4.0 RISK ASSESSMENT FOR METHYLMERCURY

4.1 BACKGROUND

Methylmercury is highly toxic to mammalian species and causes a variety of adverse effects. It is a developmental toxicant in humans and animals. It causes chromosomal effects but does not induce point mutations. The *Mercury Study Report to Congress* (MSRC) (U.S. EPA, 1997) concluded that because there are data for mammalian germ-cell chromosome aberration and limited data from a heritable mutation study, methylmercury is placed in a group of high concern for potential human germ-cell mutagenicity. There is no two-generation study of reproductive effects, but shorter term studies in rodents, guinea pigs, and monkeys have reported observations consistent with reproductive deficits. There are no data to indicate that methylmercury is carcinogenic in humans, and it induces tumors in animals only at highly toxic doses. Application of the revised Guidelines for Cancer Risk Assessment leads to a judgment that methylmercury is not likely to be carcinogenic for humans under conditions of exposure generally encountered in the environment.

The quantitative health risk assessment for a noncarcinogen is the reference dose (RfD). This is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime.

EPA has published two RfDs for methylmercury that represented the Agency consensus at that time. The original RfD of 0.3 μg/kg/day was determined in 1985. The current RfD of 0.1 μg/kg/day was established as the Agency consensus estimate in 1995. While EPA was developing the MSRC (U.S. EPA, 1997), it became apparent that considerable new data on the health effects of methylmercury in humans were emerging. Among these data sources were large studies of seafood-consuming populations in the Seychelles and Faroe Islands. Smaller scale studies were being reported on effects in populations around the U.S. Great Lakes and in the Amazon basin. Publications also included novel statistical approaches and applications of physiologically based pharmacokinetic (PBPK) models.

In 1997 the MSRC was undergoing final review; at that time many of the new data had either not been published in the peer-reviewed press or not been subjected to rigorous review. EPA decided that it was premature to make a change in the 1995 methylmercury RfD for the MSRC. This decision was in accordance with the advice of the Science Advisory Board (SAB). Since 1997 the field of

methylmercury toxicology and assessment has expanded dramatically. This criteria document presents a revised RfD that considers data from the human studies published in the 1990s, recent evaluations of health and pharmacokinetic data, and recent statistical and modeling approaches to assessing those data.

The following sections include brief descriptions of the previously published EPA RfDs as well as descriptions of some of the evaluation processes that took place at the end of the 1990s.

For this document the following definitions apply. These reflect usage in the National Research Council publication *Toxicological Effects of Methylmercury* (NRC, 2000) (see Section 1.5).

NOAEL No-observed-adverse-effect level. An exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects in a comparison between an exposed population and a control group. Effects may be seen at this level of exposure, but they are not considered to be adverse. For risk assessment the NOAEL is generally the highest level at which no adverse effects are seen.

LOAEL Lowest-observed-adverse-effect level. The lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects in a comparison between an exposed population and a control group.

BMD Benchmark dose. In common parlance this term refers to a quantitative assessment for noncancer health effects that uses a curve-fitting procedure to determine a level functionally equivalent to a NOAEL. In this chapter, BMD will be used to mean an estimated dose that corresponds to a specified risk above the background risk.

BMDL Benchmark dose lower limit, a statistical lower limit on a calculated BMD. In this document that will be the 95% lower confidence limit. The BMDL will be used as the starting point for the calculation of the methylmercury RfD.

4.1.1 Other RfDs Published by EPA

Two RfDs based on human studies have been published as consensus values for EPA. In addition, the MSRC (EPA, 1997) describes an RfD that could be estimated from animal data.

4.1.1.1 1985 RfD

A hazard identification and dose-response assessment was proposed for methylmercury in 1980 (U.S. EPA, 1980). This assessment was reviewed and consensus was achieved by the EPA RfD/RfC (reference concentration) Work Group on December 2, 1985. This RfD was published on EPA's Integrated Risk Information System (IRIS) in 1986. The critical effects were multiple central nervous system (CNS) effects, including ataxia and paresthesia in populations of humans exposed to methylmercury through consumption of contaminated grain (summarized by Clarkson et al., 1976; Nordberg and Strangert, 1976; and WHO, 1976).

The RfD for methylmercury was determined to be 3×10^{-4} mg/kg-day (0.3 μg/kg/day), based on a LOAEL of 0.003 mg/kg-day (corresponding to 200 μg/L blood concentration) and an uncertainty factor of 10 to adjust the LOAEL to what is expected to be a NOAEL. An additional uncertainty factor (UF) of 10 for sensitive individuals for chronic exposure was not deemed necessary, as the adverse effects were seen in what was regarded as a sensitive group of individuals: adults who consumed methylmercury-contaminated grain.

The RfD/RfC Work Group ascribed medium confidence to the choice of study, the database, and the RfD. The blood levels associated with the LOAEL were well supported by more recent data, but neither the chosen studies nor supporting database described a NOAEL. Medium confidence generally indicates that new data may change the assessment of the RfD.

4.1.1.2 1995 RfD

After publication of the RfD of 0.3 μg/kg/day, questions were raised as to its validity; some of these questions were in formal submissions requesting a change on the IRIS entry. In particular it was asked whether the RfD based on effects in exposed adults was protective against developmental effects. Subsequent to the RfD publication, the effects in Iraqi children of *in utero* exposure to methylmercury were reported by Marsh et al. (1987). The RfD/RfC Work Group discussed the methylmercury RfD in 1992 and again in 1994. Consensus on a revised RfD was reached in January 1995. Detailed description of the RfD derivation can be found in Volume V of the MSRC (U.S. EPA, 1997e).

Marsh et al. (1987) was chosen as the most appropriate study for determination of an RfD protective of a putative sensitive subpopulation, namely infants born to mothers exposed to

methylmercury during gestation. The data collected by Marsh et al. (1987) summarize clinical neurologic signs of 81 mother-and-child pairs. Maternal hair mercury concentrations were collected as the exposure metric. Concentrations ranging from 1 to 674 ppm mercury were determined from X-ray fluorescent spectrometric analysis of selected regions of maternal scalp. These were correlated with clinical signs observed in the affected members of the mother-child pairs. The hair concentration at a hypothetical NOAEL for developmental effects was determined by application of a BMD approach (see subsequent section for discussion of methods and data used). The analysis used the combined incidence of all neurological effects in children exposed *in utero* as reported in the Marsh et al. (1987) study. A Weibull model for extra risk was used to determine the BMD; in current terminology, this was a BMDL (95% lower confidence limit) on the dose corresponding to a 10% risk level. This level was calculated to be 11 ppm mercury in maternal hair (11 mg/kg hair). A description of BMD determination, choice of model, and issues on grouping of data is on pages 6-25 to 6-31 of Volume V of the MSRC.

The BMD of 11 ppm maternal hair mercury was converted to an exposure level of 44 µg mercury/L blood using a 250:1 ratio as described in the MSRC (U.S. EPA, 1997e, pp. 6-22 to 6-23):

$$11 \text{ mg/kg hair} / 250 = 44 \text{ µg/L blood}$$

To obtain a daily dietary intake value of methylmercury corresponding to a specific blood concentration, factors of absorption rate, elimination rate constant, total blood volume, and percentage of total mercury present in circulating blood were taken into account. Calculation was by the following equation, based on the assumptions that steady-state conditions exist and that first-order kinetics for mercury are being followed:

$$d \text{ µg/day} = \frac{C \times b \times V}{A \times f}$$

where:

d = daily dietary intake (expressed as µg of methylmercury)
c = concentration in blood (expressed as 44 µg/L)
b = elimination constant (expressed as 0.014 $days^{-1}$)
V = volume of blood in the body (expressed as 5 L)

A = absorption factor (expressed as a unitless decimal fraction of 0.95)

f = fraction of daily intake taken up by blood (unitless, 0.05)

Solving for d gives the daily dietary intake of mercury that results in a blood mercury concentration of 44 µg/L. To convert this to daily ingested dose (µg/kg-day), a body weight of 60 kg was assumed and included in the equation denominator:

$$d = \frac{c \times b \times V}{A \times f \times bw}$$

$$d = \frac{44\ \mu g/L \times 0.014\ days^{-1} \times 5\ L}{0.95 \times 0.05 \times 60\ kg}$$

$$d = 1.1\ \mu g/kg\text{-}day$$

The dose d (1.1 µg/kg-day) is the total daily quantity of methylmercury that is ingested by a 60-kg individual to maintain a blood concentration of 44 µg/L or a hair concentration of 11 ppm. The rationales for use of the hair:blood ratio and specific values for equation parameters can be found on pages 6-21 to 6-25 of Volume V of the MSRC.

A composite uncertainty factor of 10 was used. This uncertainty factor was applied for variability in the human population, in particular the wide variation in biological half-life of methylmercury and the variation that occurs in the hair-to-blood ratio for mercury. In addition, the factor accounts for lack of a two-generation reproductive study and lack of data for possible chronic manifestations of adult effects (e.g., paresthesia observed during gestation). The default value of 1 was used for the modifying factor.

The RfD was calculated using the following equation:

$$RfD = \frac{BMD}{UF \times MF}$$

$$= \frac{1.1\ \mu g/kg\text{-}day}{10}$$

$$= 1 \times 10^{-4}\ mg/kg\text{-}day$$

or 0.1 µg/kg/day.

Confidence in the supporting database and in the RfD were considered medium by the RfD/RfC Work Group. The MSRC (U.S. EPA, 1997e) says the following:

> The principal study (Marsh et al. 1987) is a detailed report of human exposures with quantitation of methylmercury by analysis of specimens from affected mother-child pairs. A strength of this study is that the quantitative data are from the affected population and quantitation is based upon biological specimens obtained from affected individuals. A threshold was not easily defined; extended application of modeling techniques was needed to define the lower end of the dose-response curve. This may indicate high variability of response to methylmercury in the human mother-child pairs or misclassification in assigning pairs to the cohort.

Further discussion of areas of uncertainty and variability are on pages 6-31 to 6-51 of Volume V of the MSRC (U.S. EPA, 1997e). A quantitative analysis of uncertainty in an RfD based on the Iraqi data is found in Appendix D of Volume V, and additional discussions of areas of uncertainty are in Volume VII, Risk Characterization, of the MSRC (U.S. EPA, 1997g).

4.1.1.3 Reference Values Derived From Animal Data

There are issues inherent to epidemiological studies, including the possibility of coexposure to other potential toxicants, that are not of concern in controlled experimental animal studies. It is therefore informative to compare RfDs that may be derived from animal studies to those derived from the epidemiological literature. RfDs derived from monkey studies are particularly relevant, as the neurotoxic effects produced by developmental methylmercury exposure in monkeys are similar to those identified in humans (Burbacher et al., 1990a; Gilbert and Grant-Webster, 1995). The studies at the University of Washington were of a relatively large cohort of macaque monkeys whose mothers were exposed throughout pregnancy to 50 µg/kg/day of methylmercury. The studies revealed deficits on cognitive tests during infancy, which may represent retarded development (Burbacher et al., 1986; Gunderson et al., 1986, 1988). These methylmercury-exposed monkeys also displayed aberrant play and social behavior (Burbacher et al., 1990b). Studies at the Canadian Health Protection Branch in the same species of monkey, dosed with 50 µg/kg/day from birth to 7 years of age, revealed visual, auditory, and somatosensory deficits, including evidence of delayed neurotoxicity identified in middle age (Rice and Gilbert, 1995, 1992, 1982; Rice, 1989a). Research in a cohort of monkeys dosed beginning *in utero* and continuing until 4 years of age revealed similar sensory system impairment (Rice, 1998; Rice and Gilbert, 1995, 1990). Three individuals dosed at 10 or 25 µg/kg/day all exhibited impaired function in at least

one sensory system in addition to evidence of delayed neurotoxicity (Rice, 1998). In none of these studies was a NOAEL identified.

Calculation of an RfD from these data according to the method typically used by the EPA would include application of a number of UFs, including dividing the LOAEL by a factor of 10 (because no NOAEL was identified), division by 10 again for extrapolation from animal to human data, and division by another factor of 10 in consideration of individual variation in sensitivity. Monkeys and humans have approximately the same brain:blood mercury ratio following chronic exposure (Burbacher et al., 1990a), although the ratio in humans may be slightly higher than in monkeys (Rice, 1989b). However, the half-life of mercury in the blood of monkeys is about 15 days (Rice, 1989c), whereas clearance times for humans averaged 45-70 days in several studies, with some individuals having even longer clearance times (see Section 4.2.3). The shorter clearance time in monkeys would result in an UF of at least 5 based on pharmacokinetic considerations alone; therefore an overall factor of 10 appears appropriate for interspecies extrapolation. This calculation would yield an RfD of 0.05 µg/kg/day from the *in utero* and postnatal exposure studies, and an RfD as low as 0.01 µg/kg/day based on combined *in utero* and postnatal exposure (Rice, 1996). Gilbert and Grant-Webster (1995) suggested an RfD of 0.025 µg/kg/day based on the same data.

4.1.2 Risk Assessments Done by Other Groups

Quantitative estimates of hazards of oral exposure to methylmercury have been considered by the Food and Drug Administration (FDA), Agency for Toxic Substances and Disease Registry (ATSDR), and other countries (WHO/IPCS), among others.

4.1.2.1 Food and Drug Administration

In 1969, in response to the poisonings in Minamata Bay and Niigata, Japan, the U.S. FDA proposed an administrative guideline of 0.5 ppm for mercury in fish and shellfish moving in interstate commerce. This limit was converted to an action level in 1974 (Federal Register *39*, 42738, December 6, 1974) and increased to 1.0 ppm in 1979 (Federal Register *44*, 3990, January 19, 1979) in recognition that exposure to mercury was less than originally considered. In 1984, the 1.0 ppm action level was converted from a mercury standard to one based on methylmercury (Federal Register *49*; November 19, 1984).

