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of fish consumed. Results from the "CHD meta-analysis model" can also be found in the second column of Table AB-6 in Appendix B.

Table V-11: CHD deaths – Current Rates and "CHD Meta-Analysis Model" Results

	Women 16-45	Women 46+	Men 16-45	Men 46+
Number of people of this age in US (2001)[21]	64,349,357	56,417,619	66,229,773	48,713,395
Annual rate of CHD death	0.14 per 10,000	38 per 10,000	1.3 per 10,000	51 per 10,000
Annual deaths per year from CHD	901	214,387	8,610	248,438
Median Change in CHD death rate due to fish consumption: Meta-analysis model	-0.007 per 10,000	-2.2 per 10,000	-0.09 per 10,000	-3.7 per 10,000
CHD deaths averted attributable to current fish consumption: Meta-analysis model	43	12,498	589	18,104

Table V-12 shows the "CHD meta-analysis" model's predictions for how different levels of fish consumption can affect the annual frequency of death from CHD in each subpopulation. Within each subpopulation eating more fish reduces the frequency of death from CHD and vice versa. Because the model is predicting the effect of eating a variety of fish on fatal CHD, the table does not include estimates for exposure to methylmercury at each percentile of fish exposure. For those who want to match the fish consumption percentiles in Table V-12 with methylmercury levels that have been estimated for women of childbearing age, see Table V-3.

Note also that we do not attempt to match frequency of fatal CHD with consumption of any particular type of fish (e.g., oily vs. non-oily). As stated previously, we did not model the specific qualities of fish that could reduce the risk. All the data that met our inclusion criteria for this assessment derive from the consumption of "fish" without differentiation as to species.

[21] (U.S. Census Bureau, 2001)

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Table V-12: Annual Frequency of Death from CHD Based on Amounts of Fish Consumed Using "CHD Meta-Analysis Model"

Fish Consumption Percentile	Women 16-45	Women 46+	Men 16-45	Men 46+
10th	0.142 in 10,000	40.2 in 10,000	1.350 in 10,000	54.4 in 10,000
25th	0.141 in 10,000	39.7 in 10,000	1.33 in 10,000	53.6 in 10,000
50th	0.139 in 10,000	39.0 in 10,000	1.30 in 10,000	52.4 in 10,000
75th	0.134 in 10,000	37.6 in 10,000	1.25 in 10,000	50.2 in 10,000
90th	0.126 in 10,000	35.1 in 10,000	1.14 in 10,000	46.0 in 10,000
95th	0.119 in 10,000	32.6 in 10,000	1.04 in 10,000	42.1 in 10,000
99th	0.098 in 10,000	25.9 in 10,000	0.71 in 10,000	29.4 in 10,000

Fish consumption percentiles are based on the median estimates of fish consumption presented in Table 2-3

Table V-13 provides outcomes from both the "CHD meta-analysis model" and the "CHD pooled analysis model," including both the central estimates and the confidence intervals surrounding each central estimate. The first two rows provide the results from the "CHD meta-analysis model." The central estimate is the median estimate (50th percentile) and the confidence intervals are the 5th and 95th percentile estimates. The last two rows of Table V-13 provide the results for these estimates from the "CHD pooled analysis model." These results in terms of death rate are shown in Table AB-6 in Appendix B.

Because the two approaches are based largely on the same data, their central estimates, i.e., their median estimates, are close to one another. Both models produce central estimates of annual deaths averted ranging from a low of 43 deaths averted ("CHD meta-analysis model" for women 16-45) to a high of nearly 23,000 deaths averted ("CHD pooled analysis model" for men 46+), depending on subpopulation.

Wider confidence intervals means that the "CHD pooled analysis model" predicts a wider range of possible outcomes, including a small possibility of some increase in risk of CHD death in the U.S. population due to fish consumption than does the "CHD meta-analysis model." As explained below, the range of possibilities within the confidence intervals indicate a much greater likelihood that deaths are being averted than being caused by fish consumption.

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The small possibility of increased risk from fish estimated by the "CHD pooled analysis model" can stem from several possible reasons, one of which could be methylmercury in the fish. For example, some people in the United States could be experiencing circumstances similar to those in eastern Finland, where risk from CHD was high. That population ate a lot of lean lake fish that were low in nutrients such as omega-3 fatty acids and selenium. Their entire diet appeared to be low in these nutrients (Salonen et al., 1995). Others reasons could include how the fish was prepared (e.g., fried vs baked); and fish serving as a surrogate for other risk factors.

Note that the terminology differs between Tables V-11 and V-13. For example, Table IV-11 lists "deaths averted" due to current fish consumption because the "CHD meta-analysis model" does not include any possibility of deaths caused by fish consumption. However, Table IV-13 refers to "change in number of deaths due to fish consumed" because the "CHD pooled analysis model" includes some possibility of death attributed to fish consumption.

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Table V-13. Median results with Confidence Intervals (5th and 95th percentiles) for Effect on CHD Death Rate from Current Levels of Fish Consumption, as predicted by the "Meta-Analysis" and "Pooled Analysis" Models

	Women 16-45	Women 46+	Men 16-45	Men 46+
Median Change in CHD Death Rate Due to Fish Consumed: Meta-Analysis Model	-0.007 per 10,000 (-0.013 per 10,000, -0.001 per 10,000)	-2.2 per 10,000 (-4.3 per 10,000, -0.4 per 10,000)	-0.09 per 10,000 (-0.17 per 10,000, -0.002 per 10,000)	-3.7 per 10,000 (-7.2 per 10,000, -0.7 per 10,000)
Change in Number of Deaths due to Fish Consumed: Meta-Analysis Model	-43 (-86, -9)	-12,498 (-24,158, -2,274)	-589 (-1,134, -106)	-18,104 (-35,151, -3,211)
Median Change in CHD Death Rate Due to Fish Consumed: Pooled Analysis Model	-0.011 per 10,000 (-0.22 per 10,000, 0.026 per 10,000)	-2.8 per 10,000 (-42 per 10,000, 9.4 per 10,000)	-0.11 per 10,000 (-1.2 per 10,000, 0.34 per 10,000)	-4.7 per 10,000 (-88 per 10,000, 6.5 per 10,000)
Change in Number of Deaths due to Fish Consumed: Pooled Analysis Model	-69 (-1400, 169)	-15,906 (-237,298, 52,076)	-728 (-8,080, 2261)	-22,922 (-428,305, 31,837)

The way to read this table is as follows: for women of child-bearing age, the "CHD meta-analysis model's" central estimate is that 43 CHD deaths are prevented annually due to current levels of fish consumption (although at the 5th and 95th percentile confidence intervals the estimated number of deaths averted are as high as 86 or as low as nine). Since the current annual number of deaths is 901 per year, the number of deaths if

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there were no fish consumption is estimated to be 901 plus 43, or 944, per the central estimate.

The "CHD pooled analysis model" produces a central estimate of 69 deaths averted due to fish consumption in this age group, although this number could be as high as 1,400 (at the 5th percentile confidence interval). It also estimates that at the 95th percentile confidence interval, up to 169 CHD deaths could be caused by fish consumption. However, the bulk of the probability distribution is less than zero, so it is more likely than not (85 percent) that increased fish consumption leads to a decrease in CHD death.

"What-If" Scenarios:

First "What If" Scenario: Women of Childbearing Age Limit Their Consumption to 12 Ounces a Week. In this scenario, women of childbearing age who are consuming 12 ounces or less of fish per week do not change their consumption but women of childbearing age who are consuming more than 12 ounces reduce their consumption to 12 ounces. This reduction is long term and does not occur solely during pregnancy. Because the models predict that a decrease in consumption causes an increase in risk, the most likely outcome would be an overall increase in the number of deaths from CHD for this population. Such an increase would be small, however, because the only people who would be eating less fish would be relatively young women. The median estimate for the "CHD meta-analysis model" is an increase of 4.6 deaths per year while the median increase for the "CHD pooled analysis model" is actually zero, but the upper confidence limit is 8.2 deaths.

NOTE: We also modeled this scenario for fetal neurodevelopment and for stroke.

Table V-14: Change in CHD Annual Deaths (vs. Baseline) Resulting from a Consumption Limit of 12 oz Per Week by Women of Childbearing Age

Population Group	CHD Death Cases Per -Year Pooled Analysis Model	CHD Death Cases Per Year Meta-Analysis Model
Women 16-45	An increase of 0.0 (-2.4, 8.2) Deaths per year	An increase of 4.6 (0.8, 10) Deaths per year

The primary values are the median cases per year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

Second "What If" Scenario: Women of Childbearing Age All Consume 12 Ounces a Week. In the next scenario, all women of child-bearing age consume exactly 12 ounces of fish. As with the first scenario, this consumption is not just during pregnancy. Because most women of childbearing age consume much less than 12 ounces per week[22]

[22] **In recent survey research by FDA, median fish consumption for the non-pregnant women of childbearing age in the survey was 2.97 ounces per week while median fish consumption for the**

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the majority of women in this age group would have to increase their consumption substantially under this scenario. Only a small minority would have to decrease consumption down to 12 ounces per week. The most likely overall impact of this scenario would be a decrease in the number of deaths from CHD in women of childbearing age.

NOTE: We also modeled this scenario for fetal neurodevelopment and for stroke.

Table V-15: Change in CHD Annual Deaths (vs. Baseline) Resulting from Consuming Exactly 12 oz per Week by Women of Childbearing Age

Population Group	CHD Death Cases Per Year Pooled Analysis Model	CHD Death Cases Per Year Meta-Analysis Model
Women 16-45	A decrease of 88 (-187, -627) deaths per year	A decrease of 108 (-21, -230) deaths per year

The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

Third and Fourth "What If" Scenarios: Men and Older Women Reduce Their Fish Consumption. One of the questions surrounding the FDA/EPA consumer advisory has been whether it would affect fish consumption throughout the population even though the target audience is limited to certain women of childbearing age and young children. The next two scenarios examine the potential impact of reductions in fish consumption by (1) young men; (2) older men; (3) older women. In one scenario, the number of fish consumers in each of these subpopulations decreases by one percent (i.e., one percent of fish eaters stop consuming all fish). In the second scenario, there is a 10 percent reduction in the amount of fish consumed by all fish consumers in these subpopulations. The "CHD meta-analysis model" predicts that a one percent reduction in the number of consumers that eat fish would be 130 additional deaths per year among for older women, 235 additional deaths per year among older men, and six additional deaths per year among young men. The "CHD pooled analysis" model's estimates are similar, although the confidence intervals are wider and include decreases in deaths per year. The predicted impact from an across the board reduction of 10 percent in the amount of fish consumed is substantially greater with 1,250 additional deaths per year among older women, 1,810 additional deaths per year among older men, and 59 additional deaths per

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pregnant women surveyed was 1.89 ounces per week (Choiniére, C.J., Timbo, B., Street, D., Trumbo, P., Fein, S., Fish Consumption by Women of Childbearing Age, Pregnant Women, and Mothers of Infants. Presented at the International Association for Food Protection Annual Meeting, Columbus, Ohio, August 3-6, 2008.) As a caveat, the study sample was from a nationally distributed consumer panel that was not representative of the whole U.S. population. The sample size was large, however, with 1,500 women in each of these groups.

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year among young men in the "CHD meta-analysis model." Again, the "CHD pooled analysis model's" estimates are similar but with wider confidence intervals.

Table V-16: Change in CHD Annual Deaths (vs. Baseline) Resulting from a One Percent Reduction the Number of Men and Older Women Who Consume Fish

Population Group	CHD Death Cases Per Year Pooled Analysis Model	CHD Death Cases Per Year Meta-Analysis Model
Women 46+	An increase of 161 (-559, 2,644) deaths per year	An increase of 130 (20, 286) deaths per year
Men 15-45	An increase of 8.0 (-23.3, 88) deaths per year	An increase of 6.1 (0.9, 14) deaths per year
Men 46+	An increase of 264 (-385, 5,168) deaths per year	An increase of 191 (29, 422) deaths per year

Estimates of increased rates of CHD Death resulting from decreased number of fish consumers in three population groups. The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

Table V-17: Change in CHD Annual Deaths (vs. Baseline) Resulting from a 10 Percent Decrease in the Amount of Fish Consumed by Men and Older Women

Population Group	CHD Death Cases Per Year Pooled Analysis Model	CHD Death Cases Per Year Meta-Analysis Model
Women 46+	An increase of 656 (-1,937, 7,674) deaths per year	An increase of 1,250 (227, 2,416) deaths per year
Men 15-45	An increase of 30 (-97, 248) deaths per year	An increase of 59 (11, 113) deaths per year
Men 46+	An increase of 1,432 (-1,721, 10,749) deaths per year	An increase of 1,810 (321, 3,515) deaths per year

Estimates of increased rates of CHD Death resulting from decreased number of fish consumers in three population groups. The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

Fifth "What If" Scenario: 50 Percent Increase In Fish Consumption by Everyone. This scenario examines the health impact of a 50 percent increase in fish consumption by all subpopulations. The models predict decreases in CHD death from such increases in consumption.

Table V-18: Change in CHD Annual Deaths (vs. Baseline) Resulting from a 50 Percent Increase in the Amount of Fish Consumed by all Population Groups

Population Group	CHD Death Pooled Analysis Model	CHD Death Meta-Analysis Model
Women 16-45	A decrease of 11, (-27, 175) deaths per year	A decrease of 22 (4, 43) deaths per year

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Women 46+	A decrease of 2,306 (-7,154, 29,691) deaths per year	A decrease of 6,249 (1,137, 12,079) deaths per year
Men 15-45	A decrease of 124 (-382, 926) deaths per year	A decrease of 294 (53, 567) deaths per year
Men 46+	A decrease of 5,243 (-6,888, 48,5154) deaths per year	A decrease of 9,052 (1,606, 17,576) deaths per year

The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

(d) Fatal Stroke

We present results from two models, which we refer to as the "stroke meta-analysis model" and the "stroke pooled analysis model" as described in Section IV.

Baseline Results

In Table V-19, the first three rows show the population numbers, rates and estimated number of stroke deaths for the four subpopulations. The fourth row shows the decrease in the death rate for each subpopulation that can be attributed to current fish consumption. As with CHD, the decreases are based on the amounts of fish consumed by each sub-population. There is only one dose-response function that is used for all four sub-populations. The fifth row shows the number of deaths averted annually for each subpopulation due to fish consumption per the "stroke meta-analysis model." .

Table V-19: Stroke deaths – Current Rates and "Stroke Meta-Analysis Model" Results

	Women 16-45	**Women 46+**	**Men 16-45**	**Men 46+**
Number of people of this age in US (2001)[23]	64,349,357	56,417,619	66,229,773	48,713,395
Annual rate of stroke death	0.25 per 10,000	18 per 10,000	0.24 per 10,000	13 per 10,000
Average baseline deaths per year from stroke	1,551	101,549	1,560	63,911

[23] (U.S. Census Bureau, 2001)

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Median stroke death rate decrease due to fish consumption ["Stroke Meta-Analysis Model"]	0.030 per 10,000	2.2 per 10,000	0.032 per 10,000	1.8 per 10,000
Stroke lives saved (deaths averted) attributable to current fish consumption ["Stroke Meta-Analysis Model"]	192	12,570	213	8,609

For women aged 16-45, the "stroke meta-analysis model" estimates that 192 stroke deaths per year are averted due to fish consumption while 12,570 stroke deaths are averted for women over age 45 due to fish consumption. Two hundred thirteen stroke deaths per year are averted for men aged 16-45 due to fish consumption while 8,609 stroke deaths per year are averted due to fish consumption by men over the age of 45.

These figures reflect the median, i.e., central estimates. In order to show the full range of uncertainty in these estimates and to present the results from the "stroke pooled analysis model" Table V-20 shows the fifth and 95th confidence intervals in addition to the central estimates. These results are also shown in Table AB-7 in Appendix B.

Both models predict that reduction in risk of fatal stroke is the most likely outcome from fish consumption. Where these models differ most notably is in the size of the confidence intervals. The "stroke pooled analysis model" produced confidence intervals that are considerably greater than those produced by the "stroke meta-analysis model." Larger confidence intervals mean a wider range of possible outcomes; consequently, the "stroke pooled analysis model" also predicts a small possibility that fish consumption can increase the risk of stroke, as revealed by the results of the 95th percentile confidence intervals in Table V-20.[24] There is an 87 percent probability that fish consumption is averting deaths rather than causing them, however.

[24] There are several possible explanations for this latter prediction, none of them mutually exclusive. First, fish consumption might increase the risk of hemorrhagic stroke. This possibility derives from a study in which Greenland Eskimos acids were found to have a higher risk of fatal hemorrhagic stroke than Danish whites (Kristensen 1983). A difference between the two groups was the higher intake of omega-3 fatty acids by the Greenland Eskimos. However, average levels of omega-3 in these Eskimos were as much as 100 time higher than average levels in the United States; consequently, the risk, if any, to U.S. residents may be low (Iso et al., 2001). Moreover, the data from the eight studies that we used in our risk assessment did not show a significant increase in risk of hemorrhagic stoke from increased fish consumption. The He et al. meta-analysis reported finding no significant association between hemorrhagic stroke and fish intake (He et al., 2004b, p. 1539).

Second, the manner of cooking could increase the risk. One study showed a decrease in risk when fish were baked or broiled but an increase in risk when fish were fried (Mozaffarian et al., 2005).

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To read Table V-20: As noted earlier, for women aged 16-45, the "stroke meta-analysis model" predicts that 192 stroke deaths are averted per year due to fish consumption. The confidence intervals around that median estimate indicate that as many as 359 or as little as 58 deaths may be averted by fish consumption.

For this same subpopulation, the "stroke pooled analysis model's" central estimate is that 238 stroke deaths are being averted annually for this subpopulation from fish consumption but at the fifth percentile confidence interval it also estimates that fish consumption could be averting up to 1,995 deaths while at the 95th percentile of the confidence interval it predicts that fish consumption may be causing 97 stroke deaths.

Third, risk assessment outcomes can be sensitive to variations in the data. Of the nine studies that provided the data for the risk assessment, four found no statistically significant association one way or another between fish consumption and stroke, four found that fish consumption reduced the risk of total stroke, three found that fish consumption reduced the risk of ischemic stroke, and three found no association between fish consumption and risk of hemorrhagic stroke one way or another. However, as reported above, one study found an increased risk from fried fish. Another study that found no overall association between fish consumption and stroke did find that the highest levels of fish consumption in its study group were associated with the highest incidence of stroke.

Finally, it is important to recognize that even where a study finds an overall decrease in risk, inevitably some members of the study population still have strokes that are modeled as being "due to" fish consumption even though the cause may involve other risk factors.

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Table V-20. Median results with Confidence Intervals (5th and 95th percentiles) for Effect on Stroke Death Rate from Fish Consumption, as Predicted by "Stroke Meta-Analysis" and "Stroke Pooled Analysis" Models

	Women 16-45	**Women 46+**	**Men 16-45**	**Men 46+**
Stroke Death Rate Change: Meta-Analysis Model	-0.030 per 10,000 (-0.056 per 0,000, -0.009 per 0,000)	-2.2 per 10,000 (-4.3 per 10,000, -0.7 per 10,000)	-0.032 per 10,000 (-0.061 per 10,000, -0.011 per 10,000)	-1.8 per 10,000 (-3.4 per 10,000, -0.7 per 10,000)
Change in Number of Deaths due to Fish Consumed: Meta-Analysis Model	-192 (-359, -58)	-12,570 (-23359, -3,994)	-213 (-402, -75)	-8,609 (-16,380, -3,233)
Stroke Death Rate Change: Pooled Analysis Model	-0.037 per 10,000 (-0.15 per 10,000, 0.016 per 10,000)	-2.2 per 10,000 (-27 per 10,000, 1.4 per 10,000)	-0.04 per 10,000 (-0.31 per 10,000, 0.03 per 10,000)	-2.4 per 10,000 (-19 per 10,000, 0.9 per 10,000)
Change in Number of Deaths due to Fish Consumed: Pooled Analysis Model	-238 (-1,995, 97)	-12,693 (-154,932, 7,938)	-294 (-2,054, 203)	-11,923 (-95,049, 4,558)

"What-If" Scenarios

First "What If" Scenario: Women of Childbearing Age Limit Their Consumption to 12 Ounces a Week. In the first scenario, women of childbearing age who are consuming 12 ounces or less of fish per week do not change their consumption but women of childbearing age who are consuming more than that reduce their consumption to 12 ounces. This reduction does not occur only during pregnancy.[25] Because the models predict that a decrease in consumption is likely to increase risk, the most likely change would be an overall increase in the number of deaths from stroke in this population. Such an increase would be small, however, because the only people who would be eating less fish would be relatively young women. The median estimate for the "stroke meta-analysis model" is an increase of 4.0 deaths per year while the median increase for the "stroke pooled analysis model" is actually zero.

[25] Where a reduction in fish consumption occurs only during pregnancy, we would expect that most of the stroke benefit from higher fish consumption before and after pregnancy would still be accrued over a lifetime.

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Table V-21: Change in Annual Stroke Deaths (vs. Baseline) Resulting from a Consumption Limit of 12 oz Per Week by Women of Childbearing Age

Population Group	Stroke Death Cases Per -Year Pooled Analysis Model	CHD Death Cases Per Year Meta-Analysis Model
Women 15-45	An increase of 0.0 (-2.0, 5.1) deaths per year	An increase of 4.0 (-8.1, 15.7) deaths per year

The primary values are the median cases per year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

Second "What If" Scenario: Women of Childbearing Age All Consume 12 Ounces a Week. In this scenario, all women of child-bearing age consume exactly 12 ounces of fish. As with the first scenario, this consumption does not just occur during pregnancy. Because most women consume much less than 12 ounces per week, the majority of women in this age group would have to increase their fish consumption substantially. Only a small minority would have to decrease consumption down to 12 ounces per week. The models predict that the most likely overall impact of this scenario would be a decrease in the number of deaths from stroke in women of childbearing age.

Table V-22: Change in Annual Stoke Deaths (vs. Baseline) Resulting from Consuming Exactly 12 oz Per Week by Women of Childbearing Age

Population Group	Stroke Death Cases Per -Year Pooled Analysis Model	CHD Death Cases Per Year Meta-Analysis Model
Women 15-45	A decrease of 250 (-258, 810) deaths per year	A decrease of 143 (-129, 417) deaths per year

The primary values are the median cases per year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

Third and Fourth "What If" Scenarios: Men and Older Women Reduce Their Fish Consumption. These scenarios model the impact of decreased consumption of fish by: (1) young men; (2) older men; and (3) older women, none of whom are targeted by the current FDA/EPA consumer advisory. In one scenario, there is a one percent reduction in the number of fish consumers (i.e., one percent of fish eaters stop consuming all fish). In the other scenario, all fish consumers in these subpopulations reduce their fish consumption by10 percent. For both scenarios, the models predict that most likely result would be a decrease in deaths averted in each of these subpopulations.

Table V-23: Change in Annual Stroke Deaths (vs. Baseline) Resulting from a One Percent Reduction in the Number of Men and Older Women Who Consume Fish

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Population Group	Stroke Death Cases Per Year Pooled Analysis Model	Stroke Death Cases Per Year Meta-Analysis Model
Women 46+	An increase in 144 (-84, 1,823) deaths per year	An increase in 134 (40, 260) deaths per year
Men 15-45	An increase in 2.9 (-1.8, 23) death per year	An increase in 2.34 (-0.7, 4.5) deaths per year
Men 46+	An increase in 134 (-45, 1,028) deaths per year	An increase in 94 (29, 193) deaths per year

Estimates of increased rates of stroke death resulting from decreased number of fish consumers in three population groups. The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

Table V-24: Change in Annual Stroke Deaths (vs. Baseline) Resulting from a 10 Percent Decrease in the Amount of Fish Consumed by Men and Older Women

Population Group	Stroke Death Cases Per Year Pooled Analysis Model	Stroke Death Cases Per Year Meta-Analysis Model
Women 46+	An increase in 751 (-688, 3,193) deaths per year	An increase in 542 (-122, 1240) deaths per year
Men 15-45	An increase in 13.9 (-13.1, 47) deaths per year	An increase in 9.0 (-3.7, 23) deaths per year
Men 46+	An increase in 575 (-419, 1,862) deaths per year	An increase in 353 (-214, 913) deaths per year

Estimates of increased rates of stroke death resulting from decreased number of fish consumers in three population groups. The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

Fifth "What If" Scenario: 50 Percent Increase In Fish Consumption by Everyone. In this scenario, all subpopulations increase their fish consumption by 50 percent. The models predict that most likely result would be an increase in deaths averted in each subpopulation.

Table V-25: Change in Annual Stroke Deaths (vs. Baseline) Resulting from a 50 Percent Increase in the Amount of Fish Consumed by All Population Groups

Population Group	Stroke Death Cases Per Year Pooled Analysis Model	Stroke Death Cases Per Year Meta-Analysis Model
Women 15-45	A decrease of 52 (-39, 193) deaths per year	A decrease of 35 (-14, 84) deaths per year
Women 46+	A decrease of 2,899 (-1,725, 10,889)	A decrease of 2,198 (-1,411, 5,678)
Men 15-45	A decrease of 53 (-57, 168)	A decrease of 40 (-38, 104)

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	deaths per year	deaths per year
Men 46+	A decrease of 2,151 (-1,810, 6,549) deaths per year	A decrease of 1,507 (-1,691, 4,074) deaths per year

Estimates of decreased rates of stroke death resulting from decreased number of fish consumers in three population groups. The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

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APPENDIX A:
TECHNICAL DESCRIPTION OF THE RISK AND BENEFIT ASSESSMENT METHODOLOGY

(a) Methylmercury and Fish Exposure Assessment

Fish Consumption

Overview – Data Sources

Estimates of daily fish consumption were developed from several different data sources: 1) The U. S. Department of Agriculture's (USDA) Continuing Survey of Food Intake by Individuals (CSFII) survey conducted between 1989 and 1991 (USDA 1993); 2) the National Health and Nutrition Survey (NHANES) conducted in 2001-02 (CDC 2004); and 3) market share data obtained from the National Marine Fisheries Service (NMFS 2002). The aspects of the consumption estimate addressed with the use data from each of these sources is listed in Table AA-1.

CSFII: As the exposure model was designed to generate estimates for each individual in the CSFII survey, the data from this source figured in just about every aspect of the estimates. Records for all fish consumption events were selected for all individuals for whom a full three-day record was included in the survey (3,525 individuals). The survey data were provided with demographic weights that were used to project the survey to the U.S. population. Although more recent data are available, the 89-91 data were accumulated from surveys which tabulated consumption over a three-day period, rather than more recent data which contained records for only two days (CSFII 94-98) or one day (NHANES) The additional day makes the 1989-91 survey a better instrument for characterizing the chronic behavior of fish consumers. Daily intakes from CSFII 89-91 and CSFII 1994-98 are similar.

NHANES: Data from the 30-day fish consumption survey from NHANES were used for two purposes. First, they were used to adjust the short-term population distribution to generate long term fish consumption frequency population distributions and to estimate. Second, they were used to estimate the extent to which different individuals eat a variety of different fish.

NMFS Market Share: Data describing the extent to which different fish species are marketed in the United States were obtained from the National Marine Fisheries Service. Market share data was used to allocate frequency of consumption under two different circumstances. First, it was used to allocate species consumption for CSFII food categories that were composed of multiple species. Second, it was used to allocate species consumption when the short-term survey was considered inadequate for a

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particular serving (see Variation in Fish Species Consumed, below). In addition, a correction factor was applied to portion sizes from the CSFII survey so that total intake matched per capita estimates from NMFS.

