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# Good Fish/Bad Fish: A Composite Benefit–Risk by Dose Curve

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***Abstract***

*Balancing risks and benefits of fish consumption is now a high visibility public health topic. Many studies identify health benefits of eating fish, both for prenatal development and adult cardiovascular conditions, partly attributed to omega-3 (n-3) polyunsaturated fatty acids or PUFAs). Many reports raise concerns about methylmercury and polychlorinated biphenyl effects on the developing fetal brain (although adults, too, can manifest methylmercury effects). Most reports and advisories focus on recreational or subsistence fish, but the vast majority of people obtain most or all of their fish from commercial sources. Our analysis of the nine most common fish in New Jersey markets, yielded a weighted average methylmercury concentration of 0.23 ug/g (ppm wet weight). There are great disparities in the amount and distribution of both PUFAs and contaminants) in different fish species. Recognizing that both benefits and harm must be related to dose, we propose a compound dose–response curve, currently based on limited data, to identify a zone of benefit, above the benefit threshold and below the harm threshold. The duration of pregnancy and birth weight improve at a benefit threshold of about 8–15 g/day maternal fish intake. Meta-analyses reveal adult cardiovascular benefits around 7.5–22.5 g/day bracket (assuming an 8 ounce/227 g typical meal), yielding a midpoint also at 15 g/day, but this is an artifact of the intake stratification. Benefit asymptotes are harder to extract, but are above 45 g/day, and in some studies exceed 100 g/day. Using the EPA Reference Dose of 0.1 ug/kg day as a methylmercury threshold, The fish intake threshold for harm converts to 27 g/day (for a selection of common commercial fish averaging 0.23 ppm MeHg) to 65 g/day for someone choosing fish low in MeHg (0.1 ppm). However, these are worst case thresholds since the RfD includes uncertainty factors. Some people eat much more than 65 g/day. The shape of the dose–benefit and dose–harm curves require better data for estimating thresholds and asymptotes, which will impact the composite curve. We propose this approach clarifies the kinds of data needed to improve risk communication on "what should I eat". Benefits from fish consumption are confounded by socioeconomic class and/or by the avoidance of more harmful foods that fish replaces, which may be as important a benefit mechanism as the PUFA content. Additional studies with better dose-reconstruction are needed and large scale intervention studies are desirable.*


**Keywords: Methylmercury; Polyunsaturated fatty acids; Fish consumption; Dose–response curve; Benefit–risk curve; Risk balancing**

## INTRODUCTION

Few environmental health controversies have captured media and public health attention as consistently as the mercury-in-fish debate. Long-term controversy and irresolvable differences of scientific opinion

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usually reflect a legitimate debate over data quantity, quality or interpretation (WHO, 2003). The fish controversy dates back to the late 1960's when researchers in Europe (Johnels and Westermark, 1969; Expert Group, 1971) and North America (Wobeser et al., 1970), triggered by the discovery of methylmercury as the cause of Minamata disease, began reporting on the high mercury levels in certain fish. While international agencies were unable to agree on an allowable intake for methylmercury (MeHg), the U.S. Food and Drug Administration in 1969 set an administrative guideline of 0.5 ppm (wet weight) of mercury in fish, later (1974) converted to an action level of 0.5 ppm above which fish were seized and removed from commerce. That level was soon (1979) changed to 1.0 ppm (Table 1).

Several studies have documented that certain cultural groups have high levels of fish consumption and high exposure to mercury (Burger et al., 1999a, 1999b; Dewailly et al., 2003; Nakagawa et al., 1997). On the other hand, fish play an important dietary role for indigenous people from tropical to Arctic latitudes, and replacement of traditional diets with "western junk food" jeopardizes health, prompting Egeland and Middaugh (1997) to argue that the benefits of fish outweigh the risks from mercury for indigenous Arctic people. We believe their optimism is not entirely warranted. A study of 38,571 Inuit, revealed that 608 had blood mercury levels exceeding 100 ug/L (maximum of 660 ug/L) and over 30% of women of child bearing age had hair mercury levels above 10 ug/g, a level associated with symptoms in adults (Wheatley and Paradis, 1998). The maximum hair level was 46 ug/g, which is within the range seen in the Minamata cohort of seriously ill adults. Tremor in adults and impaired muscle tone in newborns occurred in the Inuit cohort (Wheatley and Paradis, 1998).