The action level takes into consideration the tolerable daily intake (TDI) for methylmercury as well as information on seafood consumption and associated exposure to methylmercury. The TDI is the amount of methylmercury that can be consumed daily over a long period of time with a reasonable certainty of no harm. FDA established a TDI based on a weekly tolerance of 0.3 mg of total mercury per person, of which no more than 0.2 mg should be present as methylmercury. These amounts are equivalent to 5 and 3.3 μg, respectively, per kilogram of body weight. Using the values of methylmercury, this tolerable level would correspond to approximately 230 μg/week for a 70-kg person, or 33 μg/person/day (0.47 μg/kg bw/day). The TDI was calculated from data developed in part by Swedish studies of Japanese individuals poisoned in the Niigata episode, which resulted from the consumption of contaminated fish and shellfish and the consideration of other studies of fish-eating populations.

Based on observations from the later poisoning event in Iraq, FDA has acknowledged that the fetus may be more sensitive than adults to the effects of mercury (Federal Register *44*, 3990, January 19, 1979; U.S. FDA Consumer, September 1994). In recognition of these concerns, FDA has provided advice to pregnant women and women of childbearing age to limit their consumption of fish known to have high levels of mercury (U.S. FDA Consumer, 1994). FDA believes, however, that given existing patterns of fish consumption, few women (less than 1%) eating such high-mercury fish will experience slight reductions in the margin of safety. However, because of the uncertainties associated with the Iraqi study, FDA has chosen not to use the Iraqi study as a basis for revising its action level. Instead, FDA has chosen to wait for findings of prospective studies of fish-eating populations in the Seychelles Islands.

4.1.2.2 World Health Organization

The International Programme on Chemical Safety (IPCS) of the World Health Organization published a criteria document on mercury (WHO, 1990). In that document, it was stated that "a daily intake of 3 to 7 μg Hg/kg body weight would cause adverse effects of the nervous system, manifested as an approximately 5% increase in the incidence of paraesthesias." The IPCS expert group also concluded that developmental effects in offspring (motor retardation or signs of CNS toxicity) could be detected as increases over background incidence at maternal hair levels of 10-20 ppm mercury. These levels of concern were based on evaluation of data including the human poisoning incident in Iraq.

4.1.2.3 ATSDR

In 1993, ATSDR first published a Minimal Risk Level (MRL) for methylmercury. An MRL is derived in a manner similar to the RfD; it is defined as an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. In 1999 ATSDR published a revised methylmercury MRL using the Seychelles Islands study (SCDS) (Davidson et al., 1998) as the starting point (ATSDR, 1999). In this study (described in detail in Section 3.2.2.5 and summarized in Section 4.2.13), the investigators examined the correlation between subtle neurological effects and low-dose chronic exposure to methylmercury. No correlation between maternal hair mercury concentrations and neurological effects was seen in the SCDS 66-month-old children. ATSDR determined a minimal risk level of 0.3 μg/kg per day, based on a dose of 1.3 μg/kg per day, which reflects the average concentration of the upper quintile of the exposed population but does not necessarily correspond to a NOAEL. ATSDR used a UF of 1.5 to account for pharmacokinetic variability within the human population; they made their choice based on the analyses of Clewell et al. (1998). An additional factor of 1.5 was applied to account for any other individual variability (e.g., pharmacodynamics) as well as a modifying factor of 1.5 to account for the possibility that domain-specific tests used in the Faroe Islands study might have allowed detection of subtle neurological effects that were not evaluated in the Seychelles cohort. Although the conventional risk assessment approach is to multiply UFs, ATSDR summed these factors to develop an overall safety factor of 4.5.

4.1.3 SAB Review of the Mercury Study Report to Congress

The Science Advisory Board (SAB) is a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the EPA. The SAB is structured to provide balanced, expert assessment of scientific matters relating to problems facing the Agency. The SAB reviewed a draft of the eight-volume MSRC (U.S. EPA, 1997a-h) in the context of a public meeting held February 13 and 14, 1997. A panel of 33 scientists reviewed the entire MSRC. A subgroup focused on the health effects data, and in particular EPA's use of those data to derive the methylmercury RfD of 0.1 μg/kg/day, based on effects observed in Iraqi children exposed *in utero*.

The SAB report was published in October 1997 (EPA-SAB-EC-98-001). It made the following statement:

> In general, from the standpoint of looking at human health effects and the uncertainties, the draft report [MSRC] is a very good document and an important step forward in terms of bringing the relevant information together into one place for the first time. The current RfD, based on the Iraqi and New Zealand data, should be retained at least until the on-going Faeroe and Seychelles Islands studies have progressed much further and been subjected to the same scrutiny as has the Iraqi data.

The SAB report continued:

> Investigators conducting two new major prospective longitudinal studies—one in the Seychelles Islands, the other in the Faeroe Islands—have recently begun to publish findings in the literature and are expected to continue releasing their findings during the next 2-3 years. These studies have advantages over those cited in the previous paragraph in that they have much larger sample sizes, a larger number of developmental endpoints, potentially more sensitive developmental endpoints, and control a more extensive set of potential confounding influences. On the other hand, the studies have some limitations in terms of low exposures (to PCBs in the Faeroes) and ethnically homogenous societies. Since only a small portion of these new data sets have been published to date and because questions have been raised about the sensitivity and appropriateness of the several statistical procedures used in the analyses, the Subcommittee concluded that it would be premature to include any data from these studies in this report until they are subjected to appropriate peer review. **Because these data are so much more comprehensive and relevant to contemporary regulatory issues than the data heretofore available, once there has been adequate opportunity for peer review and debate within the scientific community, the RfD may need to be reassessed in terms of the most sensitive endpoints from these new studies.** [Emphasis theirs]

4.1.4 Interagency Consensus Process

Among the many reviews of the MSRC was one by scientists and policy-makers from interested Federal agencies, sponsored by the Committee on Environment and Natural Resources (CENR), Office of Science and Technology (OSTP). This review highlighted many divergent points of view as to the appropriate basis for quantitative assessment of the low-dose effects of methylmercury exposure. It was decided that an interagency process with external involvement would be undertaken to review new methylmercury data and evaluate new and existing data. EPA committed to participate in this process and, at its conclusion, to assess its 1995 RfD for methylmercury to determine if a change was warranted. Subsequently a workshop was organized by an interagency committee at the request of OSTP. The organizing committee was chaired by the National Institute of Environmental Health Sciences (NIEHS) and included representatives from several agencies:

Department of Health and Human Services (DHHS)
Office of the Assistant Secretary for Planning and Evaluation
Centers for Disease Control and Prevention (CDC)
Agency for Toxic Substances Disease Registry (ATSDR)
Food and Drug Administration (FDA)
Environmental Protection Agency (EPA)

National Oceanic and Atmospheric Administration (NOAA)
Office of Science and Technology Policy (OSTP)
Office of Management and Budget (OMB)

The Methylmercury Workshop was a response to the suggestion that the emerging Seychellois and Faroese data undergo a level of scrutiny beyond journal peer review if they were to be used in policy setting.

The Workshop on the Scientific Issues Relevant to Assessment of Health Effects from Exposure to Methylmercury was held in Raleigh, North Carolina, November 18–20, 1998. The purpose of the workshop was to discuss and evaluate the major epidemiologic studies associating methylmercury exposure with an array of developmental measures in children. The workshop did not attempt to derive a risk assessment, but it was assumed by participants that the workshop evaluation would facilitate agreement on risk assessment issues. The major studies considered were those that have examined populations in Iraq, the Seychelles, the Faroe Islands, and the Amazon, along with the most relevant animal studies. Study authors made detailed presentations to respond to a series of questions on study exposures, potential confounders, measurements of effect, and other related topics. Five expert panels discussed the presentations and published data; panels covered the following areas: exposure, neurobehavioral endpoints, confounders and variables, design and statistics, and experimental (animal and *in vitro*) data. The results of their deliberations were published in the Spring of 1999 (NIEHS, 1999). Conclusions of the report were reviewed by workshop panelists and by Federal scientists who had attended the workshop. The conclusions are quoted below.

1. Methylmercury is a developmental neurotoxin, but effects at low doses encountered by eating fish are difficult to evaluate.

2. All the studies reviewed were considered of high scientific quality, and the panel recognized that each of the investigations had overcome significant obstacles to produce important scientific information. The panel also stated that continued funding of the studies in the Seychelles, Faroes, and Amazon is necessary for the full potential of those studies to be realized. This is particularly the case for the Faroes and Seychelles studies, which have assessed and are currently assessing the potential developmental neurotoxic effects of methylmercury in fish-eating populations. The developmental studies would benefit by evaluation of common endpoints using similar analytical methods. It is important to note that the Amazon study did not assess developmental endpoints but assessed effects in adults.

3. Results from the Faroes and Seychelles studies are credible and provide valuable insights into the potential health effects of methylmercury.

4. Some differences are clearly present in results from the Faroes, Seychelles, and Amazon, but the panel was not able to clearly identify the sources of these differences. Among possible sources are the different effects of episodic versus continuous exposure, ethnic differences in methylmercury responses, lack of common

endpoints in the Faroes and Seychelles studies, and several other confounders or modifying factors such as those found in diet and lifestyle, as well as in chemicals present in seafood, which is the source of methylmercury to these populations. The other chemical constituents of seafood that may be explanatory include those that may be beneficial to fetal neurodevelopment (i.e., omega-3 fatty acids) and those that may be harmful to fetal neurodevelopment (e.g., PCBs).

5. These studies have provided valuable new information on the potential health effects of methylmercury, but significant uncertainties remain because of issues related to exposure, neurobehavioral endpoints, confounders and statistics, and design.

The interagency organizing committee agreed unanimously that the deliberations of the panels and the workshop report will be a key factor in subsequent public health policy actions taken by each of the participating agencies.

4.1.5 National Academy of Sciences Review

Congress directed EPA, through the House Appropriations Report for FY99, to contract with the National Research Council (NRC, a body of the National Academy of Sciences) to evaluate the body of data on the health effects of methylmercury, with particular emphasis on new data since the publication of the MSRC. NRC was asked to provide recommendations regarding issues relevant to the derivation of an appropriate RfD for methylmercury.

The NRC empaneled a group of scientific experts who held public meetings at which there were presentations from methylmercury researchers, government agencies, trade organizations, public interest groups, and concerned citizens. The panel evaluated the scientific basis for risk assessments done by EPA and other groups as well as new data and findings available since publication of the MSRC. The committee was not charged with developing an RfD as an alternative to the EPA assessment, but rather provided scientific guidance that would inform such an assessment. The NRC report, *Toxicological Effects of Methylmercury*, was released to the public on July 11, 2000 (NRC, 2000). Conclusions of that report are summarized below.

The report concludes that methylmercury is a highly toxic substance; a number of adverse health effects associated with methylmercury exposure have been identified in humans and in animal studies. Most extensive are the data for neurotoxicity, particularly in developing organisms. The nervous system is considered by the NRC committee to be the most sensitive target organ for which there are data suitable for derivation of an RfD. The committee also concludes on the basis of data from humans and from animal studies that exposure to methylmercury can have adverse effects on the developing and adult cardiovascular system. They note that some research demonstrated adverse cardiovascular effects at or

below levels associated with effects on the developing nervous system. The NRC also cites evidence of low-dose methylmercury effects on the immune and reproductive systems.

The NRC report presents some conclusions on the public health implications of methylmercury exposure; one conclusion is quoted below:

> The committee's margin-of-exposure analysis based on estimates of MeHg exposure in the U.S. population indicates that the risk of adverse effects from current MeHg exposure in the majority of the population is low. However, individuals with high MeHg exposure from frequent fish consumption might have little or no margin of safety (i.e., exposures of high-end consumers are close to those with observable adverse effects). The population at highest risk is the children of women who consumed large amounts of fish and seafood during pregnancy. The committee concludes that the risk to that population is likely to be sufficient to result in an increase in the number of children who have to struggle to keep up in school and who might require remedial classes or special education. (NRC, 2000 p. 9)

The NRC report gives an evaluation of the 1995 EPA RfD. Their conclusion is as follows:

> On the basis of its evaluation, the committee's consensus is that the value of EPA's current RfD for MeHg, 0.1 μg/kg/day, is a scientifically justifiable level for the protection of public health. However, the committee recommends that the Iraqi study no longer be used as the scientific basis of the RfD (NRC, 2000 p. 11).

The NRC report made several recommendations on the appropriate basis for a revised RfD. The Committee thoroughly reviewed three epidemiological longitudinal developmental studies: the Seychelles Islands, the Faroe Islands, and New Zealand. The Seychelles study yielded scant evidence of impairment related to *in utero* methylmercury exposure through 5.5 years of age, whereas the other two studies found dose-related effects on a number of neuropsychological endpoints. The Faroe Islands study is the larger of the latter two studies and has been extensively peer-reviewed. NRC recommended use of data from the Faroe Islands study for derivation of the RfD (NRC, 2000 p. 11).

NRC recommended BMD analysis as the most appropriate method of quantifying the dose-effect relationship. They recommend the lower limit on a 5% effect level obtained by applying a K-power model ($K \geq 1$) to dose-response data based on Hg in cord blood. NRC noted that for the Faroe Islands data the results of the K-power model under this constraint are equivalent to a linear model (NRC, 2000, pp. 11-12).

NRC recommended use of the Boston Naming Test (BNT) as the critical endpoint. This endpoint yields the second-lowest BMDL but was judged by the Committee to be more reliable than the endpoint

that yields the lowest BMDL. The BMDL for the BNT from the Faroe Islands study is 58 ppb Hg in cord blood.