Table AA-1: Where different fish consumption data sources were used in the exposure assessment

	CSFII 1989-1991	**NHANES 2003**	**NMFS Market Share as of 2005**
Portion Size	**X**		
Species Consumed	**X**		X
Demographic Characteristics	**X**		
Frequency of Fish Consumption	**X**	**X**	
Variety of Consumption	X	X	

Adjustments for Chronic Frequency of Intake

Short-term surveys often do not provide accurate estimates of long-term food consumption (Paustenbach 2000). In particular, short-term surveys tend to misrepresent infrequent consumers since they will either not account for consumers who did not eat a specific food item during the survey period and they will project a higher average intake for an infrequent consumer who did happen to eat the specific food item during the survey period. As a result, a short-term survey will underestimate the number of eaters and overestimate average daily intake for eaters for longer periods of time. Furthermore, a short-term survey may not accurately reflect the pattern of fish consumption, i.e., individuals who consume a particular species during the survey period may consume other species over a longer period of time.

To compensate for the inaccuracy of short-term food intake surveys, several adjustments were made. First, the number of fish consumption events was decreased and the number of eaters increased by a Long Term-to-Short Term Consumer Ratio (LTSTCR) with an uncertain range of 2.3 to 2.5. Adjusting the survey data for LTSTCR results in an estimate that in a given year, 85 to 95 percent of the total U.S. population consumes fish. This range is consistent with the food consumption/frequency information available from the 30-day National Human and Nutrition Estimation Survey (NHANES; CDC 2001). Since equal and opposite LTSTCRs were applied to the frequency of consumption and number of consumers, the long-term per capita mean consumption of fish was held constant to short-term consumption.

Because short term surveys are better at monitoring consumption patterns for frequent consumers than for infrequent consumers, the LTSTCR in serving frequency was reduced

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for frequent fish consumers using an exponential function that reduced the LTSTCR as the number of servings increased according to the following equation:

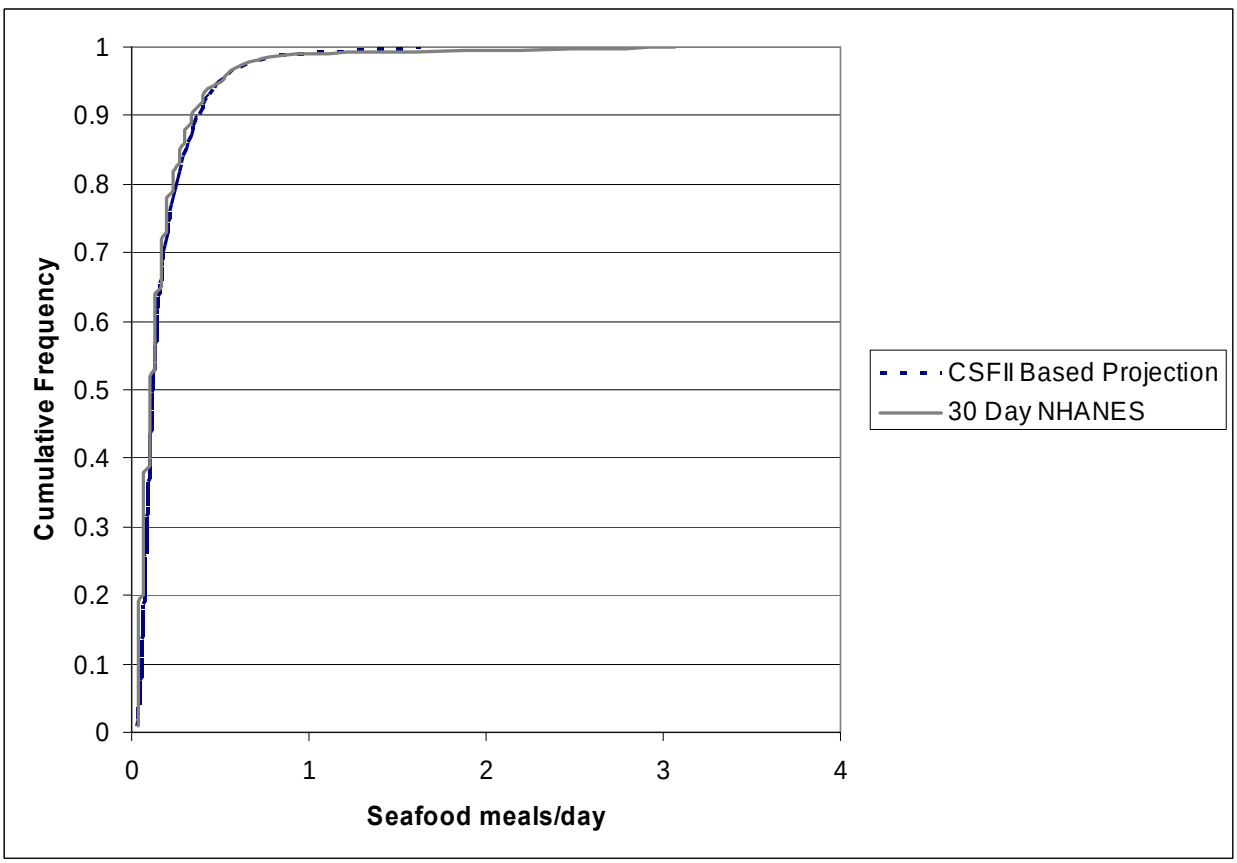
$$AS = \frac{D3S * 122}{LTSTCR^{\frac{\alpha}{D3S}^{\beta}}}$$

Where:

AS = Annual Servings
D3S = 3 Day Servings
LTSTCR = Long Term to Short Term Consumer Ratio
α, β = model parameters

The model parameters used to extrapolate long-term frequency of consumption from short- term records were chosen to be consistent with the 30-day fish consumption data collected by NHANES (see Figure AA-1).

Figure AA-1: Long-Term Frequency Extrapolation for Consumption



The CSFII based projection employed the exponential function described in Carrington and Bolger (2002b), using values of 0.696 and 0.356 for the alpha and beta parameters, respectively. These parameters

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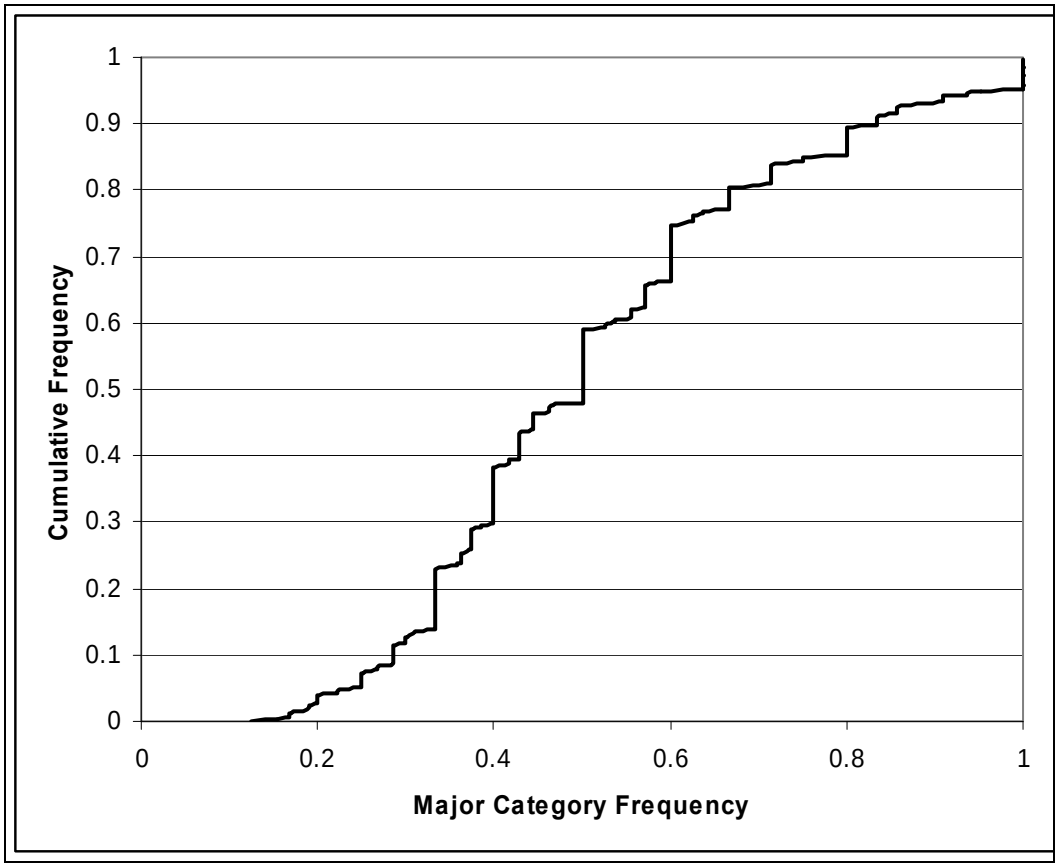
were obtained by fitting the projected frequency distribution to 30 day survey data obtained from NHANES III (CDC, 2003).

Variation in Fish Species Consumed

Short-term surveys also may also fail to portray variation in the types of fish consumed. For example, an individual who consumes a particular species every day of a three-day survey may consume other species at other times during the year. Since the levels of mercury in fish may vary considerably by species, this may significantly influence the exposure estimate for that individual. Therefore, individual exposure estimates employed both the survey data and per capita market share information to build a consumption pattern for each individual. This distribution was derived from the NHANES survey, by calculating the fraction of total fish consumption in the fish category with the highest number of eating occasions for the 403 adult women who consumed fish on four or more occasions (see Figure AA-2).

Figure AA-2: Variation among Individuals of the Variation in Species Consumed



A distribution representing the extent to which a single species dominates fish consumption over a 30-day period. This distribution was used to determine the extent to

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which the short-term survey was used to predict long-term fish consumption behavior. Specifically, the fraction of fish belonging to a single category was used to determine the fraction of the species determined by the CSFII. For example, if all the fish for an individual was an identical species, then the CSFII survey was considered to adequately characterize long term consumptions. If the fraction was low, indicating that the individual ate a wide variety of species, then most of the fish were selected from the market share distribution.

Individual variation in species consumption and overall frequency of consumption were assumed to be independent. The assumption is supported by the observation that the repetition ratio and 30-day frequency of seafood in NHANES was used to determined the extent of variation in species consumption is largely uncorrelated (r = -0.11). Some of the overall variation in species selection by each consumer also comes from CSFII. Since these data are paired, whatever correlation there is between species variation and frequency is represented in the exposure model.

Water Loss during Food Preparation

A concentration factor was applied to serving sizes to reflect water loss during food preparation. These factors were based on water loss of 11 percent for fried fish, 21 percent for poached or steamed fish, and 25 percent for baked or broiled fish (EPA 2002, pages 2-5 and 2-6). Group specific correction factors were calculated based on the frequency of different food preparation procedures (e.g. baking, steaming, or frying) within each fish group. A value of 20 percent was used for fish groups represented in the methylmercury surveillance data but not in the CSFII survey. The resulting concentration factors are listed in Table AA-3. Correction factors were not needed for canned tuna since the methylmercury concentration values in that fish group were obtained after cooking and draining of water or oil from the can.

Portion Size Adjustment

A correction factor of 1.15 was applied to portion sizes from the CSFII survey so that total intake matched per capita estimates from NMFS. This correction was factor was calculated as follows:

Average Intake from CSFII (1989-91): 14.3 g/day
Average Intake from NMFS (2005): 16.2 lbs/year = 20.1 g/day
Weight loss During Cooking: 20 percent

Correction factor = 20.1 * 0.8/ 14.2 = 1.125

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Methylmercury Levels in Fish

Mercury Concentrations in Individual Species

Most surveys of mercury in fish, as well as biomarkers in blood and hair measure total mercury, and as a result do not distinguish between inorganic mercury and methylmercury. However, when the forms are speciated it has been shown that most (over 90 percent) of the mercury in fish is methylmercury (WHO 1990; Hight & Cheng 2006).

In order to combine the fish consumption data with the levels of mercury in fish, it was necessary to map the 268 food codes employed in the CSFII survey with the groups used for reporting methylmercury levels (see Table AA-2). The mapping resulted in a total of 51 fish groups. In most cases, the correspondence was either direct or the fish ingredient in the survey food code was a member of a methylmercury contamination group. For several species, an analog (or surrogate) was chosen. If there was no other species that was very similar, several new distributions were created that combined multiple methylmercury contamination groups. Specifically, groups were created for crabs, lobster, shellfish, finfish, and all other fish. Per capita market share was used to assign histogram frequencies for each group.

Distributions of methylmercury levels in fish were constructed for each of the 51 fish groups which represented over 99 percent of the fish consumed in the United States. Three different methods were used to construct the distributions:

- For fish categories (fresh tuna, canned light tuna, canned albacore tuna, shark, and swordfish) for which there were over 100 observations, distributions were generated empirically by directly sampling from FDA surveillance data.
- For other species for which additional raw survey data are available, distributions were developed by fitting the distributions to the portions of the cumulative distribution above the levels of detection. A battery of ten distributions was fit to each data set and the four that provided the best fit were used to construct a probability tree. An example is shown in Figure AA-3. See Carrington (1996) for further description of the methodology.
- Since raw data were unavailable for some species, distributions were generated with modeled distributions that reflected reported arithmetic mean values published from a National Marine Fisheries Service survey (NMFS 1978a) for each group and a range analogous to those obtained from tuna, shark, and swordfish. Lognormal and Gamma distributions were used to represent the data, with each model assigned a probability of 0.5 to represent model uncertainty. The magnitude of the shape parameters (the geometric standard deviation of the lognormal distribution and the beta parameter of the gamma distribution) were represented as uniform distributions that encompassed the range of values resulting from fitting the shark, swordfish, and tuna data. The scale parameters

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(the geometric mean of the lognormal distribution and the alpha parameter of the gamma distribution) were calculated from the arithmetic mean in the NMFS survey and the shape parameter (Carrington and Bolger, 2002).

The type of distribution used for each species is identified in Table AA-3. The one percent of the fish market not included was presumed to follow the same distribution as the rest of the market.

Table AA-2: Summary of Mercury Concentration Data (FDA 2006)

SPECIES	MERCURY CONCENTRATION (PPM)[1]					NO. OF	SOURCE OF DATA[2]
	MEAN	MEDIAN	STDEV	MIN	MAX	SAMPLES	
ANCHOVIES	0.043	N/A	N/A	ND	0.34	40	NMFS REPORT 1978
BASS (SALTWATER, BLACK, STRIPED)[3]	0.219	0.13	0.227	ND	0.96	47	FDA 1990-04
BASS CHILEAN	0.386	0.303	0.364	0.085	2.18	40	FDA 1990-04
BLUEFISH	0.337	0.303	0.127	0.139	0.634	52	FDA 2002-04
BUFFALOFISH	0.19	0.14	‡	0.05	0.43	4	FDA SURVEY 1990-02
BUTTERFISH	0.058	N/A	N/A	ND	0.36	89	NMFS REPORT 1978
CARP	0.14	0.14	‡	0.01	0.27	2	FDA SURVEY 1990-02
CATFISH	0.049	ND	0.084	ND	0.314	23	FDA 1990-04
CLAM	ND	ND	ND	ND	ND	6	FDA 1990-02
CRAB [4]	0.06	0.03	0.112	ND	0.61	63	FDA 1990-04
CRAWFISH	0.033	0.035	0.012	ND	0.051	44	FDA 2002-04
CROAKER ATLANTIC (Atlantic)	0.072	0.073	0.036	0.013	0.148	35	FDA 1990-03
CROAKER WHITE (Pacific)	0.287	0.28	0.069	0.18	0.41	15	FDA 1990-03
FLATFISH [5]	0.045	0.035	0.049	ND	0.18	23	FDA 1990-04
GROUPER (ALL SPECIES)	0.465	0.41	0.293	0.053	1.205	43	FDA 2002-04
HADDOCK (Atlantic)	0.031	0.041	0.021	ND	0.041	4	FDA 1990-02
HAKE	0.014	ND	0.021	ND	0.048	9	FDA 1990-02
HALIBUT	0.252	0.2	0.233	ND	1.52	46	FDA 1990-04
HERRING	0.044	N/A	N/A	ND	0.135	38	NMFS REPORT 1978

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JACKSMELT	0.108	0.06	0.115	0.04	0.5	16	FDA 1990-02
LOBSTER (NORTHERN/AMERICAN)	0.31	N/A	N/A	0.05	1.31	88	NMFS REPORT 1978
LOBSTER (Species Unknown)	0.169	0.182	0.089	ND	0.309	16	FDA 1991-2004
LOBSTER (Spiny)	0.09	0.14	‡	ND	0.27	9	FDA SURVEY 1990-02
MACKEREL ATLANTIC (N. Atlantic)	0.05	N/A	N/A	0.02	0.16	80	NMFS REPORT 1978
MACKEREL CHUB (Pacific)	0.088	N/A	N/A	0.03	0.19	30	NMFS REPORT 1978
MACKEREL KING	0.73	N/A	N/A	0.23	1.67	213	GULF OF MEXICO REPORT 2000
MACKEREL SPANISH (Gulf of Mexico)	0.454	N/A	N/A	0.07	1.56	66	NMFS REPORT 1978
MACKEREL SPANISH (S. Atlantic)	0.182	N/A	N/A	0.05	0.73	43	NMFS REPORT 1978
MARLIN *	0.485	0.39	0.237	0.1	0.92	16	FDA 1990-02
MONKFISH	0.18	N/A	N/A	0.02	1.02	81	NMFS REPORT 1978
MULLET	0.046	N/A	N/A	ND	0.13	191	NMFS REPORT 1978
ORANGE ROUGHY	0.554	0.563	0.148	0.296	0.855	49	FDA 1990-04
OYSTER	0.013	ND	0.042	ND	0.25	38	FDA 1990-04
PERCH (Freshwater)	0.14	0.15	‡	ND	0.31	5	FDA SURVEY 1990-02
PERCH OCEAN	ND	ND	ND	ND	0.03	6	FDA 1990-02
POLLOCK	0.041	ND	0.106	ND	0.78	62	FDA 1990-04
SABLEFISH	0.22	N/A	N/A	ND	0.7	102	NMFS REPORT 1978
SALMON (CANNED)	ND	ND	ND	ND	ND	23	FDA 1990-02
SALMON (FRESH/FROZEN)	0.014	ND	0.041	ND	0.19	34	FDA 1990-02
SARDINE	0.016	0.013	0.007	0.004	0.035	29	FDA 2002-04
SCALLOP	0.05	N/A	N/A	ND	0.22	66	NMFS REPORT 1978

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SCORPIONFISH	0.286	N/A	N/A	0.02	1.345	78	NMFS REPORT 1978
SHAD AMERICAN	0.065	N/A	N/A	ND	0.22	59	NMFS REPORT 1978
SHARK	0.988	0.83	0.631	ND	4.54	351	FDA 1990-02
SHEEPSHEAD	0.128	N/A	N/A	0.02	0.625	59	NMFS REPORT 1978
SHRIMP	ND	ND	ND	ND	0.05	24	FDA 1990-02
SKATE	0.137	N/A	N/A	0.04	0.36	56	NMFS REPORT 1978
SNAPPER	0.189	0.114	0.274	ND	1.366	43	FDA 2002-04
SQUID	0.07	N/A	N/A	ND	0.4	200	NMFS REPORT 1978
SWORDFISH	0.976	0.86	0.51	ND	3.22	618	FDA 1990-04
TILAPIA	0.01	ND	0.023	ND	0.07	9	FDA 1990-02
TILEFISH (Atlantic)	0.144	0.099	0.122	0.042	0.533	32	FDA 2002-04
TILEFISH (Gulf of Mexico)	1.45	N/A	N/A	0.65	3.73	60	NMFS REPORT 1978
TROUT (FRESHWATER)	0.072	0.025	0.143	ND	0.678	34	FDA 2002-04
TUNA (CANNED, ALBACORE)	0.353	0.339	0.126	ND	0.853	399	FDA 2002-04
TUNA (CANNED, LIGHT)	0.118	0.075	0.119	ND	0.852	347	FDA 2002-04
TUNA (FRESH/FROZEN, ALBACORE)	0.357	0.355	0.152	ND	0.82	26	FDA 2002-04
TUNA (FRESH/FROZEN, BIGEYE)	0.639	0.56	0.184	0.41	1.04	13	FDA 2002-04
TUNA (FRESH/FROZEN, SKIPJACK)	0.205	N/A	0.078	0.205	0.26	2	FDA 1993
TUNA (FRESH/FROZEN, Species Unknown)	0.414	0.339	0.316	ND	1.3	100	FDA 1991-2004
TUNA (FRESH/FROZEN, YELLOWFIN)	0.325	0.27	0.22	ND	1.079	87	FDA 2002-04
TUNA(FRESH/FROZEN, ALL)	0.383	0.322	0.269	ND	1.3	228	FDA 2002-04
WEAKFISH (SEA TROUT)	0.256	0.168	0.226	ND	0.744	39	FDA 2002-04
WHITEFISH	0.069	0.054	0.067	ND	0.31	28	FDA 2002-04
WHITING	ND	ND	‡	ND	ND	2	FDA SURVEY

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							1990-02

1 - Mercury was measured as Total Mercury and/or Methylmercury. ND - mercury concentration below the Level of Detection (LOD=0.01ppm). NA - data not available.

2 - Source of data: FDA Surveys 1990-2006, "National Marine Fisheries Service Survey of Trace Elements in the Fishery Resource" Report 1978 , "The Occurrence of Mercury in the Fishery Resources of the Gulf of Mexico" Report 2000

3 - Includes: Sea bass/ Striped Bass/ Rockfish

4 - Includes: Blue, King, and Snow Crab

5 - Includes: Flounder, Plaice, Sole

Figure AA-3: Fitted Distributions for Mercury in Crab Meat

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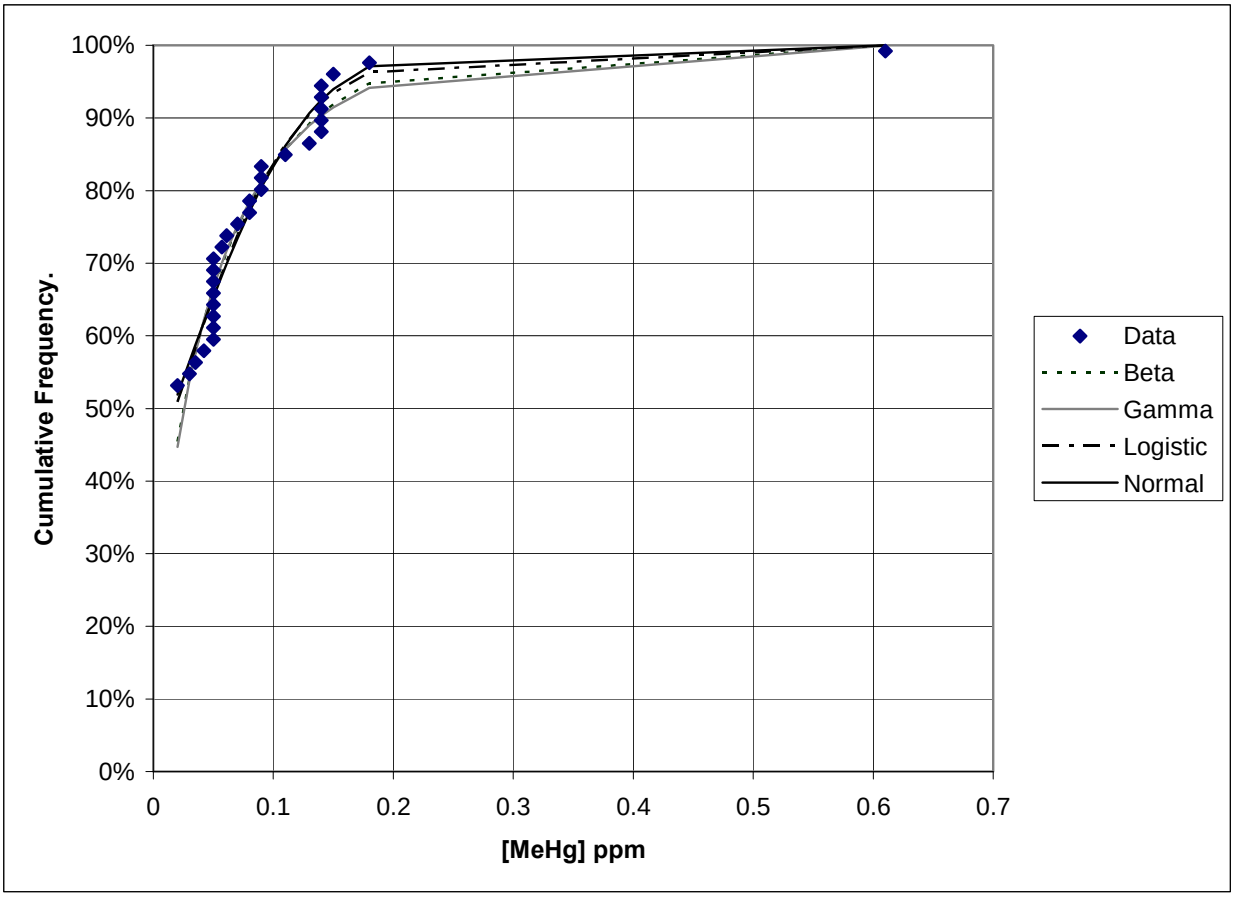

An example of a fitted distribution. Ten different distributions were fit to the sample Hg data for Crabs. The four best models were used to create a probability tree that describes the frequency distribution with a representation of model uncertainty. A primary advantage of using distributions to describe the data is that they can be used to extrapolate the concentration in the samples that are below the level of detection – which comprised about 50 percent of the crab samples.

Table AA-3: Summary of Mercury Concentration Models

Species	Market Share[1]	Mean Hg (ppm)	Distribution Type[2]	Concentration Factor[3]
Tilefish, Gulf	0.01%	1.450	Surrogate	0.839
Shark	0.07%	0.988	Empirical	0.758
Swordfish	0.44%	0.976	Empirical	0.75
Mackerel, King	0.05%	0.73	Surrogate	0.8
Orange Roughy	0.20%	0.550	Modeled	0.809
Marlin	0.02%	0.489	Modeled	0.8
Grouper	0.27%	0.46	Modeled	0.823
Tuna, Fresh	1.22%	0.384	Empirical	0.8
Mackerel, Spanish	0.05%	0.368	Surrogate	0.8

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Tuna, Albacore Canned	3.81%	0.353	Empirical	1
Bluefish	0.06%	0.34	Modeled	0.839
Bass, Freshwater	0.19%	0.318	Modeled	0.791
Lobsters, American	1.22%	0.31	Surrogate	0.758
Croaker, Pacific	0.00%	0.303	Modeled	0.871
Bass, Saltwater	0.51%	0.301	Modeled	0.797
Lingcod and Scorpion fish	0.02%	0.286	Surrogate	0.802
Sablefish	0.19%	0.273	Surrogate	0.839
Trout, Saltwater	0.10%	0.269	Modeled	0.77
Halibut	0.48%	0.22	Modeled	0.761
Carp and Buffalo fish	0.04%	0.203	Modeled	0.871
Haddock, Hake, and Monkfish	4.86%	0.17	Modeled	0.802
Perch, Freshwater	0.14%	0.162	Modeled	0.785
Snapper, Porgy, and Sheepshead	0.86%	0.137	Modeled	0.812
Skate	0.46%	0.137	Surrogate	0.758
Lobsters, Spiny	0.71%	0.121	Modeled	0.758
Tuna, Light Canned	11.41%	0.118	Empirical	1
Cod	3.36%	0.115	Modeled	0.809
Tilefish, Atlantic	0.01%	0.111	Modeled	0.839
Smelt	0.09%	0.092	Modeled	0.867
Mackerel, Chub	0.61%	0.088	Surrogate	0.8
Whitefish	0.19%	0.075	Modeled	0.752
Croaker, Atlantic	0.21%	0.073	Modeled	0.871
Squid	1.92%	0.07	Surrogate	0.818
Catfish	5.71%	0.068	Modeled	0.8
Butterfish	0.04%	0.0580	Surrogate	0.839
Pike	0.10%	0.056	Modeled	0.75
Crabs	2.12%	0.05	Modeled	0.775
Flatfish	2.42%	0.05	Modeled	0.761
Anchovies, Herring, and Shad	3.06%	0.05	Surrogate	0.737
Mackerel, Atlantic	1.04%	0.049	Surrogate	0.8
Pollock	7.32%	0.049	Modeled	0.794
Perch, Ocean and Mullet	0.47%	0.04	Surrogate	0.809
Trout, Freshwater	0.60%	0.037	Modeled	0.752
Crawfish	0.47%	0.033	Modeled	0.773
Salmon	6.83%	0.028	Modeled	0.77
Clams	2.04%	0.023	Modeled	0.764
Oysters and Mussels	2.22%	0.023	Modeled	0.782
Scallops	1.46%	0.023	Modeled	0.793
Tilapia	4.83%	0.02	Modeled	0.8
Sardines	1.73%	0.016	Modeled	0.75
Shrimp	22.21%	0.012	Modeled	0.776

1 – Market share calculation based on 2005 National Marine Fisheries Service published landings, imports and exports data (NMFS 2005; NMFS 2008) .

