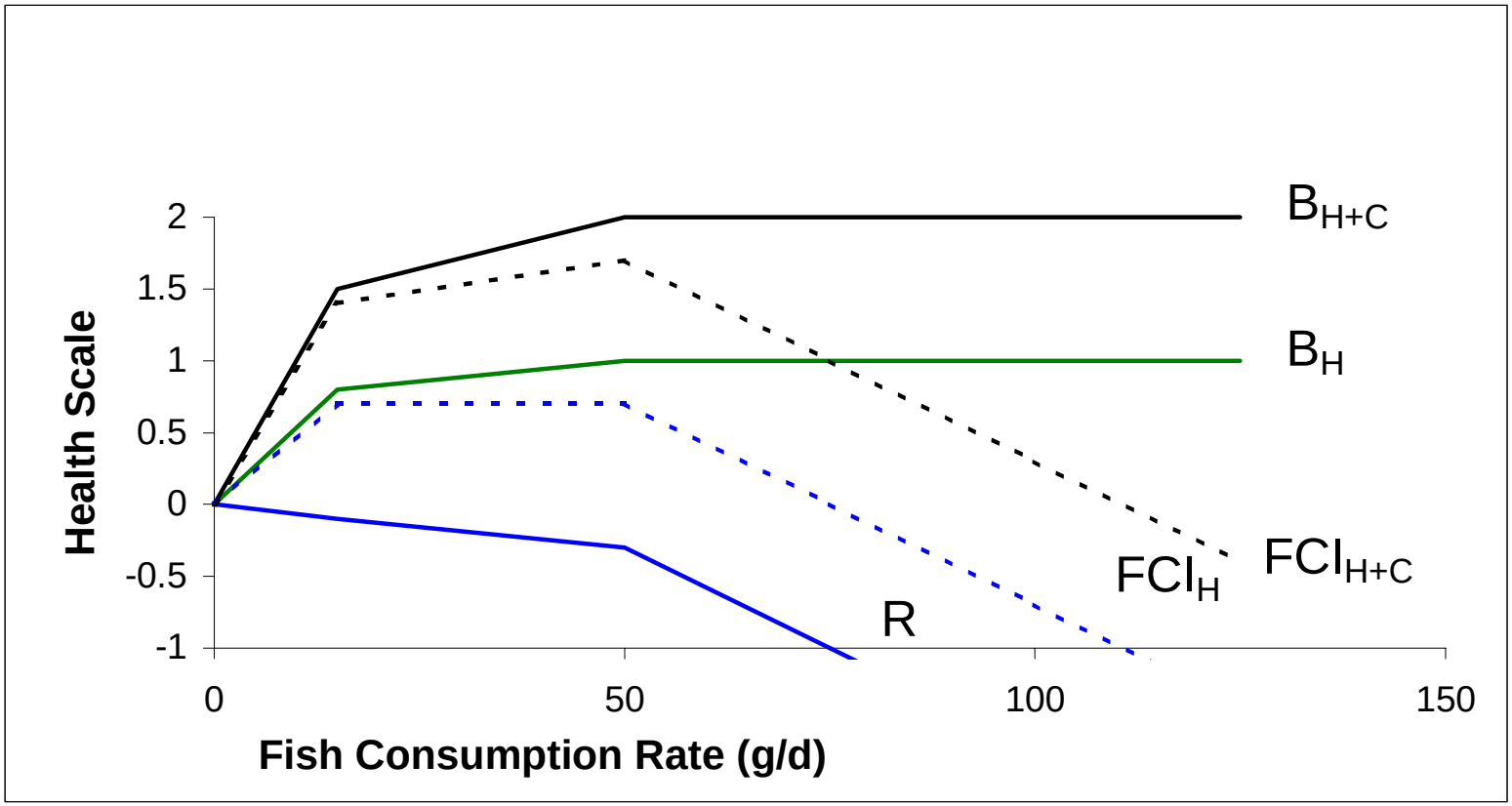
6.5.5 Cultural Benefits

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:

$$(R_i \times S_i) \times (-1) \times PPS = Risk_{iPPS}$$

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 1E-4 for methylmercury (see Chapter 4 for details). The estimated methylmercury dose extrapolated from the adjusted mean mercury hair concentration is 2E-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 (1E-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).

		Response		
Multiple of RfD (1E-4 mg/kg-day)	Dose (mg/kg-day)	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 1E-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.

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

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).

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 mg Hg/kg fish x 6.5 g/day consumed ÷ 60 kg body weight x 1 kg/1000 mg = 3E-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 (50^{th} 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 (95^{th} 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 (50^{th} 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 ED_{50} 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.