NRC described alternative dose conversion processes using a one-compartment model similar to that used in the MSRC.

In their discussion of uncertainty factors, NRC reviewed several sources of variability and uncertainty and recommended that an uncertainty factor of at least 10 be used. NRC recommended a factor of 2 to 3 for biological variability in dose estimation. They also recommended an additional factor to account for data gaps relating to possible long-term neurological effects not evident in childhood, as well as possible effects on the immune and cardiovascular systems (NRC, 2000, p. 327).

4.1.6 External Peer Review of Draft RfD

A draft EPA RfD document was submitted for external scientific peer review in late October 2000; the reviewers are listed at the front of this document. At the same time the draft RfD document was circulated for comment to other Federal Agencies through CENR and OSTP. A public scientific review meeting was held November 15, 2000; the final peer review report was delivered to EPA on December 7, 2000, and is available in the docket. The external peer reviewers supported the use of the Faroes data, derivation of a BMD as described by NRC, and application of a tenfold uncertainty factor to the BMDL. They agreed with EPA's use of a one-compartment model for dose conversion as well as with most of the parameter estimates; they commented correlation among some of the parameters. The peer reviewers disagreed with NRC's recommendation to set the RfD on the BNT results from the full Faroese cohort. They felt that the BNT scores showed an effect of concomitant PCB exposure in some analyses. They preferred a PCB-adjusted BMDL of 71 ppb mercury in cord blood for the BNT. They also offered suggested alternatives to use of the BNT test reslts. The peer reviewers validated a final RfD of 0.1 µg/kg bw /day.

4.1.7 Revised RfD

The development of this RfD considered the NRC recommendations and followed them for the most part. Most recommendations of the peer-review panel were incorporated as well. The following sections provide rationales for choices made by EPA in determining the basis for the RfD.

4.2 CHOICE OF CRITICAL STUDY AND ENDPOINT

NRC concluded, and EPA agrees, that the data from human studies showing developmental neurotoxicity are the most appropriate basis for the RfD. NRC concluded that human studies on methylmercury carcinogenicity are inconclusive and that the renal tumors observed in mice were found only when animals were exposed at or above the maximally tolerated dose (MTD). In the MSRC, EPA noted that if one applied the principles of the revisions to the Risk Assessment Guidelines for Carcinogenicity, the following conclusions would be reached:

> Methylmercury is not likely to be a human carcinogen under conditions of exposure generally encountered in the environment. Data in humans were inadequate; interpretation is limited by inappropriate study design and incomplete descriptions of methodology. Dietary exposure in two strains of mice resulted in increased renal adenomas and adenocarcinomas. Tumors were observed only in dose groups experiencing profound nephrotoxicity. Studies in rats exposed to an MTD showed no increased tumor incidence. Several studies show that methylmercury can cause chromosomal damage in somatic cells. While evidence is good for chromosomal effects, it does not appear that methylmercury is a point mutagen. The mode of action in renal tumor induction is likely to be related to reparative changes in the tissues. Human exposure is likely to be from consumption of contaminated foods, especially fish. It is expected that exposure, even in groups consuming large amounts of fish from contaminated sources, will be to levels far below those likely to cause the tissue damage associated with tumor formation in animals (U.S. EPA, 1997).

NRC concluded that human data, as well as results of animal tests, indicate the cardiovascular system is a sensitive target for methylmercury effects. This is particularly true for developing organisms. Their report also cites animal and *in vitro* data linking methylmercury exposure to immunotoxic and reproductive effects (summarized in NRC, 2000, pp. 190-191). It is clear, however, that at the current time the human data set on developmental neurotoxicity is the most extensive, best reviewed, and most thoroughly evaluated. The RfD will thus rely on those data. It is expected that an RfD based on developmental neurotoxicity will be protective against adverse effects likely to occur at higher levels of mercury exposure. Following NRC's recommendation, EPA's choice of critical study was limited to those developmental studies of populations experiencing long-term, low-dose exposure. Only those studies are summarized in subsequent sections of this document.

4.2.1 Summary of Available Data

This section gives brief summaries of studies on the developing central nervous system that were described by NRC. This section follows the format used by the NRC report; studies are grouped into subsections by endpoint and chronologically within subsection. Section 4.2.1.1 describes the evidence for effects of methylmercury on neurological status; Section 4.2.1.2 describes the effects on attainment of

developmental milestones during infancy; Section 4.2.1.3 describes other effects during infancy and early childhood; Section 4.2.1.4 presents evidence for cognitive deficits during childhood (school age); and Section 4.2.1.5 describes sensory and other effects of methylmercury.

For more detailed study descriptions refer to Section 3 of this document or to the MSRC.

4.2.1.1 Status on Neurological Examination

Cree Population—McKeown-Eyssen et al. (1983)

McKeown-Eyssen et al. (1983) studied a population of 234 12- to 30-month-old Cree Indian children for whom prenatal methylmercury exposure was estimated on the basis of maternal hair samples. The subjects lived in four communities in northern Quebec. Hair samples were collected on 28% of the mothers during pregnancy; prenatal exposure for the rest of the cohort was estimated from hair segments assumed to date from the time the study child was *in utero*. No child was judged to have any abnormal physical findings. Overall, 3.5% (4) of the boys and 4.1% (5) of the girls were considered to have abnormal neurological findings. The most frequent abnormality (observed in 11.4% [13] of the boys and 12.2% [14] of the girls) involved tendon reflexes. Abnormalities of muscle tone or reflexes in boys were the only neurological finding for which there was a statistically significant association with prenatal methylmercury exposure, either before or after adjustment for confounding. The risk of an abnormality of tone or reflexes increased seven times with each 10 ppm increase in maternal hair mercury. When exposure was categorized, the prevalence of tone or reflex abnormality did not increase in a clear dose-response manner across categories. In girls, incoordination was negatively associated with prenatal methylmercury exposure. The authors noted that these mild, isolated neurological findings were different from those described in previous reports of neurological abnormalities after prenatal exposure to higher levels of methylmercury.

Mancora, Peru—Marsh et al. (1995)

Neurological examination was done on 194 children in Mancora, Peru. Although the study was conducted in the early 1980s, it was not published until 1995 (Marsh et al., 1995). Fish consumption was the primary route of methylmercury exposure and maternal hair was used as the index of exposure (geometric mean 7.05 ppm; range 0.9 to 28.5 ppm). Comparison of peak and mean hair-mercury concentration suggested that the women's exposure was at steady state because of stability in their fish-

consumption patterns. Maternal hair samples and data on child neurological status were available for 131 children. Several elements of the study design are not described: the size of the eligible population from which the 131 children were sampled, the specific elements of the neurological assessment conducted, and the ages at which the children were examined. Frequencies were reported for the following endpoints: tone decreased, tone increased, limb weakness, reflexes decreased, reflexes increased, Babinski's sign, primitive reflexes, and ataxia. No endpoint was significantly associated with either mean or peak maternal hair mercury.

SCDS Pilot Study—Myers et al. (1995b)

In the cross-sectional or pilot study of the SCDS (Myers et al., 1995b), 789 infants and children between the ages of 5 and 109 weeks were evaluated by a pediatric neurologist. Mean maternal hair mercury in the cohort was 6.1 ppm (range 0.6 to 36.4 ppm). The endpoints assessed were mental status, attention, social interactions, vocalizations, behavior, coordination, postures and movements, cranial nerves, muscle strength and tone, primitive and deep tendon reflexes, plantar responses, and age-appropriate abilities such as rolling, sitting, pulling to stand, walking, and running. The statistical analyses focused on three endpoints chosen on the basis of their apparent sensitivity to prenatal methylmercury exposure in the Iraq and Cree studies: overall neurological examination, increased muscle tone, and deep tendon reflexes in the extremities. There was no association between maternal hair mercury and questionable and abnormal results. The frequency of those results ranged from 16.5% in the group with hair mercury at 0 to 3 ppm to 11.7% in the group with Hair mercury at more than 12 ppm. The frequencies of abnormalities of limb tone or deep tendon reflexes were about 8%; there was no dose-dependent variation in frequency of either endpoint.

SCDS Main Study—Myers et al. (1995c)

The main cohort of the SCDS consisted of 779 mother-infant pairs, representing approximately 50% of all live births during the period of recruitment. The final sample size was 740. When the infants were 6.5 months old, a pediatric neurologist administered essentially the same neurological examination that had been used in the pilot phase; testing was blinded as to child's exposure. A total of 3.4% (25) of the children had overall neurological scores considered abnormal or questionable; this frequency was too low to permit statistical analysis of the overall neurological examination. The frequency of abnormalities was 2% for both limb tone and abnormal deep tendon reflexes. Questionable limb tone was identified in approximately 20% of the children, and questionable deep tendon reflexes in approximately 15%.

Although such findings were not considered pathological, they were combined with abnormal findings for statistical analyses. The frequency of abnormal and questionable findings for limb tone or deep tendon reflexes was not significantly associated with maternal hair mercury concentrations.

Faroes Population—Dahl et al. (1996)

A functional neurological exam was part of a general physical examination administered to a cohort of 7-year-old children from the Faroe Islands. Of 1,386 infants eligible at recruitment, cord-blood and maternal hair samples were obtained from 1,022 singleton births (75%), and 917 children were examined (66%) (Grandjean et al., 1992). The mean cord-blood concentration was 22.9 μg/L; the mean maternal hair mercury concentration was 4.3 ppm. The examination focused on motor coordination and perceptual-motor performance (Dahl et al., 1996). Results were scored as automatic, questionable, or poor. There was no association between cord-blood mercury and the number of tests on which a child's performance was considered automatic or performed optimally. On the tests of reciprocal motor coordination, simultaneous finger movement, and finger opposition, fewer than 60% of the children achieved a score of automatic for optimal performance. On the finger opposition test, children with questionable and poor performance (425 children) had a significantly higher mean cord-blood mercury concentration than children with automatic performance (465 children) (23.9 versus 21.8 μg/L, $p = 0.04$) (Grandjean et al., 1997).

Faroes Population—Steurwald et al. (2000)

A cohort of 182 singleton, full-term infants born in the Faroe Islands between 1994 and 1995 was recruited. The cohort represented 64% of all births in the study area. Data were collected on maternal hair mercury, cord whole-blood mercury, and cord serum mercury. A total of 15 maternal hair measurements exceeded 10 ppm. Measurements were also taken of 18 pesticides or metabolites and 28 polychlorinated biphenyl (PCB) congeners in maternal serum. At 2 weeks of age infants were given a neurological examination designed to assess functional abilities, reflexes and responses, and stability of behavioral status during examination. Responses were categorized as optimal, questionable, or suboptimal. The neurological optimality score (NOS) was the number of items rated as optimal out of a total of 60. Two subscores were generated (muscle tone and reflexes) and a variety of thyroid-function indices were also assessed. Maternal hair mercury concentrations were not significantly associated with NOS score, but there was a significant inverse relationship between NOS scores and cord whole-blood mercury. The mean mercury concentration was 20.4 μg/L (range 1.9 to 102 μg/L). Based on NOS

score, a tenfold increase in cord-blood mercury was associated with the equivalent of a 3-week reduction in gestational age. Adjustments for total PCBs and fatty acid concentrations had no effect on results, and selenium was not an effect modifier. Muscle-tone and reflexes subscores were not significantly associated with any exposure biomarker.

Cordier and Garel (1999)

Cordier and Garel (1999) studied a cohort of Amerind children from a gold-mining area in French Guiana. Median maternal hair concentration was 6.6 ppm with a range of 2.9 to 17.8 ppm; 35% of maternal hair mercury levels were greater than 10 ppm. Neurological examination included the following: neuromotor examination of the upper an lower limbs, body axis, deep reflexes, and postural reactions; neuromotor functions; neurosensory examination; and cranial growth. The authors report that for children greater than 2 years of age, increased reflexes were found with greater incidence as a function of maternal hair mercury; the effect was greater in boys than in girls. When 10 children were retested 9 months later by a different examiner, only 3 were found to have the increased reflex response. The authors commented that this poor reproducibility makes the reflex response difficult to interpret.

Conclusions

There is some evidence that neurological status in children is associated with low-dose *in utero* exposure: (1) an increased incidence (not dose dependent) of tone or reflex anomalies in boys associated with increased maternal hair mercury (McKeown-Eyssen et al., 1983); (2) an inverse association between newborn neurological optimality score and cord-blood mercury in Faroese children (Steurwald et al., 2000); (3) a statistically significant increase in the mean cord-blood mercury of 7-year-old Faroese children who performed less than optimally on a finger opposition test, compared with Faroese children with normal performance (Grandjean et al., 1997); (4) the association of increased reflexes with increasing maternal hair mercury in a group of children aged 9 months to 6 years in French Guiana (Cordier and Garel, 1999). NRC notes that a particular limitation of the use of neurological status is the categorical nature of the response; in other words, the subject has either an abnormal response or a normal response. This may have been a factor in the evaluation of results from the SCDS. The number of abnormal responses in this population was very low; thus there was reduced statistical power for hypothesis testing.

4.2.1.2 Age at Achievement of Developmental Milestones

SCDS—Myers et al. (1997) and Axtell et al. (1998)

The association between achievement of developmental milestones and prenatal methylmercury exposure was evaluated in the main cohort of the SCDS (Myers et al., 1997). Data were available for 738 of the 779 children enrolled. The mean average age for walking was 10.7 months for girls and 10.6 months for boys; for talking it was 10.5 months for girls and 11.0 months for boys. The mean age at which a child was considered to talk was not significantly associated with maternal hair mercury in any of the regression models used. In regressions stratified by child sex, a positive association was found between age at walking and maternal hair mercury in boys only. The interaction between mercury and sex was not statistically significant in the analyses of the complete cohort. The authors considered the magnitude of the delay in boys' walking to be clinically insignificant; a 10-ppm increase in maternal hair mercury was associated with approximately a 2-week delay. This association in boys was not significant when four statistical outliers were excluded from the analysis. Authors concluded that hockey-stick models provided no evidence of a threshold for developmental delay, as the fitted curves were essentially flat.