Most studies of fish consumption focus on recreational or subsistence anglers, people who fish and tend to like and eat fish (Knuth et al., 2003). In our series of studies of anglers in South Carolina (Savannah River, Burger et al., 1999b, 2001a), New Jersey (Newark Bay, Burger et al., 1999a), and Puerto Rico (Burger and Gochfeld, 1991), we found that many subgroups substantially exceeded the EPA's (1997) default assumptions of 5 kg/year average and 19 kg/year for subsistence fishers, used in their risk assessments. However, most people in most countries obtain their fish from secondary commercial sources. Therefore, we recently surveyed supermarkets and fish markets for fish availability (Burger et al., 2004) and analyzed nine of the most commonly available fish types and canned tuna for mercury (Burger and Gochfeld, 2004a; Burger et al., 2005).

In the past decade there has been increasing emphasis that consuming fish has many health benefits for the

Table 1
Allowable daily intakes (ug/kg day) derived from various international and national agencies

| Country and agency | Basis | Standard | Convert to ADI (ug/kg day) |
|---|---|---|---|
| US Food & Drug Administration (de facto extrapolated from advisories) | Extrapolated from advisories | | 0.4 |
| Japan Provisional Tolerable Weekly Intake | | 170 ug/week | 0.37 |
| US Agency for Toxic Substances and Disease Registry (ATSDR) | Maternal hair level associated with delayed walking in Iraq (ATSDR 1993) | Chronic oral minimal risk level for methylmercury | 0.12 |
| | NOAEL derived from preliminary Seychelles data (ATSDR, 1997). Incorporate a composite UF = 4.5 | | 0.3 |
| | Based on conversion from the NOAEL of 15.3 ppm in hair from the Seychelles data (ATSDR, 1999) | | 0.5 |
| US Environmental Protection Agency (based on Iraq epidemic) | Based on paresthesias in adults from Iraq epidemic | Former RfD for adults | 0.3 |
| US Environmental Protection Agency reassessment 1999, based on Faroe Islands | Based on neurodevelopmental endpoints from Faroe Islands using Benchmark Dose and UF = 10. | Revised RfD for adult and developmental effects | 0.1 |
| World Health Organization (2003) | Based on FAO Joint Expert Committee on Food Additives and Contaminants | 1.6 ug/kg week, revised in 2003 from prior level of 3.3 | 0.23 |

general public, due in part, at least, to high concentrations of omega-3 (*n*-3) polyunsaturated fatty acids (PUFAs), and some of the benefits of fish can be achieved, by consuming fish oil extracts. Some people have replaced meat and fowl with fish, consuming 10 or more meals per week of fish, resulting in some cases of clinical mercury poisoning (Hightower and Moore, 2003; Gochfeld, 2003). Balancing the benefits and harm remains a risk communication challenge (Knuth et al., 2003).

## Objectives

In this paper we examine dose–response information for the benefits and harm of fish consumption, and present a composite dose–response curve which elucidates the benefit–harm paradox, identifies data needs (thresholds and asymptotes), and can inform personal decisions about which and how much fish to consume as well as enhancing the fish advisory process. We focus here on methylmercury, although other contaminants such polychlorinated biphenyls (PCBs; Jacobson and Jacobson, 2002) and radionuclides (Burger et al., 2001b) pose risks. It will be helpful to provide a more extensive database on the PUFA and contaminant content of various fish. We recognize also that the benefits of consuming fish are partly independent of their PUFA content, while the harm may involve interactions between MeHg and other contaminants including PCBs as well as interaction with the PUFAs themselves (Guallar et al., 2002).

## METHODS

To develop the composite benefit–harm curve we searched MEDLINE in various ways to obtain literature on fish consumption, on risks from methylmercury and polychlorinated biphenyls in fish, on the benefits of fish consumption, as well as studies of PUFA and fish oil supplementation. We used various combinations of terms, and although the MEDLINE 'hits' were numerous, the number of papers yielding dose–response shape information was not. We found 13 cohort studies on adult cardiovascular risks and fish consumption, of which 7 yielded threshold data and asymptote (Table 2). We also reviewed recently published meta-analyses by He et al. (2004a, 2004b) and extracted threshold and asymptote data as well (Table 3). We drew a traditional logistic dose–response curve (for benefits) aligned as well as possible with our estimate of threshold and asymptote (Fig. 1) and displayed these with the dose–response curve (for harm). Summing the curves yields the composite curve, and the area of interest lies between the benefit and harm thresholds.