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As a result of species not included in the list, the sum of the market share values is about 99 percent.
2 - *Empirical* – Direct sampling of data set, used for large data sets with very few values below the limit of detection. *Fitted* – Modeled distribution with uncertainty about model form (see text for additional explanation). Used for data sets with a limited number of observations, often with many values below the level of detection. *Surrogate* – Two generic distributional forms (lognormal or gamma) were employed, with a mean value from 1978 National Marine Fisheries Survey, and a shape parameter shape derived from distributions for other species. This technique was used when only mean values are available.
3 – These values reflect weight after food preparation as a percentage of initial weight. Mercury concentrations for fish as eaten were calculated by dividing initial concentration by the correction factor. No correction factor was applied for canned tuna, since the mercury measurements were made after cooking.

Biomarker Calculations: Mercury in Blood and Hair

Diet-Blood Relationship

While many studies have attempted to relate dietary methylmercury exposure to blood mercury levels, in most cases the correlation is very poor, with r values of 0.3 or less (reviewed in WHO 1990). This lack of correlation may be attributed in large part to the failure of short-term measurements of mercury exposure to gauge long-term dietary exposure (Sherlock & Quinn 1988). The study by Sherlock et al. (1984), in which 20 male volunteers consumed controlled fish diets with known methylmercury concentrations over a 100-day exposure period, was selected for use in this assessment. Mercury blood values monitored for the duration of the study were used to project equilibrium values for a chronic diet-blood relationship. The mean body weight for the subjects was 71 kg, with a range of 52 to 102 kg. The relationship between dietary exposure and mercury blood level appeared to be linear with respect to dose. Although the ratio of mercury blood level to dietary exposure was inversely related to body weight, it was not directly proportional to body weight. Therefore, Sherlock et al., (1984) suggested using a body weight (BW) dose conversion factor of $BW.^{1/3}$ We have determined that a conversion factor of $BW^{0.44}$ will result in corrected values that have no correlation with body weight (i.e. r=0; see Figure AH-4) .

Sherlock et al. (1984) extrapolated steady-state blood levels from two other parameters (a and b). The extrapolated steady-state levels reported in the paper were not corrected for body weight. Therefore, the values for each of the 20 subjects were recalculated using $BW^{0.44}$ to normalize all values to a BW of 70 kg. In order to characterize the measurement error for each subject, 40 bootstrap data sets were generated from the standard deviations reported for each parameter estimate. Each bootstrap set was then fit by 10 different frequency distributions using least squares regression. Three weighted models were retained per bootstrap, which were assigned probabilities on the basis of goodness-of fit and number of parameters (Carrington 1996). The resulting 120 models were then employed as a probability tree to characterize uncertainty from measurement

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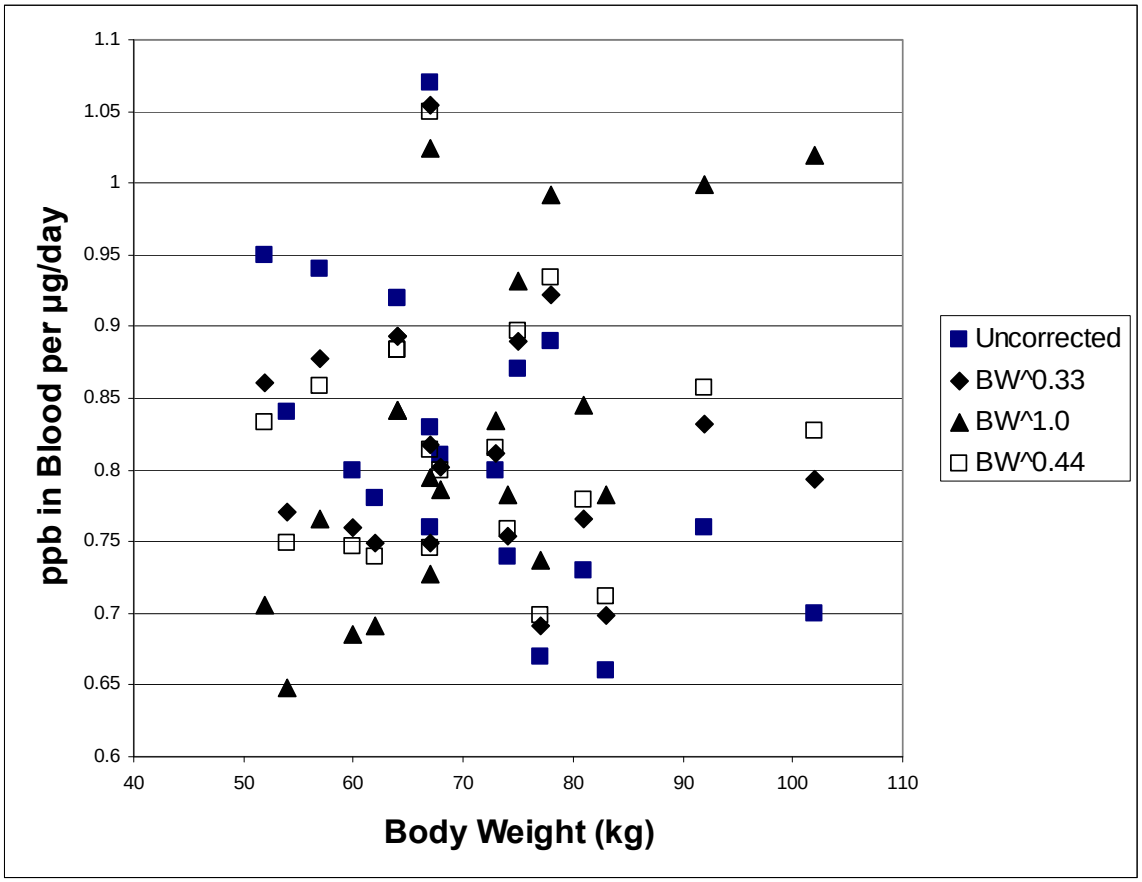
error and model selection. When used in a simulation, the contribution of body weight was calculated by applying $BW^{0.44}$ to the weight of each subject in the food consumption survey.

Figure AA-4: Influence of Body Weight on Blood/Diet Ratio



Exposure to Other Sources of Methylmercury

Since the present model is intended to represent methylmercury exposure from fish, background mercury blood levels were added to the model to acknowledge the possibility of minor exposures from sources other than fish. This range reflected the levels at the low end of the NHANES 30-day fish survey (CDC 2003). Virtually everyone in the NHANES survey had a blood mercury level above zero, yet 10-20 percent of the NHANES survey population reported no fish consumption, suggesting that there are contributions to blood mercury levels from other sources (e.g., dental amalgams) other

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than fish. To model the population distribution for background blood methylmercury (i.e., methylmercury from sources other than fish), a normal distribution with an uncertain range of 0.05 to 0.1 ppb for the mean and a standard deviation of 0.02 ppb was used. The distribution was truncated at zero.

Blood-Hair Relationship

For the purposes of predicting hair levels from given blood levels, an empirical distribution was constructed from paired observations from the NHANES 1999-2000 survey (CDC 2003). Since this data is more recent, has a larger sample size, and reflects exposures ranges found in the United States, it was used in favor of other data used in previous versions of the model (Carrington et al., 2002; Carrington et al., 2004). The data were used as follows:

- In order to avoid potential errors arising from analytical imprecision at low concentration levels, only individuals with total mercury levels above one ppb were used.
- The 1999-2000 NHANES survey measured both total mercury and inorganic mercury in blood. In order to avoiding confounding contributions from inorganic mercury, only individuals with an inorganic contribution of 25 percent or less of the total were used.
- The survey consisted of children aged one-five and adult women. Since the present model is only concerned with exposure of adults to mercury, only the data from adult women were used.
- An individual with an extremely high hair level (849 ppm) was excluded since this hair level almost certainly did not result from the consumption of fish (see McDowell et al., 2004 for further discussion; see also Section II of this report).
- Methylmercury concentrations for the 526 individuals who met the above criteria were calculated by subtracting the inorganic mercury concentration from the total concentration.
- Hair/Blood ratios were calculated for each individual to develop a population distribution of ratios. This approach presumes that the ratio is independent of dose (i.e. the relationship between blood methylmercury and hair methylmercury is linear.) The ratio is also presumed to be independent of body weight.
- Not all of the variation observed may be true variation in the pharmacokinetic relationships between blood and hair (or blood and hair, which hair is used as a marker for). Of particular concern is the fact that blood measurements fluctuate and are dependent on the time since the last fish meal, and as a result, measurements made at a single time point may not accurately reflect long-term exposure. Since inorganic mercury was not measured independently in hair, it is also possible that there is some contamination of hair from inorganic mercury – perhaps from environmental sources. Regardless of the explanation, because actual pharmacokinetic variation is almost certainly narrower that the apparent distribution, the distribution was truncated with uncertainty ranges of 20 percent

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at both ends.

Paired measurements of hair and blood mercury concentrations are plotted in Figure AA-5. The distribution of ratios is shown in Figure AA-6. The tails of the distribution of ratios, which were partially (i.e. as an uncertainty) excluded are shown in Figure AA-7 and Figure AA-8. The figures illustrate that while the majority of the hair/blood ratios fall in a relatively narrow range of 0.1 to 0.3, there is significant departure from this range at both the upper and lower tails.

Figure AA-5: Hair and Blood Concentrations in Women of Childbearing Age in the U.S. (from NHANES)

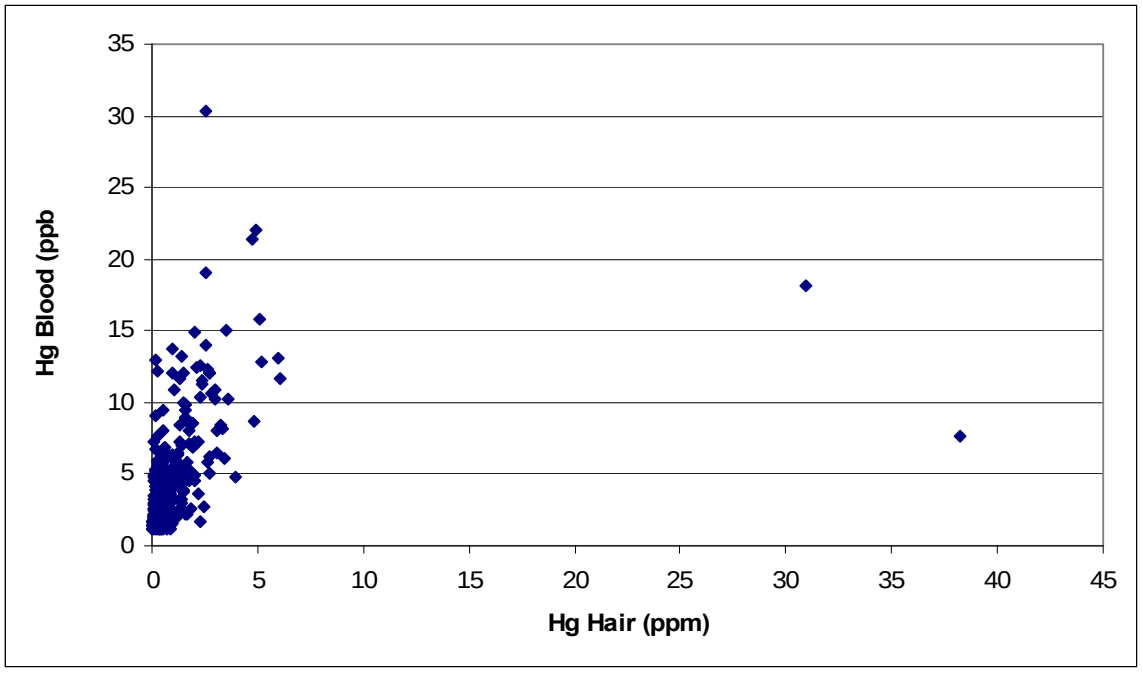

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Figure AA-6: Hair/Blood Ratios in Women of Childbearing Age in the U.S. (from NHANES)

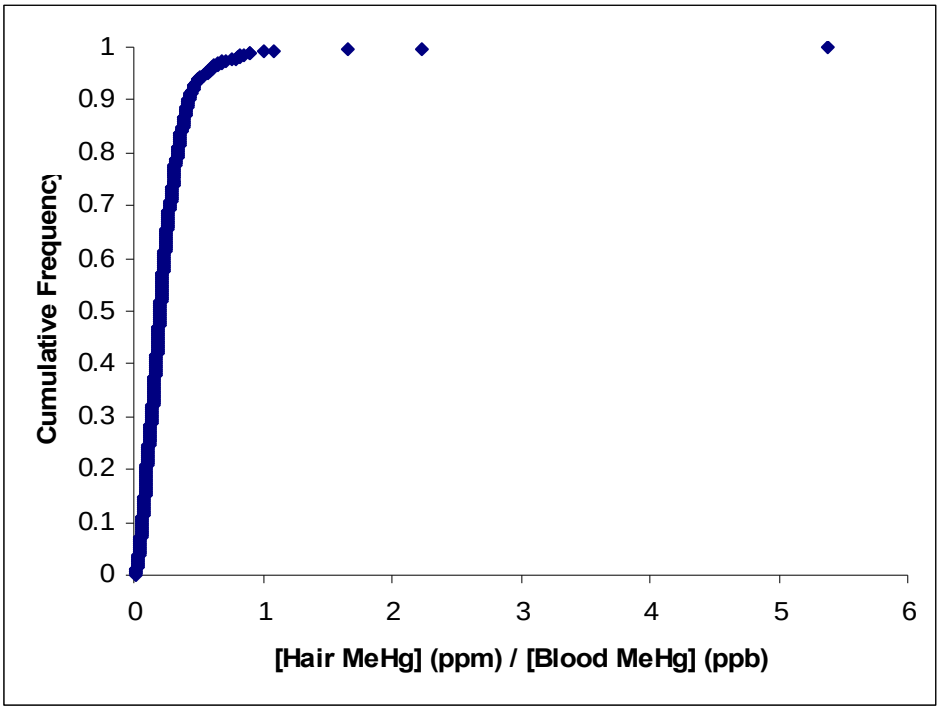

Figure AA-7: Hair-Blood Ratios, the Lower Tail of the Distribution (from NHANES)

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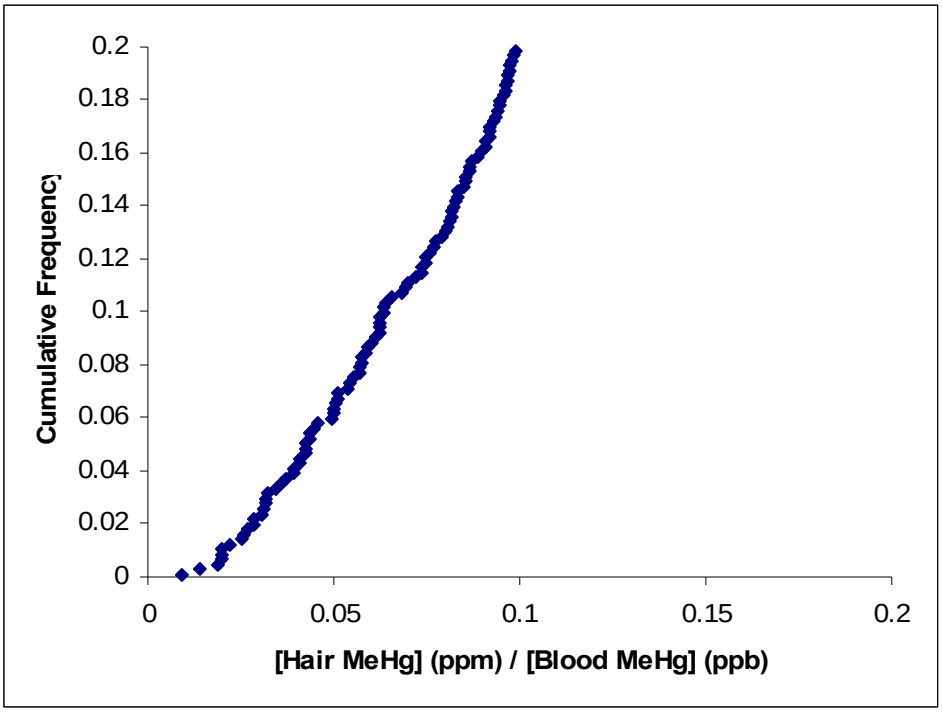

Figure AA-8: Hair-Blood Ratios, the Upper Tail of the Distribution (from NHANES)

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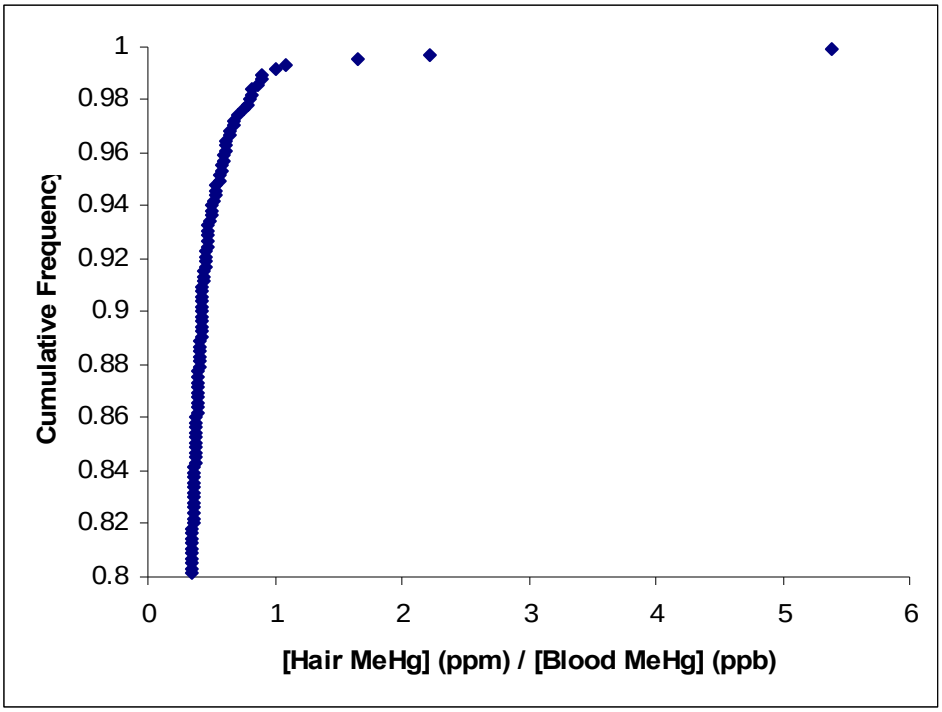

(b) Dose-Response Functions

Methylmercury and Neurological Endpoints

Milestones at Two Years – FDA (Carrington & Bolger 2000)

The dose-response function used to represent the relationship between maternal exposure to mercury, using hair mercury as a marker for dose, and the age of onset of walking and talking was based on the analysis described in Carrington and Bolger (2000). This analysis is based on pooled data from the Iraqi poisoning episode in early 1970's and data obtained from the prospective epidemiology study in the Seychelles. The models used in Carrington and Bolger (2000) differ in one or more of 5 different aspects: 1) The primary model used to describe the relationships between methylmercury exposure and outcome, 2) the statistical model used to describe variation the use of background terms, 3) background terms used to describe variation independent of dose, 4) study variables that accounted for differences between Iraq and Seychelles, and 5) the order in which the above components are assembled, which in at least some cases, determined how they interacted with one another. Additional details, including a list of the alternative model components, are given in Appendix C.

One modification was made to the prior analysis. Since the onset of walking and talking in Iraq was recorded in sixth month increments, the reported ages were 0-6 months higher than the actual age of onset. Since milestones in the Seychelles study were recorded in

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one month increments, this accounts for some, but not all, of the differences in the baseline age of onset between the two populations. To correct for this reporting imprecision, three months were subtracted from the reported milestone ages for the data obtained from Iraq. The data were the reanalyzed as described previously. Although this correction reduced the importance of the study parameter used to account for differences in the two populations, it had little impact on model fitness the other parameter estimates.

IQ at Seven Years – Axelrad et al. (2007)

The analysis developed by Axelrad et al (2007) for the U.S. Environmental Protection Agency (EPA) developed separate integrated estimates of IQ for three different prospective epidemiology studies: New Zealand, Seychelles, and the Faroe Islands which are presented in the following table.

Table AA-4: IQ Decrement per ppm of Maternal Hair Mercury in Axelrad (2007) Analysis)

Study	Linear Slope[1]	Pop. Size[2]	Notes
New Zealand	-0.50 ± .027	237	Reported in Table III of Crump (1998); outlier child omitted; rescaled to study population variance
Seychelles	-0.17 ± 0.13	643	Reported in Table 2 of Myers (2003); rescaled to study population variance
Faroe Islands	-0.124 ± .057	917	Reported in Axelrad et al (2007), based on structural equation modeling of three IQ subtests by Budtz-Jørgensen *et al.* (2005).

1 ± .Standard Error of the Mean
2 –Population size reflects final study group size used to for the dose-response evaluation.

Axelrad et al. (2007) used a Bayesian analysis to generate an estimate of a single slope of -0.153 and confidence intervals based on the standard error of the mean that ranged from -0.047 to -0.259. That estimate is employed in our analysis as a normal distribution, per Axelrad, with a mean of -0.153 and standard deviation of 0.064.

IQ at Seven Years – Harvard Center for Risk Analysis (HCRA): Cohen et al. (2005b)

Cohen et al. (2005b) conducted an analysis that is very similar to that of Axelrad et al. (2007). However, there are two noteworthy differences. First, the uncertainty analysis was based on a limited number of alternative assumptions. Although it was based on the same three epidemiology studies, it did not generate separate IQ estimates for each study. It was noted that much lower estimates were obtained from the Seychelles than from the other two studies. It is also not clear whether the confidence ranges are statistical (i.e. fifth and 95th percentiles) or encompass the entire range of IQ estimates. Second, the analysis developed linear coefficients from the Faroe Islands study using the low end of the log(dose)-linear slope reported in the study. This range was chosen because it most closely matches exposures in the United States. The results using this analysis yielded a central estimate of -0.7 IQ points per ppm in maternal hair. The confidence range for this

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estimate was 0 to -1.5 IQ points per ppm in hair. However, because the NAS committee deemed the log(dose) transform used in the Faroe study to be "biologically implausible" (NRC, 2000), Cohen et al. (2005b) also calculated from the first and third quartiles, which yielded an estimate of -0.2 IQ points per ppm in hair – which is much closer to the Axelrad et al. (2007) estimate derived from the entire range.

As pointed out in the National Academy of Sciences methylmercury report (NRC, 2000), the log(dose)-linear and linear models provide a similar description of at least some of the data from the Faroe Islands study. However, the models diverge greatly at doses both below and above the ranges encountered in the study. In addition to the more esoteric and theoretical criticisms of the log(dose) regression, there are empirical grounds for discounting the log(dose) transform from other data in the literature and from common experience. First, the log(dose) transformation implausibly predicts that the size of the effect increases as the dose decreases. In fact, the predicted increase in IQ approaches infinity as the dose approaches zero. If this were even approximately true there would be huge differences in the IQ of populations who do not consume fish. Second, the log(dose) transformation predicts that there is relatively little additional effect on IQ at doses higher that those encountered in the Faroe Islands study. This prediction is inconsistent with the results from Iraq and Minamata where clinical effects that were much more severe than those modeled in the Faroe Islands study occurred at higher levels of exposure. The log(dose) scale yields an estimated decrease of about seven IQ points per 10-fold increase in mercury level. Since the levels in various tissues were 10-100 times higher in Iraq and Minamata than in the Faroe Islands, the log linear model predicts relatively modest further effects corresponding to seven-14 IQ points at the higher dose levels (i.e. less than one standard deviation). However, two children in Iraq were unable to walk or talk at five years of age. Since the standard deviation for these milestones is roughly two months, this represents a developmental delay of about 18 standard deviations, or about 270 points on an IQ scale. Many other children in the Iraq study also displayed overt neurological symptoms that are not predicted by the log linear model (see Figure AA-11). On the other hand, the observations from Iraq are consistent with a linear model (Carrington & Bolger, 2000, and see above) that is close to the slope noted in the secondary analysis from Cohen et al. (2005b). Given its implausibility, the log(dose) transformed doses does not merit serious consideration as a mathematical tool for drawing conclusions from the Faroe Islands study. The secondary analysis based on the range of the Faroe Islands data is more reliable.

Finally, the Cohen et al. (2005b) analysis did not yield a formal quantitative representation of uncertainty. They did present a plausible range of values that was based on various combinations of scores that were grouped by the similarity of the individual measures (e.g. cognitive, motor, language) or the study in the test was conducted (i.e. New Zealand Seychelles, or Faroe Islands). The uncertainty ranges in our simulation models employ a probability tree comprised of the individual measures using the weights assigned in the original paper. Also this approach yields a wider confidence interval than the plausible range in the original report, the average is identical.

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Bayley Scales at 12 months – Poland Study (Jedrychowski et al., 2005)

A small study of 233 infants in Krakow, Poland conducted by Jedrychowski et al. (2005) recorded the concentration of mercury in maternal and cord blood and subsequently examined the infants at 12 months of age. The range of mercury exposures was relatively narrow and lower than either the Seychelles or the Faroe Islands. Two test domains were reported – the Bayley Cognitive and the Bayley Psychomotor. After obtaining the raw data from the authors, the relationship between both biomarkers and both test scores was examined by linear regression. It may be observed from Figure AA-9 and Figure AA-10 that the regression slopes are relatively flat relative to the overall variation in the scores. Nonetheless, there is a small negative slope for three of the four regression results which are similar in magnitude (see Table AA-5).