Axtell et al. (1998) reanalyzed the milestone data, applying semiparametric generalized additive models that are less restrictive than the approaches used by Myers et al. (1997). Their major finding was that the association between age at walking and maternal hair mercury in boys was nonlinear. In their modeled estimates, walking was delayed as maternal hair concentrations increased from 0 to 7 ppm but was observed at a slightly earlier age as mercury concentration increased beyond 7 ppm. The size of the effect associated with the increase from 0 to 7 ppm was very small, corresponding to a delay of less than 1 day in the achievement of walking. Because of the contradictory nature of the dose-response relationships above and below 7 ppm, the authors expressed a doubt that the association found below 7 ppm reflected a causal effect of mercury exposure on age at walking.

Mancora, Peru—Marsh et al. (1995)

Data on developmental milestones were collected in the Peruvian study conducted by Marsh et al. (1995). The study was conducted prospectively, and data were apparently collected in an ongoing manner over the course of a mother's visits to a postnatal clinic. Regression analyses, including analyses stratified by child sex, did not reveal any significant associations between maternal hair mercury

concentrations and the ages at which children sat, stood, walked, or talked. The rates of developmental retardation, especially in speech (13 of 131), were substantial. Children's birthweight, height, and head circumference were unrelated to maternal hair mercury concentrations.

Faroes Population—Grandjean et al. (1995)

Ages at achievement of motor development milestones were investigated in a 21-month birth cohort (1,022 infants born in 1986-1987) of children in the Faroe Islands. Complete data were available for 583 children. Three motor-development milestones commonly achieved between 5 and 12 months of age were selected for analysis: "sits without support," "creeps," and "gets up into standing position with support." There was no significant association between age at achievement and either cord-blood or maternal hair mercury for any of the three milestones. For all three, however, the authors reported a significant inverse association between age at achievement and the child's hair mercury concentration at 12 months. Children's hair mercury was interpreted as an index of postnatal exposure to methylmercury. Breastfeeding was associated with both increased hair mercury concentrations and more rapid achievement of milestones. Therefore, the authors concluded that the inverse association reflected residual confounding by duration of breastfeeding.

Conclusions

The recent human studies provide little evidence of an association between maternal hair mercury below 30 ppm and delayed developmental milestones. The NRC report noted that in the SCDS, mean age of walking was higher in the part of the population born to mothers with higher hair mercury. The association was for male children only and it was not dose related. In the Faroese population, there was a negative association for maternal hair mercury and three developmental milestones. The study authors attributed this to higher mercury exposure in the breastfed population and the salutary effect of breast milk on development. The NRC report commented on the reported developmental delays in the Iraqi population, which has been the subject of much discussion as to the degree of uncertainty in the estimates (see also MSRC Volumes V and VII). NRC cites analyses by Cox et al. (1995) and Crump et al. (1995), which indicate that the earlier estimates of the Iraqi threshold for late walking were too low. The threshold for late walking appears highly dependent on assumptions on background incidence, the definition of delayed walking, and the effect of a small number of influential data points.

4.2.1.3 Infant and Preschool Development

Cree population—McKeown-Eyssen et al. (1983)

In the study of a Cree population, the Denver Developmental Screening Test (DDST) was administered to the 12- to 30-month-old children in the cohort (n = 234). Scores were reported as the percentage of items passed on each subscale as well as on the entire test. The authors did not provide estimates of significance of association between test scores and maternal hair mercury concentrations; they concluded that there was no significant association indicative of an adverse effect of methylmercury before or after adjustment for confounding variables.

New Zealand population—Kjellstrom et al. (1986)

Kjellstrom et al. (1986) studied a cohort of New Zealand children for whom prenatal methylmercury exposure was estimated on the basis of maternal hair samples as well as dietary questionnaires collected during the period when the study child was *in utero*. Exposure information was collected on nearly 11,000 women; the study focused on 935 women who reported eating fish more than three times per week during pregnancy. Seventy-three women had hair mercury concentrations greater than 6 ppm. The 74 children of those women were designated as the high-mercury group. Efforts were made to match each child in the high-mercury group with a reference child on the basis of maternal ethnicity, hospital of birth, maternal age, and child age. In the followup evaluations at 4 years of age, a total of 38 exposed and 36 reference children were tested; this data set included 30 completely matched pairs. Fifty-two percent of the children in the high-mercury group had an abnormal or questionable DDST score compared with 17% of the children in the control group ($p < 0.05$). That result corresponds to an odds ratio of 5.3. Results were similar when pairs that were poorly matched on ethnicity were excluded.

SCDS pilot study—Myers et al. (1995b)

In the SCDS cross-sectional study, a revised version (DDST-R) of the DDST was administered to 789 children between the ages of 1 and 25 months. No association was found between maternal hair mercury concentration during pregnancy (mean 6.6 ppm) and DDST-R results when normal and questionable examinations were combined. The prevalence of abnormal findings was so low (three children <1%) that the statistical analysis was not meaningful. When abnormal and questionable results

were grouped (in 65 children, 8%), high maternal hair mercury concentrations were significantly associated with poor outcomes (p = 0.04, one-tailed test). That result was largely attributable to the higher frequency of abnormal and questionable results among children in the highest maternal hair mercury category (greater than 12 ppm), by contrast to the frequency of approximately 7% among children in each of the other four groups (0-3, 3-6, 6-9, and 9-12 ppm).

SCDS main study—Myers et al. (1995c)

In the main SCDS study, the DDST-R was administered to a cohort of 740 children at age 6.5 months. The frequency of examinations considered to be abnormal or questionable was very low, precluding meaningful statistical analysis of the DDST-R data. The researchers also administered the Fagan Test of Infant Intelligence, an assessment of visual-recognition memory or novelty preference. Results were not related to maternal hair mercury concentrations.

SCDS main cohort at 19 and 29 months—Davidson et al. (1995)

The Bayley Scales of Infant Development (BSID) were administered to children in the SCDS cohort at ages 19 and 29 months. In addition, at 29 months, six items of the Infant Behavior Record, a rating scale, were completed by the examiner. There are two primary scores on the BSID: the mental development index (MDI) and psychomotor development index (PDI). At both ages, MDI scores were similar to the expected mean for U.S. children. At both ages, however, the Seychellois children performed markedly better on PDI than the expected mean for U.S. children. There was no association between MDI scores at 19 or 29 months with maternal hair mercury concentration during pregnancy. Similar results were obtained in a secondary analysis that included only children with the lowest or highest maternal hair mercury concentrations. Assessments of perceptual skills at 19 months were not associated with mercury exposure. Scores on that test at 29 months could not be evaluated because of a pronounced ceiling effect; that is, there were so many high scores on the test that no difference would be detectable. Likelihood of a PDI score below the median was not significantly associated with maternal hair mercury concentration in the full logistic regression model, but was associated with this exposure index in a model that included limited covariates.

Conclusions

There is some indication of low-dose mercury effects in very young children, but there are difficulties in the measurement of such effects. The DDST was administered to four study populations. When abnormal and questionable results were combined, there was a significant association with increasing maternal hair mercury in the New Zealand cohort and in the SCDS cross-sectional study (but not the main study). The NRC report comments on the bases for the different findings: age at examination, different rates of abnormal and questionable scores, and the possibility that test items or criteria for judging scores differed among studies. NRC offered the general conclusion that screening tests such as the DDST are not useful in neurobehavioral toxicology studies; such tests are insufficiently sensitive to variations in the range of normal performance (NRC 2000, p. 200).

The NRC panel noted that the BSID is currently considered to be the best available instrument for infant assessment and is useful for measurement of prenatal exposures to neurotoxicants (NRC 2000, p. 200). In the SCDS main study there was no significant association between young children's scores on the BSID and maternal hair mercury. At 19 and 29 months, the Seychellois children scored higher than the means for U.S. children on the PDI portion of the scales.

4.2.1.4 Childhood Development

New Zealand population—Kjellstrom et al. (1989)

Children in the New Zealand cohort were followed up at 6 years of age. Children were given a battery of 26 psychological tests, tests of scholastic aptitude, and behavioral tests. The following domains were assessed: general intelligence, language development, fine and gross motor coordination, academic attainment, and social adjustment. Maternal hair mercury concentration was associated with poorer scores on full-scale IQ tests (Wechsler Intelligence Scale for Children, Revised [WISC-R]), language development (Test of Language Development, spoken language quotient), and visual-spatial and gross-motor skills (McCarthy Scales of Children's Abilities). Multiple regression analyses were done on these endpoints: Test of Language Development, spoken language quotient (TOLD-SL); WISC-R, performance IQ; WISC-R full-scale IQ; McCarthy Scales, perceptual performance; and McCarthy Scales, motor scales. Covariates in the regressions were these: maternal ethnic group, maternal age, maternal smoking and alcohol use during pregnancy, length of maternal residence in New Zealand, social class, primary language, siblings, sex, birthweight, fetal maturity, Apgar score, and duration of

breastfeeding. Observations were weighted in the regression to deal with outliers. In the analyses there were statistically significant associations between maternal hair mercury and poorer scores on the following measures: full-scale IQ; language development (spoken language quotient), visual-spatial skills (perceptual-performance scale), and gross motor skills (motor scale). The poorer mean scores of the children in the high-mercury group were largely attributable to children of mothers with mercury concentrations above 10 ppm. In this group, mean average hair mercury was 13 to 15 ppm and mean peak was 25 ppm. Maternal hair mercury concentrations accounted for relatively small amounts of variance in the outcome measures and generally accounted for less than covariates such as social class and ethnic group.

In the original analyses of five test scores (Kjellstrom et al., 1986), hair mercury was used in regression analyses as a binary variable; that is, either >6 ppm or between 3 and 6 ppm. Analyses found an association between high prenatal mercury exposure and decreased test performance. Later regression analyses by Crump et al. (1998), which used maternal hair mercury level as a continuous variable, did not find significant associations between mercury and children's test scores. However, this finding was highly influenced by a single child whose mother's mercury hair level (86 ppm) was more than four times that of any other. When this child was excluded, there were significant associations between hair mercury and TOLD-SL and MC-PP scores. When regression analyses were done on scores from all 26 scholastic and psychological tests, and the data on the influential point were omitted, scores on six tests were significantly associated with mothers' hair mercury: Clay Reading Test-concepts, Clay Reading Test-letter test, McCarthy Scales-general cognitive index, McCarthy Scales-perceptual-performance scale, Test of Language Development-grammar completion, and Test of Language Development-grammar understanding.

SCDS pilot study— Myers et al. (1995a), Davidson et al. (2000), Davidson et al. (1998), Myers et al. (2000) .

A portion of the pilot cohort of 789 children were given developmental assessments; these were children who were 66 months old within a 1-year testing window (Myers et al., 1995a). Of the 247 eligible children, 217 were administered a test battery consisting of the McCarthy Scales of Children's Abilities, the Preschool Language Scale, and two subtests of the Woodcock-Johnson Tests of Achievement (letter-word identification and applied problems). The median maternal hair mercury concentration in that subsample of the pilot cohort was 7.1 ppm. Maternal hair mercury was associated with significantly lower general cognitive index (GCI) scores on the McCarthy scales. Scores declined

approximately five points between the lowest and highest exposure categories. Similar associations were found on the perceptual-performance scale of the McCarthy scales and on the auditory comprehension scale of the Preschool Language Scale. Scores declined approximately 2.5 points across the range of maternal hair mercury concentrations. When outliers and influential points were removed from the regressions the statistical significance of the associations was lost for all except auditory comprehension (Preschool Language Scale Auditory Comprehension subscale). In the pilot phase of the SCDS, information was not collected on several key variables that frequently confound the association between neurotoxicant exposures and child development. Those variables are socioeconomic status, caregiver intelligence, and quality of the home environment.

Further evaluation was performed on a portion of the Seychelles pilot cohort at 108 months of age (Davidson et al., 2000). Eighty-seven children were tested on five subtests of the WISC-III (Information, Block Design, Vocabulary, Digit Span, and Coding), CVLT, BNT, Beery-Buktenica Development Test of Visual Motor Integration (VMI) (copying geometric figures), Finger Tapping, grooved pegboard, Trailmaking (tracing the correct route through a form with a pencil), and the design memory subtest of the Wide Range Assessment of Memory and Learning (WRAML) (drawing each of four geometric designs from memory). Performance on BNT, VMI, and grooved pegboard showed a positive association related to mercury exposure in males, whereas there were trends toward poorer performance related to mercury exposure for grooved pegboard in females ($p = 0.07$). Given the small number of subjects, the power of the study was probably quite low; these largely negative results should be interpreted with caution.

No effect of mercury was identified on the Child Behavior Check List (CBCL) at 66 months of age in the main cohort of Seychelles study as determined by the total T score (Davidson et al., 1998). The CBCL is a report inventory scored by the caregiver that assesses eight domains: withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems, delinquent behavior, and aggressive behavior. An analysis of these subscales was performed on the 711 children assessed on this test (Myers et al., 2000). No effect of mercury was identified on individual subscales.