Studies cited presented data on fish consumption either in meals per month or grams per day (g/day). We converted the former to g/day, assuming a typical meal = 8 oz (227 g). Since many studies reported categories (e.g. 1–3 meals/month), we used the mid-point to estimate thresholds (i.e. 2 meals/month = 454 g = 15 g/day). Where intake in the reference group was given as "less than", we assigned it to the next lower category. Thus "less than one meal per week" was assumed to mean "1 meal per 2 weeks".

Table 2
Benefits of fish consumption with respect to heart disease and stroke

| Citation | Country | Endpoint | Estimated threshold | Estimated asymptote |
|---|---|---|---|---|
| Daviglus et al. (1997) | Chicago men | Fatal heart disease | 15 | >35 |
| | | Nonsudden death | 26 | >35 |
| Ascherio et al. (1995) | USA men | Any MI | 14 | 80 |
| | | Nonfatal MI | 18 | 80 |
| | | Fatal CHD | 28 | 80 |
| Gramenzi et al. (1990) | Italy women | MI (non-fatal) | 32 | >64 g |
| Siscovick et al. (2000) | USA both sexes | Cardiac arrest | 15 | 200 |
| Albert et al. (1998) | USA male physicians | Sudden death | 14 | 100 |
| Kromhout et al. (1985) | Netherlands men | Fatal heart disease | 7 | >45 |
| Hu et al. (2001) (heart) | USA nurses | Heart disease | 14 | 90 |
| Iso et al. (2001) (stroke) | | Stroke | 32 | 160 |

The relative risk for zero fish consumption or less than 1 meal per month is set at 1. A "meal" is considered equivalent to 8 ounces = 227 g. Thresholds and asymptotes estimates by interpolation; a = if reference group intake given as "less than" assume that the average is in the next lowest category of consumption (i.e. <1/week = 1 every 2 weeks); MI = myocardial infarction [95% CL shown in square brackets]; ND = unable to detect threshold from data given.

Table 3
Results from meta-analyses by He et al. (2004a, 2004b) for coronary heart disease and stroke

| Published intake intervals | Extrapolated daily fish intake (227 g/meal) in g/day | Coronary heart disease (13 cohorts) Pooled RR (95% CL) | Stroke (9 cohorts) Pooled RR (95% CL) | Ischemic stroke Pooled RR | Hemorrhagic stroke Pooled RR |
|---|---|---|---|---|---|
| 0 to <1/month | <7.5 | 1 | 1 | 1 | 1 |
| 1–3×/month | 7.5–22.5 | 0.89 [0.79–1.01] | 0.82 [0.72–0.94] | 0.69 | 1.47 |
| 1/week | 32 | 0.85 [0.76–0.96] | 0.87 [0.77–0.98] | 0.68 | 1.21 |
| 2–4×/week | 64–128 | 0.77 [0.66–0.89] | 0.82 [0.72–0.94] | 0.66 | 0.89 |
| >4/week | >128 | 0.62 [0.46–0.82] | 0.69 [0.54–0.88] | 0.65 | 0.8 |

| | Heart disease Trend ($P = 0.03$) | All stroke Trend ($P = 0.06$) | Ischemic stroke Trend ($P = 0.24$) | Hemorrhagic stroke Trend ($P = 0.31$) |
|---|---|---|---|---|
| Estimated threshold[a] | 15 g/day (midpoint of 1–3 meals/month) | 15 g/day (midpoint of 1–3 meals/month) | <15 g/day | 96 g/day |
| Estimated asymptote[a] | ≥128 g/day | ≥128 g/day | 15 g/day | Not discernable |
| Reference | He et al. (2004a) | | He et al. (2004b) | |

95% confidence limits around the relative risk (RR) are shown. The last two columns show that the main benefits are for ischemic stroke.
[a] We estimated the thresholds and asymptotes by inspection of the meta-analysis results.