Figure AA-9: Regression Analysis for Poland Study – Maternal Blood Hg

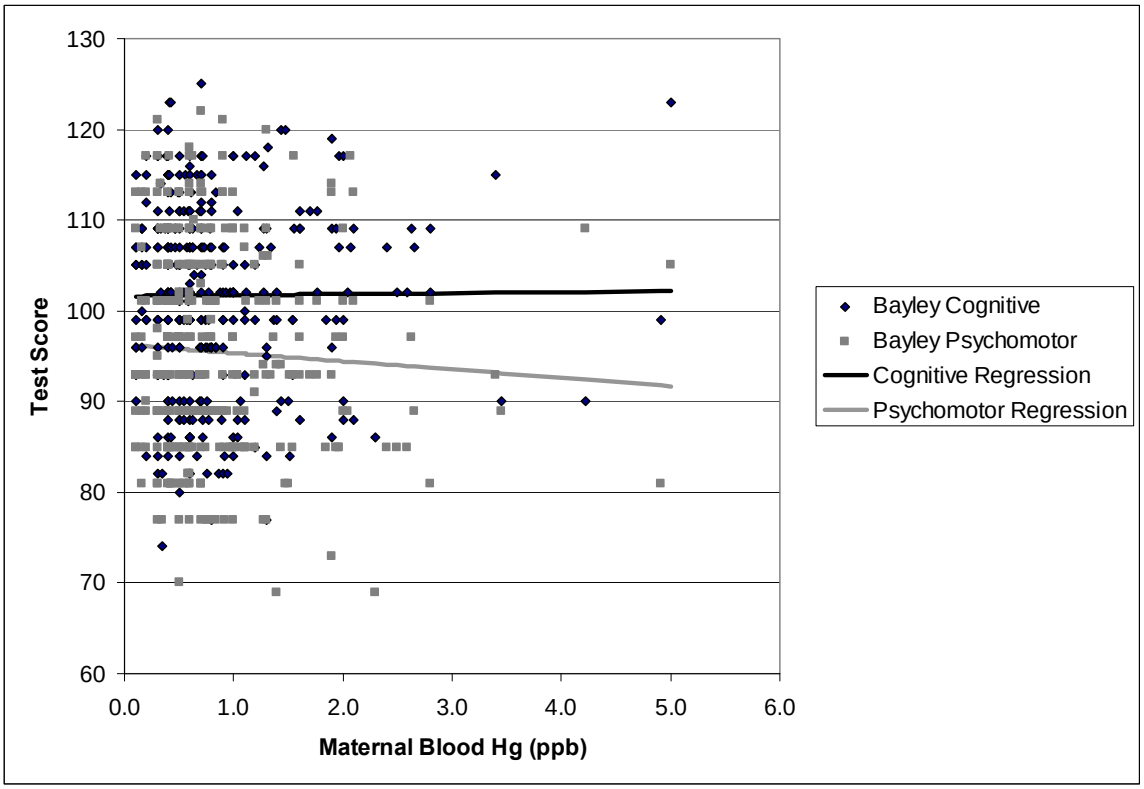

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Figure AA-9: Regression Analysis for Poland Study – Cord Blood Hg

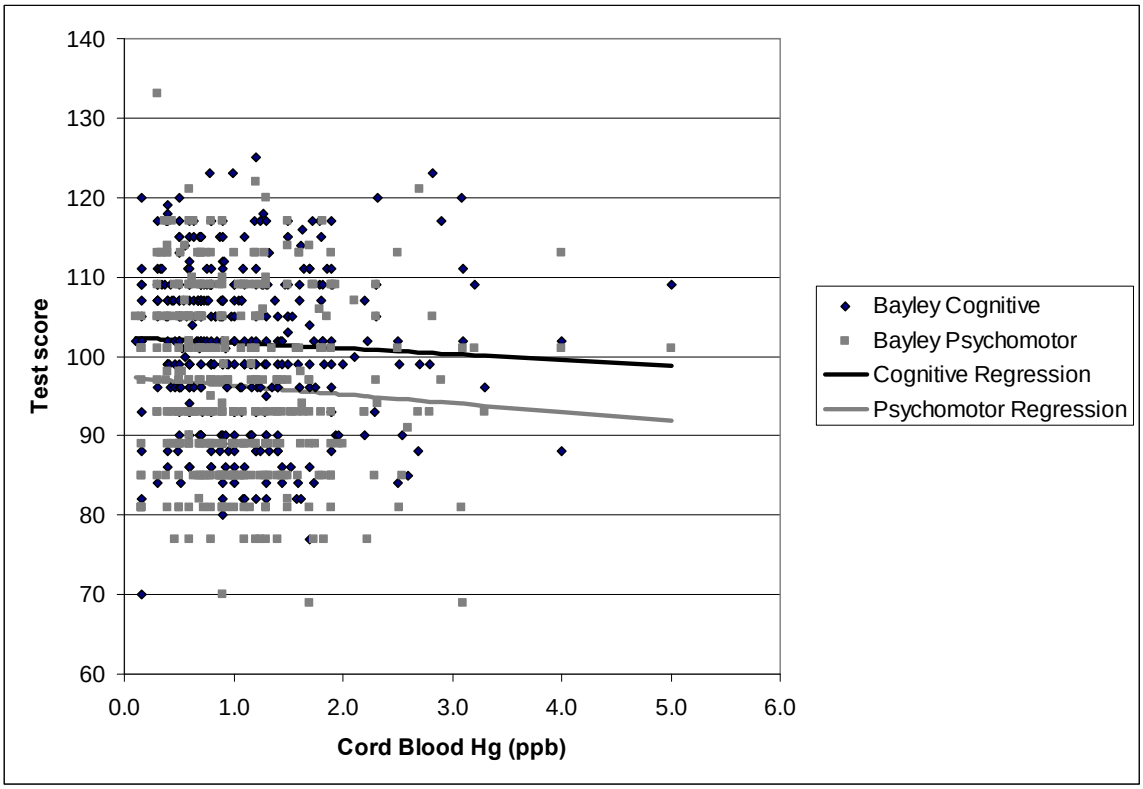

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Table AA-5: Linear Regression Analysis for Poland Study

Hg Biomarker	Bayley Test Score	Regression Slope	Test SD	Z slope	Z Slope Hair Equivalent[1]
Maternal Blood	Cognitive	0.1	10.3	0.01	0.05
Maternal Blood	Psychomotor	-0.9	11.0	-0.08	-0.37
Cord Blood	Cognitive	-0.7	9.8	-0.07	-0.22
Cord Blood	Psychomotor	-1.1	11.0	-0.10	-0.30

1-Conversion factors of 5 and 3.3 were used to convert maternal and chord blood concentrations to hair equivalents, respectively.

Comparison of Neurodevelopmental Dose-Response Functions

Quantitatively, the dose-response functions developed from Iraq, New Zealand, Seychelles, and the Faroe Islands can be grouped into three categories (see Figure AA-11 and Figure AA-12):

1. The dose-response functions developed from developmental milestone data from the Iraqi poisoning episode, the IQ functions derived from the Faroe Islands using a linear dose-response model, and the Myers et al. (2003) slope for IQ in the Seychelles are all similar at both high and low doses. Since the Iraqi estimates are anchored on high dose data, only this group of dose-response functions is consistent to what was observed with the Iraqi study where there are data to anchor the high dose estimates.
2. The two estimates derived from New Zealand and the linear slope derived from the lower quartile of the log-dose transformation of the Faroe Islands study by Cohen et al. (2005b) yield slopes that are much higher than those in the first group. These slopes are not consistent with Iraq. The Faroe Islands slope is demonstrably different because it is derived from a supralinear dose-response function. However, the New Zealand study does seem to indicate a higher neurodevelopmental effect relative to normal variation than would be expected from the Iraqi epidemic. Although the slope derived from the Poland study might also be placed in the "high" category, it is not so much higher than Iraq that it is necessarily unrealistic.
3. The slope for IQ derived by Cohen et al. (2005b) from the Seychelles study is slightly positive (i.e. the net decrease is negative). When extrapolated to high doses, this is also clearly inconsistent with the epidemics in Iraq and Japan. This discrepancy can be explained without resorting to uncontrolled variables. First, a sublinear dose-response model is plausible. Second, the fact that the methylmercury exposure in the Seychelles is almost entirely from fish may provide a beneficial effect of fish consumption that equals or exceeds the negative effect of methylmercury.

The bases of the confidence intervals for the three dose-response functions considered in this analysis are different. These differences reflect the scientific rationale behind the derivation of the dose-response functions from their associated data. Although these

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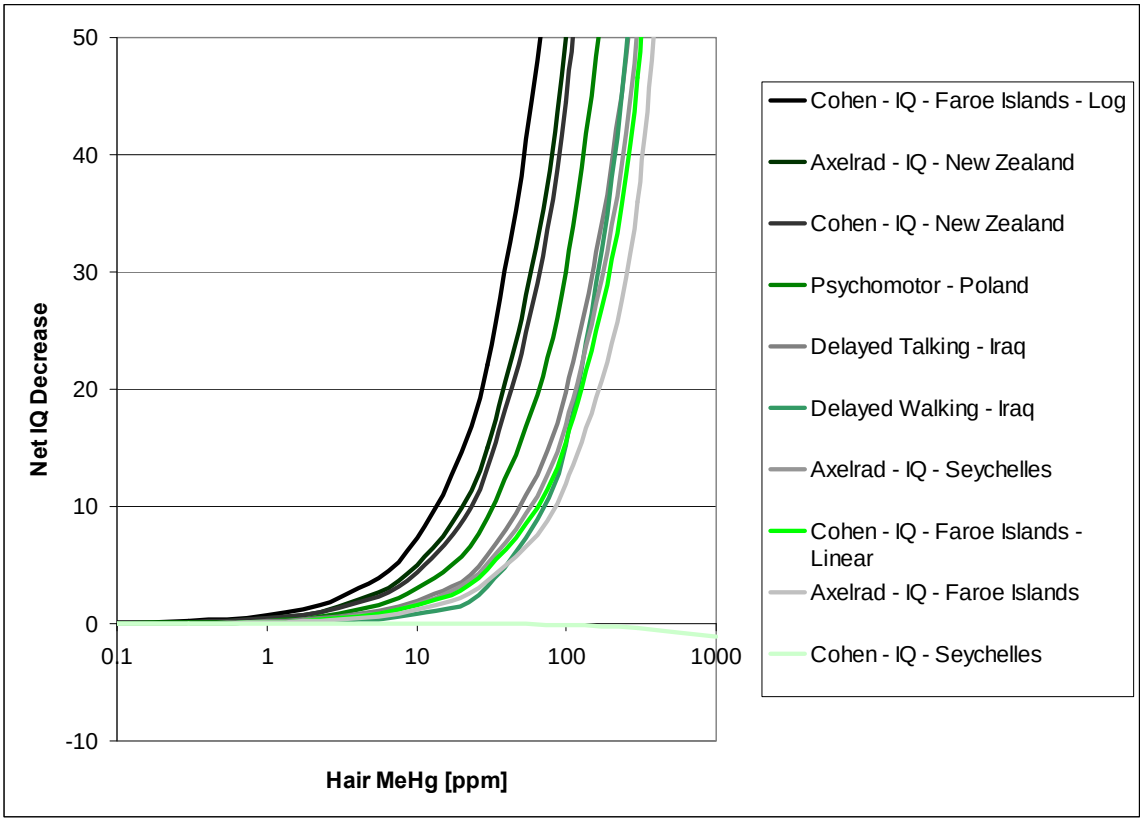
differences have relatively little effect on the central estimates, they do affect the width and shape of the confidence intervals. In particular, some dose-response functions reflect statistical notions of probability (i.e., the uncertainty is related to an underlying frequency), while some do not. Uncertainties based on notions of frequency can be represented by continuous statistical distributions. The other sources of uncertainty may be represented with probability trees, where the sum of the probabilities of each model, study, or measure is one (Hacking, 1976; Rescher, 1993). The sources of uncertainty for each dose-response function considered are summarized in Table AA-6. In spite of the differences in approach, the confidence intervals for the neurobehavioral dose-response functions have a breadth that is quite comparable (see Figure AA-12).

Figure AA-11: Developmental Effects of Methylmercury: High Doses on a Log Scale



The values plotted are the median estimates of the uncertainty distributions. The dose-response functions are listed in the legend in the order in which they appear on the graph, from left to right at the high-dose end of each function.

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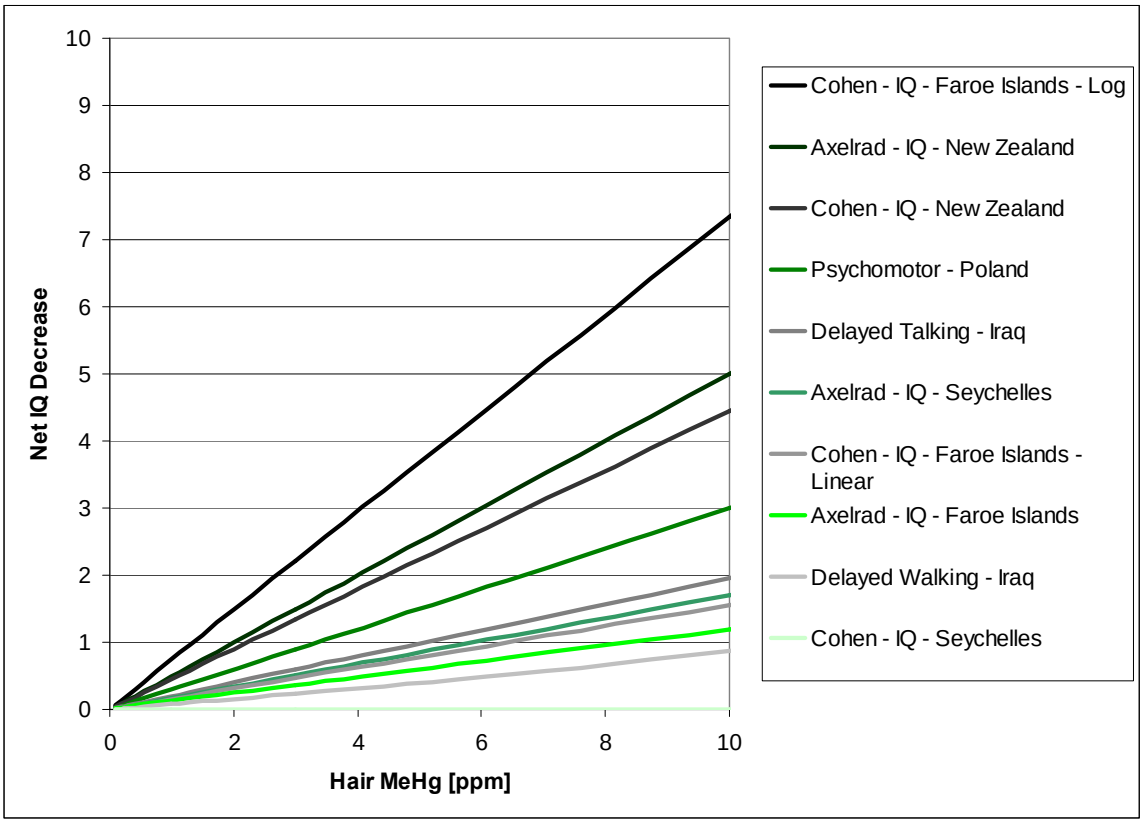
Figure AA-12: Developmental Effects of Methylmercury: Low Doses on a Linear Scale



The values plotted are the median estimates of the uncertainty distributions. The dose-response functions are listed in the legend in the order in which they appear on the graph, from top to bottom at the high-dose end of each function. The functions labeled from Iraq also include data from the Seychelles.

Table AA-6: Sources of Uncertainty Represented in the Neurobehavioral Dose-Response Functions

Dose-Response Analysis	Sampling Error[1]	Model Uncertainty[2]	Study Uncertainty[3]	Measure Uncertainty[4]
Carrington & Bolger (2000)	No	Yes	Yes	No
Axelrad et al.(2007)	Yes	No	Yes	No
Cohen et al. (2005b)	No	No	Yes	Yes

1. *Sampling Error*. This statistical notion of probability arises when generalizations about a large population are drawn from a smaller population. The confidence intervals reflect the notion that the small sample is randomly drawn from the entire population and that the subset may not be entirely representative of the whole population.

2. *Model Uncertainties*. Different mathematical equations can often be used to draw a generalization from data. As long as the models are in roughly the same range as the data, then it may make little difference which mathematical form is used since all will be constrained by the data. On the other hand, when extrapolating from high to low doses, the models are often not sufficiently constrained by

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data at low doses to make model selection an irrelevant issue. Since it is generally not possible to establish that one and only one dose-response model is correct, potential model bias may be eliminated by including model uncertainty in the analysis by using more than one model.

3. *Study Uncertainties.* It is not uncommon for different studies that are concerned with causal relationships between the same variables to yield different results. This can generally be attributed to the presence of one or more uncontrolled variables in at least one of the studies. Not surprisingly, variations in apparent causal relationships are especially common in epidemiology studies where there are many uncontrolled variables. While epidemiologists try to address this issue by modeling variables that are known to influence an outcome, this introduces additional model uncertainties (i.e. the relationships of the other variables may not be modeled correctly), and there always may be additional factors that are unaccounted for. The Axelrad estimate presumes that an underlying mean value common to all the studies is the true value, and therefore the confidence interval does not reflect differences between studies. Although Cohen et al. (2005b) produced an analysis that averaged the results from all three studies into a single estimate, the confidence intervals reflect the differences in the studies.

***4. Measure Uncertainties*. The relative public health significance of different measures can also be a source of significant uncertainty. This is particularly apt to occur in an economic or cost-benefit analysis where an abstract concept of value is used. In addition, there may be uncertainties in how different measures are related. This is especially true for "IQ" measures which are generally a collection of different measures that are partially related. This issue can be treated as a statistical problem by modeling the extent to which two measures are correlated. However, there can still be additional uncertainty over whether or not two scales are measuring the same attribute, even if they are highly correlated.**

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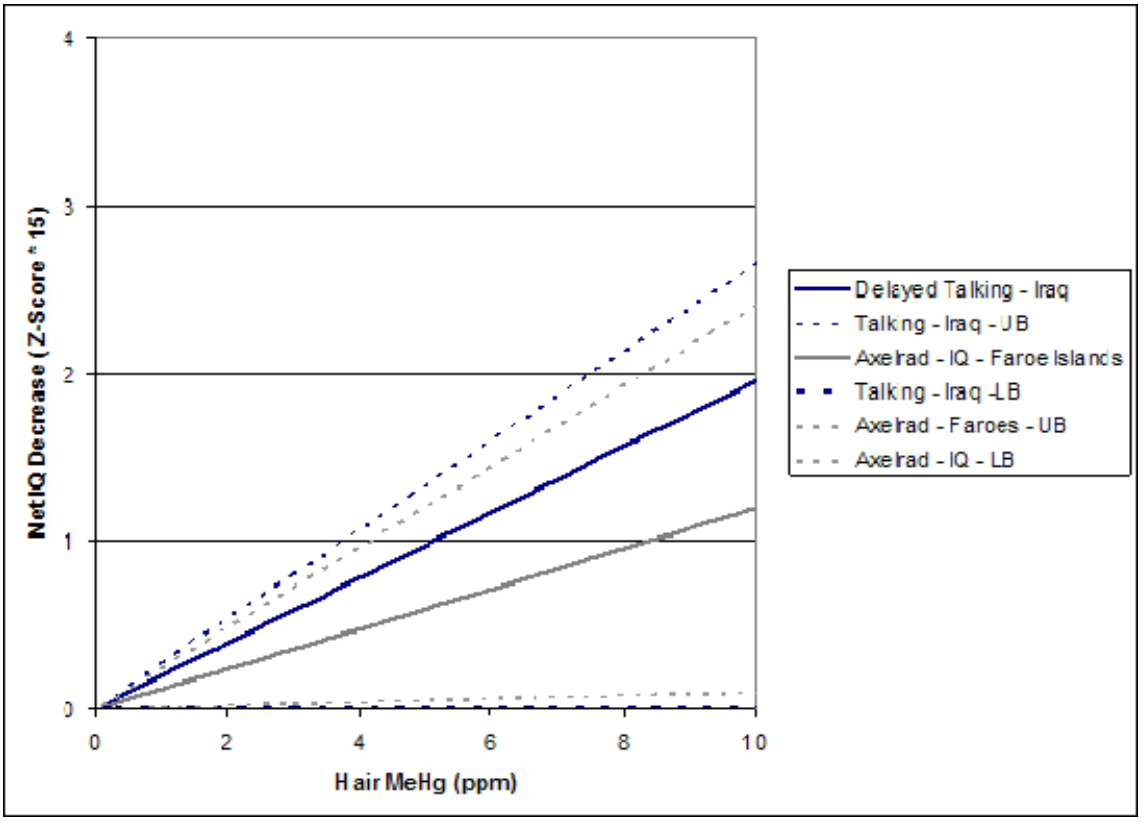
Figure AA-13: Developmental Effects of Methylmercury: Comparison of Confidence Intervals

The upper and lower bounds are 95 percent percentile confidence intervals



Fish Consumption and Neurodevelopmental Endpoints

Daniels et al. (2004)

Daniels et al. (2004) studied the relationship between maternal fish intake during pregnancy and cognitive development from questionnaires posed to mothers of 7,421 English children born in 1991-1992. In a subset of that population, they also studied the relationship between pre-natal exposure to methylmercury and cognitive development. Finally, they studied the relationship between postnatal fish intake by the children themselves and their cognitive development. Each individual child's cognitive development was evaluated using adaptations of the MacArthur Communicative Development Inventory at 15 months of age and the Denver Developmental Screening Test at 18 months.

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Their study measured and categorized the maternal fish intake (mum) of oily and white fish intake as follows: rarely or never, once per two weeks, one to three times per week, and four or more times per week. The estimated average fish intake per meal was 4.5 ounces or 127.6 grams. The child's fish intake was monitored at ages six months (child6) and 12 (child12) months by simply noting whether or not at least one fish meal was consumed per week. The study also recorded the age of the child in weeks (age) at the completion of the MacArthur Communicative Development Inventory (MCDI) and the Denver Developmental Screening Test (DDST).

We analyzed the data from this study using multivariate linear regression analysis. Each of the six outcomes (i.e., three different MCDI scores and three different DDST scores) was analyzed four different ways:
Each of the six outcomes was analyzed four different ways:

1. Maternal fish intake; age of child at testing; children's fish intake at six months, mercury concentration in cord tissue;
2. Maternal fish intake; age of child at testing; children's fish intake at 12 months; mercury concentration in cord tissue;
3. Maternal fish intake; age of child at testing; children's fish intake at six months;
4. Maternal fish intake; age of child at testing; children's fish intake at 12 months;

Results are shown in Tables AA-7-10. Children's fish intake was a discrete (zero or one) variable and was used as such in the regression analysis. However, for the purpose of deriving a slope for the relationship between the child's intake and test outcome, we employed an estimated average fish intake per meal of two ounces, which yields an average daily intake of eight grams/day.

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Table AA-7: Linear regression slope estimates with four variables and six outcome measures; 6 month fish intake (Daniels et al., 2004)

	Mum (g/d)	Child6 (g/d)	Cord Mercury (ppm)	Age (weeks)	Subjects (n)
MCDI Comprehension	0.030	0.98	3.15	2.38	1007
MCDI Production	-0.032	0.39	-1.92	0.85	1007
MCDI Social activity at 15m	0.0058	0.16	0.71	0.32	1053
Denver total development score (18m)	0.0055	0.18	0.23	0.39	1009
Denver communication score (18m)	0.0009	0.06	0.61	0.19	1013
Denver social achievement score (18m)	-0.0002	0.05	-0.90	0.13	1013

Table AA-8: Linear regression slope estimates with four variables and six outcome measures; 12 month fish intake (Daniels et al., 2004)

	Mum (g/d)	Child6 (g/d)	Cord Mercury (ppm)	Age (weeks)	Subjects (n)
MCDI Comprehension	0.00	0.00	-0.002	0.99	1007
MCDI Production	-0.02	-0.04	-2.2	0.85	1007
MCDI Social activity at 15m	0.007	0.06	0.44	0.33	1053
Denver total development score (18m)	0.0085	-0.0008	-0.08	0.39	1009
Denver communication score (18m)	0.0021	-0.012	0.50	0.20	1013
Denver social achievement score (18m)	0.0005	0.006	-0.99	0.14	1013

Table AA-9: Linear regression slope estimates with three variables and six outcome measures; 6 month fish intake (Daniels et al., 2004)

	Mum (g/d)	Child6 (g/d)	Age (weeks)	Subjects (n)
MCDI Comprehension	0.037	0.66	1.94	7136
MCDI Production	0.0023	0.26	0.79	7136
MCDI Social activity at 15m	0.0113	0.099	0.34	7466
Denver total development score (18m)	0.0042	0.093	0.38	7204
Denver communication score (18m)	0.0024	0.032	0.15	7223
Denver social achievement score (18m)	0.0004	0.028	0.10	7215

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Table AA-10: Linear regression slope estimates with three variables and six outcome measures; 12 month fish intake (Daniels et al., 2004)

	Mum (score per g/d)	Child12 (score per g/d)	Age (weeks)	Number of Subjects
MCDI Comprehension	0.035	0.71	1.98	7136
MCDI Production	0.0056	0.057	0.81	7136
MCDI Social activity at 15m	0.011	0.10	0.34	7466
Denver total development score (18m)	0.0042	0.084	0.38	7204
Denver communication score (18m)	0.0026	0.020	0.146	7223
Denver social achievement score (18m)	0.00022	0.031	0.10	7215

In order to evaluate the relative importance of each variable, the relative contribution of each variable on each outcome measure was gauged calculating a "maximum Z-score," which was calculated as follows:

Maximum Z = Variable Range * Slope / Test Score SD

The extent to which these values (Table AA-10 and Table AA-12) deviate from zero (i.e. positive or negative) indicate the relative strength of the relationship between the independent and dependent variables. The following general conclusions may be drawn from Tables AA-7 through AA-12:

- Since it has a much bigger contribution to the variation in outcome, age of testing is clearly an important variable for all outcomes (see Table AA-7 through AA-10. The slopes are uniformly positive and the magnitudes of the slopes are not greatly affected by which of the other variables are included.

- With the smaller data set that included mercury (Table AA-7 and Table AA-8), there are no clear trends for cord mercury, maternal fish intake, or children's fish intake. Not only are both positive and negative slopes attained from the regression analyses, somewhat discrepant results are obtained when child's fish consumption at 12 months is used instead of a 6 months.

- With the full data set (without mercury; Table AA-9 and Table AA-11), there a consistent, albeit small, positive relationship between fish intake by both mother and child and test outcomes. On a per gram basis (i.e. if one meal is assumed to correspond to eight grams per day), the slopes are considerably higher for direct consumption by the children. More of the total variation is accounted for by children's intake as well (Table AA-10 and Table AA-12).

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Table AA-11: Maximum Z-Score Contribution from Maternal Fish Consumption, Toddler (12 months) Fish Consumption, Cord Mercury, and Age on Development Measures (Daniels et al., 2004)

	Maximum Z-score				Standard Deviation
	Mum	Child12	Trace Hg	Age	
MCDI Verbal Comprehension	0.00	0.00	0.00	0.26	30.7
MCDI Production	-0.10	-0.02	-0.08	0.39	17.5
MCDI Social activity at 15m	0.10	0.09	0.05	1.20	5.4
Denver total development score (18m)	0.11	0.00	-0.01	0.56	5.6
Denver communication score (18m)	0.06	-0.04	0.12	0.64	2.4
Denver social achievement score (18m)	0.02	0.02	-0.28	0.49	2.2

Table AA-12: Maximum Z-Score Contribution from Maternal Consumption, Children (12 month) Consumption and Age on Development Measures (Daniels et al., 2004)

	Maximum Z Score			Standard Deviation
	Mum	Child12	Age	
MCDI Verbal Comprehension	0.08	0.18	0.57	31.5
MCDI Production	0.02	0.03	0.43	16.9
MCDI Social activity at 15m	0.15	0.15	1.61	5.5
Denver total development score (18m)	0.06	0.12	0.62	5.6
Denver communication score (18m)	0.08	0.07	0.55	2.4
Denver social achievement score (18m)	0.01	0.12	0.42	2.2

In order to evaluate potential net benefits to infants from mothers eating fish, Z-score slope from MCDI Verbal Comprehension and DDST Communication Scores were used. The results from the various regression analyses are given in Table AA-12. It may be observed that the slopes derived from the full data set all fall in a range of 0.0010 to 0.0012. The slopes derived from the partial data set that included cord mercury as a variable are less consistent. In particular, in the analyses where the cord slope mercury was positive (i.e. better scores were obtained from mothers with higher mercury levels) the slope for maternal fish consumption was diminished. This result may be explained by the fact that blood and fish consumption are highly correlated.