SCDS Main Study—Davidson et al. (1998), Axtell et al. (2000), Palumbo et al. (2000)

As part of the main SCDS, 711 children 66 months of age (from the original cohort of 779) were evaluated with a battery of standardized neurodevelopmental tests. At this evaluation, mercury was measured in a 1-cm segment of the child's hair as an indicator of postnatal exposure. The following were assessed: general cognitive ability (McCarthy Scales of Children's Abilities), expressive and receptive

language (Preschool Language Scale, PLS), reading achievement (letter-word recognition subtest of the Woodcock-Johnson Tests of Achievement), arithmetic (applied problems subtest of the Woodcock-Johnson Tests of Achievement), visual-spatial ability (Bender Gestalt Test), and social and adaptive behavior (CBCL). The scores of the six primary endpoints indicated no adverse effect of either prenatal or postnatal mercury exposure. The only significant associations were consistent with enhanced performance among children with increased exposure to methylmercury. Increased pre- and postnatal mercury concentrations were significantly associated with better scores on the total score of the Preschool Language Scale. For the applied problem test, increased postnatal mercury concentrations were associated with better scores. Among boys, increased postnatal mercury concentrations were associated with fewer errors on the Bender Gestalt Test.

The investigators published additional analyses of the 66-month data evaluating the possibility of non-linear relationships associated with mercury exposure (Axtell et al., 2000). Endpoints included the six primary variables analyzed previously: McCarthy GCI, PLS, Woodcock-Johnson (WJ) applied problems, WJ letter/word recognition, Bender copying errors, and CBCL total T score. Generalized additive models, which make no assumptions about the relationship between exposure and test score, were used. Nonlinearities were identified between prenatal exposure and PLS and CBCL, and between postnatal exposure and McCarthy GCI. For the PLS the trend involved a decrement of 0.8 points (poorer performance) from 0 to 10 ppm and an increase of 1.3 points above 10 ppm. For the CBCL there was an increase (representing a poorer score) between 0 and 15 ppm and a decrease above 10 ppm. The GCI increased (improved) by 1.8 points through 10 ppm in the child's hair and declined by 3.1 above 10 ppm. Although these results are difficult to interpret, they provide limited evidence of an adverse effect of mercury exposure below 10 ppm maternal hair on two measures, and are associated with child's hair mercury concentration above 10 ppm on the GCI. As pointed out by the authors, there are fewer data points above 10 ppm (this is especially true for child's hair mercury), and therefore trends above this level are estimated less precisely.

The SCDS investigators used multiple linear regression to assess the results of the McCarthy GCI administered at 66 months (Palumbo et al., 2000). They analyzed the standard MSCA subscales and also constructed specific subscales to approximate the domains of cognitive functioning assessed in the Faroe Islands study: attention, executive function, expressive language, receptive language, nonverbal memory, visuospatial, and gross motor visuomotor development. They found a positive association between the child's hair mercury at 66 months and the standard memory subscale, with no other associations identified. As with all the previous analyses of these variables, the raw scores were converted to "normative" scores. As pointed out by the OSTP panel (NIEHS, 1999, Section 3.5 of the Confounders

and Variables Section), the applicability of U.S. norms to this population is unclear, and the use of standardized scores may decrease sensitivity by collapsing different raw scores to one standard score.

Faroes Population—Grandjean et al. (1997)

Testing was done at approximately 7 years of age on 917 of the surviving members of a 1986-1987 birth cohort of 1,022 singleton births. Maternal hair was sampled at parturition (geometric mean 4.3 ppm); children's hair mercury was measured at 12 months (geometric mean = 1.1 ppm) and 7 years of age (geometric mean = 3.0 ppm). Mercury was also measured in cord blood. The neuropsychological tests were these: computer-administered tests from the Neurobehavioral Evaluation System (NES) (Finger Tapping, hand-eye coordination, and continuous performance test); Tactual Performance Test; three subtests of the WISC-R (digit span, similarities, and block design); Bender Gestalt Test; CVLT; the BNT; and Nonverbal Analogue Profile of Mood States. Not all children could complete the entire battery; this was associated with increased mercury exposure for some tests such as the finger opposition test and mood test.

In multiple-regression analyses, increased cord-blood mercury concentration was significantly associated with worse scores on Finger Tapping, continuous performance test (CPT) (in the first year of data collection), WISC-R digit span, BNT, and CVLT. The investigators estimated that a tenfold increase in cord mercury concentration was associated with delays of 4 to 7 months in those neuropsychological domains. The maternal hair mercury concentration showed regression coefficients that were generally lower than those obtained with cord-blood mercury as the exposure indicator. For the Finger Tapping test, maternal hair mercury was a better predictor of effect, especially for the both-hands condition. The child's hair mercury measured at 12 months was a significant predictor for Finger Tapping with both hands and CPT reaction time; by contrast, hair mercury at the time of examination was significantly associated with continuous performance test reaction time, block designs, and Bender Visual Motor Gestalt errors.

When the Peters-Belson method for covariate adjustment was used, two additional endpoints (WISC-R block design, Bender Gestalt Test errors) were found to be associated with mercury exposure. Associations remained significant when the part of the cohort with maternal hair mercury concentrations greater than 10 ppm was excluded from the analyses. A term for the interaction between mercury and sex was not statistically significant, indicating that the effects were similar among boys and girls. In general, children's test scores were more strongly associated with cord-blood mercury concentration than

with either maternal hair mercury concentration or mercury concentrations in samples of children's hair collected at 1 and 7 years of age.

Grandjean et al. (1998) also analyzed the Faroese data in a case-control fashion. Two groups were assembled: a case group of 112 children with maternal hair concentrations of 10 to 20 ppm at parturition, and a control group of 272 children with maternal hair mercury concentrations less than 3 ppm. Controls were matched to cases on age, sex, year of examination, and caregiver intelligence. The median maternal hair mercury concentrations in the two groups were 1.8 and 12.5 μg/g, constituting a sevenfold difference. Median cord-blood mercury concentrations also differed substantially (59.0 μg/L in the case group versus 11.9 μg/L in the control group). On 6 of the 18 endpoints, the case group scored significantly lower than did the control group. The results of those analyses differ in certain respects from those of the main analyses. First, the set of endpoints on which the cases and controls differed is similar but not identical to the set of endpoints that was significantly associated with cord blood mercury concentration found in the main analyses. In the case-control analyses, a term for the interaction between mercury and sex was statistically significant for several scores: the Bender Gestalt Test error score, short-term reproduction on the CVLT, all three Finger Tapping conditions, CPT reaction time, and average hand-eye coordination score. For all scores, adverse mercury effects were noted for boys but not girls.

Amazon Valley—Grandjean et al. (1999)

A study cohort was assembled numbering 351 children ages 7 to 12. The population, which was drawn from four riverine communities in Amazonian Brazil, had increased exposures to methylmercury because of their consumption of fish contaminated by upstream gold-mining activities. When data on all four villages were combined, children's hair mercury concentrations were significantly associated with their scores on Finger Tapping, Santa Ana dexterity test, WISC-III digit span, Stanford-Binet copying and recall, and Stanford-Binet bead memory. Adjustment for community generally reduced the magnitude of the associations, sometimes dramatically. It was noted that hair mercury concentrations and village residence were so highly confounded, however, that adjustment for village might be inappropriate.

French Guiana population—Cordier and Garel (1999)

Cordier and Garel (1999) studied a cohort from a gold-mining area in French Guiana. Median maternal hair concentration was 6.6 ppm with a range of 2.9 to 17.8 ppm. Children ages 5 to 12 years old (n = 206) were administered a battery of neuropsychological tests: Finger Tapping, three subtests from

the Stanford-Binet (block design, copying designs, bead memory), and two subtests from the McCarthy scales (numerical memory, leg coordination). After adjustment for potential cofounders, increased maternal hair mercury concentrations were significantly associated with copying-design score; the effect was greater in boys. The data were reanalyzed to include only those observations from the region with highest mercury exposures (Upper Maroni). When observations were separated by gender, there was an association in boys between mercury exposure and poorer leg coordination, and with poorer block-design scores in girls.

Conclusions

There is ample evidence of low-dose *in utero* mercury effects on neuropsychological indices in school-age children. In the New Zealand population, maternal hair mercury was associated with poorer scores on several measures: full-scale IQ, language development (spoken language quotient), visual-spatial skills (perceptual-performance scale), and gross motor skills (motor scale). The poorer mean scores in the high-mercury group were largely attributable to the children of mothers with hair mercury above 10 ppm. One analysis by Crump et al. (1998) used maternal hair mercury as a continuous, rather than binary, variable; in this analysis there was no significant association with hair mercury. These analyses were heavily influenced by a single data point (a child with purported high developmental exposure who showed no abnormal scores). If data for this child are excluded, and parental education and age at testing are included as covariates, there are significant associates between mercury exposure and six scores.

In the SCDS pilot (cross-sectional) study, increasing maternal hair mercury was associated with the GCI and the perceptual performance scale of the McCarthy scales. Exclusion from analyses of several influential points reduced the significance of the mercury effect. As it was intended as a feasibility study, the pilot SCDS did not collect information on socioeconomic status, caregiver intelligence, or quality of home environment. In the SCDS main study there was no observation of any adverse effect of prenatal or postnatal mercury exposure. The NRC report commented on the regression model for the GCI score:

> The R^2 (square of the multiple correlation coefficient) value (0.10) of the reduced regression model for the GCI score in the main SCDS study was identical to that in the pilot study. That also appeared to be true for scores on the Preschool Language Scale.... That finding is puzzling because the pilot-study models...did not include several key covariates...and because the regression coefficients for socioeconomic status and caregiver intelligence were statistically significant for total scores of the GCI and Preschool Language Scale in the main

study cohort. Those differences suggest that maternal hair Hg concentration is very highly confounded with those key covariates in the Seychelles population, or they suggest that the associations between child neurodevelopment and the covariates differ substantially in the pilot and main study cohorts, or both (NRC 2000, pp. 203, 205).

In the Faroes population, mercury exposure measured in cord blood was associated with deficits on several measures: Finger Tapping, preferred hand; CPT (first year of data collection, two scores); mean reaction time, WISC-R digit span; BNT (with and without cues); and CVLT (short-term and long-term reproduction). The mercury effect was similar in males and females. Most test scores were more strongly associated with cord-blood mercury than with maternal hair mercury. In the case-control analysis, the case group scored significantly lower than the control group on 6 of 18 endpoints.

In two smaller populations there were observed effects of mercury exposure. Combining results from four communities in the Amazon basin showed a significant association of children's hair mercury with deficits on four measures. In a French Guiana cohort (n = 206), it was shown that maternal hair mercury was associated with one measure (a Stanford-Binet subtest), particularly in boys.

4.2.1.5 Sensory, Neurophysiological, and Other Endpoints in Children

Faroes population—Grandjean et al. (1997)

In the Faroe Islands cohort, the evaluation of 7-year-old children included assessments of visual acuity, near-contrast sensitivity, otoscopy and tympanometry, and some neurophysiological tests. Visual acuity, contrast sensitivity, auditory thresholds, and visual-evoked potentials were not significantly associated with prenatal methylmercury exposures. For brainstem auditory-evoked potential, peaks I, III, and V were slightly delayed at increased cord-blood mercury concentrations at both 20 and 40 Hz; interpeak latencies were not associated with mercury at either frequency.

Madeira population—Murata et al. (1999b)

Many of the same neurophysiological tests that had been done in the Faroe Islands study were administered to 6- to 7-year-old children living in Madeira. This was a cross-sectional study of 149 subjects. For brainstem auditory-evoked potential, maternal hair mercury was significantly associated with I-III and I-V interpeak latencies at both 20 and 40 Hz, as well as with total latencies for peaks III and V at both frequencies. Those results are similar to the findings in the children tested in the first year of

the Faroes cohort. For visual-evoked potentials on a pattern-reversal task, maternal hair mercury concentration was significantly associated with one of the three latencies, as well as with the N75-N145 and P100-N145 latencies.

Ecuador—Counter et al. (1998)

Auditory function in children and adults was investigated by Counter et al. (1998). The study sample consisted of 75 individuals (36 children and 39 adults) from a gold-mining region in Ecuador and 34 individuals (15 children and 19 adults) from nonmining areas as a control. Blood mercury concentrations were significantly higher in individuals (both adults and children) from the gold-mining area than in individuals from the control region (mean level of 17.5 μg/L versus 3.0 μg/L). Neurological examinations were carried out on all individuals. In children, blood mercury was significantly associated with hearing threshold at 3 kHz in the right ear only. No association was found for adults. A borderline association was found between blood mercury concentration and I-III interpeak transmission time on the left side in both children and adults. The authors concluded that overall auditory sensory-neural function and neural conduction time at the brainstem level were generally unaffected by elevated blood mercury levels in either children or adults.

Conclusions

There is increasing evidence of adverse endpoints other than cognitive development in mercury-exposed children. In the Faroes cohort, there were delays in some auditory-evoked potential peaks as a function of cord-blood mercury. Similar findings were reported for a smaller population from a fishing village in Madeira. A population of children in a gold-mining region of Ecuador showed an association between blood mercury and hearing threshold in the right ear at 3 kHz.

4.2.2 Choice of Study

Of the three large human developmental studies, two reported associations between low-dose *in utero* exposure to methylmercury and performance on standardized neurobehavioral tests. The Faroes investigators reported effects in the domains of attention, fine-motor function, confrontational naming, visual-spatial abilities, and verbal memory. Although similar results were reported for the New Zealand population (and in the Seychelles pilot study), there were no observations of adverse effects attributable to methylmercury in the main SCDS.

This section discusses issues relevant to the choice of critical study for calculation of a reference dose from among these three studies.