For the dose–response for harm, where asymptote is probably not an issue, we sought different ways of estimating a harm threshold. For the sake of illustration, we used the lowest allowable daily intake recognized by national or international agencies (Table 1). This is currently the U.S. Environmental Protection Agency (EPA) Reference Dose of 0.1 ug/kg day. Conveniently this is based on a neurodevelopmental endpoint. We also considered a less strict value of 0.3 ug/kg day which is the minimum risk level (MRL) proposed by the Agency for Toxic Substances and Disease Registry (ATSDR) based on lack of neurodevelopmental effects in the Seychelles.

We combined these data with results from our recently completed analyses of mercury levels in a variety of commonly consumed commercial fish (Burger et al., 2004, 2005), to estimate allowable fish consumption levels. There are numerous papers on fish oil supplementation, some involving megadoses (>1 g/day), but these report conflicting results, and we chose to focus on papers reporting fish ingestion rates. Our analysis is seriously constrained by the fish-consumption intervals (grouped intake data), particularly the lowest intake bracket, provided by the original papers.

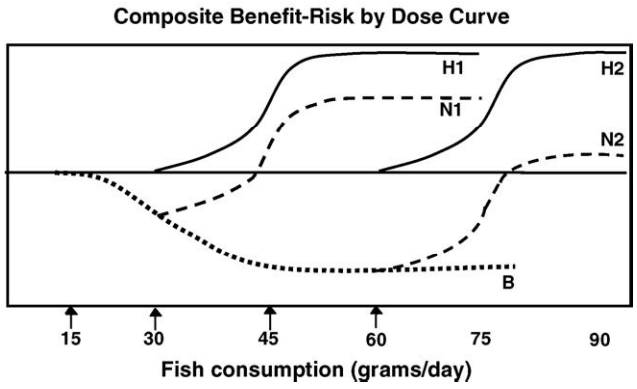


Fig. 1. Composite benefit and risk by dose curve, summing the dose–response curves for harm (H1, H2) and benefit (B) to arrive at net benefit–harm composites (N1, N2). Up-arrows under *X*-axis indicate thresholds. 15 g/day appears to be a common benefit threshold from several studies and endpoints (developmental benefits may occur as low as 5 g/day). 27 g/day corresponds to the worst case harm threshold for a person consuming fish averaging 0.23 ug/g of methylmercury (based on New Jersey study, Burger et al., 2005). Sixty corresponds to a harm threshold for a person selecting fish known to be low in methylmercury (0.10 ug/g). 45 g/day corresponds to the lowest asymptote for benefits from fish consumption. Thus two harm curves and two net benefit–harm curves are shown in conjunction with a single benefit curve. Used by permission of the Environmental and Occupational Health and Sciences Institute.

## RESULTS

Our results extracting threshold and asymptote data from the literature are presented in Tables 2 and 3, and our composite curve is Fig. 1. It was challenging to detect threshold and asymptote parameters from papers not originally designed to yield these parameters. It is fortunate that the benefit threshold for several endpoints, pregnancy duration and development, and adult cardiovascular, consistently lie below the thresholds for harm from methylmercury. To the extent that benefit is due to PUFA and harm to mercury, one could construct similar curves for each kind of fish, once adequate data on PUFA content and mercury levels are published for each species.

## Fish Consumption: Dose and Toxicity

We calculated the amount of fish that could be consumed per week, before reaching any one of the harm thresholds (Table 1). We selected two "thresholds". The EPA Reference Dose (RfD) of 0.1 ug/kg day (derived from the Faroe Island study; EPA, 2001) and the ATSDR Minimum Risk Level MRL) of 0.3 ug/kg day (ATSDR, 1999) are both designated as levels that can be consumed daily without causing harm, and are designed to protect unusually susceptible individuals. EPA's RfD of 0.1 ug/kg day also is extended to adults, although it is based on the developmental endpoints. Prior to the mid-1990s, EPA's RFD was 0.3 ug/kg day for adults based on paresthesias, and some jurisdictions such as New Jersey, retain 0.3 ug/kg day as a basis for fish advisories for otherwise healthy adults (A. Stern, pers. comm.). In 1995 EPA revised the RfD to 0.1 ug/kg day based on neurodevelopmental effects in Iraq (EPA, 2001), and in 1999 EPA arrived at the same RfD using the Faroe Island data (Grandjean et al., 1997). The RfD and MRL include uncertainty factors which would place the threshold for the average person at a higher level. For fish that average 0.1 ug/g (ppm) of mercury (for example, salmon or canned light tuna), a 60 kg woman could consume 65 g/day (16 ounces/week), before exceeding the RfD and 182 g/day without exceeding the MRL. But commonly available commercial fish manifest great variation in mercury levels.