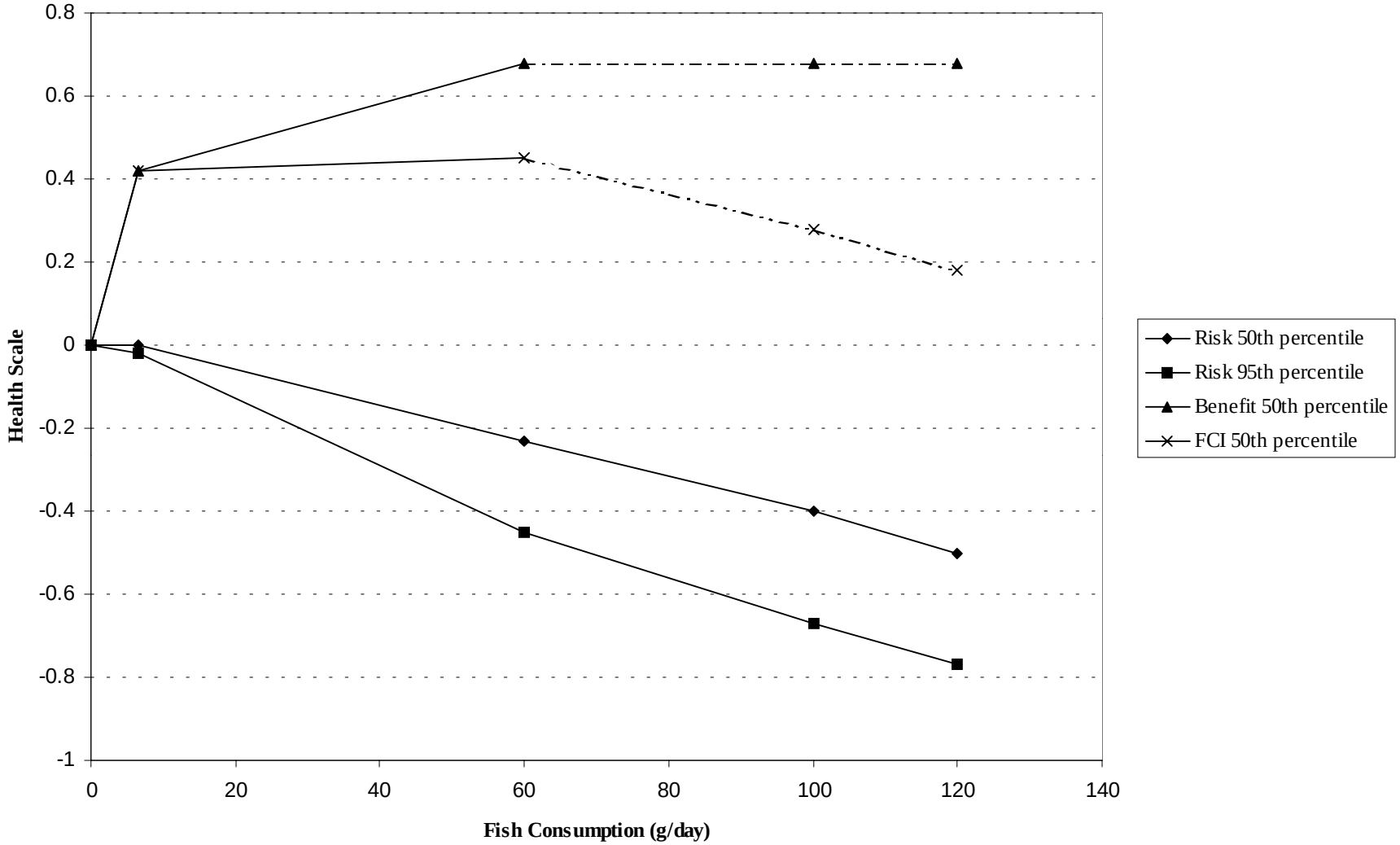
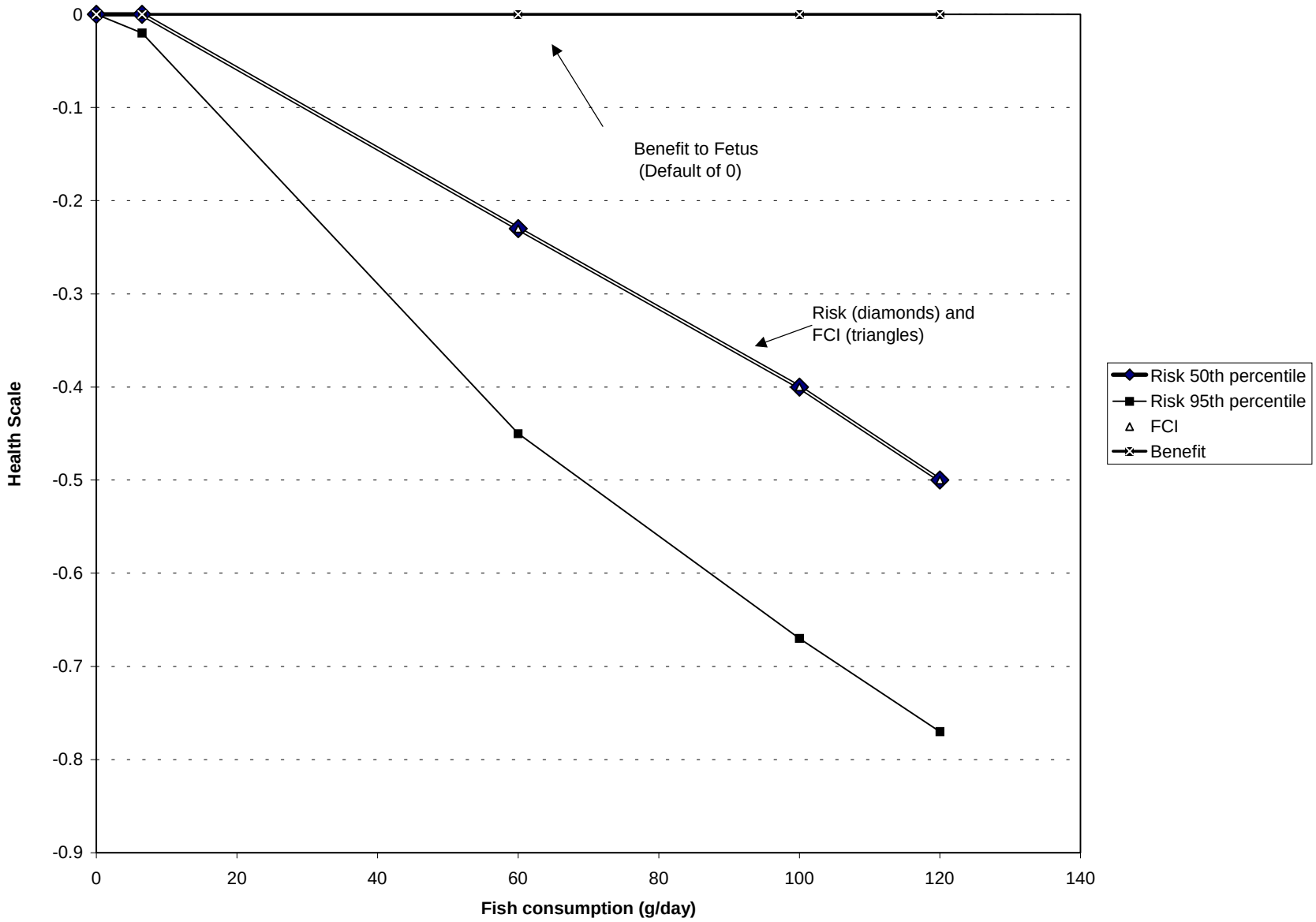