4.2.2.1 Critique of New Zealand Study

The study by Kjellstrom et al. (1986) included 57 fully matched groups of four 6-year-old children each as well as four incomplete sets, for a total of 237. As was the case for the Faroes study, these authors reported deficits in measures associated with methylmercury exposure. NRC noted (NRC, 2000 p. 251) that the New Zealand population's sources of methylmercury exposure and the study endpoints were similar to those examined in the Seychelles. While EPA was developing its RfD for the MSRC, the New Zealand data were available as a report that had not been subjected to standard peer-review procedures. In 1998, Crump and associates published a reanalysis of the New Zealand data that was peer reviewed. This paper reported associations of prenatal methylmercury exposure with several endpoints (when one extreme outlier was excluded), including four endpoints that were not found to be related to methylmercury in the Seychelles study. The New Zealand study has been criticized for errors in matching exposed children to controls and for testing exposed children and controls at different ages (Myers et al., 1998). Those errors occurred in the 4-year followup but were corrected in the 6-year followup. NRC notes (NRC, 2000, p. 209) that there is no reason to expect differential measurement error across the studies. An error of that type is likely to be nondifferential (i.e., unbiased), and it would reduce the likelihood of detecting associations between methylmercury exposure and neurobehavioral test scores.

The Kjellstrom et al. (1986) study collected data on several potential confounding factors and used a broad battery of standardized measures that were administered by trained examiners. It is likely that the exposure was relatively low-dose and not episodic, reflecting well-established food consumption patterns. The section below discussed controls for possible confounders in the SCDS and Faroes studies. An important variable is the concomitant exposure to organochlorine compounds such as PCBs and pesticides that could have neurotoxic effects. There is essentially no information on the extent of such exposures in the New Zealand study population, either in the original report or in follow-up analyses (e.g. Crump, 1998).

4.2.2.2 Control for Possible Confounding

Both the Faroes study and the SCDS evaluated most of the variables that have been linked to childhood cognitive development. Table 6-2 of the NRC report lists these and notes which study

controlled for the particular variable. Although neither study controlled for all potential confounders, it was felt by the authors of the NRC report that the influences of those variables on cognitive outcome are probably too weak to account for any major inconsistencies between the two studies. The Confounders and Variables Panel of expert workshops sponsored by OSTP had earlier concluded that neither the SCDS nor the Faroese study was critically flawed and that these studies were suitable for determination of the upper limit of a methylmercury NOAEL (NIEHS, 1999).

Place of Faroese residence—town versus country

At the 1998 OSTP workshop, the Faroes investigators noted that the maternal Ravens scores and the child verbal-test scores were generally higher among families residing in one of the three towns in the Faroes compared with those living in the countryside (NIEHS, 1999). This was thought to be due to social-class differences. It was suggested that because more fish and, in particular, whale meat was consumed by rural residents, the associations of mercury exposure with child verbal-test scores could in fact reflect those social-class differences. However, analyses presented at the workshop showed that these associations remained significant even after controlling for a dichotomous town-country control variable (Table 6-3 in the NRC report). NRC felt it would not be appropriate to control for town residence in all analyses. They made the following statement:

> Because fish and whale consumption constitute a large proportion of the rural diet, the disappearance of associations after controlling for residence could be due to the fact that residing in a rural area leads to increased Hg exposure which, in turn, causes an adverse outcome. It would not necessarily indicate that the lower social class associated with rural residence is the true cause of the Hg-associated deficit. The disappearance of an association between Hg and neurobehavioral effects under those circumstances would be very difficult to interpret, because the interpretation would depend upon what condition is considered the reason for the association between living in a rural area and poor outcome (i.e., lower social class or greater Hg exposure) (NRC, 2000, p. 261).

Another source of town versus country difference could be the distance traveled to the testing site, with resulting fatigue in the children from the countryside. However, analyses showed that the regression coefficients for prenatal mercury exposure remain significant even after controlling for child's residence.

Test administration

The neuropsychological test examiner was routinely controlled for in the Faroe Islands study (see NIEHS, 1999, Section 3.5), but not the SCDS. It was suggested at the OSTP workshop that if an examiner who is less adept at eliciting optimal performance from the subjects tested a large proportion of less-exposed children, the results could be affected (NIEHS, 1999). NRC noted:

> If those children performed more poorly than they otherwise would have on the test, an association between Hg concentration and test scores might be obscured by failure to control for the examiner. That result could also occur if an adept tester tested a large proportion of the more heavily exposed children, leading them to achieve higher scores than they would have if tested by other examiners (NRC, 2000 p. 263).

Age at testing

The SCDS controlled for age at testing by converting the raw test scores to age-corrected standard scores with conversion tables based on U.S. norms (NIEHS, 1999). The Faroes investigators analyzed the raw scores by adjusting statistically for the child's age (measured in days since birth). NRC found the latter approach to be preferable (NRC, 2000, p. 263). They noted, first, that the applicability of U.S. norms to these study populations is uncertain. In this context it should be noted that the Seychellois scores on the BSID were higher than U.S. averages at both 19 and 29 months. Second, NRC felt that the use of age-corrected standard scores could reduce the sensitivity of the test, because several adjacent raw scores are treated as equivalent in converting to standard scores. Last, they noted that age-corrected standard scores use 3-month intervals, which introduces a degree of arbitrariness in assigning a child to a particular group. The NRC report found the approach of controlling statistically for age by multiple regression to be appropriate, because the effect of age is likely to be linear across the relatively short age period (3 months in both studies); that is, over short time periods, development is most likely to take place at a constant rate.

Some members of the scientific community have noted the possibility that the most important difference in the design of the two studies is the age of the child at assessment; 7-year-olds were tested in the Faroes as opposed to children 5.5 years of age in the SCDS. Developmental assessments are likely to be less sensitive in detecting subtle neurotoxic effects when they are administered during a period of rapid developmental change. Individual differences in the rate of neurocognitive maturation may mask subtle differences in function attributable to toxic exposures. NRC (2000, pp. 257-258) also noted that

infant assessments in the SCDS (namely the 19 and 29 month Bayley Scale examinations) were not given at optimal age points for detecting effects, particularly in this developmentally robust population.

Selection bias from exclusion of individuals with severe impairments

The OSTP workshop Confounders and Variables Panel (NIEHS, 1999) identified what they considered a serious potential issue with the SCDS. They noted that recruitment was limited to children with no severe debilitating conditions. This panel felt that such a restriction could lead to underestimation of effect when the shape of the dose-response curve is not known.

PCB exposure in the Faroese population

PCB exposure through maternal consumption of whale blubber was discussed at length at the OSTP workshop and in the report of the Confounders and Variables Panel (NIEHS, 1999). Using the data from the part of the cohort for which cord PCB was measured, Grandjean et al. (1997) performed a series of analyses to ascertain if the PCB and mercury effects could be separated. Of the eight outcomes for which there was a significant association with cord-blood mercury, four were also associated ($p<0.1$) with log transformed PCB levels in cord tissue before adjustment for mercury. These four endpoints were also significantly related to mercury cord-blood concentrations. These were CPT reaction time, BNT with and without cues, and CVLT long-term reproduction (Table 4-1). When PCBs were included in the regression analysis, only the CPT reaction time remained significantly associated with mercury. CVLT and BNT with no cues were not significantly associated with either agent, whereas BNT with cues was about equally associated with both ($p \leq 0.10$). It is important to recognize that such an analysis removes the shared variance related to both mercury and PCBs, thereby reducing the *p* value associated with either agent.

The Faroes investigators considered CPT reaction time to be a test of attention, BNT to assess language, and CVLT to assess memory (Grandjean et al., 1997). Deficits in overall cognitive functioning and verbal comprehension have been found to be associated with *in utero* PCB exposure in a study of 4.5-year-old children in the Netherlands (Patandin et al., 1999a), whereas deficits on a vigilance task similar to the CPT were associated with cord PCB levels (commission errors) as well as the child's concurrent PCB exposure (reaction time) (Patandin et al., 1999b). In the Patandin et al. study, PCB and dioxin exposure was through diet unrelated to fish consumption. Another study reported effects of exposure to children through their mothers' consumption of contaminated Lake Michigan fish. Deficits in attention, language processing (reading comprehension), and memory related to prenatal PCB

Table 4-1. Regression coefficients (betas) for effects of logarithmic transformations of mercury before and after adjustment for PCB concentrations on Faroese neuropsychological tests: results from 7-year-old children from the first year of testing.

	Before Adjustment		After Adjustment for PCB			
				p-Values		
Neuropsychological Test	Beta	p-Value	Beta	Mercury	PCB	Both
Continuous Performance Test						
Average reaction time (ms)	39.3	<0.001	37.8	0.002	0.64	0.001
Boston Naming Text						
No cues	-1.58	0.04	-1.04	0.21	0.16	0.05
With cues	-2.03	0.007	-1.36	0.10	0.08	0.008
California Verbal Learning Test (Children)	-0.99	0.03	-0.78	0.11	0.26	0.05
Long-term reproduction						

From Grandjean et al., 1997.

exposure were identified in 11-year-old children (Jacobson and Jacobson, 1996). Other contaminants undoubtedly present in the fish, including methylmercury, were not assessed in this study; the potential contribution of methylmercury exposure to the observed effects could not be evaluated.

It is informative to compare PCB levels in other studies reporting adverse effects associated with PCBs with PCB levels in the Faroese women. No breast milk or blood PCB levels from the mothers or infants in the Faroe Islands cohort have been published. However, a recent study compared levels of PCB congener 153 in human blood in pregnant women from the Faroe Islands consuming 0-1 blubber meals/month ("low") or 2-3 blubber meals/month ("high") with other populations (Fängström et al., 2000). "Low" Faroese exposure was comparable to blood PCB levels in an unspecified number of pregnant women in the Netherlands, whereas "high" Faroese blood PCB levels were comparable to those in an identified highly exposed population in the Quebec Arctic. The Faroese samples in the Fängström et al. (2000) analysis were collected in 1994-1995, and the cohort for the Faroe study of developmental neurotoxicity was recruited in 1986-1987. It is unclear when the Dutch samples in the Fängström et al. (2000) study were collected; the cohort in the Dutch developmental study was recruited in 1990-1992. Blood levels cannot be directly compared between the Dutch study and the Fängström et al. (2000) data because one was on lipid-adjusted serum and the other on non-lipid-adjusted plasma. Similarly, breast

milk levels cannot be directly compared (Grandjean et al., 1995a; Steurwald et al., 2000; Lanting et al., 1998). In general, human body burdens of PCBs have decreased by about 50% over the past decade, so it is possible that blood levels in the Dutch study were higher than those reported in the Fängström et al. (2000) paper. It is also quite probable that PCB levels in the Faroe Islands were higher in the mid-1980s than the mid-1990s, suggesting that the "low" Faroe exposure is comparable to levels in the Dutch study. It is important to reiterate that whereas there may have been effects of PCBs in addition to those of methylmercury, statistical analyses indicated that the effects were independent in this population (Budtz-Jørgensen et al., 1999).

The Confounders and Variables Panel at the OSTP meeting (NIEHS, 1999) concluded that both PCB and mercury had adverse effects on the CVLT score and on the BNT scores with and without cues. They felt that it was not possible to determine the relative contribution of each. NRC concluded that there was no empirical evidence or theoretical mechanism to support the opinion that *in utero* Faroese exposure to PCBs exacerbated the reported methylmercury effect. They note that statistical tests for interaction between PCB and mercury show no interaction. NRC reached a similar conclusion to the Confounders and Variables Panel; a likely explanation is that both PCB and mercury adversely affect some test outcomes, but their relative contributions cannot be determined given their co-occurrence in the Faroes population. NRC states it is unlikely that a difference in PCB exposure between the two populations explains the lack of developmental neurotoxic effects in the Seychelles (NRC, 2000, pp. 220 and 223).

In a second set of analyses, Budtz-Jørgensen et al. (1999) found that the effect of prenatal PCB exposure was reduced when the data were sorted into tertiles by cord PCB concentrations. Regressions assessing mercury exposure and the five principal test outcomes were then run separately for each of the three groups. The regression coefficients for a mercury effect in the lowest PCB tertile were no weaker than those for the higher two PCB groups. This lends additional credence to a conclusion that the associations between mercury and test outcomes are not attributable to confounding by prenatal PCB exposure. Calculations of benchmark doses and lower limits (BMDLs) were done using the whole cohort, after a PCB correction and for the portion of the cohort with the lowest PCBs (NRC 2000 , Table 7-4, reproduced here as Table 4-2). In this table results are reported separately for methylmercury measured in hair and cord blood and are calculated using the K-power model described in Section 4.3.4. NRC commented on the results for the low-PCB-exposed subset for the two endpoints that were related to PCB exposure, the BNT and the CVLT. They noted that the BMDs for these outcomes did not differ from the BMDs for the total sample by any more than the BMDs for the two endpoints that were not related to PCB exposure. NRC opined that the variability seen in Table 4-2 is no more than that expected

by chance; the BMDs and BMDLs for both the PCB-adjusted and the low-PCB subset analyses are within the intervals defined by the BMDs and corresponding BMDLs derived for the full cohort. The difference between the BMDs based on the full cohort and the low PCB subset is less than one standard error of the low PCB subset (NRC, 2000, p. 288). These analyses support a conclusion that there are measurable effects of methylmercury exposure in the Faroese children that are not attributable to PCB toxicity.