We sampled the nine types of fish most commonly available in New Jersey markets (Burger et al., 2005), from which we compute a weighted mean total mercury level of 0.25 ug/g (ppm wet weight) corresponding to about 23 ug/g of MeHg (assuming that about 90% of total Hg is MeHg). This sample did not include canned tuna which we had previously shown averaged 0.1 ug/g MeHg for "light" tuna and 0.37 ug/g MeHg for "white" tuna (Burger et al., 2004). Thus women who consume a variety of fish, could eat 26.5 g/day or 80 g/day (3–9 eight oz meals/month) before exceeding the RfD and MRL, respectively. In Fig. 1, the harm threshold is represented at 27 g/day.

## Fish Consumption: Dose and Benefits

The data on the benefits of fish consumption can be divided into developmental and adult benefits, with most studies focusing on the latter (Table 2). In addition, studies either looked at outcome as a function of fish consumption (usually by dietary recall) or outcome in patients given fish oil supplements versus controls. We consider only the former.

The most useful reproductive data were reported by Olsen and Secher (2002) from a prospective study of pre-term births involving 8998 women. They found that women who consumed no fish were 3.6 times more likely (95% confidence limit 1.15–11.2×) to have a pre-term birth than women who consumed 38 g of fish per day (Olsen and Secher, 2002). They found a benefit threshold at about 5–15 g/fish per day (depending on meal size assumptions) within the range of the thresholds for adult cardioprotective effects. Though positive, the Helland et al. (2003) study showing a benefit for IQ, used only a single dose of cod liver oil supplementation, and does not provide threshold data.

In adults, several studies have shown reduction in various cardiovascular risk factors, including improvement of lipid profiles, inhibition of lipid peroxidation, reduction of platelet aggregation, and an anti-arrythmic effect. The clinical endpoints have included both fatal and non-fatal coronary heart disease (CHD), myocardial infarction (MI), and stroke. Several studies have shown substantial benefit from fish consumption, while others have been mainly negative. Ascherio's (1995) report on the health professional study, found benefit for some endpoints (see Table 2), but no benefit for preventing cardiac bypass surgery. Katan's editorial (1995) reported this as simply a negative study. Moreover, mercury content of fish in the diet may interfere with the cardioprotective effects (Guallar et al., 2002).

Table 2 summarizes benefit–response data for heart disease and stroke endpoints. In a study of male workers in a Western Electric Company study, men who ate any fish had slightly reduced deaths from CHD and MI, with more obvious benefit above about 26 g day (interpolated between 18 and 34 g/day). Above 35 g fish/day the relative risks were 0.62, 0.56 and 0.33 for fatal CHD, fatal MI, and non-sudden death from heart disease compared with 0 fish intake (Daviglus et al., 1997). That study provided no clear (maximum benefit). Ascherio et al. (1995) reported on the Harvard Health Professionals study, finding an unexpected increased likelihood of heart surgery in the high PUFA intake group. However, there was a protective effect against MI and CHD, with thresholds in the 14–28 g range, and an asymptote around 80 g/day. Similar results were obtained by Gramenzi et al. (1990) on Italian women, yielding a threshold for non-fatal MI around 32 g/day with an asymptote above 64 g/day. Siscovick's et al. data (2000) on American men and women and reveals a threshold for cardiac arrest around 15 g, with continued benefit among frequent

fish-eaters. Albert et al. (1998) studying physicians, found a relative risk for sudden death of 0.44 for those who ate 1 fish meal per week (c32 g/day) with a threshold around 14 g/day and an asymptote somewhere above 45 g/day. In the Zutphen (Netherlands) study, men who reported eating fish had a lower rate of coronary heart disease death, and the authors identify a threshold at 30 g/day (Kromhout et al., 1985). However, their data are compatible with an RR of 0.60 for 14 g/day, and show a benefit plateau achieved after 44 g/day. The meta-analysis by He et al. (2004a) reviewed 11 papers on cardiac benefits (including most of the above) and found a significant risk reduction even in the 1–3 meals/month category (7.5–22.5 g/day) compared with the less than 1 meal/month category. Moreover, there appeared to be a plateau at about 1 meal/week followed by even further improvement (hence no asymptote) at >4 meals/week (see Table 3).