Figure 6.21b Estimated Risk to the Fetus As a Function of Everglades Fish Consumption.



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 6E-2 mg/day or 8E-2 mg/day (i.e., 0.028 x 2 or 3 = 6E-2 or 8E-2). Assuming a body weight of 60 kg this corresponds to a dose of 1E-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 triglyercides. 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 $\pm$ 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 $\pm$ 89.9) of fish from inland locations, and 3 to 306 meals (mean $\pm$ SD = 111 $\pm$ 80.4) of purchased or processed fish. Their total fish consumption over 12 months was 83 to 751 meals (mean $\pm$ SD = 322 $\pm$ 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 (95^{th} 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.

Table 6-8. 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	Mercury	Arsenic
Fish tissue Concentration*	45.08	834.58	64	13	200	23	1.8	2.4	6.7	110	27	0.043	1	0.341	0.06
6.5 g/day	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	4E-8	7E-9
38 g/day	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	2E-7	3E-8
60 g/day	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	3E-7	6E-8
120 g/day	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	7E-7	1E-7
RfD	NA	**2E-5†**	5E-2	NA	NA	5E-4	3E-5	5E-5	1E-5	2E-4	NA	5E-4	NA	1E-4	3E-4
Organ	NA	**Immune**	Kidney	NA	Liver	Liver	Liver	Liver	Liver	Liver	NA	Kidney	CNS	CNS	Skin
Exceedance at 38 g fish/day	NA	**25 fold**	No	NA	NA	No	No	No	No	No	NA	No	NA	No	No

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

* All 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 the PCB mixtures found in fish. The RfD for Aroclor 1254 is used as a surrogate for the mixture found in fish.

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.

Consumption	Total PCB	Biphenyl	DDT	Aldrin	Dieldrin	Heptachlor epoxide	Mirex	Cadmium	Mercury	Arsenic	**Total HI**	**Liver HI**	CNS HI	**Immune HI**	Kidney 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**	1E-4
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**	9E-4
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**	1E-3
120	5E+01	2E-3	8E-2	1E-1	1E-1	1	1	2E-4	7E-3	4E-4	**50**	**2**	6E-3	**50**	2E-3
Critical Effect/Organ	Immune	Kidney	Liver	Liver	Liver	Liver	Liver	Kidney	CNS	Skin	Total	Liver	CNS	Immune	Kidney

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_{aldrin}	$R_{dieldrin}$	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 (50^{th} 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 (50^{th} 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 that one chemical.