PCB body burdens in the Seychellois are very low by comparison to North American and European populations. In 28 serum samples obtained from Seychelles study children, there were no detectable concentrations of any PCB congeners. In the Faroes study, prenatal PCB exposure was measured in 436 stored umbilical cord tissue samples. It was noted at the OSTP workshop that cord tissue PCB concentration has never been validated in relation to blood or milk concentration; because cord tissue is lean and PCBs are lipophilic, the panel felt that it may not be the most reliable indication of total PCB body burden (NIEHS, 1999). The cord samples were analyzed for a small subset of PCB congeners that were used to represent the biologically significant PCB exposure. In an earlier publication (Grandjean, et al., 1995) it was shown that these congeners predominate in samples from the Faroes cohort; comprise these three congeners comprise approximately 50% of the PCBs in breast milk lipid. These same three congeners, along with one other, were used to quantify PCB body burdens in milk and plasma in a study of children in the Netherlands (Lanting et al., 1998). The approach taken in the Faroes for quantifying PCB exposure (adding three key congeners together and multiplying by 2) appears to be a reasonable approach for estimating total PCB exposure and is not expected to introduce a bias into the analysis.

4.2.2.3 Population Differences in Susceptibility

Populations may be more or less susceptible to effects of a toxicant as a consequence of predisposing factors, such as nutritional status, exposure to other agents (see Section 4.2.2.1), or genetic susceptibility.

The SCDS cohort is predominantly African in descent; the Faroes cohort is Caucasian. The latter population has been somewhat isolated and thought to be descended from a small number of "founders." This homogeneity in the Faroes could increase or decrease genetic susceptibility to effects of toxic insult. NRC noted that methylmercury neurodevelopmental effects were observed in a genetically heterogeneous and racially diverse sample studied in New Zealand, a population that was predominantly non-Caucasian.

Table 4-2. BMD (BMDL) Estimates from the Faroe Islands Study with and without adjustment for PCBs and in the subset of Low PCB-exposed children (reproduced from NRC 2000)

		Full Cohort	Adjusted for PCBs	Low PCB subset
Exposure	**Endpoint**	**BMD (BMDL)[a]**	**BMD (BMDL)**	**BMD (BMDL)**
Hair	Finger Tapping	20 (12)	17 (9)	7 (4)
	CPT Reaction Time	18 (10)	27 (11)	13 (5)
	Boston Naming Test	15 (10)	24 (10)	21 (6)
	CVLT: Delayed Recall	27 (14)	39 (12)	32 (7)
Cord Blood	Finger Tapping	140 (79)	149 (66)	41 (24)
	CPT Reaction Time	72 (46)	83 (49)	53 (28)
	Boston Naming Test	85 (58)	184 (71)	127 (40)
	CVLT: Delayed Recall	246 (103)	224 (78)	393 (52)

[a] BMDs are calculated under the assumption that 5% of the responses will be abnormal in unexposed subjects (P_0 = 0.05), assuming a 5% excess risk (BMR = 0.05).
Source: E. Budtz-Jørgensen, Copenhagen University, N. Keiding, Copenhagen University, and P. Grandjean, University of Southern Denmark, unpublished material, April 28, 2000.

Data on birthweight and gestation length in the Faroes and Seychelles show no indication of energy or macronutrient (protein and carbohydrate) deficiency. It is possible that members of either population could be deficient in micronutrients. It has been suggested that certain nutrients found in fish eaten by the Seychelles residents (e.g., omega-3 fatty acids and selenium) could attenuate adverse effects of methylmercury exposure. It should be noted that both the Faroese and New Zealand populations would be considered "high fish consumers" by comparison to U.S. norms, and both populations were observed to have measurable effects of mercury exposure. It is unlikely that general health status of the Faroese and Seychellois was a factor in enhancement or attenuation of mercury effects. Both populations receive excellent health care.

The point was made in Section 4.2.2.2 that recruitment in the SCDS was limited to children with no severe debilitating conditions. In the opinion of some scientists this may contribute to making the Faroes sample more representative of the population at risk in the United States in that it includes infants with some degree of initial perinatal risk.

It has been noted in several scientific forums that the cohort in the main Seychelles study appears to have been robust for psychomotor development at early ages. The SCDS authors report a number of abnormal scores on the Denver Developmental Screening Test that are considered to be exceptionally low by U.S. norms. The population also was observed to have an unusually high mean PDI score and a very low rate of referral for mental retardation. The means and standard deviations of the cognitive measures administered at later ages were similar to U.S. norms. It is not clear what, if any, effect this

developmental robustness has on susceptibility to adverse effects of prenatal Hg exposure. Statistical power to find an adverse effect is discussed in Section 4.2.2.8.

4.2.2.4 Assessment of Prenatal Mercury Exposure

In the Faroes study, mercury in cord blood and maternal hair was measured; in the Seychelles, maternal hair mercury was the biomarker of exposure. The maternal hair samples obtained in the Faroes and Seychelles studies did not necessarily reflect the same period of pregnancy. The Seychelles samples were 9-cm lengths of hair reflecting average mercury exposure during pregnancy. The Faroes study analyzed mercury from hair samples of variable length, some 3 cm (reflecting late second and third trimester) and some 9 cm (presumably reflecting the entire pregnancy).

In the analyses of the Faroese data, cord-blood mercury concentration was significantly associated with a slightly larger number of endpoints than was maternal hair mercury. Given the estimated half-life of methylmercury and what is known of PBPK, it could be assumed that cord-blood mercury reflects the latter part of gestation. Hair mercury could reflect the entire pregnancy or could be segmentally analyzed to provide snapshots of various times in gestation. Some of the effects reported in the Faroese cohort could be related to toxic responses in the latter stages of prenatal development. However, hair mercury concentrations in the Faroe Islands study were only a slightly weaker predictor of methylmercury effects than was cord blood. NRC concluded that it would be reasonable to expect that, if children were affected in the main Seychelles study, some indication of an association between child development and maternal hair mercury concentration would have been observed (NRC, 2000, p. 252). It noted that the findings of developmental effects reported in New Zealand were based solely on maternal hair sample data averaged across the entire period of pregnancy. The difference in the observation of effects between the Faroes study and the SCDS is thus not an artifact of biomarkers of exposure.

4.2.2.5 Level of Exposure

In their analyses the SCDS authors used maternal hair mercury as the biomarker of exposure; the Faroes investigators used both cord blood and maternal hair mercury. A comparison of maternal hair mercury levels indicates that exposure in the two studies was in the same range. For the main SCDS, the median hair mercury was 5.9 ppm with a range of 0.5 ppm to 26.7 for the whole cohort. In the Faroes birth cohort (n = 1,020), the median hair mercury was 4.5 ppm with a range of 2.7 to 42.6 ppm (Grandjean et al., 1992) . That the Seychelles Islands study may entail a lower exposure level than the Faroe Islands study could be concluded from two lines of evidence: the hair:blood ratio from the

Seychelles Islands and laboratory studies suggesting that dietary factors can influence tissue levels of methylmercury.

The ratio of hair mercury to blood mercury in the Seychelles study was estimated to be 416, a value that is higher than ratios reported elsewhere, which span 190 to 367 (Stern, 1997). The hair: cord blood ratio for the Faroes cohort was 191 (Grandjean et al., 1992). The value commonly used in dose conversion models is 250 (Stern, 1997; U.S. EPA, 1997e). If the value of 416 is used in estimating maternal or fetal blood mercury then estimates of the dose experienced by the Seychellois fetuses would be lower, by almost twofold, than assumed.

The hair: blood ratio of 416 is plausible for the Seychellois population considering their high fish diet and suggestions in the literature that diet can influence tissue levels of mercury. Average fish consumption in that population is 12 fish meals/week, which is likely to result in comparatively high levels of n-3 fatty acids and selenium. Such a diet may alter the kinetics of mercury by lowering blood or organ levels of mercury associated with a certain level of intake.

4.2.2.6 Episodic Versus Continuous Exposure

Exposure to methylmercury in the Seychelles is through daily consumption of fish. Although the Faroese eat fish more frequently than does the average consumer in the United States (about three meals a week), a significant source of methylmercury exposure in this population is from eating pilot whale meat. Pilot whale meals are relatively infrequent (less than once per month on the average) (Grandjean et al., 1992) with additional intermittent snacks of dried whale (Grandjean et al., 1998). The whale meat mercury concentration varies with the pod. An analysis of 466 whales showed an average concentration of 1.9 ppm, with a range of 0.59 to 3.30 ppm (Faroese Food Agency data quoted in NIEHS, 1999). There is no evidence to indicate that methylmercury bioavailability from the muscle of pilot whale is any different from that of fish tissue.

In the New Zealand study, there was the assumption of regular consumption of a relatively high-mercury fish (shark) in fish and chips, the major fast food of the area; the actual frequency and pattern of exposure are unavailable.

The degree to which differences in exposure pattern among studies account for differences in outcome is uncertain. It has been suggested that the mercury body burden in the Faroe Islands study was the consequence of a “spike” exposure pattern, in contrast to a more continuous exposure pattern in the

Seychelles study, which nonetheless resulted in a similar body burden. The Faroese investigators did segmental analyses of a small number of long hair strands from cohort mothers. Their results indicated a few instances of hair mercury peaks that implied temporal variation or spiking. They noted, however, that the peak level was only about twice the lowest hair mercury concentration (Budtz-Jørgensen et al., 1999).

The pattern of exposure can be a critical determinant of *in utero* toxicity. For example, the NRC report cites data in animals that showed that maternal ingestion of a given dose of alcohol over a short time caused greater neuronal impairment (Bonthius and West, 1990) and behavioral impairment (Goodlett et al., 1987) than that caused by gradual ingestion of the same total dose over several days. The frequency of exposure has a significant influence on the variation in blood levels, even under steady-state conditions, and is dependent on blood half-life (Rice et al., 1989).

It is probable that both episodic and continuous patterns of exposure are present in the population of the United States. Individuals in some ethnic groups engage in a subsistence-type fishing pattern, consuming fish as their major protein source. Most sport fishers, however, consume fish on an intermittent basis. It is not uncommon for piscivorous fish in inland waters to have mercury levels exceeding 1 to 2 ppm (U.S. EPA, 1997), so that the body burden of mercury in this group of fish consumers would presumably be the result of episodic exposure to food sources with levels of mercury similar to those in the Faroe Islands (see also Section 5.4.4 of this document). It may be that the consumption pattern of the Faroe Islands population better represents the pattern of exposure in the majority of the U.S. population exposed to elevated levels of methylmercury than does the consumption pattern of the population of the Seychelles Islands.

4.2.2.7 Endpoints Assessed

As described in Section 4.2.1, there have been inconsistent indications of adverse effect in newborns or preschool children of mothers experiencing low-dose, long-term exposure to methylmercury. The lack of consistent positive findings using standard newborn neurological tests has been considered unsurprising. Neurological examination of the newborn and young infant presents testing challenges that are difficult to meet in large-scale studies. The state of the newborn determines to a significant degree the quality and intensity of response to stimulation during an examination. “The state of an infant is usually dependent upon factors that are often outside the examiner’s control, such as hunger, hydration, illness, and the temporal location of an infant in its sleep-wake cycle. The recognition that state is a key variable in newborn behavior can be found in the fact that neonatal behavioral and

neurologic assessments usually indicate what state the newborn should be in before a given item series is administered..." (K. Deitrich, in U.S. EPA, 2000f).

It has been observed that most of the deficits associated with low-level prenatal exposure to developmental toxicants would not be revealed in a pediatric neurological examination and that gross neurological findings are unlikely in such studies. It has also been shown in studies not related to methylmercury that minor neonatal neurological deviations from the norm are not predictive of later neurobehavioral morbidity (U.S. EPA, 2000f).

Screening tests such as the Denver Developmental Screening Test have been used with highly variable results in methylmercury studies. Section 4.2.1 reports the differences in results among the New Zealand, SCDS pilot, and SCDS main cohorts. Recent research suggests that screening tests are not as sensitive as once believed and are no longer recommended for use in studies of low-level environmental chemical exposures to the fetus or infant (U.S. EPA, 2000f).

In the opinion of most developmental scientists, the Faroes and Seychelles studies used very different neurobehavioral test batteries. The tests selected for use in the SCDS are considered apical or omnibus tests (e.g., the McCarthy Scales of Children's Abilities); these provide global scores that integrate performance over many separate neuropsychological domains. The investigators studying the Faroes population were working from a hypothesis that mercury would have multifocal domain-specific neuropsychological effects. The OSTP Neurobehavioral Endpoints Panel was similarly disposed. They noted that it is plausible that prenatal exposure to methylmercury may not affect IQ, but rather domain-specific areas such as memory deficits, motor delays, or effects on so called "executive functions" – the complex domains that involve planning and cognitive flexibility (NIEHS, 1999). The Faroese test battery consisted of highly focused tests selected from those commonly used in clinical neuropsychology (e.g., CVLT and BNT) and did not include an apical test of global function. They observed effects in areas of language, memory, motor skills, visual-spatial abilities, and attention.

Many of the subscales of the McCarthy Scales might be expected to provide measures comparable to some tests administered to the Faroese children. However, there was no evidence from the McCarthy subtests of domain-specific effects in the Seychelles. These included verbal, perceptual-performance, quantitative memory, and motor scores. One conclusion is that if there were actually domain-specific effects occurring in the 5-year-old Seychellois, they should have been observed in the analyses of the McCarthy Scales results. The NRC panel came to a different conclusion: "Although the Faroe Islands and SCDS test batteries include tests of language and memory, it is not appropriate to view the endpoints

used in the studies to assess each domain to be equivalent either in terms of the specific skills assessed or the test sensitivity." (NRC, 2000, pp. 256-257).

One test was administered to both populations: the Bender-Gestalt Test. The investigators used different scoring systems; the SCDS used the Koppitz system whereas the Faroes used the Gottingen system. The NRC report noted that in a paper by Trillingsgaard et al. (1985) scores derived using the more detailed Gottingen system were significantly associated with low-dose lead exposure, whereas scores on the Koppitz system were not. Thus the Gottingen system used in the Faroe Islands might be more sensitive.