As a summary of these results, a triangular distribution with a minimum of 0, and most likely value of 0.001 and a maximum value of 0.0012 was used in our simulation model intended to illustrate combined effects. An illustration of the combined dose-response

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with methylmercury concentrations fixed at the market average is shown in Figure AA-14.

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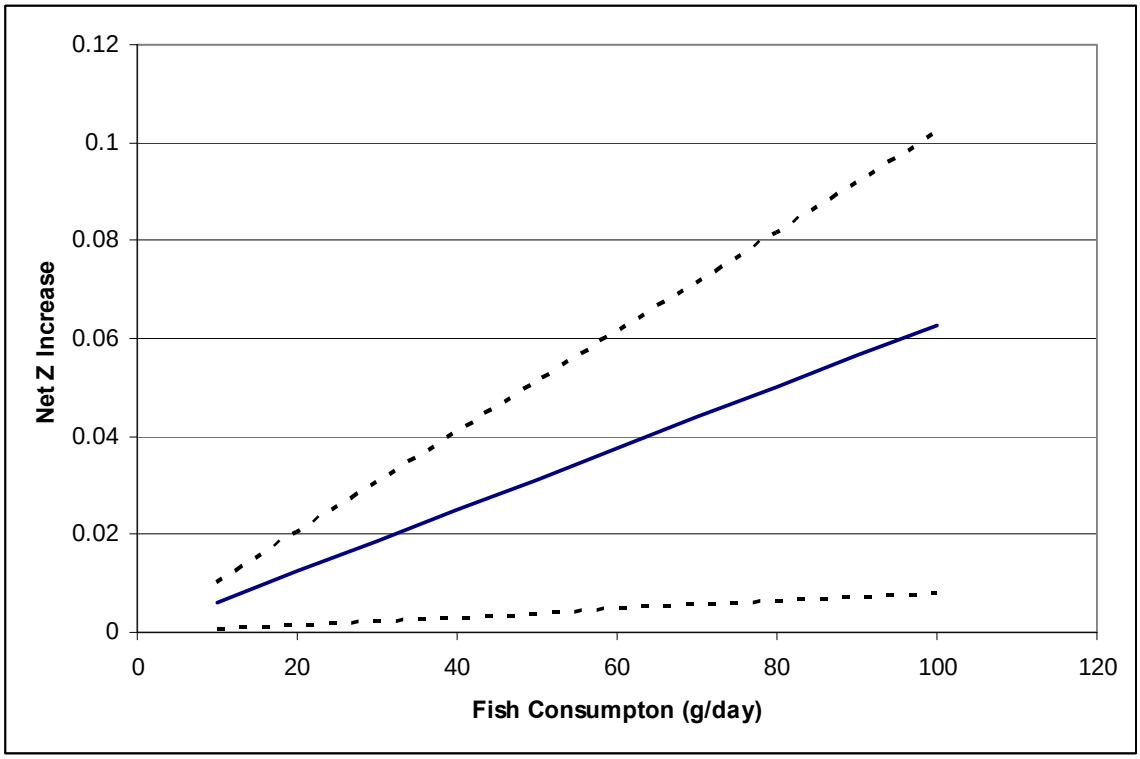
Table AA-13: Summary of Z-Score Slopes from Verbal Test Scores (Daniels et al., 2004)

Analysis	MCDI Comprehension	Denver Communication
Partial Data Set, with Cord Hg, Children at 6 months	0.0010	0.0003
Full Data Set, without Cord Hg, Children at 6 months	0.0012	0.0010
Partial Data Set, with Cord Hg, Children at 12 months	0.0000	0.0009
Full Data Set, without Cord Hg, Children at 12 months	0.0011	0.0011

All units are for ΔZ per g of fish consumed per day.

Figure AA-14: Combined Dose-Response For Methylmercury and Fish (Daniels et al., 2004)



A combined dose-response function for fish and mercury on neurobehavioral development that combines the methylmercury-delayed talking dose-response function and the Daniels et al. (2004) fish-verbal test score dose-response function. For this graph, it was assumed that all fish contained a market average concentration of 0.086 ppm. Only the median response is displayed. Although there is no variability represented in the fish dose-response, the dose-response function for mercury includes population variability from the biomarker relationships and the hair-response model. Although the results displayed in the graph are entirely positive (i.e. increased fish consumption results in increased neurobehavioral performance), at the low end of the population distribution there is a small negative component.

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Fish Consumption and Cardiovascular Disease

Cardiovascular Death – He et al. (2004a)

The main result of the meta-analysis produced by He et al. (2004a) was an estimate of the relative risk associated with each of four different rates of fish consumption. This analysis was based on studies 1-13 in Table AA-14. However, they also reported the results of a regression analysis of the pooled data which yielded a slope of seven percent per 20 grams of fish per day with a confidence interval (CI) of one to 13 percent. The confidence intervals were used to calculate the standard error of the mean (SEM) of 3.65 percent. This translates to a linear slope with a normal distribution of 0.35 percent per g-day and an SEM of 0.18 percent.

Stroke – Bouzan et al. (2005)

Bouzan et al. (2005) conducted a regression analysis with data from multiple epidemiological studies that related the frequency of fish consumption to stroke. They included data from studies numbered two, three, five and six in Table AA-16 and an additional case control study (Caicoya 2002). Their regression analysis generated both linear slope and an intercept. Bouzan et al. (2005) interpreted the intercept as an indicator of the benefit or risk associated with any fish consumption. Since the idea that a nanogram of fish would have a substantial health impact is implausible, the Bouzan model was modified to attribute the low dose effect to the first 50 grams of fish per week, which roughly corresponds to the low end of the range of exposures in the analysis. Thus, the reduced risk of 12 percent (CI: - one percent, 25 percent) attributed to the intercept was translated to a slope of 1.68 percent per g/day, an SEM of 1.1 percent, and a maximum response at 7.1 grams/day. For higher doses, and additional reduction was based on the slope estimates provided by Bouzan et al (2006); the reported values of two percent per 100 grams/week (CI: -2.7 percent, 6.6 percent) were translated to a normal distribution with a mean of 0.14 percent per grams/day with an SEM of 0.2 percent. For uncertainty characterization, paired slope and intercept parameters were generated that matched the reported correlation coefficient of 0.77 (Cohen et al., 2005a).

Cardiovascular Death and Stroke – FDA, 2007

Two meta-analyses conducted by He et al. (2004a,b) were used as a starting point for the development of dose-response function for the relationship of average fish consumption (grams/day) and the population frequency of two endpoints -- cardiovascular death and stroke. Although based on the same data, a second analysis (referred to throughout this report as "the stroke pooled analysis model" due to the pooling of models of individual studies, as described below) differs from the work of He in the following respects:

- Dose-response models were fit to data from individual studies rather than pooled data from all of the studies. This allowed for analysis of the uncertainty arising from the

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idea that the studies may be imperfectly analogous to the U.S. population. The models of the individual studies were pooled into a common dose-response function with a probability tree. Since it is not assumed that all the studies are measuring the same underlying population rate (i.e. there is an underlying "true" mean value for the complete set of cohorts), the confidence intervals in our analysis are greater than those of He. This difference is analogous to using the standard deviation rather than the standard error of the mean to characterize uncertainty.

- Sampling error was represented by binomial sampling from each individual data point instead of assuming a common variance across all studies and dose groups. Specifically, after generating 300 bootstrap data sets from each study, dose-response functions were estimated for each set by using nonlinear regression and weighted least squares as a goodness-of-fit measure. The data points were weighted by the number of person-years associated with each observation.
- The data were fit using a linear model, with a maximum effective dose parameter (Hockey Stick) and two sigmoidal models; a three parameter Michaelis-Menten function (KD, minimum, and maximum) and a Hill function (KD, power, minimum, and maximum). The inclusion of both maximum and minimum parameters allowed the model to indicate that a subset of the disease occurrences are reduced or increased by fish consumption. The sigmoidal models were also permitted to have both positive and negative relationships between disease outcome and fish consumption. Since the Hill function has four parameters, it was only used for studies with at least four dose groups. More specifically, the following equations were used:

Hockey Stick:

$$\text{Dose} < \text{MaxDose}: \text{Disease Rate} = \text{Intercept} + \text{Dose} * \text{Slope}$$
$$\text{Dose} >= \text{MaxDose}: \text{Disease Rate} = \text{Intercept} + \text{MaxDose} * \text{Slope}$$

Michaelis-Menten:

$$\text{Disease Rate} = \text{Min} + (\text{Max-Min}) * (K_D/(\text{Dose}+K_D))$$

Hill:

$$\text{Disease Rate} = \text{Min} + (\text{Max-Min}) * (K_D^k/(\text{Dose}^k+K_D^k))$$

- The relationship between dose and frequency of outcome was modeled for each study instead of pooling the data from all the studies. A probability tree was used to integrate the results of each study into a single dose-response function, instead of averaging the results by either pooling the data or using Bayesian Model Averaging (e.g. the techniques used by Axelrad et al. (2007) for methylmercury and IQ). The probabilities assigned to the studies were weighted by the square root of the sample size. The fundamental difference in this approach is that it is not assumed that there is necessarily a common effect across studies. Instead, the effect may be different in magnitude between studies, and therefore each study is considered independently as a

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plausible prediction. The net effect of this approach is that the confidence intervals associated with the dose-response function are much wider.

- As a means of accounting for known differences among dose groups in each study, adjusted rate estimates were used instead of the relative risks. These were calculated for each non-referent group by calculating the number of events yielding the published relative risk, using the following equation:

$$\text{Adjusted Group Events} = \frac{\text{Adjusted Relative Risk} * \text{Referent Events} * \text{Group PersonYears}}{\text{Referent PersonYears}}$$

The main difference in this approach compared to that of He is that it allows sampling error from the low dose group to be represented instead of being fixed to a value of one.

- One stroke study (Keli et al. (1994) that was included in the He et al. (2004b) meta-analysis was not included in the present analysis because it only contained two groups, which is insufficient for modeling a dose-response relationship. In addition several studies published after the He meta-analyses that met the original criteria were included: Folson and Demissie (2004), Nakamura et al. (2005), and Iso et al. (2006) were added for CHD, and Nakamura et al. (2005) and Mozaffarian et al. (2005) were added for stroke.

Table AA-14: Cardiovascular Mortality Studies

Study	Pop. Size	Events	Average Age at Baseline	Average Follow Up	Study Median Age	% Male	Nationality
1. Kromhout et al. (1985)	852	78	72.5	20	82.5	100	Netherlands
2. Fraser et al. (1992)	26,473	260	52	6	55	38	USA
3. Ascherio et al. (1995)	44,895	264	55	6	58	100	USA
4. Daviglus et al. (1997)	1,822	430	47.6	30	62.6	100	USA
5. Mann et al. (1997)	10,802	64	34	13	40.65	38	UK
6. Albert et al. (1998)	20,551	308	53.2	11	58.7	100	USA
7. Oomen et al. (2000) – Finland	1,088	242	57.8	20	67.8	100	Finland
8. Oomen et al. (2000) - Italy	1,097	116	58.3	20	68.3	100	Italy
9. Oomen et al. (2000) – Netherlands	553	105	58.4	20	68.4	100	Netherlands
10. Yuan et al. (2001)	18,244	187	54	12	60	100	China
11. Hu et al. (2002)	84,688	484	42	16	50	0	USA
12. Mozaffarian et al. - (2003)	7,389	247	72.5	11	78	39	USA
13. Osler et al. (2003)	3,910	247	47	9	51.65	53	Denmark
14. Folsom & Demissie (2004)	41,836	922	62	14	69	0	USA
15. Nakamura et al. (2005)	8,879	142	51	19	60.5	44	Japan

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16. Iso et al. (2006)	41,578	62	49.5	12	55.5	48	Japan

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Table AA-15: Individual Group Data for Cardiovascular Death

Cohort	Person-Years	Fish Consumption (g/day)			Adjusted Relative Risk	Unadjusted Events	Adjusted Events
		Most Likely	Lower Bound	Upper Bound			
1	3,180	0	0	0	1	23	23.0
1	5,660	2	2	2	0.64	25	26.2
1	4,300	22	22	22	0.56	18	17.4
1	2,320	36	36	36	0.36	7	6.0
1	1,580	67	67	67	0.39	5	4.5
2	80,517	0	0	0	1	94	114.2
2	88,007	5.3	0.1	10.5	1.01	145	126.1
2	18,725	20.25	10.6	29.9	0.74	16	19.7
3	10,975	0	0	0	1	16	16
3	17,886	7	7	7	0.74	19	19.3
3	66,367	18	18	18	0.86	80	83.2
3	91,370	37	37	37	0.71	93	94.6
3	33,779	69	69	69	0.54	28	26.6
3	21,652	119	119	119	0.77	28	24.3
4	4,754	0	0	0	1	48	48.0
4	16,681	9	1	17	0.88	157	148.2
4	19,350	26	18	34	0.84	179	164.1
4	6,368	54.95	35	74.9	0.62	46	39.9
5	51,536	0	0	0	1	26	26.0
5	31,179	7	3.5	10.5	1.21	13	19.0
5	60,951	20.25	10.6	29.9	1.23	25	37.8
6	7,715	1.65	0	3.3	1	9	9.0
6	15,465	6.6	3.4	9.8	0.79	12	14.3
6	79,561	18.9	9.9	27.9	0.71	38	65.9
6	123,693	48.95	28	69.9	0.7	64	101.0
6	27,343	84	70	98	0.73	10	23.3
7	9,520	9.5	0	19	1	100	100.0
7	5,260	29.5	20	39	0.97	52	53.6
7	6,980	57.45	40	74.9	1.25	90	91.6
8	5,480	0	0	0	1	32	32.0
8	6,940	10	1	19	0.94	37	38.1
8	6,460	29.5	20	39	0.93	34	35.1
8	3,260	57.45	40	74.9	0.67	13	12.8
9	3,140	0	0	0	1	29	18.3
9	3,380	10	1	19	1	30	19.7
9	4,540	29.5	20	39	1.1	46	29.2
10	36,892	4.2	4.2	4.2	1	33	33.0
10	55,115	10.9	10.9	10.9	0.55	28	27.1
10	32,499	17.7	17.7	17.7	0.69	21	20.1
10	25,767	25.3	25.3	25.3	0.64	17	14.8
10	29,194	46.0	46.0	46.0	0.44	14	11.5
11	67,537	1.7	0	3.4	1	111	111.0
11	337,393	7	3.5	10.5	0.8	386	443.6

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11	690,479	20.25	10.6	29.9	0.65	752	737.6
11	157,711	52.45	30	74.9	0.72	182	186.6
11	54,525	90	75	105	0.55	76	49.3
12	1,099	1.8	0.0	3.6	1	7	11.1
12	1,577	7.1	3.6	10.7	1.033	10	19.6
12	166	17.9	14.3	21.4	1.068	14	2.7
12	434	32.1	25.0	39.3	0.722	11	5.0
12	48	64.3	42.9	85.7	0.722	16	0.7
12	2,697	7.1	3.6	10.7	1	7	21.2
12	3,870	14.3	7.1	21.4	1.033	10	37.4
12	406	26.8	17.9	35.7	1.068	14	5.1
12	1,065	39.3	28.6	50.0	0.722	11	9.6
12	118	71.4	46.4	96.4	0.722	16	1.3
12	2,461	17.9	14.3	21.4	1	7	19.1
12	3,531	26.8	17.9	35.7	1.033	10	33.7
12	371	35.7	28.6	42.9	1.068	14	4.6
12	971	50.0	42.9	57.1	0.722	11	8.6
12	108	80.4	60.7	100.0	0.722	16	1.1
12	1,879	32.1	25.0	39.3	1	7	10.0
12	2,697	39.3	28.6	50.0	1.033	10	17.7
12	283	50.0	42.9	57.1	1.068	14	2.4
12	742	60.7	50.0	71.4	0.722	11	4.5
12	82	92.9	71.4	114.3	0.722	16	0.6
12	3,833	64.3	42.9	85.7	1	7	18.2
12	5,501	71.4	46.4	96.4	1.033	10	32.1
12	578	80.4	60.7	100.0	1.068	14	4.4
12	1,513	92.9	71.4	114.3	0.722	11	8.2
12	168	119.6	89.3	150.0	0.722	16	1.1
13	14,076	1.7	0	3.4	1	57	57.0
13	20,825	7	3.5	10.5	0.81	70	68.3
13	26,690	20.25	10.6	29.9	0.92	100	99.4
13	6,341	52.45	30	74.9	0.9	25	23.1
14	50,038	3.3	0	7	1	121	220.0
14	77,410	10.6	7	14.3	1.11	181	207.8
14	174,852	17.9	14.3	21.4	0.86	337	363.6
14	48,325	28.6	21.4	35.7	0.75	80	92.3
14	92,341	60	35.7	100	1.04	203	232.2
15	4,433	7	0	14.3	1.47	7	5.3
15	39,149	21.4	14.3	28.6	1	32	32.0
15	50,066	50	28.6	75	1.07	39	43.8
15	50,488	100	75	150	0.91	37	37.6
15	9,738	200	150	300	0.91	9	7.2
16	102,044	23	23	23	1	11	11.0
16	97,984	51	51	51	0.4	5	4.2
16	93,879	78	78	78	1.38	16	14.0
16	91,229	114	114	114	1.05	14	10.3
16	92,189	180	180	180	1.08	16	10.7

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The cohort numbers refer to the studies listed in Table AA-1.

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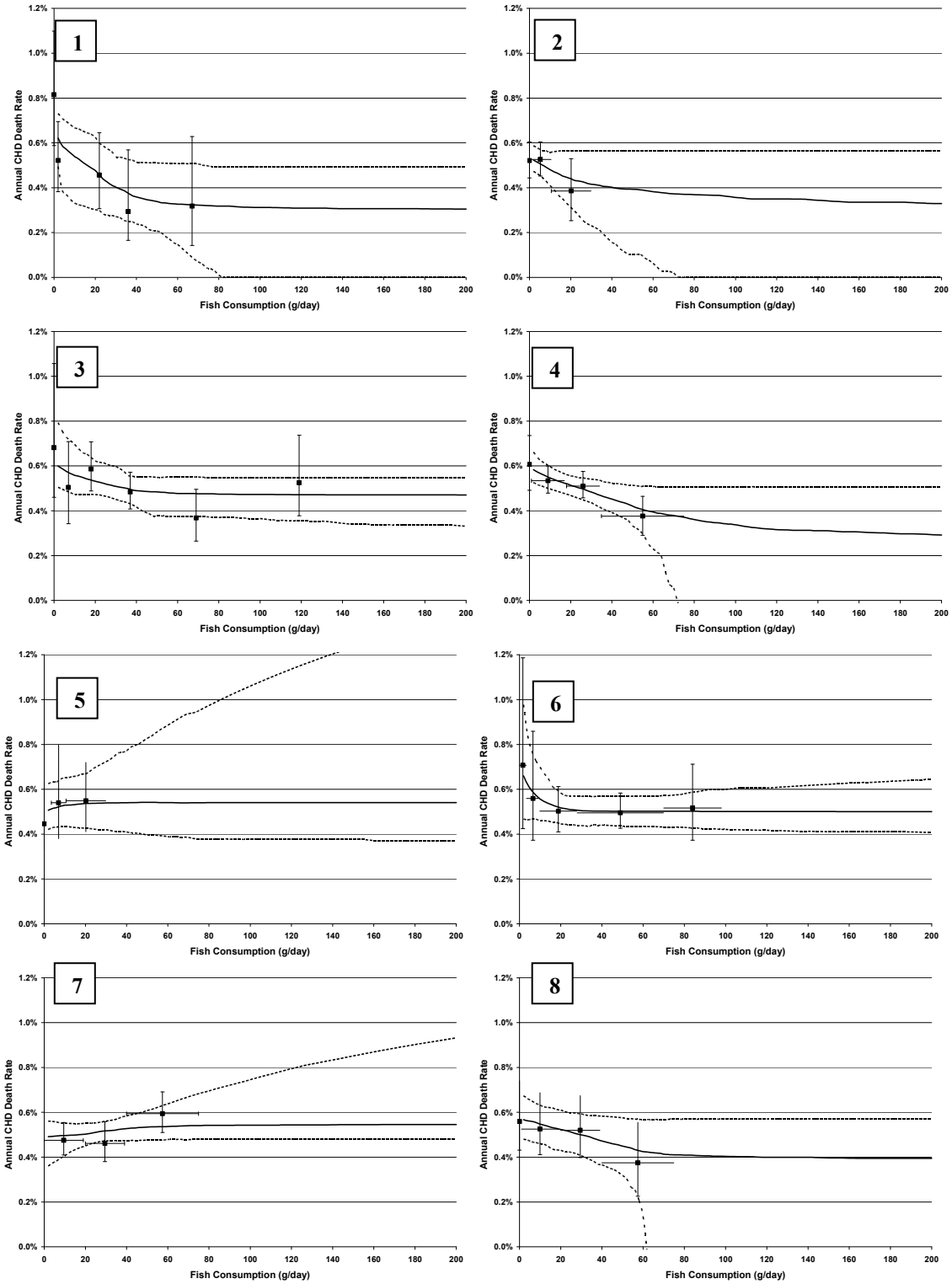
Figure AA-15: CHD Mortality Dose-Response Models for Individual Studies



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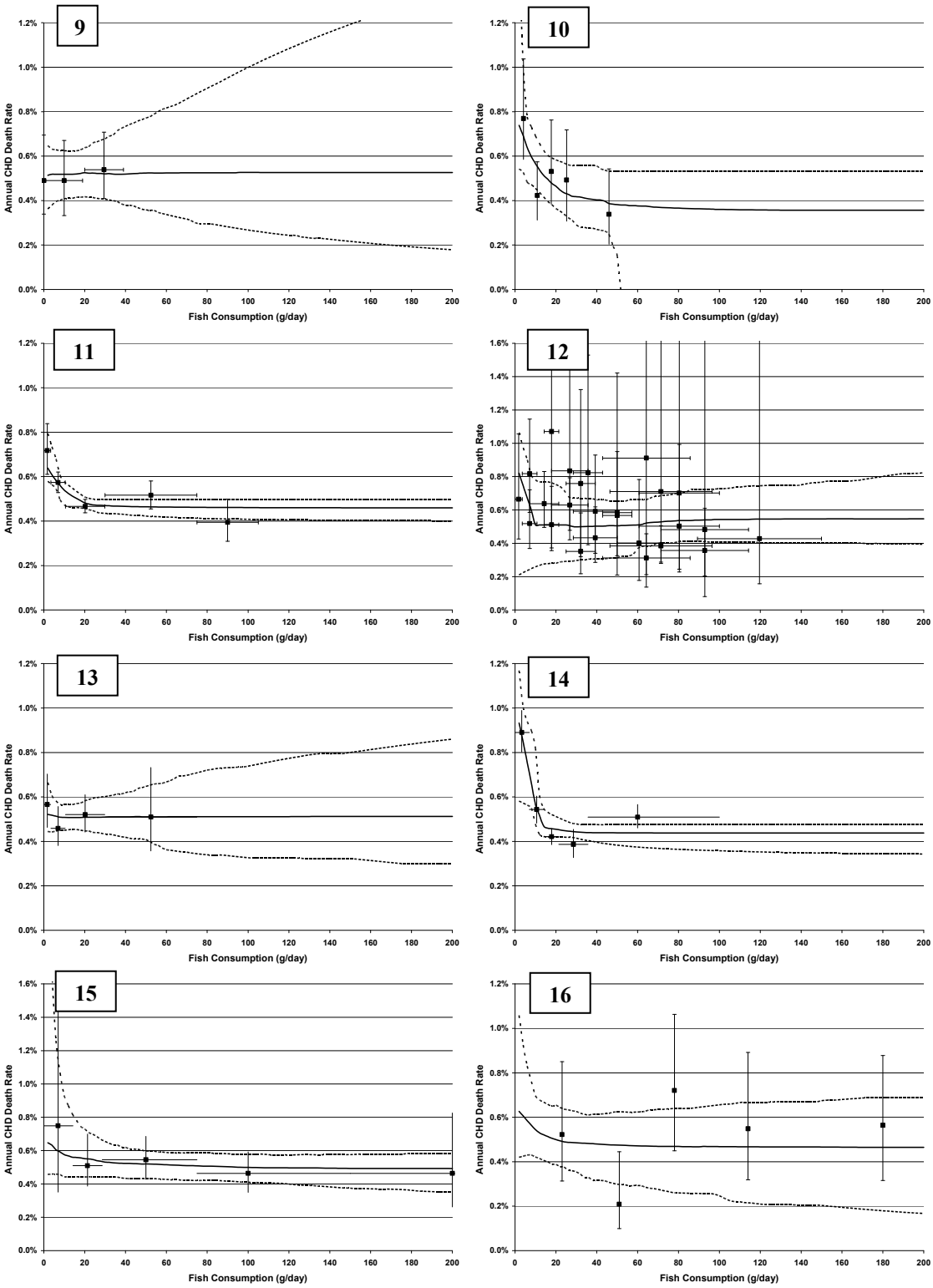

The figure numbers refer to the studies listed in Table AA-14. The dose-response functions from each study was normalized to the rates for U.S. males aged 45 and above.

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Figure AA-16: Dose-response Function for Fish Consumption and CHD Death in Men Aged 45+

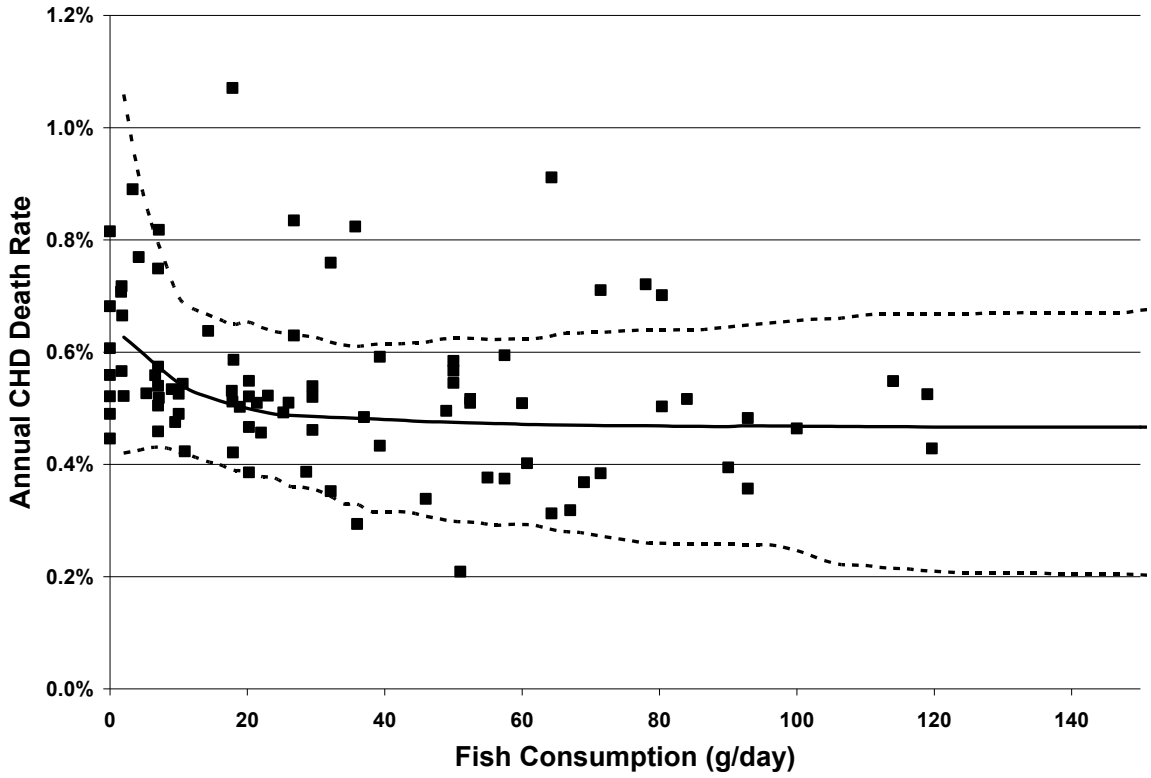

Table AA-16: Stroke Studies

Study	Pop. Size	Events	Average Age at Baseline	Average Follow Up	Study Median	% Male	Location
1. Morris et al. (1995)	21,185	281	52	4	54	100	USA
2. Orencia et al. (1006)	1,847	76	47.6	30	62.6	100	USA
3. Gillum (1996)	2,059	262	62	12	68	100	USA
4. Gillum (1996)	2,351	252	62	12	68	0	USA
5. Yuan et al. (2001)	18,244	460	54	12	60	100	USA
6. Iso et al. (2001)	79,839	574	34	14	41	0	USA
7. He et al. (2002)	43,671	608	53.4	12	59.4	100	USA
8. Sauveget et al. (2003)	40,349	1462	56	16	64	100	Japan
9. Mozaffarian et al. (2005)	8,879	288	58.3	12	64.3	44	Japan
10. Nakamura et al. (2005)	4,775	626	58.3	12	64.3	42	USA

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Table AA-17: Individual Group Data for Stroke. Cohort numbers are the studies in Table AA-16.