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

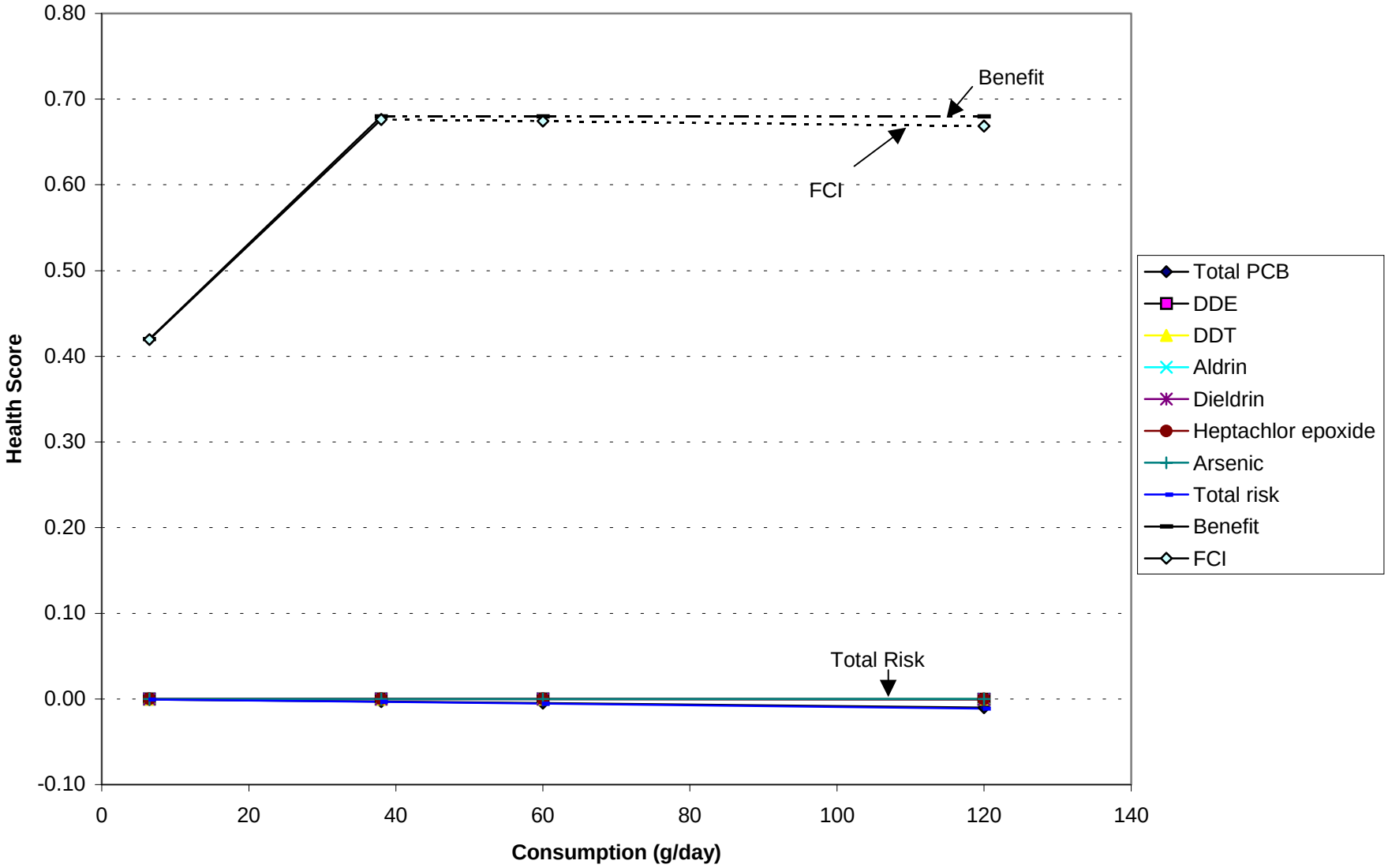


Figure 6-23. Total Cancer Risk and Individual Components for Salmon Taken from the Credit River.

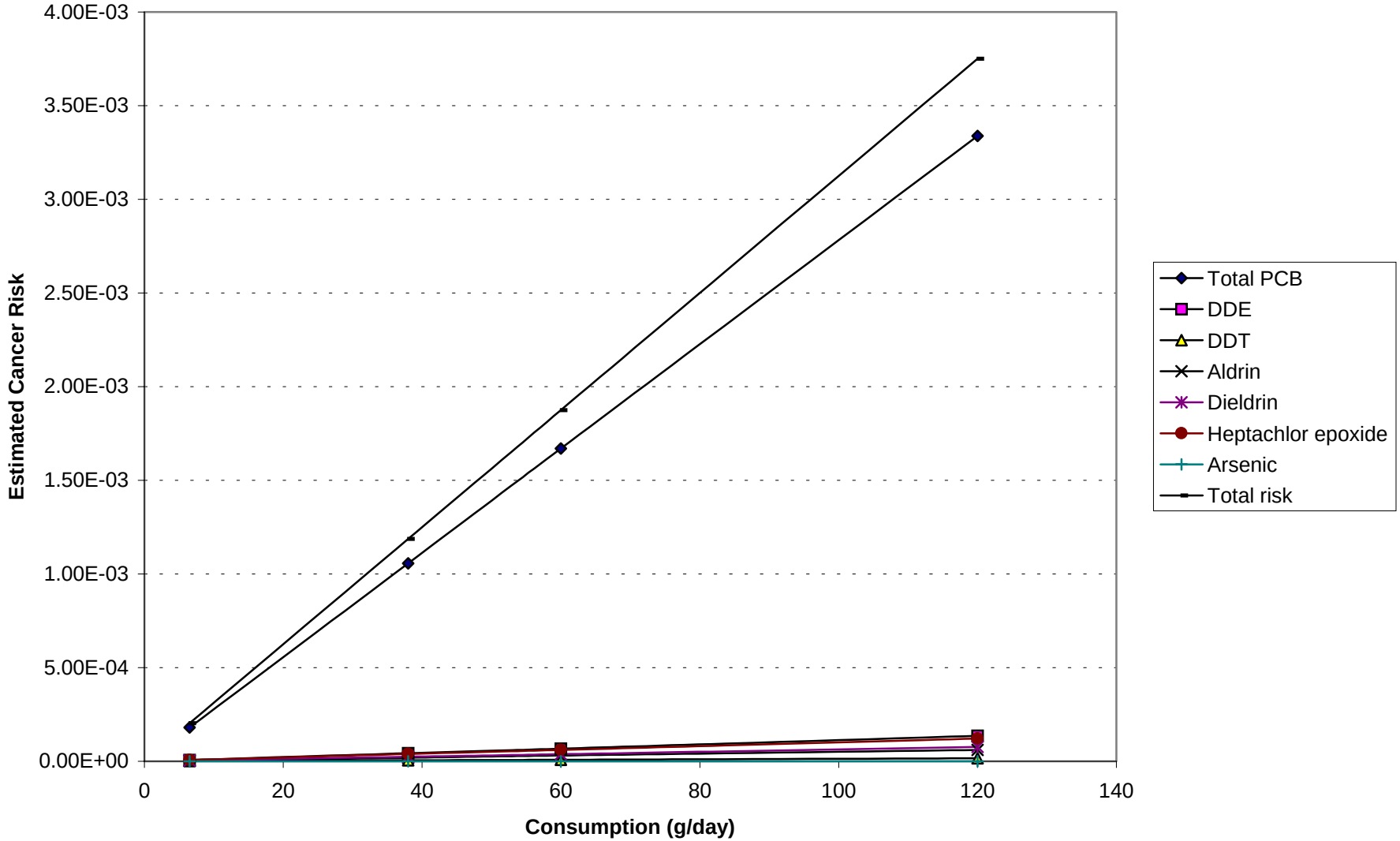


Figure 6-24 Hypothetical Risk, Benefit, and FCI Assuming that the Shape of the Noncancer Dose-Response Curve for PCBs is the Same as that for Methylmercury for Salmon from the Credit River.