There was also a protective effect against stroke with a threshold possibly as low as 8 g/day (Keli et al., 1994). However, Caicoya (2002) reported a greater stroke risk with increasing fish consumption. A large U.S. study of physicians found a stroke-protective benefit at 1–3 meals/month (midpoint = 15 g/day) (He et al., 2002) with no added benefit from greater fish consumption. The meta-analysis by He et al. (2004b) based on review of eight papers, resolved some of the inconsistency. The main protection was against ischemic strokes, with protection against hemorrhagic stroke only in the most frequent fish eater groups. There was also no clear asymptote.

The Nurses Health study with a very large sample size yielded valuable data for women. Women who ate fish 1–3 times per month had a relative risk of 0.79, and those who ate fish weekly had an RR of 0.71, with little added benefit from more frequent consumption (Hu et al., 2002). Using the midpoint of 1–3 meals/month yields a daily intake of about 15 g/day as a putative threshold for benefit with a benefit plateau reached around 45 g/day. In the same study, a threshold for protection against stroke was reached at about 30 g/day (Iso et al., 2001). The benefit was mainly for thrombotic rather than hemorrhagic stroke (Skerrett and Hennekens, 2003).

The common denominator of the above studies is that people who ate fish at least once a month had lower relative risks (not always statistically significant at the 0.05 level) than those who ate fish less frequently or not at all. The studies show that benefits for both heart disease and stroke begin in the 15–35 g/day range. The reproductive benefits appear to have a threshold in the same range, albeit based on very limited data. Asymptotes are harder to detect, some studies show little benefit to increasing above 45 g/day (e.g. Kromhout et al., 1985) whereas others show benefit in the highest consumption group (Siscovick et al., 2000; He et al., 2004a, 2004b). As Guallar et al. (2002) cautioned, at higher consumption, the risks from contaminants may erase the benefits.

## DISCUSSION

### Mercury and Development

Despite a recent (2003) attempt by the U.S. Environmental Protection Agency to downgrade the classification of mercury toxicity, mercury and all its compounds are toxic to virtually all life forms, and a wide range of biocides from familiar antiseptics to anti-fouling paints, incorporate mercury. Many uses of mercury are being phased out and much industrial effluent has been diminished, leaving coal-fired powerplants and metal smelters as major sources of air emissions with long range atmospheric transport a significant contributor (New Jersey, 2001). Methylmercury, one of the most toxic forms of mercury, is produced in aquatic ecosystems by microbial action on inorganic mercury; it is readily bioavailable and biomagnifies in the food chain, reaching relatively high concentrations in large fish. Consuming fish is the main pathway for human exposure to methylmercury. Although mercury, particularly methylmercury, is toxic to humans at all ages, the developing nervous system is generally considered the most sensitive endpoint for risk assessment and prevention, and fetal Minamata Disease is a classic case in environmental toxicology (Chang and Guo, 1998). Although the profound retardation seen at Minamata is a hallmark of MeHg toxicity, today there is much more concern for the subclinical end of the spectrum, where a small excess of MeHg may affect the construction of the CNS.

Some of the mechanisms by which mercury (and other developmental neurotoxicants) interfere with nervous system development (e.g. microtubule assembly) are well-established (Brown et al., 1988). Lagunowich et al. (1991) demonstrated that neural cell adhesion molecules (NCAMs) are a target for MeHg, and Dey et al., (1999) showed that MeHg affects the timing of NCAM gene expression in

rodents, thus establishing one mechanism for different critical periods (Rice and Barone, 2000).

## Harmful Effects of Fish

The literature on harm from fish is extensive. These include acute toxic effects of ciguatoxin, tetrodotoxin (from puffer fish), and saxitoxin (paralytic shellfish poisoning), as well as bacterial contamination (Institute of Medicine, 1991). For our purposes, however, the main concern lies in the concentrations of methylmercury (MeHg) and polychlorinated biphenyl compounds (PCBs) in edible fish tissue.