Cohort	Person-Years	Fish Consumption (g/day)			Adjusted Relative Risk	Unadjusted Events	Adjusted Events
		Most Likely	Lower Bound	Upper Bound			
1	22,321	7	0	14	1	46	46
1	40,525	22	14	29	0.9	65	75
1	37,115	67	29	100	0.8	55	61
1	5,292	150	100	200	0.6	7	9.0
2	4,721	0	0	0	1	7	7.0
2	16,467	8	1	17	1	25	24.4
2	18,980	26	18	34	0.96	29	27.0
2	6,258	52	35	70	1.34	15	12.4
3	2,832	0	0	0	1.00		25.7
3	9,516	7	0	14	1.27		109.9
3	8,940	22	14	29	1.23		100.0
3	3,420	67	29	100	0.85		26.4
4	2,988	0	0	0	1		34.8
4	10,968	7	0	14	0.78		99.7
4	10,164	22	14	29	0.77		91.2
4	4.092	67	29	100	0.55		26.2
5	36,892	4.2	4.2	4.2	1	101	101.0
5	55,115	10.9	10.9	10.9	0.93	141	140.3
5	32,499	17.7	17.7	17.7	0.79	70	70.3
5	25,767	25.3	25.3	25.3	1.01	71	71.2
5	29,194	46.0	46.0	46.0	1.11	97	88.7
6	53,008	1.7	0	3.4	1	37	37.0
6	285,973	7	3.5	10.5	0.93	169	185.6
6	576,099	20.25	10.6	29.9	0.78	291	313.7
6	147,026	52.45	30	74.9	0.73	69	74.9
6	24,155	90	75	105	0.48	8	8.1
7	22,883	1.7	0	3.4	1	40	40.0
7	44,629	7	3.5	10.5	0.73	57	56.9
7	214,851	20.25	10.6	29.9	0.74	282	277.9
7	143,507	52.45	30	74.9	0.67	174	168.1
7	36,154	90	75	105	0.83	55	52.5
8	167,670	17	11	18	1	552	552.0
8	204,704	30	25	35	0.85	471	572.8
8	194,528	48	46	65	0.85	439	544.4
9	6,024	8	2	10	1	78	78.0
9	13,476	13	11	15	0.88	154	153.6
9	26,712	42	35	50	0.74	284	255.9
9	11,124	95	80	110	0.77	110	110.9
10	4,433	7	0	14.3	1.34	14	10.2
10	39,149	21.4	14.3	28.6	1	67	67.0
10	50,066	50	28.6	75	1.09	80	93.4
10	50,488	100	75	150	1.2	101	103.7

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10	9,738	200	150	300	1.26	26	21.0

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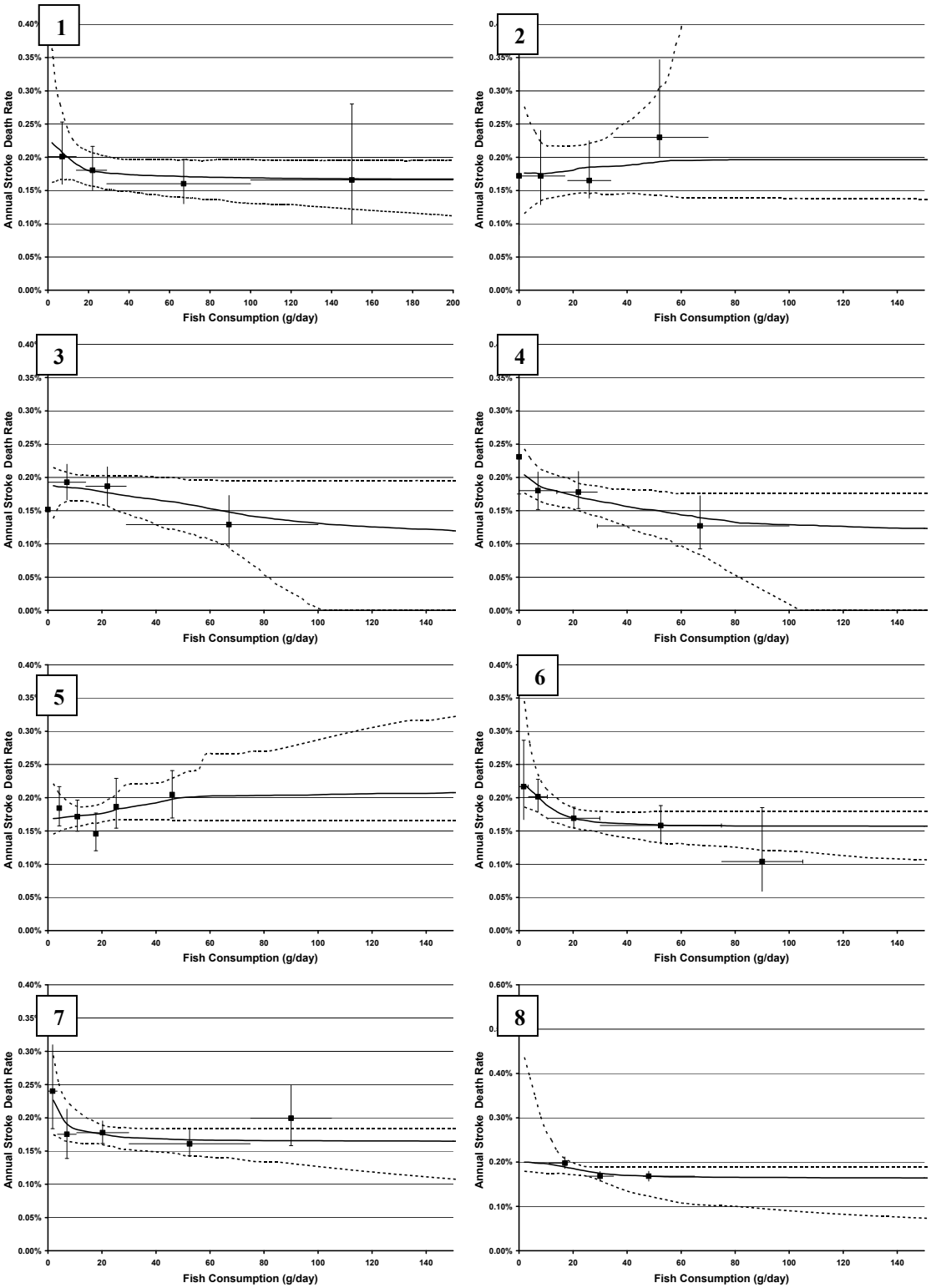
Figure AA-17: Stroke Mortality Dose-Response Models for Individual Cohorts



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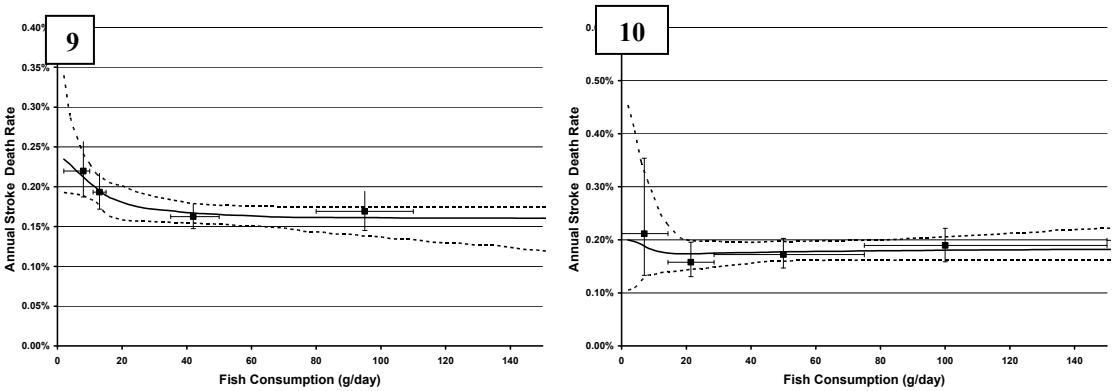
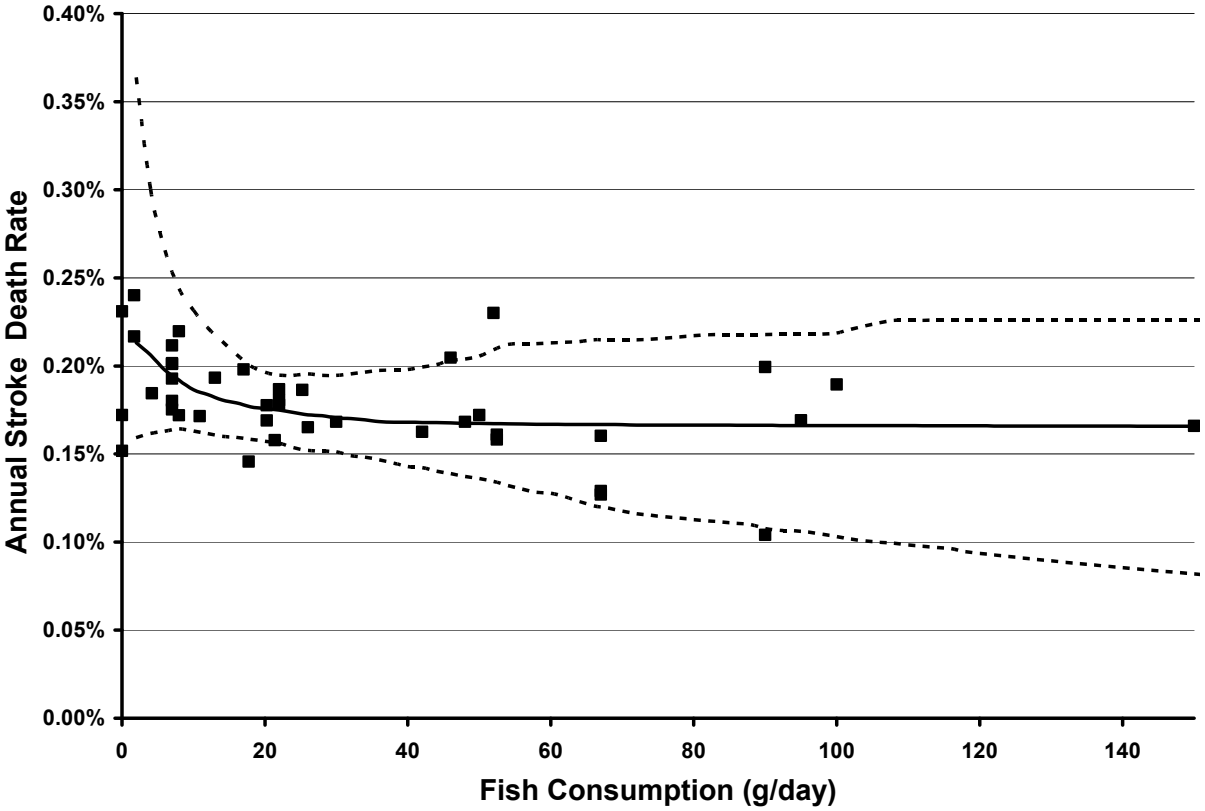


The figure numbers refer to the studies listed in Table AA-16. The dose-response functions from each study was normalized to the rates for U.S. females aged 45 and above.

Figure AA-18: Dose-response Function for Fish Consumption and Stroke Death in Women Aged 45+



As an alternative, in addition to cohort size, studies were also weighted by sex and age relative to each subpopulation. This results in dose-response functions that vary by sex and age (results not shown). There are some small, but noticeable, differences. The impact of seafood consumption on CHD mortality appears to be somewhat greater in

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males than females, and greater in older populations. For stroke, while there is virtually no evidence to suggest that age is an important factor, there appears to be a greater impact in females.

Cardiovascular Disease Rates in the United States

All of the cardiovascular dose-response models used predict relative rates of disease as a function of fish consumption. In order to predict the number of cases, baseline rates of disease were calculated and all the estimates were normalized to U.S. population rate using the rate from each study irrespective of fish consumption. For CHD death rate, data from National Center for Health Statistics (NCHS 2006) and the U.S. Census Bureau (2001) were used to calculate age-specific rates for each population group which were then adjusted for sex differences using data from Ho et al. (2004). Since the latter article did not contain rate information for persons under the age of 45, the relative rates for men and women in the youngest age group (45-50) were used to correct for sex differences in the 15-44 subpopulations of both sexes. For Stroke, Age and sex specific population rates were calculated from data compiled by NCHS (NCHS 2006). The resulting rate estimates are presented in Table AA-18.

Table AA-18: Cardiovascular Disease Rates for each Subpopulation in the United States

Sex	Age	CHD Death Rate	Stroke Death Rate
Male	45+	5.1E-03	1.3 E-03
Male	15-44	1.3E-04	2.4 E-05
Female	45+	3.8E-03	1.8 E-03
Female	15-44	1.4E-05	2.5 E-05

(c) Simulation Models

Exposure Simulations

The exposure assessment was constructed using data from the 3,524 selected individuals in the CSFII survey dataset. This strategy maintained the information about individual characteristics associated with each estimate of mercury exposure. It also retained the limited information present in the three-day survey about long-term consumption patterns.

The simulation model, constructed in Microsoft Excel, consisted of three iterative loops with the following logical structure:

Begin Uncertainty Loop
    Randomly Select Distributions for Fish methylmercury Concentration
    Randomly Select percent Consumers (85-95 percent - from NHANES)

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Randomly Select Annual Serving Variability Parameter
Begin Population Loop (3,525 Individuals in CSFII)
Calculate Average Serving Size for Individual (from CSFII)
Calculate three-Day Servings (from CSFII)
Calculate Annual Servings (using model)
Randomly Select Fish Consumption Individual Variability
Begin Annual Exposure Simulation (# of Annual Servings)
Randomly Select Survey Source (CSFII vs. Market Share)
If Market Share, Randomly Select Species
Randomly Select methylmercury Concentration for Identified Species
Correct for Water Loss During Cooking
Calculate methylmercury Intake
Sum Total Fish Intake for Individual
Sum Total Methylmercury Intake for Individual
Next Serving
Calculate and Record Average Daily Methylmercury and Fish Intake
Record Demographic Characteristics for Individual (from CSFII)
Next Individual
Next Plausible Set of Assumptions

The Uncertainty loop consisted of 200 iterations and contained the uncertainty distributions developed for methylmercury concentration in the various fish groups and projection of the short-term consumer survey to long-term fish consumption patterns were re-sampled within this loop. The random numbers used for each iteration were generated prior to running the simulation. This allows post-hoc investigation of individual results and allowed the LTSTCR to be carried forward to the biomarker simulation. Each iteration of the second Variability loop consisted of an individual from the CSFII survey who consumed one or more servings of fish during the three-day survey. The number of servings and average serving size for each individual are calculated at this step.

The annual number of servings was then used to set the number of iterations for the third loop, in which in each iteration simulated a fish consumption event. First, a random number was used to select the information source (CSFII or per capita) to be used for the serving. Specifically, if the random number was less than the percentile ranging from 0.2 to 0.8 selected at the outset of the uncertainty iterations, a randomly selected CSFII record for the individual was used to identify the species and the serving size. Otherwise, a species was randomly selected from a histogram distribution based on per capita disappearance rate, and the average serving size for the individual was used. Second, the mercury concentration for the species consumed by randomly sampling from either an empirical distribution (shark, swordfish, and tuna) or a modeled distribution using a mean value from NMFS data and a distribution selected at the outset of the uncertainty iteration. Methylmercury exposure from the serving was then calculated by multiplying

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serving size by concentration. After completion of the specified number of servings, total methylmercury exposure for the year was summed from all the servings, and then divided by 366 to yield an average daily methylmercury. This number was recorded along with the age, sex, body weight, and demographic weight for the individual. After completion of the middle and outer loops, a two-dimensional array was produced with dimensions of 200 uncertainty iterations by 3,525 variability iterations. These were stored and used as the basis for the subsequent biomarker simulation.

At the end of each variability loop, per capita population percentiles were calculated. This was accomplished by generating a frequency histogram from the 3,525 estimates where the width is proportional to the demographic weight provided with the survey. Individuals not consuming fish were included in the distribution by introducing a value of zero for the fraction of non-consumers. The percentage of fish consumers was calculated by multiplying the number of consumers in the three-day survey by the LTSTCR for the current uncertainty iteration. Subtraction of the resulting value from one yielded the fraction of non-consumers.

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Dose-Response Simulations

Dose-response simulations were constructed to predict responses for each of the four subpopulations modeled. Individuals belonging to each subpopulation were extracted from the exposure assessment.

Table AA-19: Individual from Exposure Assessment in Each Subpopulation

Subpopulation	N
Women 15-45	882
Women 46+	623
Men 15-45	757
Men 46+	513

Each simulation consisted of a two-dimensional Monte-Carlo routine with an outer uncertainty loop and an inner variability loop with the following logical structure:

Begin Uncertainty Loop
    Randomly Select Uncertainty Iteration from Exposure Assessment
    Randomly Select Population Model for Diet-Blood Ratio
    Randomly Select Dose-Response Models
    Begin Population Loop
        Randomly Select Individual from Exposure Assessment
        Randomly select Diet-Blood Ratio from Population Model
        Correct for Body Weight
        Add other Mercury Exposures
        Calculate Blood methylmercury
        Randomly select Blood-Hair Ratio from Empirical Distribution
        Calculate Predicted Hair Value
        Calculate methylmercury-Dependent Neurobehavioral Outcomes
        Calculate Fish-Dependent Cardiovascular Outcomes
        Record Output
    Next Individual
    Calculate Population Distributions for Neurobehavioral Outcomes
    Calculate Average Population Rates for Cardiovascular Outcomes
Next Plausible Set of Assumptions

A simulation for the entire population was run with 5,000 variability iterations and 500 uncertainty iterations.

At the outset of each uncertainty iteration, one of the 200 uncertainty iterations from the exposure assessment and a population model for the diet to blood ratio were randomly selected. The variability loops were then run with random selection of the individual from the exposure assessment, the diet/blood ratio from the population model, and the

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blood/hair ratio from the empirical distribution. Random numbers for the variability iterations were generated prior to the simulation and the same set of values were used for each uncertainty iteration. These values were then used to calculate blood and hair values for each individual. At the conclusion of each variability loop, per capita population percentiles were calculated in the same manner the percentiles for daily methylmercury exposure.

The logic of the dose-response model is also illustrated in AA-19. Since some of the items displayed pertain to populations and other pertain to individuals, the statistical relationships are not illustrated. In particular, note the following:

- The population value of "% Consumers" is used to randomly determine if the individual is a fish consumer. If not, the methylmercury contribution from fish is ignored.
- The cardiovascular rate calculated as a response in not an individual outcome. For this reason, average or total population rates are reported rather than population distributions.

Also, the arrow indicating a relationship between Fish Intake and Neurobehavioral outcome applies only to the simulation model that includes a Daniels et al. (2004)-derived benefit from fish consumption. The simulation models for men and older women only include cardiovascular outcomes.

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APPENDIX B
MODELING RESULTS

(a) Baseline Estimates

The estimates generated by the model for the U.S. population are presented in this section. Results are presented for each of four population groups, Younger Women aged 15-45, Younger Men aged 15-45, Older Women aged 46 and older, and Older Men aged 46 and older. The results for the first group, which includes women of childbearing age, also address neurobehavioral effects on children resulting from maternal exposure.

Fish Consumption

The distributions for fish consumption of each subpopulation are presented in Table AB-1.

Table AB-1: Estimates Average Daily Intake of Fish (in grams) for all Four Subpopulation Groups

Population Percentile	Women 15-45	Women 46+	Men 15-45	Men 46+
Average	13.1 (12.4, 13.8)	14.9 (14.3, 15.7)	17.9 (16.8, 19.0)	18.8 (17.7, 20.0)
10th Percentile	0.1 (0.0, 0.9)	0.2 (0.0, 1.3)	0.2 (0.0, 1.3)	0.2 (0.0, 1.7)
25th Percentile	2.8 (2.0, 3.4)	3.4 (2.5, 4.3)	3.7 (2.5, 4.6)	4.5 (3.1, 5.6)
Median	7.0 (6.1, 7.7)	8.2 (7.2, 8.9)	9.3 (8.1, 10.4)	10.7 (9.1, 11.6)
75th Percentile	16.0 (14.8, 17.3)	18.0 (16.8, 19.2)	21.3 (19.1, 23.1)	22.3 (20.4, 24.1)
90th Percentile	31.3 (29.2, 33.9)	36.3 (33.3, 38.7)	42.9 (39.2, 47.5)	43.9 (39.8, 49.0)
95th Percentile	45.4 (41.2, 51.3)	53.3 (47.7, 59.8)	63.9 (58.4, 73.2)	64.8 (57.4, 77.5)
99th Percentile	88.0 (73.6, 112.9)	100.0 (84.9, 126.6)	132.4 (109.7, 170.3)	127.4 (100.8, 167.7)
NHANES Average	10.3	14.2	16.8	20.8

All units are grams of fish consumed per day. The daily consumption was derived for each individual in the population by averaging daily consumption for one year. The central estimates are the median estimates of the uncertainty distribution. The 5th and 95th uncertainty percentiles are given in parentheses as confidence intervals.
Because our model is based in part on data from 1989-1991, the table includes average daily consumption taken from the 2003-2004 NHANES survey in order to verify that our results are consistent with current consumption patterns. The reference for this is the Documentation, Codebook, and Frequencies, Dietary Interview – Individual Foods (First Day), for the National Health and Nutrition Examination Survey for 2003-2004 (USDA/HHS 2007). This document is primarily involved with survey methodology. The data we used are in a file referenced in the document, i.e., SAS Transport File DR1IFF_C and DR2IFF_C.XTP.

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Blood and Hair Mercury Levels

The distributions for blood and hair mercury levels in younger women are presented in Table AB-2. For purposes of comparison, the model estimates are compared to results from NHANES in Figures AB-1 and AB-2. It may be observed that the blood levels model are generally 20-25 percent lower than the levels observed in NHANES, while the hair levels are 30-40 percent lower. These discrepancies may be explained, at least in part, by two factors:

- While the NHANES measurements are for total mercury in both blood and hair, the model is intended to estimate concentrations on just methylmercury.
- The model has been updated with more recent (2005) market data indicating that the consumption patterns have changed somewhat so that the average commercial fish weighted by frequency of consumption, now has less methylmercury in it than when the most recently reported NHANES mercury biomarker survey data were conducted (2000 for hair and 2002 for blood).

Table AB-2: Model Estimates of Blood and Hair Methylmercury levels in Women of Childbearing Age

Population Percentile	Dietary Hg from Fish (µg/day)	Blood Hg (µg/L):	Hair Hg (ppm)
Average	1.4 (1.3, 1.4)	1.2 (1.2, 1.3)	0.3 (0.2, 0.3)
10th Percentile	0.0 (0.0, 0.1)	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
25th Percentile	0.2 (0.1, 0.3)	0.3 (0.2, 0.3)	0.0 (0.0, 0.1)
Median	0.7 (0.6, 0.7)	0.6 (0.5, 0.7)	0.1 (0.1, 0.1)
75th Percentile	1.6 (1.5, 1.8)	1.5 (1.3, 1.6)	0.3 (0.2, 0.3)
90th Percentile	3.4 (3.1, 3.6)	2.9 (2.7, 3.2)	0.6 (0.5, 0.7)
95th Percentile	4.9 (4.5, 5.5)	4.3 (3.8, 4.8)	1.0 (0.8, 1.2)
99th Percentile	10.3 (8.1, 12.8)	8.8 (7.4, 10.7)	2.2 (1.8, 2.7)

Table AB-3: Model Estimates of Blood and Hair Methylmercury levels in Men Aged 16-45

Population Percentile	Dietary Hg from Fish (µg/day)	Blood Hg (µg/L):	Hair Hg (ppm)
Average	1.8 (1.7, 1.9)	1.4 (1.3, 1.5)	0.3 (0.3, 0.4)
10th Percentile	0.0 (0.0, 0.1)	0.1 (0.1, 0.1)	0.0 (0.0, 0.0)
25th Percentile	0.3 (0.2, 0.4)	0.3 (0.2, 0.4)	0.1 (0.0, 0.1)
Median	0.9 (0.7, 1.0)	0.7 (0.6, 0.8)	0.1 (0.1, 0.2)
75th Percentile	2.1 (1.9, 2.3)	1.7 (1.5, 1.9)	0.3 (0.3, 0.4)
90th Percentile	4.3 (3.9, 4.7)	3.3 (3.0, 3.7)	0.7 (0.6, 0.8)
95th Percentile	6.4 (5.6, 7.5)	5.0 (4.4, 5.7)	1.1 (0.9, 1.3)
99th Percentile	13.4 (10.9, 17.3)	10.4 (8.5, 12.8)	2.4 (2.0, 3.2)

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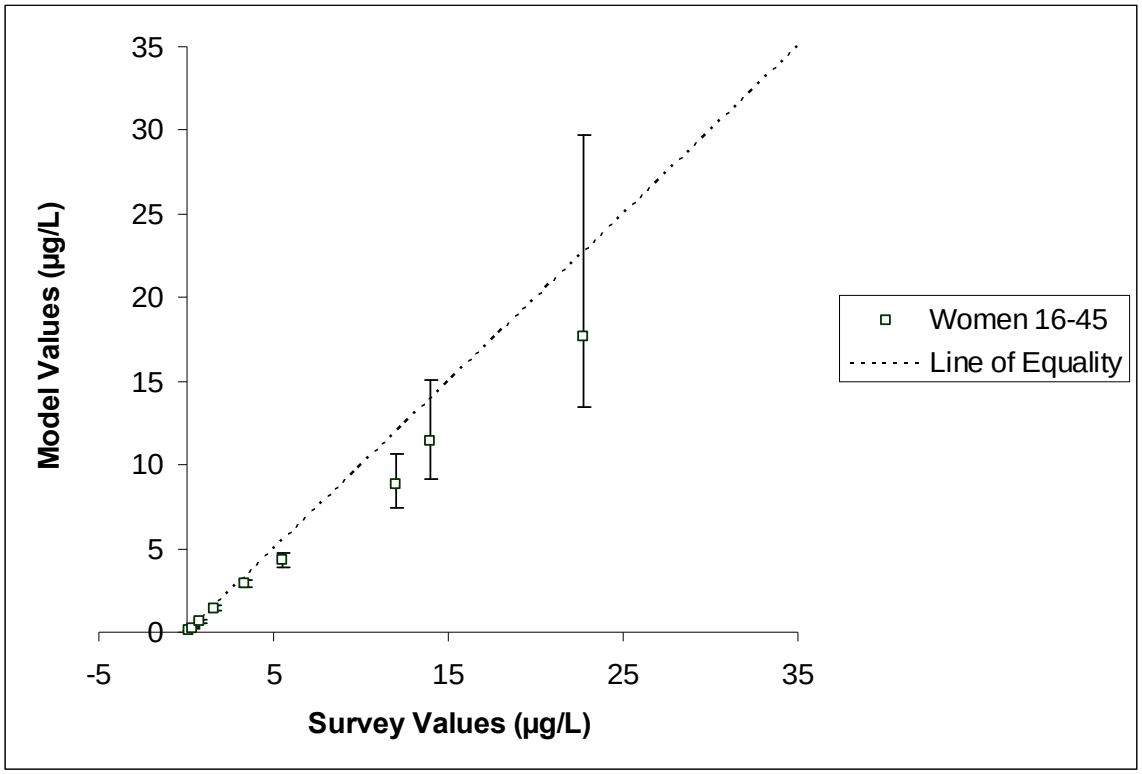
Figure AB-1: Quantile-Quantile Comparison of Model Estimates of Blood Mercury with Values from NHANES



NHANES survey data are taken from the 199-200, 2001-2002, and 2003-2004 surveys (CDC 2004). The following percentiles are plotted: 10th, 25th, 50th, 75th, 90th, 95th, 99th. 99.5th, and 99.9th. Percentiles were calculated with the demographic weights provided with the survey data.