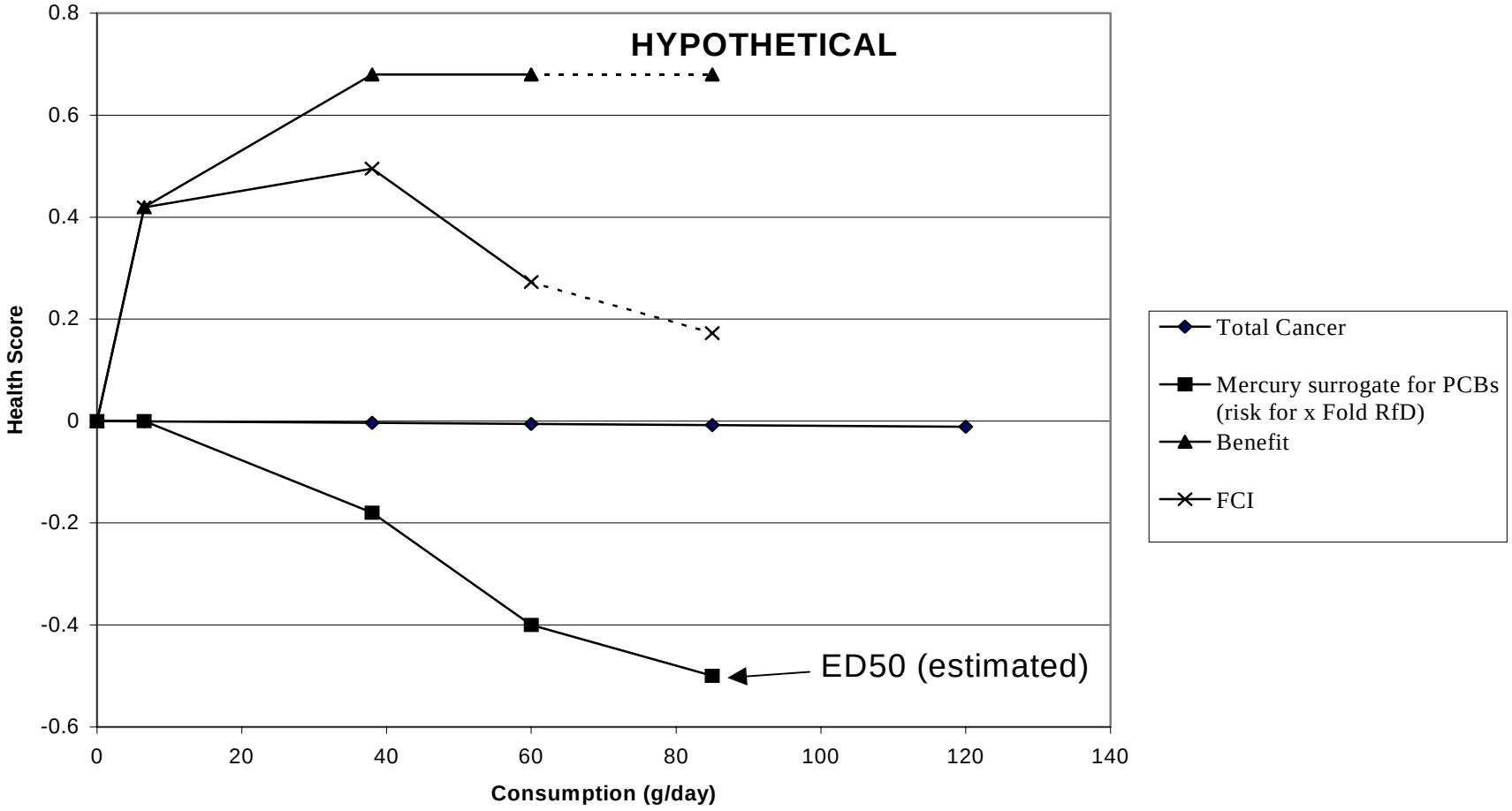
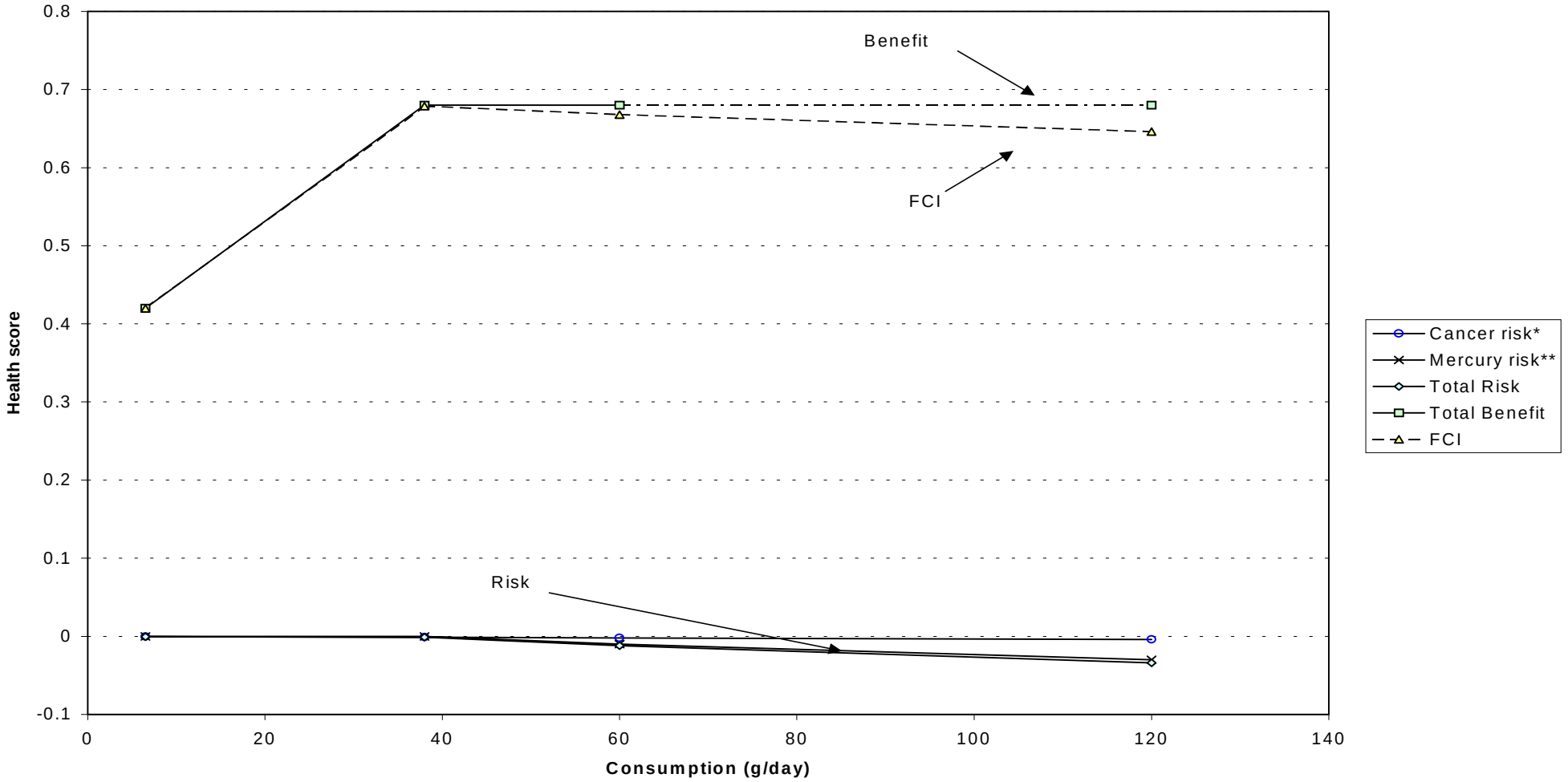