Several major studies of mercury exposure and neurobehavioral development have been conducted including in the Faroe Islands, Seychelles, New Zealand, and Amazonia (summarized in NRC, 2000). Of the two largest prospective cohorts, the Faroe Island study is interpreted as positive and the Seychelles study is reported to be negative (NRC, 2000). Strongly positive results were obtained in a New Zealand study of 74 children born to mothers who ate fish frequently and had elevated hair mercury (Kjellström et al., 1986). That study was constrained by sample size, but found deficits in performance in a range where the Seychelles study reported none. The New Zealand data provide an independent validation of the Faroe Island data (EPA, 2001). The possibilities of ethnic or dietary influences on susceptibility require attention. Rice (2004) argued that there is no detectable threshold for MeHg effects on development.

For adult neurotoxicity, there does seem to be a threshold. Recent attention to adult mercury poisoning comes from health-conscious adults, switching to high fish diets for nutritional benefits and avoidance of ''red meat'' (Hightower and Moore, 2003). Since fish lovers develop a fondness for Swordfish and Tuna and can easily consume 9–12 fish meals per week (ca 8 oz/meal), they can accumulate a toxic burden of mercury. Such a person can consume over 2 kg of fish per week, and using a level of 0.5 ug/g (lower than the average for tuna steaks, Burger et al., 2005), yields an estimate of 1000 ug/week MeHgHgH, or about 2.4 ug/kg day which is 24 times the EPA reference dose and eight times the ATSDR's Minimum Risk Level (ATSDR, 1999; EPA, 2001; Table 1). By taking in more mercury each day than is excreted, the mercury level in target organs will quickly accumulate, and the hair mercury level would soon exceed 12 ug/g, which reflects a level at which there can be clinical evidence of toxicity, such as impaired fine motor function (Hightower and Moore, 2003; Gochfeld, 2003).

## Benefits of Eating Fish

On the positive side of the equation are the social and health benefits attributed to fish, and the recognition that fishing and fish-consumption have important recreational, social, and cultural features. Fish plays an important role in the diet of certain cultures and nations including those populations studies in the Faroes, Seychelles and Amazonia. Aside from these sociocultural benefits, biochemical/nutritional benefits. The literature on both the reproductive and cardiovascular benefits of eating fish is growing (He et al., 2004a, 2004b).

Some of the benefits are attributable to the PUFA content of fish while we suspect that fish consumption itself is a surrogate for better health awareness, practices, and status. The benefits of fish consumption may occur mainly in high risk individuals (Folsom and Demissie, 2004). The extent to which the benefits of fish consumption can be replaced by fish oil supplements remains uncertain. The beneficial PUFAs are docosahexaenoic acid (DHA = 22:6*n*-3) and to a lesser extent eicosopentanoic acid (EPA = 20:5*n*-3). DHA is an essential component of nervous system cell membranes and is transported across the placenta and delivered post-natally in milk.

Post-natal DHA is positively correlated with visual and language development in breast-fed infants (Innis et al., 2001). For adults, Siscovick et al. (2000) speculated that the protective effects of the fish consumption on stroke were mediated by cell membrane concentrations of the PUFAs.

The benefits for fetal growth and development include reduction in pre-term delivery (possibly because of local action on uterus (Allen and Harris, 2001). Odent (2002) reported a 31% reduction in prematurity among 499 pregnant woman encouraged to eat sea fish before 20 weeks compared to 462 controls, although his study lacked power and he misleadingly reported it as negative. Olsen and Secher (2002) study of 8729 pregnant women, found that preterm delivery and low birth weight occurred more frequently (7.1%) among those never consuming fish to 1.9% among those eating fish once a week, a statistically significant difference. They identify a clear benefit threshold at 15 g of fish/day using our estimate of an 8 ounce (227 g) average meal size, but they estimated meal size at about 100 g, which would yield a benefit threshold possibly as low as 5 g/day.

Dunstan et al. (2003) found that fish oil capsules during pregnancy did increase PUFA levels in neonatal red cell membranes and also lowered plasma interleu-

kin-13 levels. Visual acuity and neural pathways associated with language acquisition showed a positive relationship to DHA in breast milk (Innis et al., 2001). DHA supplementation, however, reduces arachidonic acid which is also essential for CNS development (Innis, 2003). Methylmercury may influence the release of arachidonic acid in neurons (Shanker et al., 2004). Helland et al. (2003) provide evidence of both a pre-natal and post-natal (lactational) benefit on IQ of maternal supplementation with cod liver oil.