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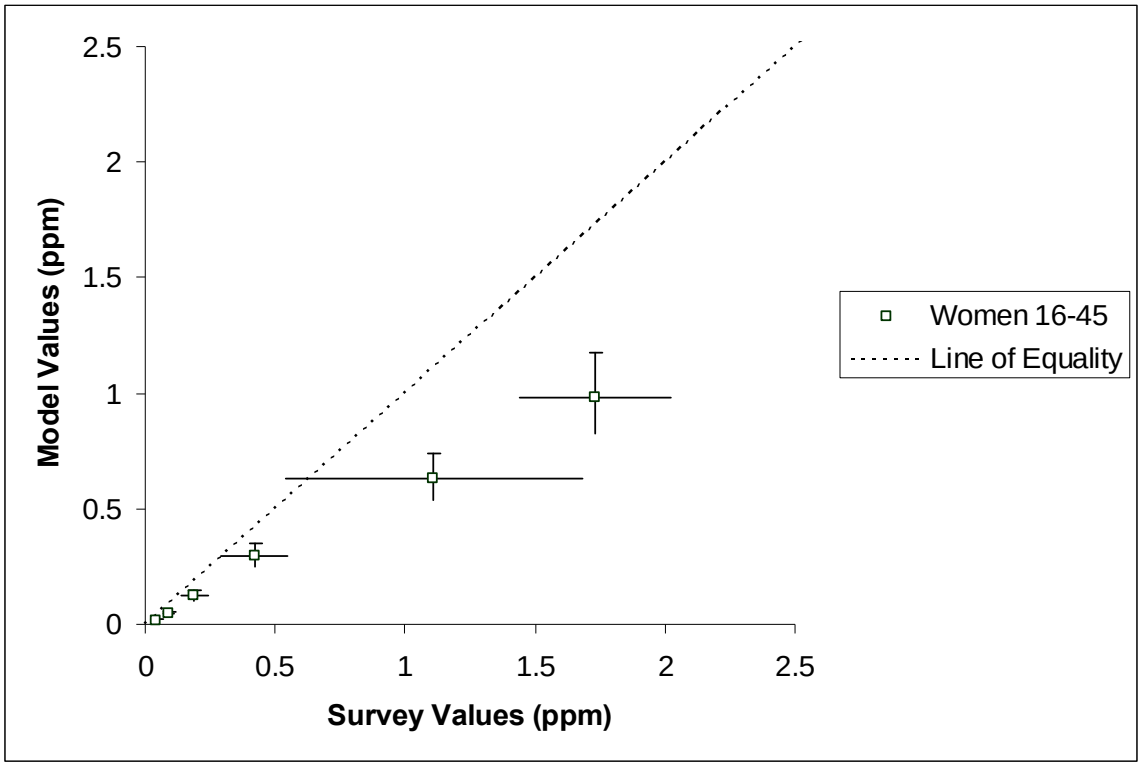
Figure AB-2: Quantile-Quantile Comparison of Model Estimates of Hair Mercury with Values from NHANES



NHANES survey data are taken from CDC (2001), which reflects data collected from 1999-2000. The following percentiles are plotted: 10th, 25th, 50th, 75th, 90th, and 95th.

Neurobehavioral Effects Attributable to Methylmercury Exposure

The predicted neurobehavioral effects resulting from current levels of methylmercury on verbal performance in toddlers with and without taking into account potential offsetting effects from fish consumption are presented in Table AB-4. Since the endpoints or responses modeled are not identical, the results are all represented as a Z-score where the outcome is expressed relative to normal variation (i.e. each Z unit = one standard deviation). The Carrington and Bolger (2000) model for delayed talking was normalized using the standard deviation from Seychelles of 2.76 months. In order to investigate the possible consequences of beneficial effects of maternal consumption of fish, a simulation model was constructed that included both methylmercury effects characterized with the Carrington and Bolger (2000) delayed talking analysis, and an uncertain range of beneficial effects based on the verbal comprehension regression analyses from the Daniels et al. (2004) study. This analysis presumes that the contribution of fish to the slope for delayed talking (which was dominated by the data from Iraq, where methylmercury was ingested in bread) and the contribution of mercury to the apparent benefit observed in the Daniels study are both negligible.

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Table AB-4: Baseline Estimates for Z-score Change Attributable to Methylmercury With and Without Offsetting Fish Benefits

Population Percentile	Carrington (2000), Age of Talking	Net Verbal ΔZ
Average	-2.9E-3 (-4.5E-3, -6.1E-4)	0.008 (0.000, 0.012)
1st Percentile	-2.7E-2 (-4.2E-2, -8.5E-3)	-0.001 (-0.020, 0.000)
5th Percentile	-1.2E-2 (-1.8E-2, -3.3E-3)	0.000 (-0.006, 0.001)
10th Percentile	-7.3E-3 (-1.1E-2, -1.7E-3)	0.001 (-0.003, 0.002)
25th Percentile	-3.2E-3 (-4.8E-3, 2.2E-4)	0.002 (0.000, 0.004)
Median	-1.1E-3 (-1.8E-3, 0.0E0)	0.005 (0.000, 0.008)
75th Percentile	-2.9E-4 (-5.2E-4, 0.0E0)	0.010 (0.001, 0.016)
90th Percentile	0.0E0 (-6.8E-5, 0.0E0)	0.020 (0.003, 0.030)
95th Percentile	0.0E0 (6.8E0, 0.0E0)	0.026 (0.005, 0.039)
99th Percentile	0.0E0 (0.0E0, 0.0E0)	0.035 (0.010, 0.048)

The values in the second column represent the net (added) change in Z-score from the Carrington (2000) delayed talking dose-response function and the Daniels et al. (2004) verbal test score dose-response function.

For comparison, predicted neurobehavioral effects for several other dose-response functions are presented in Table AB-5. Since IQ is defined as the Z score x 15, the Axelrad et al. (2007) and Cohen et al. (2005b) models were converted by dividing by 15. The Carrington (2000) model for delayed walking was normalized using the standard deviation from Seychelles of 1.96 months.

Table AB-5: Baseline Estimates for Z-score Change Attributable to Fish Consumption With Benefits from Maternal Consumption of Fish

Population Percentile	Carrington (2000), Age of Walking	Cohen et al. (2005b) IQ	Axelrad et al. (2007) IQ
Average	-6.0E-3 (-9.3E-3,	-1.8E-3 (-1.3E-2, 1.3E-3)	-3.0E-3 (-5.6E-3, -7.0E-4)
1st Percentile	-6.0E-2 (-1.0E-1, 0.0E0)	-1.6E-2 (-1.2E-1, 0.0E0)	-2.6E-2 (-5.0E-2, -6.1E-3)
5th Percentile	-2.4E-2 (-3.7E-2, 0.0E0)	-7.1E-3 (-5.2E-2, 0.0E0)	-1.2E-2 (-2.2E-2, -2.8E-3)
10th Percentile	-1.4E-2 (-2.3E-2, 0.0E0)	-4.5E-3 (-3.2E-2, 7.4E-6)	-7.5E-3 (-1.4E-2, -1.6E-3)
25th Percentile	-5.8E-3 (-1.0E-2, 0.0E0)	-2.0E-3 (-1.5E-2, 1.5E-4)	-3.4E-3 (-6.4E-3, -7.5E-4)
Median	-1.8E-3 (-3.5E-3, 0.0E0)	-7.4E-4 (-5.6E-3, 5.5E-4)	-1.3E-3 (-2.4E-3, -2.7E-4)
75th Percentile	-3.7E-4 (-9.3E-4, 0.0E0)	-2.1E-4 (-1.7E-3, 1.4E-3)	-3.6E-4 (-7.6E-4, -7.8E-5)
90th Percentile	0.0E0 (-1.2E-4, 0.0E0)	0.0E0 (-1.9E-4, 3.1E-3)	-4.1E-6 (-1.0E-4, 0.0E0)

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Cardiovascular Effects Attributable to Fish Consumption

Table AB-6 and Table AB-7 give the estimated annual reduction in the rate of occurrence of CHD Death and Stroke Death attributable to current levels of fish consumption.

Table AB-6: Baseline Estimates for CHD Death Benefit Attributable to Fish Consumption

	CHD Death Cases Per Person-Year Pooled Analysis Model	CHD Death Cases Per Person-Year Meta-Analysis Model
Women 15-45	-1.1E-6 (-2.2E-5, 2.6E-6)	-6.8E-7 (-1.3E-6, -1.3E-7)
Women 46+	-2.8E-4 (-4.2E-3, 9.2E-4)	-2.2E-4 (-4.3E-4, -4.0E-5)
Men 15-45	-1.1E-5 (-1.2E-4, 3.4E-5)	-8.9E-6 (-1.7E-5, -1.6E-6)
Men 46+	-4.7E-4 (-8.8E-3, 6.5E-4)	-3.7E-4 (-7.2E-4, -6.6E-5)

The values are median estimates of cases per person-year, with the 5th and 95th percentiles of the uncertainty distributions given as confidence intervals.

Table AB-7: Baseline Estimates for Stroke Death Benefit Attributable to Fish Consumption

	Stroke Death Cases Per Person-Year Pooled Analysis Model	Stroke Death Cases Per Person-Year Meta-Analysis Model
Women 15-45	-3.7E-6 (-3.1E-5, 1.5E-6)	-3.0E-6 (-5.6E-6, -9.1E-7)
Women 46+	-2.2E-4 (-2.7E-3, 1.4E-4)	-2.2E-4 (-4.1E-4, -7.1E-5)
Men 15-45	-4.0E-6 (-3.1E-5, 3.1E-6)	-3.2E-6 (-6.1E-6, -1.1E-6)
Men 46+	-2.4E-4 (-2.0E-3, 9.2E-5)	-1.8E-4 (-3.4E-4, -6.6E-5)

The values are median estimates of cases per person-year, with the 5th and 95th percentiles of the uncertainty distributions given as confidence intervals.

(b) Intervention Scenarios

Advisory Scenario: 12 oz Limits for Women of Childbearing Age

To examine the impact of fish consumption advisories, several scenarios were developed. The first scenario introduced a 12 oz. per week consumption limit for all women of childbearing age. This modification of the exposure model involved truncating consumption of fish at the specified limit. Whereas individuals coming more that 12 oz. /week are reduced to 12 oz., those individuals who are already consuming under that limit do not modify their consumption. The impact of the advisory on neurobehavioral outcome occurring as a result of the reduction in exposure to methylmercury, expressed as a Z-score, is presented in Table AB-8.

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Table AB-8: Z-score Change with a 12 oz Limit (vs. Baseline) for All Women of Childbearing Age

Population Percentile	Carrington (2000), Age of Talking	Axelrad (2007) IQ	Net Verbal ΔZ
Average	2.6E-4 (3.7E-5, 4.5E-4)	2.2E-4 (4.6E-4, 7.1E-5)	-7.3E-4 (-1.5E-3, -2.8E-5)
1st Percentile	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	-1.3E-1 (-3.0E-1, -3.0E-2)
5th Percentile	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	-2.1E-2 (-4.6E-2, -2.7E-3)
10th Percentile	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	0.0E0 (-1.3E-3, 0.0E0)
25th Percentile	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)
Median	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)
75th Percentile	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)
90th Percentile	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)
95th Percentile	0.0E0 (0.0E0, 3.2E-4)	0.0E0 (2.6E-4, 0.0E0)	0.0E0 (0.0E0, 0.0E0)
99th Percentile	7.8E-3 (1.8E-4, 1.3E-2)	6.8E-3 (1.3E-2, 1.9E-3)	0.0E0 (0.0E0, 0.0E0)

A second scenario used a 12 oz limit in conjunction with a stipulation that only fish species with average concentrations below 12 ppb are consumed by all women of childbearing age. This modification of the exposure model involved substituting fish species below the concentration limit for species above the limit. The impact of the advisory, relative to current levels of consumption, is presented in Table AB-9.

Table AB-9: Z-score Change with a 12 oz Limit and Low-Mercury Fish (vs. Baseline) for All Women of Childbearing Age

Population Percentile	Carrington (2000), Age of Talking	Axelrad (2007) IQ	Net Verbal ΔZ
Average	1.3E-3 (1.6E-4, 1.9E-3)	1.2E-3 (4.3E-4, 2.0E-3)	5.2E-4 (-8.7E-4, 1.4E-3)
1st Percentile	0.0E0 (0.0E0, 0.0E0)	-4.1E-5 (-2.4E-4, -6.4E-6)	-3.4E-2 (-6.8E-2, -9.3E-3)
5th Percentile	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	-1.3E-2 (-2.3E-2, -3.1E-3)
10th Percentile	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	-6.5E-3 (-1.2E-2, - 1.5E-3)
25th Percentile	2.5E-5 (0.0E0, 7.1E-5)	2.9E-5 (2.3E-6, 8.4E-5)	-1.5E-3 (-3.2E-3, -1.3E-4)
Median	3.1E-4 (0.0E0, 4.6E-4)	3.1E-4 (1.0E-4, 5.5E-4)	3.7E-5 (0.0E0, 4.9E-4)
75th Percentile	1.1E-3 (0.0E0, 1.6E-3)	1.0E-3 (3.5E-4, 1.8E-3)	2.9E-3 (1.3E-3, 4.9E-3)
90th Percentile	3.0E-3 (7.5E-5, 4.3E-3)	2.6E-3 (9.3E-4, 4.5E-3)	9.2E-3 (4.1E-3, 1.5E-2)

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95th Percentile	5.3E-3 (3.8E-4, 7.8E-3)	4.6E-3 (1.7E-3, 7.7E-3)	1.6E-2 (7.0E-3, 2.3E-2)
99th Percentile	1.7E-2 (3.0E-3, 2.5E-2)	1.4E-2 (5.1E-3, 2.5E-2)	2.8E-2 (1.6E-2, 4.2E-2)

The change in cardiovascular risk for both these scenarios (fish consumption is identical) are presented in Tables AB-10 and AB-11.

Table AB-10: CHD Death Risk with a 12 oz Limit (vs. Baseline) in Women of Childbearing Age

Population Group	CHD Death Cases Per Person-Year Pooled Analysis Model	CHD Death Cases Per Person-Year Meta-Analysis Model
Women 15-45	0.0E0 (-3.7E-8, 1.3E-7)	7.1E-8 (1.3E-8, 1.6E-7)

The values are median estimates of cases per person-year, with the 5th and 95th percentiles of the uncertainty distributions given as confidence intervals.

Table AB-11: Stroke Death Risk with a 12 oz Limit (vs. Baseline) in Women of Childbearing Age

Population Group	Stroke Death Cases Per Person-Year Pooled Analysis Model	Stroke Death Per Person-Year Meta-Analysis Model
Women 15-45	0.0E0 (-3.1E-8, 8.0E-8)	6.3E-8 (-1.3E-7, 2.4E-7)

The values are median estimates of cases per person-year, with the 5th and 95th percentiles of the uncertainty distributions given as confidence intervals.

As a third variation on the 12 oz limitation, a scenario where all women of childbearing age consume exactly 12 oz of fish was examined. For this scenario, the methylmercury concentration was presumed to correspond to the market average of 0.086 ppm, resulting in an exposure of 4.3 µg/day of methylmercury. The impact of the advisory, relative to current levels of consumption, is presented in Table AB-12.

Table AB-12: Z-score Change with Fixed 12 oz Consumption (vs. Baseline) for Women of Childbearing Age

Population Percentile	Carrington (2000), Age of Talking	Cohen (2005b) IQ	Axelrad (2007) IQ
Average	-5.2E-3 (-7.2E-3, -4.0E-4)	-3.1E-3 (-2.3E-2, 2.3E-3)	-4.6E-3 (-8.1E-3, -1.6E-3)
1st Percentile	-2.1E-2 (-3.4E-2, -7.4E-3)	-2.3E-2 (-1.8E-1, -1.5E-3)	-1.5E-2 (-3.2E-2, -5.4E-3)
5th Percentile	-1.5E-2 (-2.1E-2, -3.6E-3)	-1.1E-2 (-8.4E-2, -8.3E-4)	-1.1E-2 (-2.0E-2, -4.1E-3)
10th Percentile	-1.2E-2 (-1.7E-2, -2.1E-3)	-8.1E-3 (-6.0E-2, -1.7E-4)	-9.6E-3 (-1.7E-2, -3.4E-3)

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25th Percentile	-7.9E-3 (-1.1E-2, 0.0E0)	-6.8E-3 (-5.0E-2, 2.6E-4)	-7.0E-3 (-1.2E-2, -2.4E-3)
Median	-4.8E-3 (-6.7E-3, 0.0E0)	-4.7E-3 (-3.6E-2, 1.3E-3)	-4.5E-3 (-7.7E-3, -1.5E-3)
75th Percentile	-2.5E-3 (-3.6E-3, 0.0E0)	-3.0E-3 (-2.4E-2, 2.2E-3)	-2.6E-3 (-4.6E-3, -8.3E-4)
90th Percentile	-4.5E-4 (-1.1E-3, 0.0E0)	-1.7E-3 (-1.3E-2, 3.5E-3)	-5.3E-4 (-1.3E-3, 0.0E0)
95th Percentile	1.8E-3 (0.0E0, 3.2E-3)	-2.0E-4 (-3.7E-3, 4.7E-3)	1.7E-3 (4.7E-4, 3.3E-3)
99th Percentile	1.4E-2 (1.7E-3, 2.1E-2)	1.9E-3 (1.2E-4, 9.5E-3)	1.2E-2 (4.4E-3, 2.2E-2)

The change in cardiovascular and stroke risk for the fixed 12 oz scenario are presented in Table AB-13 and Table AB-14, respectively.

Table AB-13: CHD Death Risk with 12 oz Consumption (vs. Baseline) in Women of Childbearing Age

Population Group	CHD Death Cases Per Person-Year Pooled Analysis Model	CHD Death Cases Per Person-Year Meta-Analysis Model
Women 15-45	-1.4E-6 (-9.7E-6, 2.9E-6)	-1.7E-6 (-3.3E-6, -1.8E-7)

The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

Table AB-14: Stroke Death Risk with 12 oz Consumption (vs. Baseline) in Women of Childbearing Age

Population Group	Stroke Death Cases Per Person-Year Pooled Analysis Model	Stroke Death Cases Per Person-Year Meta-Analysis Model
Women 15-45	-3.9E-6 (-1.3E-5, 4.0E-6)	-2.2E-6 (-6.5E-6, 2.0E-6)

The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

As an exploration of potential unintended consequences of an advisory, the impact of reductions in the fish consumption in other population groups was modeled. Tables AB-15 through AB-18 present the estimate changes in CHD and cardiovascular death rates resulting from either a 10 percent reduction in the amount of fish consumed by all consumers or a one percent increase in the number of consumers who do not eat fish at all.

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Table AB-15: CHD Death Risk from a One Percent Reduction in Persons Consuming Fish in Men and Older Women

Population Group	CHD Death Cases Per Person-Year Pooled Analysis Model	CHD Death Cases Per Person-Year Meta-Analysis Model
Women 46+	2.9E-6 (-9.9E-6, 4.7E-5)	2.3E-6 (3.5E-7, 5.1E-6)
Men 15-45	1.2E-7 (-3.5E-7, 1.3E-6)	9.2E-8 (1.4E-8, 2.1E-7)
Men 46+	5.4E-6 (-7.9E-6, 1.1E-4)	3.9E-6 (6.0E-7, 8.7E-6)

Estimates of increased rates of CHD Death resulting from decreased number of fish consumers in three population groups. The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

Table AB-16: Stroke Death Risk from a One Percent Reduction in Persons Consuming Fish in Men and Older Women

Population Group	Stroke Death Cases Per Person-Year Pooled Analysis Model	Stroke Death Cases Per Person-Year Meta-Analysis Model
Women 46+	2.5E-6 (-1.5E-6, 3.2E-5)	2.4E-6 (7.1E-7, 4.6E-6)
Men 15-45	4.3E-8 (-2.8E-8, 3.4E-7)	3.5E-8 (1.1E-8, 6.8E-8)
Men 46+	2.8E-6 (-9.1E-6, 2.1E-5)	1.9E-6 (6.0E-7, 4.0E-6)

Estimates of increased rates of Stroke Death resulting from decreased number of fish consumers in each of three population groups. The primary values are the median cases per person-year, with the 5th and 95th percentiles given as confidence intervals.

Table AB-17: Comparison of CHD Death Risk from a 10 Percent Reduction in Persons Consuming Fish in Men and Older Women

Population Group	CHD Death Cases Per Person-Year Pooled Analysis Model	CHD Death Cases Per Person-Year Meta-Analysis Model
Women 46+	1.2E-5 (-3.4E-5, 1.4E-4)	2.2E-5 (4.0E-6, 4.3E-5)
Men 15-45	4.5E-7 (-1.5E-6, 3.7E-6)	8.9E-7 (1.6E-7, 1.7E-6)
Men 46+	2.9E-5 (-3.5E-5, 2.2E-4)	3.7E-5 (6.6E-6, 7.2E-5)

Estimates of increased rates of CHD Death resulting from decreased fish consumption in three population groups. The primary values are the median cases per person-year of the uncertainty distribution, the 5th and 95th percentiles given as confidence intervals.

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Table AB-18: Stroke Death Risk from a 10 Percent Reduction in Persons Consuming Fish in Men and Older Women

Population Group	Stroke Death Cases Per Person-Year Pooled Analysis Model	Stroke Death Cases Per Person-Year Meta-Analysis Model
Women 46+	1.3E-5 (-1.2E-5, 5.7E-5)	9.6E-6 (-2.2E-6, 2.2E-5)
Men 15-45	2.1E-7 (-2.0E-7, 7.2E-7)	1.4E-7 (-5.6E-8, 3.4E-7)
Men 46+	1.2E-6 (-8.6E-5, 3.8E-5)	7.3E-6 (-4.4E-6, 1.9E-5)

Estimates of increased rates of Stroke Death resulting from decreased fish consumption in each of three population groups. The primary values are the median cases per person-year, with the 5th and 95th percentiles given as confidence intervals.

Advisory Scenario: Limiting Species Without Limiting Amount Consumed

This scenario limited the species consumed without altering the amount consumed. Specifically, this putative advisory stipulates that only fish species with average concentrations below 12 ppb (see Table AA-2 in "methodology" Appendix A) are consumed by all women of childbearing age. This modification of the exposure model involved substituting fish species below the average concentration limit for species above the limit. The impact of the advisory, relative to current levels of consumption, is presented in Table AB-19. The presence of the negative values at the first percentile is a result of the possibility of substituting an individual fish from a species with a lower average concentration with a mercury level that higher than the individual fish that would have been consumed from the species with a higher average concentration. Since the amount of fish consumed is unchanged in this scenario, there is no impact on neurobehavioral benefits from fish or on cardiovascular endpoints, and as a result, the predicted effects with and without the inclusion of the Daniels benefit dose-response function are identical.

Table AB-19: Z-score Change with Low-Methylmercury Fish and No Consumption Limit (vs. Baseline) for All Women of Childbearing Age

Population Percentile	Carrington (2000), Age of Talking	Axelrad (2007) IQ	Net Verbal ΔZ
Average	1.1E-3 (0.0E0, 1.7E-3)	1.0E-3 (0.0E0, 1.7E-3)	1.1E-3 (0.0E0, 1.7E-3)
1st Percentile	-3.9E-5 (0.0E0, 0.0E0)	-4.2E-5 (0.0E0, -6.8E-6)	-3.9E-5 (0.0E0, 0.0E0)

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5th Percentile	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)
10th Percentile	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)	0.0E0 (0.0E0, 0.0E0)
25th Percentile	2.5E-5 (0.0E0, 7.0E-5)	2.9E-5 (0.0E0, 8.3E-5)	2.5E-5 (0.0E0, 7.0E-5)
Median	3.0E-4 (0.0E0, 4.6E-4)	3.0E-4 (0.0E0, 5.4E-4)	3.0E-4 (0.0E0, 4.6E-4)
75th Percentile	1.1E-3 (0.0E0, 1.5E-3)	1.0E-3 (0.0E0, 1.7E-3)	1.1E-3 (0.0E0, 1.5E-3)
90th Percentile	2.8E-3 (0.0E0, 4.1E-3)	2.5E-3 (0.0E0, 4.3E-3)	2.8E-3 (0.0E0, 4.1E-3)
95th Percentile	4.8E-3 (0.0E0, 6.9E-3)	4.1E-3 (0.0E0, 6.9E-3)	4.8E-3 (0.0E0, 6.9E-3)
99th Percentile	1.3E-2 (0.0E0, 1.9E-2)	1.1E-2 (0.0E0, 1.9E-2)	1.3E-2 (0.0E0, 1.9E-2)

Advisory Scenario: 50 Percent Increased Fish Consumption

This scenario examines the potential impact of an advisory that recommends increasing fish consumption. The model was modified by presuming an across the board increase in fish consumption of 50 percent. Table AB-20 and Table AB-21 present the estimated changes in CHD and Stroke Death relative to current levels of exposure, respectively.

Table AB-20: CHD Death Benefit from a 50 Percent Increase in the Amount of Fish Consumed, Relative to Baseline

Population Group	CHD Death Pooled Analysis Model	CHD Death Meta-Analysis Model
Women 15-45	-1.7E-7 (-2.7E-6, 4.2E-7)	-3.4E-7 (-6.7E-7, -6.7E-8)
Women 46+	-4.1E-5 (-5.3E-4, 1.3E-4)	-1.1E-4 (-2.1E-4, -2.0E-5)
Men 15-45	-1.9E-6 (-1.4E-5, 5.8E-6)	-4.4E-6 (-8.6E-6, -8.0E-7)
Men 46+	-1.1E-4 (-1.0E-3, 1.4E-4)	-1.9E-4 (-3.6E-4, -3.3E-5)

The negative values represent a decrease in estimated mortality.