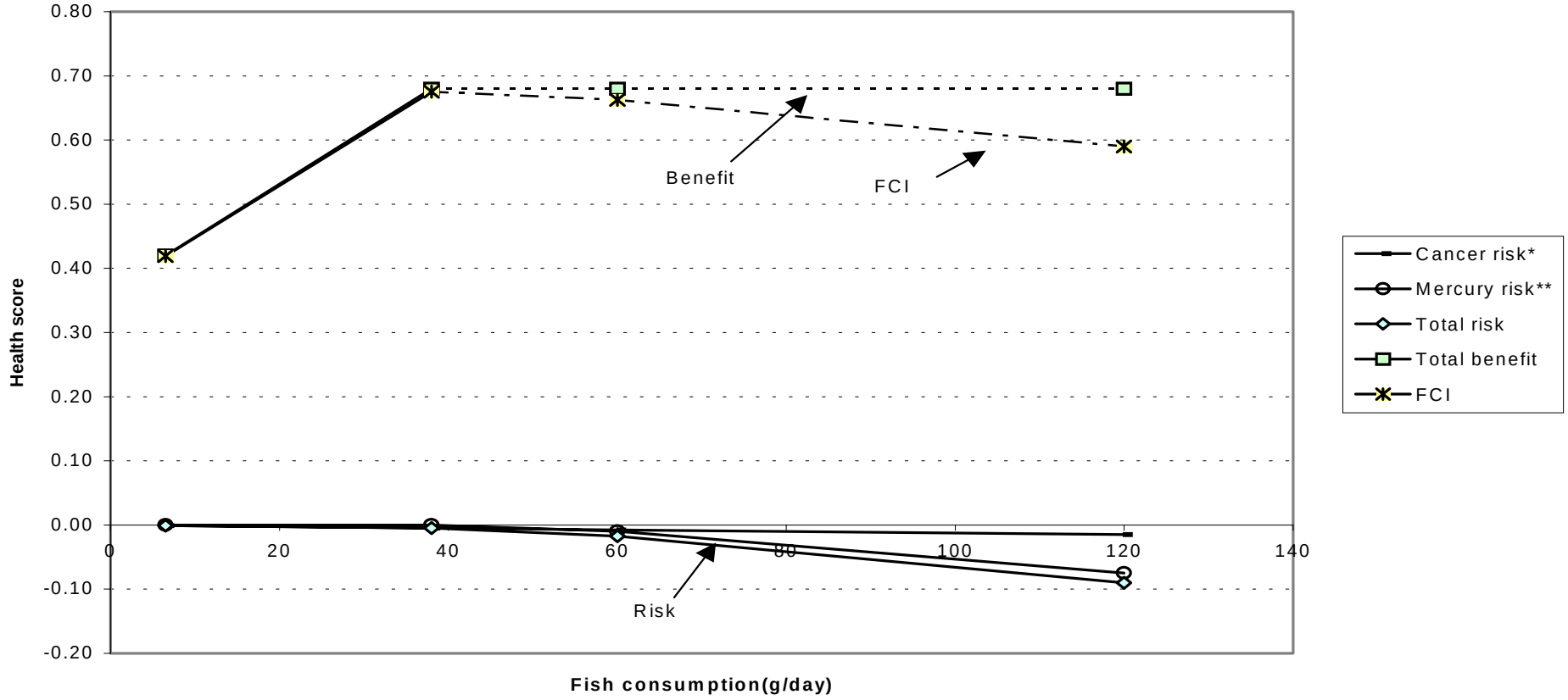