## Utility of the composite curve

To reconcile the risk–benefit balance for fish, we have assembled both dose–response dose–benefit curves into a composite curve (Fig. 1) with daily fish consumption on the X-axis. A typical dose response curve for mercury would graph adverse outcome against mercury intake. Likewise a typical dose response curve for PUFA would graph beneficial outcome against PUFA intake. Our composite curve aims to reduce these to a common and useful denominator, grams of fish per day, taking into account that the concentration of both mercury and PUFA vary greatly among fish. Although the data are sparse (Table 2), it indicates that the main benefits accrue from consuming some fish, at least 15 g/day up to 60 g of fish/day, with a flattening of the benefit curve beyond that. Unfortunately, by grouping data in the 1–3 fish meals/month category, the thresholds have been obscured in many studies.

If one ate fish with MeHg levels around 0.23 ppm, there would be a very slim margin of safety between the 15 g/day benefit threshold and 27 g/day worst-case harm threshold (using the RfD). People would require strong encouragement to choose fish lower in mercury. The same person choosing fish with mercury around 0.1 ppm would have a comfortable margin between 15 g and 65 g. A person who is less risk-averse might choose to be guided by the MRL rather than the RfD, in which case there is a comfortable margin for fish below 0.7 ppm, which allows eating almost anything other than sharks and Swordfish.

The worst situation exists when a harm threshold is lower than a benefit threshold, which for MeHg in fish is unlikely from existing data. However, the data currently support the interpretation that the harm threshold lies below the benefit asymptote. As more extensive data accumulates on both dose–benefit and dose–harm accrue, this approach will allow people to adjust their intake to exceed the benefit threshold while remaining below the harm threshold. Optimality involves choosing fish high in omega-3 fatty acids and low in MeHg and/or PCBs. People who prefer large predatory fish, high in MeHg and PCBs, are likely to exceed a harm threshold. Conversely those who can choose fish low in mercury (0.1 ppm or less)=, would not exceed the EPA RfD until they ate 60 g of fish/day. Data on mercury concentration in various fish species is available from several sources (FDA, 2004; Burger et al., 2005). Data on PUFAs in fish is increasingly available from various world wide web pages.

## Temporal Effects

There are two relevant issues of temporality: critical periods and dose rate. From the current literature we were not able to sort out the issue of critical periods for benefit and harm (Rice and Barone, 2000). Innis and Elias (2003) suggest that DHA accumulation in the third trimester, when the brain undergoes rapid allometric growth, is particularly important, while the harmful effects of MeHg, may be more critical earlier during a period of neuronal migration and differentiation. As data accrue, recommendations might be tailored to stage of pregnancy (“eat less now”; “eat more later”), but this will require studies designed specifically to obtain this temporally sensitive data.

Likewise, the effect of dose-rate has not been assessed. Eating an 8 ounce (227 g) fish once a month may translate into a daily average of 8 g/day, but is not equivalent to eating 8 g each day. Although dose-rate studies are critical in the development and testing of pharmaceuticals, they are remarkably sparse in metal toxicology.

## Previous Proposals

An anonymous referee called our attention to a paper by Anderson et al. (2002) not accessible on MEDLINE, in which a very similar composite benefit–harm curve approach was proposed. Unfortunately, the title of that valuable paper “Framework and Case Studies” would give little clue as to its content. Anderson et al. (2002) examine a Comparative Dietary risk Framework combining benefits and harm, and discuss in detail the strengths and current limitations of the method and available data sets. Their more theoretical work did not focus particularly on mercury, and is reported as preliminary, but clearly reflects an approach similar to ours.

## CONCLUSIONS

It is apparent that there are benefits to eating fish, and to some extent these benefits derive from their PUFA content which is increasingly being analyzed and publicized. Choosing fish low in MeHg and PCBs and high in PUFA is clearly desirable, although many people who like fish show a preference for the taste of predatory species, high in MeHg, and not necessarily high in PUFAs (these fish are also increasingly rare because of overfishing pressures). Ongoing research should clarify the dose–benefit and dose–harm curves. Given the uncertainties in existing studies over the threshold, it would be desirable for studies to stratify their samples to illuminate more precisely the benefit threshold and asymptote issues. Documenting the margin of safety between the benefit threshold and the harm threshold is both an individual and public health priority.

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