Table AB-21: Comparison of Stroke Death Risk from a 50 Percent Increase in the Amount of Fish Consumed, Relative to Baseline

Population Group	Stroke Death Pooled Analysis Model	Stroke Death Meta-Analysis Model
Women 15-45	-8.1E-7 (-3.0E-6, 6.0E-7)	-5.4E-7 (-1.3E-6, 2.2E-7)
Women 46+	-5.1E-5 (-1.9E-4, 5.5E-5)	-3.9E-5 (-1.0E-4, 2.5E-5)
Men 15-45	-8.0E-7 (-2.5E-6, 8.6E-7)	-6.0E-7 (-1.6E-6, 5.7E-7)
Men 46+	-4.4E-5 (-1.3E-4, 3.7E-5)	-3.1E-5 (-8.4E-5, 3.5E-5)

The negative values represent a decrease in estimated mortality.

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Appendix C
Methodology and Results from Carrington and Bolger (2000)

This is a slightly modified excerpt from Carrington and Bolger (2000) that describes the methodology used to model developmental milestone data from Iraq and Seychelles. The excerpt provides modeling details that are referenced in Appendix A but not specifically included.

Data

Sources

The concern for exposure to mercury is primarily a result of two poisoning epidemics that occurred in Japan and Iraq. The latter epidemic, that occurred after exposure to contaminated grain, was the subject of an extensive epidemiological investigation that included an effort to relate the magnitude of exposure to methylmercury to health impact (Marsh et al, 1987). Because these were not prospective studies, the reports concerned with the Iraqi episode do not reflect the same degree of experimental control as subsequent studies. For risk assessment purposes, perhaps the major shortcoming of the Iraqi study is the presence of relatively few individuals at low doses. For instance, because there is little data on the extent of normal variation for the observed measures of development, it is difficult to discern whether a slightly higher frequency of "abnormal" responses (e.g. delayed walking) is attributable to mercury effects or normal variation. However, in spite of numerous shortcomings, the Iraqi study has a major advantage over more recent reports – there were high-dose health effects that were unequivocally attributable to methylmercury exposure.

More recent prospective studies have searched for health effects of methylmercury in populations consuming whale or fish with much lower levels of exposure than those encountered in Iraq (Kjellstrom, et al, 1986; Marsh et al, 1995a, Grandjean et al, 1997). For the present analysis, the results of the Iraqi study are combined with a more recent study in the Seychelles Islands (Marsh et al, 1995a), where the exposure to methylmercury is from the consumption of marine fish. Data from the Seychelles study were used because of the presence of some of the same measurements as those collected from Iraq and because the individual subject data was made available to us. The Seychelles study has many more individual subjects and the range of mercury hair levels were much lower and more representative of levels typically found in consumers of fish, but which are still much higher than those typical of infrequent consumers of fish.

Response Measures

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To combine results from two or more studies in an analysis, it is necessary that there be a common measure. For the present analysis, two endpoints that were collected in both the Iraqi and Seychelles studies were used as the common measure: 1) Age of Talking (AOT) – the age at which the infants started talking, and 2) Age of Walking (AOW) -- the age at which the infants became toddlers. Not only were these measures available from both studies, they have the advantage of being simple measures of neurological development.

Construction of Cumulative Frequency Tables

The data were used to construct separate (one for each study) two dimensional cumulative frequency tables for each study which tabulated frequency for groups spanning the range of hair levels and observed response. These were constructed by grouping the subjects from each study by dose, and calculating the frequency at which each of series of response levels were exceeded. Tables were then constructed for AOT and AOW. Plots of cumulative frequency tables for both the Iraqi and Seychelles studies for AOT and AOW are shown in Figure AC-2, respectively.

Modeling

Comparative Modeling

The analysis presented here is an exercise in comparative modeling where a large number of alternative mathematical models are examined with respect to their ability to describe historical data. Analyses of epidemiological data often undertake evaluation that are designed to identify which of a number of different parameters (e.g. confounding variables or modifying factors) are to be included in a final model. The present analysis differs in two important respects. First, it evaluates models that are different in form rather than just complexity. Second, rather than concluding the analysis with a final or best model, a probability tree that employs probabilities for a set of alternative models to characterize the uncertainty associated with an estimation.

To conduct a comparative modeling exercise, the first step is to assemble a list of candidate models. Dose-response models often have multiple sources of theoretical uncertainty. These include the dose-response relationship itself, the influence of factors other than dose on the outcome, and the extent of the variability among individual subjects. In addition, when multiple studies are being used to evaluate the models, it may be desirable to accommodate differences in the studies within the model. As a result, models were formulated from four submodels, each of which had several theoretical alternatives. Each of the four submodels represent a potential source of model uncertainty: 1) A dose-response function (relating hair level to AOT or AOW); 2) a statistical distribution describing population variability; 3) dose-independent factors; and 4) study dependent factors. With several variations of the mathematical form (see Table) and relative position of each of the submodels (AC-1), a series of 1092 candidate models

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were assembled. All the models were relatively simple and contained 3 to 7 adjustable parameters (*e.g*. slope, standard deviation, dose-independent AOT) which could be altered to improve the fit.

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As an example of what the dose response equations looked like when assembled, a model that fit the data well was constructed from a linear dose response function, a background response parameter, a background study parameter, and a Weibull distribution to account for population variability at position 4. To predict cumulative frequency as a function of dose and response, this yielded the following function:

$$= 1 - \exp((-\text{Response} / (\text{Dose}*P_1 + P_3 + P_4) / ((\log 2) \wedge (1/P_2))) \wedge P_2)$$

To predict response as a function of dose and frequency, the following function was used:

$$= (\text{Dose}*P_1 + P_3 + P_4) / ((\log 2) \wedge (1/P_2)) (\log(1/(1- \text{Frequency})]) \wedge (1/ P_2)$$

where
P_1 is the dose-response slope
P_2 is the Weibull alpha parameter
P_3 is the background response (*i.e.* age in months)
P_4 is a study-dependent background term (also age in months)

Software

The analysis was conducted in Microsoft Excel using procedures written in Visual Basic for Applications, which are available on request.

Goodness-of-Fit

Fitness was judged by a composite least residual squares measure that gave equal weight to residuals for predicted population percentiles (frequency as a function of dose and response) and for predicted magnitude of effect (response as a function of frequency). The fit for each dose-group was weighted by the original number of observations – which gave the values from the Seychelles considerably more weight in the low dose regions.

Optimization

The parameters were adjusted to fit the data (minimize the measure of fit) with Excel Solver. Simple equations were used to assign initial estimates for the parameters – some of these used information from the study such as the range of doses and responses. If an obviously poor fit was obtained, different initial estimates were used in order to find a better fit – usually by adopting estimates from simpler models with the same parameters that produced a better fit.

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Model Weighting and Model Uncertainty

The models were judged with an algorithm that rewards a model for goodness-of-fit and penalizes for the use of extra parameters:

$$\text{Model Weight} = (((1 + n / Pn) \wedge O) * ((1 - gof) \wedge H)$$

where
n = number of observations
Pn = Number of Model Parameters
gof = Goodness-of-Fit
O = The Parameter Penalty, an arbitrary constant that determines the relative importance of model simplicity
H = The Association factor, an arbitrary constant that determines the relative importance of goodness-of-fit.

In the present analysis, values of 0.3 and 100 were used for O and H, respectively. These values were chosen because they appeared to generate a reasonable balance between fit and model simplicity (see Carrington, 1996 for further discussion of this approach). The uncertainty associated with the predictions made was represented by weighting the 200 best models. The algorithm used for model weighting was also used to select the best models.

Two of the dose-response models employed have a biochemical heritage – the Mass Action model is an equation that is able to describe reversible (ionic) competitive ligand-receptor binding interactions. The first order equation is a function that describes irreversible (covalent) ligand-receptor interactions. Evidence that methylmercury acts by either of these mechanisms could be construed as an increase in the weight (and probability) accorded theories that employ those functions. However, it should be noted that even if a particular biochemical mechanism of action is conclusively established, the *in vivo* reaction will often be vastly more complicated that a biochemical reaction taking place *in vitro*. As a result, a model reflecting the wrong mechanism, or no mechanism, may still describe the data and still make a better prediction. Although it would be possible to include theoretical support for a theory in the calculation of each models evidential weight, the biochemical mechanism for methymercury is presently unknown.

Results

Age of Talking. For the AOT endpoint, the best model was comprised of a linear dose-response relationship, a Weibull population distribution, and a background response parameter, and a study-dependent dose parameter (see Figure AC-1). The exponential, hockey stick, and mass action dose-response relations were also heavily represented among the top-rated models (see Table AC-2). The first-order and logistic models tended

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to not fit as well. The Weibull distribution was clearly the best fitting population distribution - regardless of the dose-response function used. The lognormal distribution consistently provided a better fit than the other two distributions. The poorer fit with either the normal or logistic distribution functions is indicative of a skewed distribution. All the top rated models included parameters for both dose-independent and study-dependent effects, reflecting the notions that a) children do not speak at age 0, and that there are differences in the Iraqi and Seychelles studies that are not attributable to methylmercury.

Age of Walking. For the AOW endpoint, the best model was comprised of a linear dose-response relationship, a Weibull population distribution, a background dose and response parameters, and a study-dependent dose parameter (see AC-3). All the dose-response functions were represented among the top-rated models. The Weibull and lognormal distributions were again the clear favorites for modeling population variability. All the top rated models included two parameters for dose-independent effects. All of the best models also included a study dependent parameter, again reflecting differences in the Iraqi and Seychelles populations.

Function Output. The output of the best model for each of the three endpoints is plotted in Figures AC-2 and AC-3 for both the Iraqi and Seychelles studies. Probability trees comprised of the top 200 models yield uncertainty distributions when used as a predictive tools. As an example, sample output from the AOT function that weights the frequency of use of the best 200 models is given in AC-3. In a two-dimensional Monte-Carlo simulation used to simulate both variability and uncertainty, this function will impact the distribution in both dimensions.

Because the models contain study-dependent variables, the study for which a prediction is required must be specified. If the resulting models are to be used in a risk assessment, this requires a decision about which study population is more representative of the population of concern to the assessment. This decision would revolve around speculation about the source of the differences between the studies (e.g. cultural or genetic), and would be a source of both variability and uncertainty. For instance, the population of concern may be variable with regard to the percentage of the population for which each study is more appropriate, while the extent of that frequency for each may be uncertain.

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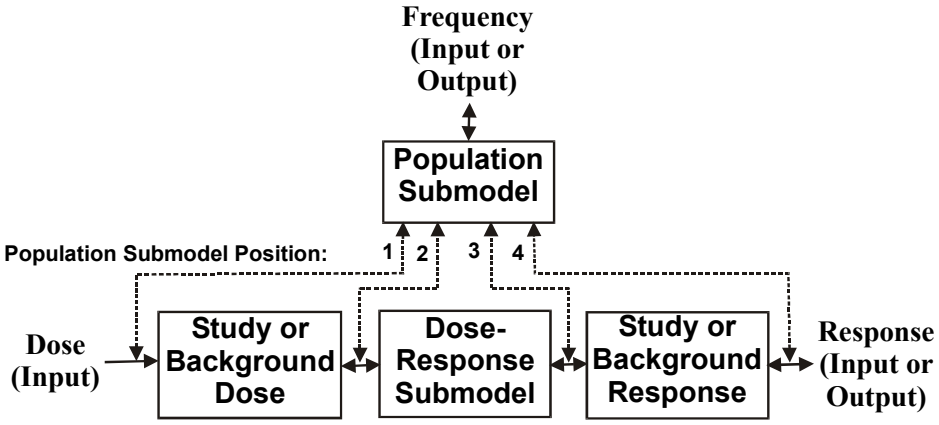

Figure AC-1: **Model Assembly from Four Components**

General structure of the models used to integrate the results from the Iraqi and Seychelles studies. The central component is the dose-response function that relates dose to the magnitude of an individual outcome (i.e. AOT or AOW). The background and study functions add parameters to account for dose-independent influences that are study-independent or study-dependent. The population submodel converts the individual model into a population model by introducing a statistical distribution at one of four positions in the individual model.

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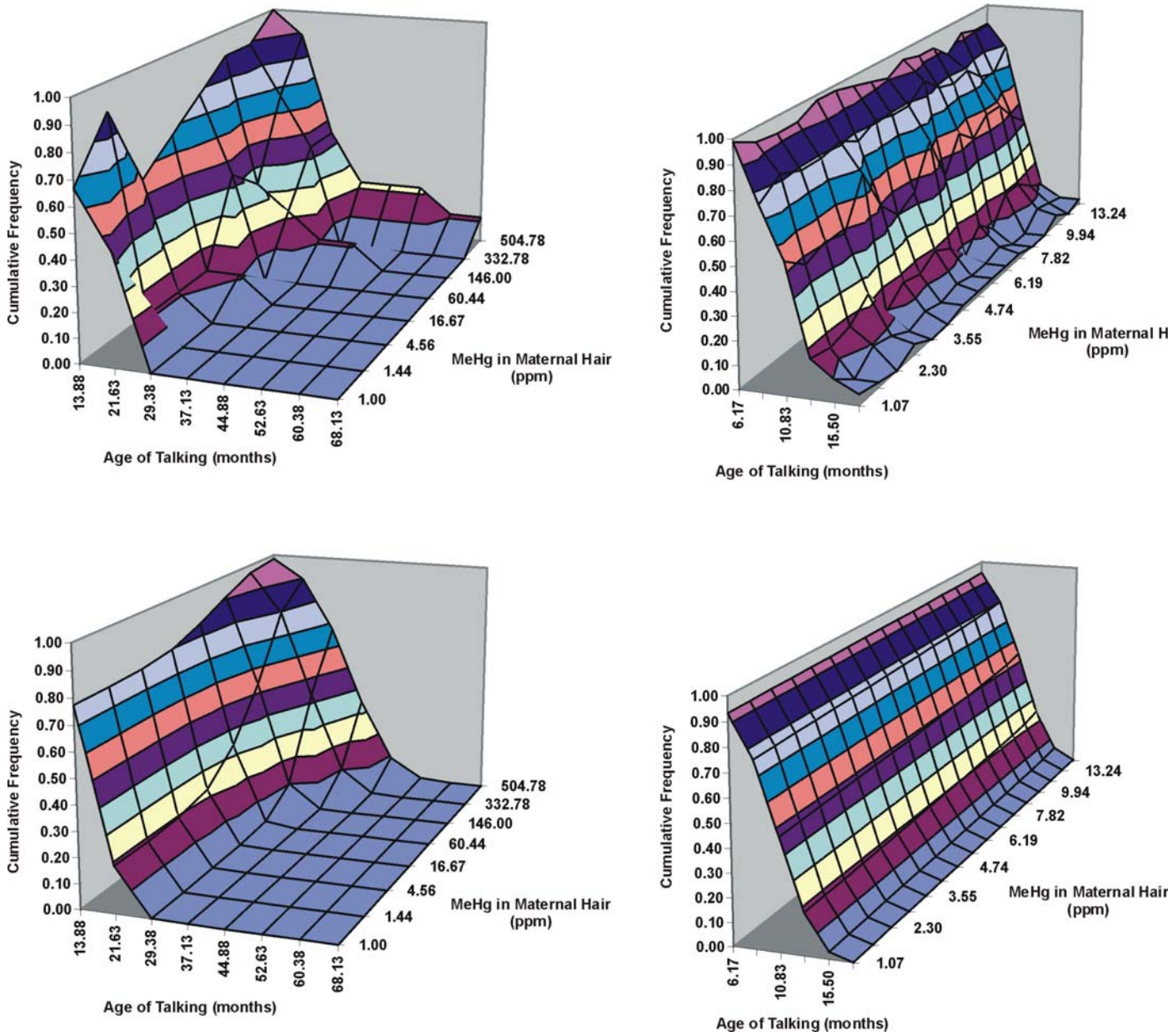
Figure AC-2: Age of Talking, Data and a Model



The charts at the top reflect the cumulative incidence tables constructed from the raw data (Age of Talking) from the Iraqi (left) and Seychelles (right). The charts at the bottom reflect a common model fit to both data sets. The Z-axis reflects the percent of the population in each dose group (Y-axis) with a AOT above the X-axis value. The X-axis values are chosen to represent the range of value encountered in the studies, and therefore do not necessarily generate incidences of 0 or 1 at all dose groups

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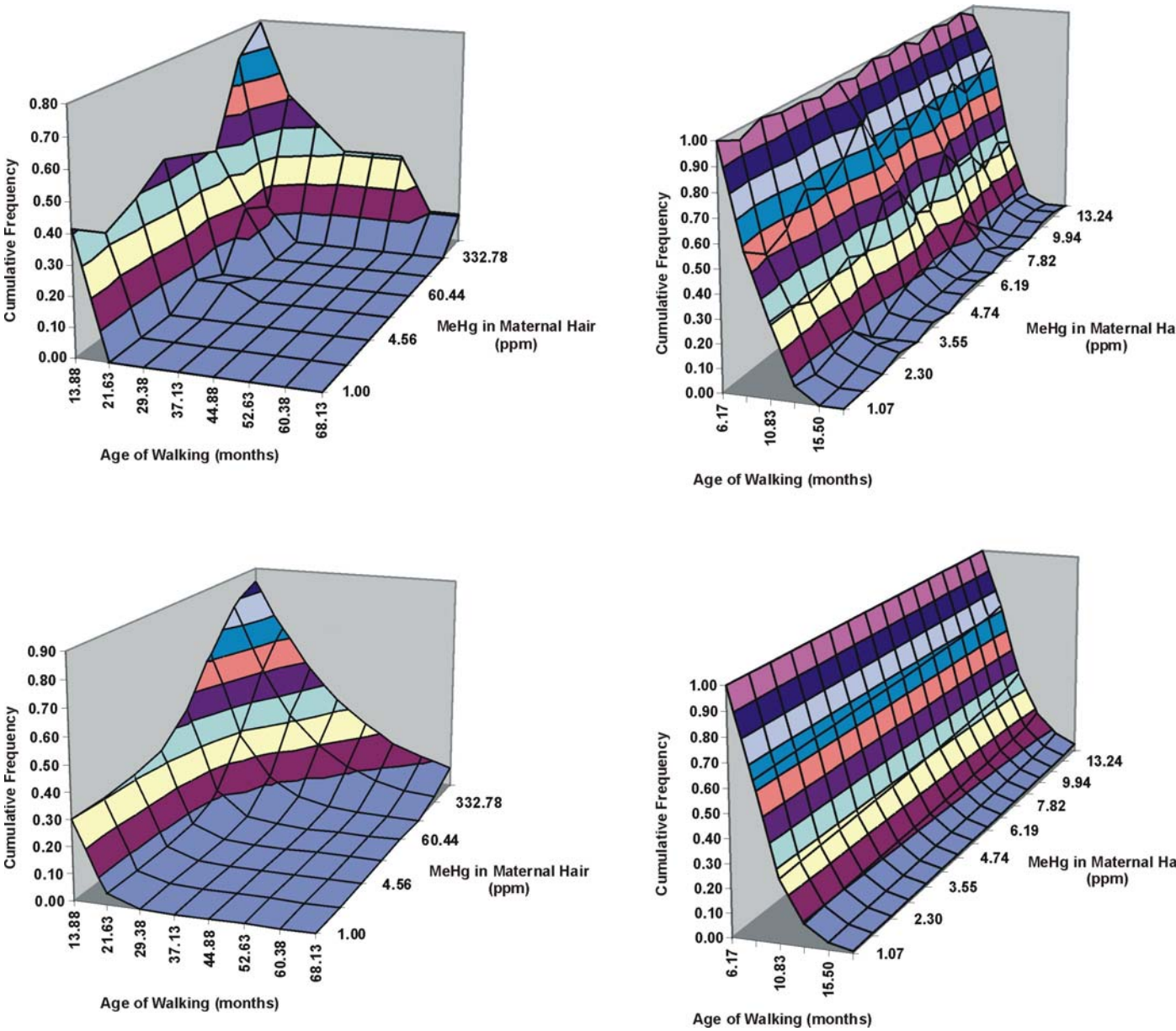
Figure AC-3: Age of Walking, Data and a Model



The charts at the top reflect the cumulative incidence tables constructed from the raw data (Age of Walking) from the Iraqi (left) and Seychelles (right). The charts at the bottom reflect a common model fit to both data sets. The Z-axis reflects the percent of the population in each dose group (Y-axis) with a AOW above the X-axis value. The X-axis values are chosen to represent the range of value encountered in the studies, and therefore do not necessarily generate incidences of 0 or 1 at all dose groups.

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Table AC-1: Functions Used to Construct Models of Methylmercury Effects

Submodel	*Functions*
Dose vs Individual Response	Linear, Hockey Stick, Mass Action, First Order, Exponential, Logistic
Population Variability	Normal, Lognormal, Weibull, Logistic
Dose Independent Factors	None, Background Dose, Background Effect, Background Dose and Background Effect
Study Factors	None, Study Dose, Study Effect, Study Dose and Study Effect

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Table AC-2: The Top Twenty Models for the Age of Talking Endpoint

Response Submodel	*Population Submodel*	*Position*	*Background Submodel*	*Study Submodel*	*Fit*	*n*	*Weight*	*Map Value*
Linear	Weibull	4	Response	Dose	0.0078	4	1.3951	0.0064
Linear	Weibull	3	Response	Response	0.0078	4	1.3951	0.0128
Exponential	Weibull	4	Response	Dose	0.0074	5	1.3642	0.0191
Exponential	Weibull	3	Response	Response	0.0075	5	1.3480	0.0253
Exponential	Weibull	3	dose and response	Dose	0.0071	6	1.3250	0.0314
Hockey Stick	Weibull	3	dose and response	Dose	0.0072	6	1.3165	0.0374
Exponential	Weibull	3	Dose	Dose	0.0078	5	1.3094	0.0434
Hockey Stick	Weibull	4	Response	Response	0.0078	5	1.3072	0.0494
Hockey Stick	Weibull	4	Response	Dose	0.0078	5	1.3072	0.0554
Linear	Weibull	4	Response	dose and response	0.0078	5	1.3072	0.0614
Hockey Stick	Weibull	4	Dose	Response	0.0078	5	1.3072	0.0674
Linear	Weibull	4	dose and response	Response	0.0078	5	1.3072	0.0734
First Order	Weibull	3	Response	Response	0.0078	5	1.3043	0.0794
Linear	Weibull	4	dose and response	Dose	0.0078	5	1.3035	0.0854
Mass Action	Weibull	3	Response	Response	0.0078	5	1.3012	0.0914
Mass Action	Weibull	4	Response	Dose	0.0079	5	1.2966	0.0974
First Order	Weibull	4	Response	Dose	0.0079	5	1.2944	0.1033
Mass Action	Weibull	4	Dose	Response	0.0079	5	1.2870	0.1092
Exponential	Weibull	4	Response	dose and response	0.0074	6	1.2844	0.1151
Hockey Stick	Weibull	3	Dose	Dose	0.0080	5	1.2823	0.1210

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Table AC-3: Sample Output for Maternal Hair MeHg (ppm) vs. Child AOT (months)

Dose (ppm in Hair)	*Population Frequency*	*Study*	*Uncertainty*		
			Average	*Median*	*0.95*
1	0.5	Seychelles	10.42	10.46	10.52
1	0.95	Seychelles	15.33	15.06	16.23
10	0.5	Seychelles	10.74	10.79	10.87
10	0.95	Seychelles	15.77	15.38	16.70
100	0.5	Seychelles	13.88	13.91	15.11
100	0.95	Seychelles	20.15	19.63	23.28
10 vs. 1	0.5	Seychelles	0.32	0.31	0.47
10 vs. 1	0.95	Seychelles	0.45	0.43	0.73
1	0.5	Iraq	16.82	16.93	17.91
1	0.95	Iraq	23.55	23.66	27.36
10	0.5	Iraq	17.13	17.25	18.00
10	0.95	Iraq	23.98	24.11	27.76
100	0.5	Iraq	20.23	20.39	20.95
100	0.95	Iraq	28.28	28.67	32.23
10 vs. 1	0.5	Iraq	0.31	0.31	0.42
10 vs. 1	0.95	Iraq	0.44	0.43	0.63

The average, median, and 95th percentiles for predicted AOT is given for various combinations of dose, population frequency, study population, and likelihood. The values for the doses "10 vs 1" represent the net difference in expected AOT with maternal concentrations of methylmercury in hair at 10 ppm vs 1 ppm.

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APPENDIX D

ESTIMATED EXPOSURE IN THE DANIELS ET AL. ((2004) COHORT

Because we used the Daniels et al. (2004) data in our risk and benefit assessment for fetal neurodevelopment, we were interested in understanding the exposure to methylmercury in this cohort. We obtained the individual subject data for the cohort and were able to estimate exposure as described below.

Daniels et al. (2004) performed a mercury analysis for a subset of 1,054 mother-child pairs. This subset was drawn from a sample of 1,225 children in the ALSPAC study population from whom umbilical cord tissue had been taken at birth. The cord tissue was analyzed for mercury concentration to provide a measure of prenatal exposure to methylmercury for these children.

Using umbilical cord tissue to measure exposure is somewhat unorthodox as compared to more typical measurements involving mercury in hair and blood that have been conducted in the United States and elsewhere. Nonetheless, we can estimate how exposures in this population compare to U.S. exposures by converting mercury in umbilical cord tissue to mercury in blood and hair as follows:

- Cord blood = cord tissue divided by 8.9 (Sakamoto et al., 2007);
- Maternal blood = cord blood divided by 1.7 (Stern 2005b);
- Maternal hair = cord blood divided by 5 (Axelrad et al., 2007; Butz-Jorgensen et al., 2004).

We can then compare the blood and hair estimates to the results from the NHANES database. We do so in terms of percentiles of exposure as shown in Table IIA-3.

Table C-1: Estimated prenatal mercury exposure in the ALSPAC study population (Daniels et al., 2004) in the United Kingdom and prenatal exposure in the United States as reported by NHANES.

Population Percentile	UK (ALSPAC) Cord Tissue/Hg Levels (µg/g)	UK (ALSPAC) Estimated Cord Blood/Hg Levels (µg/L)	UK (ALSPAC) Estimated Maternal Blood/Hg Levels (µg/L)	US (NHANES) Maternal Blood/Hg Levels* (µg/L)	UK (ALSPAC) Estimated Maternal Hair/Hg Levels (ppm)	US (NHANES) Maternal Hair/Hg Levels (ppm)**

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Average	0.023	2.6	1.5	1.6	0.51 ppm	0.47 ppm
10th Percentile	0.004	0.5	0.3	0.2	0.10 ppm	0.04 ppm
25th Percentile	0.008	0.9	0.5	0.4	0.17 ppm	0.09 ppm
50th Percentile	0.013	1.5	0.9	0.8	0.30 ppm	0.19 ppm
75th Percentile	0.023	2.6	1.5	1.7	0.51 ppm	0.42 ppm
90th Percentile	0.041	4.6	2.7	3.7	0.91 ppm	1.11 ppm
95th Percentile	0.066	7.4	4.4	5.6	1.48 ppm	1.73 ppm
99th Percentile	0.186	20.8	12.3	12.4	4.17 ppm	3.50 ppm

***From the 1999-2004 NANES survey years.**

**** From the 1999-2000 NHANES survey years. These were the only years during which NNANES measured hair mercury levels.**

As the table shows, our estimate of exposure in this U.K. study population was similar to exposure in the United States across the spectrum. The U.K. population's exposure to methylmercury was lower than we would expect because per capita consumption of commercial fish in the U.K. is about 2.8 times higher than it is in the United States (NMFS 2005) while methylmercury concentrations in fish available in the U.K. are similar to concentrations in fish in the U.S. marketplace (Montwill 2007). The lower than expected exposure in this U.K. study population might be due to consumption of mostly low methylmercury fish and avoidance of higher methylmercury fish.

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