Figure 6-25. Risk, Benefit, and FCI as a Function of Niagara River Rockbass Consumption.



* 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

Aberg, B., L. Ekman, R. Falk, *et al*. 1969. Metabolism of methyl mercury (203Hg) compounds in man. Arch. Environ. Health. 19: 478-484. (As cited in U.S. EPA, 1999)

AFS (American Fisheries Society). 1997. Proceedings of the 1997 American Fisheries Society forum on contaminants in fish. December 8-10. EVS consultants. Seattle, Washington.

Anderson, P.A. and J.B. Wiener. 1995. Eating Fish. In: Risk vs. Risk: Tradeoffs In: Protecting Health and the Environment. J.D. Graham and J.B. Wiener, eds. Harvard University Press, Cambridge, Massachusetts. pp. 104-124.

Buck, G.M., L.E. Sever, and P. Mendola. 1997. Consumption of contaminated sport fish from Lake Ontario and time-to-pregnancy. Am. J. Epid. 146: 949-954.

Burger, J., J. Sanchez and M. Gochfeld. 1998. Fishing, consumption, and risk perception in fisherfolk along an east coast estuary. Environ. Res. 77A: 25-35.

Choi, S.C., R. Bartha. 1994. Environmental factors affecting mercury methylation in estuarine sediments. Bull. Environ. Contam. Toxicol. 53(6): 805-12

Cox, C., T.W. Clarkson, D.O. Marsh, *et al*. 1989. Dose-response analysis of infants prenatally exposed to methylmercury: An application of a single compartment model to single-strand hair analysis. Environ. Res. 49: 318-332. (As cited in U.S. EPA, 1999)

Davidson, P.W., G.J. Myers, C. Cox, *et al*. 1998. Effects of renatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: Outcomes at 66 months of age in the Seychelles Child Development Study. J.A.M.A. 280(8): 701-707.

Daviglus, M.L., J. Stamler, A.J. Orencia, *et al*. 1997. Fish consumption and the 30-year risk of fatal myocardial infarction. N. Engl. J. Med. 336(15): 1046-1053.

DeRosa, C.T., J.F. Stara, and P.R. Durkin. 1985. Ranking chemicals based upon chronic toxicity data. Toxicol. Ind. Health. 1(4): 177-92.

DeRosa, C.T., M.L. Dourson, and R. Osborne. 1989. Risk assessment initiatives for noncancer endpoints: Implications for risk characterization of chemical mixtures. Toxicol. Ind Health. 5(5): 805-824.

Dourson, M.L., R.C. Hertzberg, R. Hartung, *et al*. 1985. Novel approaches for the estimation of acceptable daily intake. Toxicol. Ind. Health. 1(4): 23-41.

Dewailly, E., P. Ayotte, C. Laliberte, *et al*. 1996. Polychlorinated biphenyl (PCB) and dichlorodiphenyl dichloroethylene (DDE) concentrations in the breast milk of women in Quebec. Am. J. Pub. Health. 86: 1241-1246.

Dewailly, E., J-P Weber, S. Gingras, *et al*. 1991. Coplanar PCBs in human milk in the province of Quebec, Canada: are they more toxic than dioxin for breast fed infants? Bull Environ Contam Toxicol. 47: 491-498.

Durkin, P. 1998. Personal communication with Michael Dourson. December.

Feely, M.M., and S.A. Jordan. 1998. Dietary and tissue residue analysis and contaminant intake estimations in rats consuming diets composed of Great Lakes salmon: a multigeneration study. Reg. Toxicol. Pharmacol. 27: S8-S17.

Fleming, L.E., S. Watkins, R. Kaderman, *et al*. 1995. Mercury exposure in humans through food consumption from the everglades of Florida. Water Air Soil Pollut. 80: 41-48.

Gillum, R.F. 1996. Fish consumption and stroke incidence. Stroke. 27(7): 1254

Grandjean, P., P. Weihe, R.F. White, *et al*. 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol. Teratol. 19: 417-428.

Hartung, R. and P.R. Durkin. 1986. Ranking the severity of toxic effects: potential applications to risk assessment. Comments on Toxicology. 1(1): 49-63.

Hutchison, R. and C.E. Kraft. 1994. Hmong fishing activity and fish consumption. J. Great Lakes Res. 20: 471-478.

Ip, H.N.H. 1990. Chlorinated pesticides in foodstuffs in Hong Kong. Arch. Environ. Contam. Toxicol. 19: 291-296.

Jacobson, J.L. and S.W. Jacobson. 1996. Intellectual impairment in children exposed to Polychlorinated biphenyls *in utero*. N. Engl. J. Med. 335: 783-789.

Jarabek, A.M. 1994. Inhalation RfC methodology: dosimetric adjustments and dose-response estimation of noncancer toxicity in the upper respiratory tract. Inhal. Toxicol. 6(suppl): 301-325.

Kannan, K., S. Tanabe, H.T. Quynh, *et al*. 1992. Residue pattern and dietary intake of persistent organochlorine compounds in foodstuffs from Vietnam. Arch. Environ. Contam. Toxicol. 22: 367-374.

Krabbenhoft, D.P. 1996. Mercury studies in the Florida Everglades. U.S. Department of the Interior, U.S. Geologic Survey. Fact Sheet FS-166-96.

Kromhout, D., E.B. Bosschieter and C.L. Coulander. 1985. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N. Engl. J. Med. 312(19): 1205-1209.

Marsh, D.O., T.W. Clarkson, C. Cox, *et al*. 1987. Fetal methylmercury poisoning: relationship between concentration in single strands of maternal hair and child effects. Arch. Neurol. 44: 1017-1022.

Mendola, P., G.M. Buck, L.E. Sever, *et al*. 1997. Consumption of PCB-contaminated freshwater fish and shortened menstrual cycle length. Am. J. Epid. 146: 955-960.

Meek, M.E., R. Newhook, R.G. Liteplo, *et al*. 1994. Approach to assessment of risk to human health for priority substances under the Canadian Environmental Protection Act. Environmental Carcinogenesis and Ecotoxicology Reviews. C12(2): 105-134.

Mes, J. and D. Weber. 1989. Non-orthochlorine substituted coplanar polychlorinated biphenyl congeners in Canadian adipose tissue, breast milk, and fatty foods. Chemosphere. 19 :1357-1365.

Miettinen, J.K., T. Rahola, T. Hattula, *et al*. 1971. Elimination of 203-Hg methylmercury in man. Ann. Clin. Res. 3: 116-122. (As cited in U.S. EPA, 1998)

Minnesota Department of Health. 1998. Fish Consumption Advisory. Minnesota.

N.Y. DEC (New York State Department of Environmental Conservation). 1994. Memorandum concerning chemical contaminants in fish from the Niagara River from Lawrence C. Skinner, Section Head, Environmental Monitoring Section, New York State Department of Environmental Conservation, Bureau of Habitat..

Newsome, WH, D.J. Davies, and W.F. Sun. 1998. Residues of polychlorinated biphenyls (PCB) in fatty foods of the Canadian Diet. Food Additives and Contaminants. 15: 19-29.

Phelps, R.W., T.W. Clarkson, T.G. Kershaw, *et al*. 1980. Interrelationships of blood and hair mercury concentrations in a North American population exposed to methylmercury. Arch. Environ. Health. 35: 161-168. (As cited in U.S. EPA, 1999)

Pohl, H. R. and H. G. Abadin. 1995. Utilizing uncertainty factors in minimal risk levels derivation. Reg. Toxicol. Pharmacol. 22: 180-188.

Ponce, R.A., S.M. Bartell, D. LaFlamme, *et al*. 1998. Quantitative analysis of risks and benefits for public health decisions applied to fish consumption. The Toxicologist. 42(1-S): 45.

Price, P., R. Keenan, J. Swartout, *et al*. 1997. An approach for modeling noncancer dose responses with an emphasis on uncertainty. Risk Anal. 17: 427-437.

Science Subgroup. 1997. Ecologic and precursor success criteria for South Florida ecosystem restoration: A Report to the Working Group of the South Florida Ecosystem Restoration Task Force. Online: http://everglades.fiu.edu/TASKFORCE/PRECURSOR/toc.html

Shapiro, Jean A., *et al*. 1996. Diet and rheumatoid arthritis in women: A possible protective effect of fish consumption. Epidemiology. 7(3): 256-263.

Sherlock, J.C., D.G. Lindsay, J. Hislop, *et al*. 1982. Duplication diet study on mercury intake by fish consumers in the United Kingdom. Arch. Environ. Health. 37(5): 271-278. (As cited in U.S. EPA, 1999)

Siscovick, D.S., *et al*. 1995. Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and the risk of primary cardiac arrest. J.A.M.A. 274 (17): 1363-1367.

Suzuki, T., T. Hongo, J. Yoshinaga *et al*. 1993. The hair-organ relationship in mercury concentration in contemporary Japanese. Arch. Environ. Health. 48: 221-229. (As cited in U.S. EPA, 1999)

Tsubaki, T.K. and K. Irukayama. 1977. Minamata Disease: Methylmercury Poisoning in Minamata and Niigata, Japan. Elsevier Science Publishers, New York. p. 143-253. (As cited in U.S. EPA, 1999)

U.S. EPA. 1988. Technical support document on risk assessment of chemical mixtures. Office of Research and Development. EPA/600/8-90/064.

U.S. EPA. 1989. Risk Assessment Guidance for Superfund. Volume I: Human Health evaluation Manual (Part A). Interim Final, December 1989. EPA/540/1-89/002.

U.S. EPA. 1992. National Study of Chemical Residues in Fish. Office of Science and Technology. EPA 823-R-92-008b.

U.S. EPA. 1995. Use of the benchmark dose approach in health risk assessment. EPA/630/R-94/007

U.S. EPA. 1996. Proposed Guidelines for Carcinogen Risk Assessment. Office of Research and Development. Washington, DC. EPA/600/P-92/003C

U.S. EPA. 1998. Comparative Risk Framework: methodology and case study. SAB review draft. National Center for Environmental Assessment. Cincinnati, OH. NCEA-C-0135

U.S. EPA. 1999. Integrated Risk Information System (IRIS). Substance file for methyl mercury. Online: http://www.epa.gov/ngispgm3/iris/subst/0073.htm.

Weihe, P., P. Grandjean, F. Debes, *et al*. 1996. Health implications for Faroe Islanders of heavy metals and PCBs from pilot whales. Sci Total Environ. 186: 1-179.

WHO (World Health Organization). 1990. Environmental Health Criteria 101: Methylmercury. Geneva. (As cited in U.S. EPA, 1998)