A second important difference in the assessment batteries used in the Faroes study and SCDS is the age of the child at assessment; 7-year-olds were tested in the Faroe Islands in contrast to children 5.5 years of age in the SCDS. Assessments in the New Zealand cohort were done at 4 and 6 years of age. It is generally thought that developmental assessments are likely to be less able to detect subtle neurotoxic effects when they are administered during a period of rapid developmental change. The period covering ages 60 to 72 months (when the SCDS and New Zealand cohorts were evaluated) is such a time; individual differences in the rate of cognitive maturation are likely to eclipse subtle differences in function attributable to a teratogenic exposure (Jacobson and Jacobson, 1991). The NRC panel also felt that in the SCDS, assessments of infants (particularly the 19- and 29-month BSID) were not given at optimal age points. Their report makes the following statement:

> Studies of prenatal exposure to alcohol and other substances that have administered the Bayley scales at multiple ages have repeatedly failed to detect effects at 18 months, probably because it too is a period of rapid cognitive maturation, involving the emergence of spoken language. Twenty-nine months is likely to be an insensitive testing point for the Bayley scales because it is at the end of the age range for which the version of this test used in the Seychelles was standardized, leading to a substantial risk of a "ceiling effect" (i.e., too many children receiving the highest possible scores on numerous items) (NRC, 2000 pp. 257-258).

The overall conclusion of NRC, however, was that discrepancies between the Faroe Islands and the main Seychelles studies are probably not due to differences in the assessments. They point out that the New Zealand study observed associations between methylmercury exposure and scores on the McCarthy Scales of Children's Abilities (the primary outcome measure used in the SCDS) at about the same age of assessment as in the Seychelles study (NRC, 2000, p. 258).

4.2.2.8 Power of Studies

NRC commented on the power to detect subtle effects in the admittedly large human studies (NRC, 2000, pp. 266-267). They noted that it is possible that the differences in response between the Faroes study and the SCDS could be due to between-sample variability in the expression of neurotoxicity at low doses. NRC remarked that even large samples can have insufficient power to detect adverse effects if a relatively small number of subjects are exposed in the upper ranges of the exposure distributions, where those effects will presumably be found.

NRC said that the magnitude of the associations found in the methylmercury studies resembles that reported for other environmental contaminants, such as low-dose lead and PCBs. If the magnitude of an association is not large, it is not likely that it would be detected in every cohort studied. NRC noted by comparison that it is well established in the scientific community that a blood lead concentration in excess of 10 μg/dL places a child at increased risk of poor developmental outcomes. However, not all lead studies have found an association between exposure at this level and decreased performance, and substantial variability exists in the magnitudes of the reported effects (Bellinger, 1995). NRC noted for the SCDS, "the evidence consistent with such effects found in the pilot phase, coupled with the suggestion of unusual developmental robustness in the main study, suggest that the failure to detect apparent adverse effects in the main study could be due to the substantial sample-to-sample variation expected when trying to identify weak associations in an inherently 'noisy' system of complex, multi-determined neurobehavioral endpoints" (NRC, 2000, p. 267).

In another comment on power, NRC says that power analyses based on total sample size can be misleading if adverse effects occur primarily among the most heavily exposed individuals, who typically constitute a small proportion of the sample. They note that of 700 children in the SCDS, only about 35 were exposed at levels concordant with maternal hair mercury of 15 ppm or higher. Because multiple-regression analysis examines associations that are averaged across the entire distribution of exposure, associations that hold only for the most highly exposed children can be difficult to detect. "Thus, if adverse effects of prenatal MeHg exposure occur primarily in the upper range, the power to detect them will be limited, and it would not be surprising if associations found in one Seychelles cohort (the pilot study) were not detected in the next cohort (the main study)" (NRC, 2000, p. 267).

In this context it should be noted that Grandjean et al. (1997) published an analysis of their neuropsychological test data on 7-year-old children, wherein they excluded all scores from children born to mothers with 10 ppm or higher hair mercury. This decreased the number of observations by 15%. In

the multiple-regression analyses, regression coefficients and p values were very similar to those obtained when data on the full cohort were used. This indicates that in this study population, adverse effects of mercury were detectable at exposures below 10 ppm maternal hair mercury.

4.2.2.9 Selection of Study

There is a large database on potential neurodevelopmental effects of methylmercury. In particular, three large, well-designed, prospective longitudinal studies have been peer reviewed and intensively analyzed. Some results from these studies of large populations are in apparent conflict. The previous sections reviewed some of the factors that have been suggested to account for the finding of adverse outcomes associated with *in utero* mercury exposure in the Faroes and New Zealand and the lack of this association in the SCDS. None of these factors represents a critical flaw in study design or execution. None of the factors adequately explains the differences in the study outcomes.

The NRC (NRC, 2000, p. 221) suggests that the finding of a low-dose methylmercury effect in a culturally and genetically heterogenous population in New Zealand study decreases the importance of population sensitivity issues in comparing the Seychelles and Faroes studies. The New Zealand study had a higher baseline rate of abnormal and questionable DDST scores in the test (8%-17% in controls) than did the Seychelles study (8% in the complete pilot cohort, 1.9% of the complete main cohort). This observation is consistent with the suggestion that the lack of effects in the Seychelles population is related to its relatively higher level of neurological performance at critical early life stages. Another possibility is that the manner in which the tests were given in the Seychelles led to better test performance, resulting in a less sensitive measure (i.e., an easier test for children to pass). The SCDS may also have had reduced power because of the small number of maternal-child pairs with methylmercury over 15 ppm. A comparison of the numbers in the relatively high-exposure range is instructive. If one uses 10 ppm maternal hair mercury as the high-exposure cutoff, there are about 150 Faroes subjects, at least 100 Seychelles subjects, and only 16 New Zealand subjects in this category (see Fig. 5-6, p. 166, NRC report).

One strength of the New Zealand study is that an effect was shown in an ethnically heterogeneous sample; another advantage was that the study used developmental endpoints with predictive validity. However, EPA acknowledges and shares the NRC reservations about using the New Zealand study as the basis for the methylmercury RfD. The New Zealand study is relatively small, with 237 subjects, by comparison with the population of up to 900 for the Faroes tests. Moreover, the New Zealand data have

not had the exhaustive scientific scrutiny that have been applied to the SCDS and Faroes study. The advantages of the Faroes study include these:

- large sample size;
- good statistical power as calculated by conventional means;
- the use of two different biomarkers of exposure;
- comprehensive and focused neuropsychological assessment;
- assessment at an age and state of development when effects on complex neuropsychological functions are most likely to be detectable;
- statistically significant observations that remain after adjusting for potential PCB effects; and
- extensive scrutiny in the epidemiological literature.

The Faroes data have also undergone extensive reanalyses in response to questions raised by panelists in the NIEHS (1999) workshop and by NRC (2000). The SCDS shares many strengths of the Faroes study. However, EPA agrees with NRC that a positive study, one that shows statistically significant associations between prenatal mercury exposure and adverse outcomes, is the strongest public health basis for an RfD (NRC, 2000, p. 6). Moreover, although one can model the nonpositive results of the SCDS, the resulting estimates of no effect level are difficult to interpret.

The study selected by EPA as the basis of the methylmercury RfD is the report of developmental neurotoxicity in 7-year-old children in the Faroes. The next section discusses issues in choice of endpoint for the RfD calculation. Many of the arguments in study selection pertain to choice of endpoint as well.

4.2.3 Choice of Critical Effect (endpoint)

EPA considered recommendations of NRC and the external peer reviewers in making the choice of a critical effect or endpoint from the Faroese data on neuropsychological effects in children. Rather than choosing a single measure for the RfD critical endpoint, EPA considers that this RfD is based on several Faroese test scores. These test scores are all indications of neuropsychological processes that are involved with the ability of a child to learn and process information. The issues and decision points in coming to this choice are described in the following sections.

4.2.3.1 Endpoints Suitable for RfD Derivation

Several studies have reported significant associations between increased numbers of combined abnormal and questionable scores on standardized neurological examinations. NRC opined that the functional importance of these effects is uncertain. There is little evidence that relatively low-dose, long-term exposure has any significant effect on language or motor-skill developmental milestones. There is some evidence of an association between *in utero* mercury exposure and deficits on the DDST. The NRC put forth the opinion that this screening test is not as useful as others in developmental neurotoxicological testing.

As is shown in Table 4-3, the tests used in the Seychelles and New Zealand studies in general were apical tests, assessing broad functional categories. These tests are widely used clinically and have been validated and normed for the U.S. population (but not the populations in which they were used). In contrast, the tests used in the Faroe Islands study were chosen to assess specific behavioral domains. The global clinical instruments such as the McCarthy, WISC-R, and CBCL have manuals that describe the tests and domains assessed, as well as the predictive validity of scores on these instruments to "real-world" behavior such as school performance. For the tasks used in Faroe Islands, Finger Tapping is a commonly used assessment of motor speed (Letz, 1990), and the Bender is a standardized test of childhood development. The other three endpoints also have demonstrated clinical relevance and predictive value As outlined in the table, most of these endpoints are predictive of ability in various academic skills, and therefore school performance. These tests, whether designed to be relatively global or domain-specific, were adversely affected by methylmercury exposure in the Faroe Islands and New Zealand, but not the Seychelles Islands, studies. In addition, motor performance was adversely affected in both New Zealand and the Faroe Islands. The only study that assessed social and adaptive behavior was the SCDS. BMD analysis performed by the NRC committee identified adverse effects on the CBCL at maternal hair levels comparable to those at which effects were observed in the Faroe Islands study (NRC, 2000, Table 7-5, p. 291). As concluded by the NRC (NRC, 2000, p. 325), the deficits observed in the New Zealand and Faroe Islands study can be considered predictive of problems in cognitive and academic performance associated with methylmercury exposure.

NRC presented BMDs and BMDLs for several endpoints in the positive Faroes and New Zealand studies as well as for the nonpositive Seychelles study (the next section discusses choices of model and choices made in BMDL calculation). Reproduced below is Table 7-2 from the NRC report (here as Table 4-4), which compares BMDs from the three studies in terms of maternal hair mercury. Included in this table are the New Zealand BMDs calculated after exclusion of the data from the highest exposed

individual. NRC suggested that this hair mercury concentration of 86 ppm is not plausible. The text reads:

> a hair Hg concentration of 86 ppm is more than 4 times the next highest hair Hg concentration in the study. If the one-compartment pharmacokinetic model and EPA's standard default input assumption are used, it can be estimated that a 60-kg woman would have to eat an average of 0.5 pounds (227 g) of fish containing 2.2 ppm of Hg to reach a hair Hg concentration of 86 ppm. Consistent exposure at such a dose seems unlikely when the mean Hg concentration in fish from fish-and-chips shops, a principal source of exposure in New Zealand (Kjellström et al., 1986), is 0.72 ppm (Mitchell et al., 1982). On the basis of those considerations, the committee concluded that analyzing the New Zealand data without the data from that individual is appropriate. (NRC, 2000, p. 282).

The range of BMDL values is relatively small (4 to 25 ppm maternal hair mercury). Inspection of this table shows that all the BMDs (and corresponding BMDLs) from the New Zealand study are lower than those from the other positive study in the Faroes. Often the most sensitive adverse endpoint is selected as the critical effect for calculation of a RfD. The most common surrogate for "most sensitive" is the lowest BMDL or bounded NOAEL (that is, NOAEL from a study wherein an effect was observed). The lowest BMDL is 4 ppm maternal hair mercury for the McCarthy Perceptual Performance Test calculated by Crump et al. (1998, 2000) on the New Zealand data (Kjellstrom et al., 1986). NRC had reservations about using the Kjellstrom (1986) data as the basis for the methylmercury RfD, with which EPA agreed (see Section 4.2.2.9). In this instance the choice is not of the lowest BMDL, but will be made from among the measures in the Faroese data.

Grandjean and colleagues reported significant associations between either maternal hair mercury or cord-blood mercury and decrements in several neuropsychological measures in 7-year-old Faroese children:

- Finger Tapping—preferred hand ($p = 0.05$)
- Continuous Performance Test—first year of data collection
  - – false negatives—($p = 0.02$)
  - – mean reaction time—($p = 0.001$)
- WISC-R Digit Span ($p = 0.05$)
- Boston Naming Test
  - – no cues ($p = 0.0003$)
  - – with cues ($p = 0.0001$)

Table 4-3. Tests modeled by NRC, functions assessed, and potential societal relevance

Study	Test	Domain/Function Assessed	Societal Relevance
Seychelles	Bender Copying Errors	Visuospatial	Math performance
	McCarthy GCI	Full-scale IQ	School performance, intelligence
	WJ Applied Problems	Ability to solve problems	Academic skills
	CBCL	Social and adaptive behavior	Antisocial behavior, need for therapeutic services
	Preschool Language Scale	Broad-based language	Learning, intelligence, school performance
	WJ letter/word recognition	Word recognition	Reading ability, school performance
Faroes	Finger Tapping	Motor performance	Motor speed/neuropathy
	CPT Reaction Time	Vigilance, attention, information processing speed	Intelligence, school behavior and performance
	Bender Copying Errors	Visuospatial	Math performance
	Boston Naming Test	Expressive vocabulary	Reading, school performance
	CVLT: Delayed Recall	Memory	Learning ability, school performance
New Zealand	TOLD Language Development	Broad-based language	Literacy skills, learning, school performance
	WISC-R: PIQ	Performance IQ, e.g. visuospatial, sustained attention, sequential memory	Learning, school performance
	WISC-R: FSIQ	Full-scale IQ, e.g. PIQ + verbal processing, expressive vocabulary	Learning, school performance
	McCarthy Perceptual Performance	Performance IQ, e.g. visuospatial, audition, memory	Learning, school performance
	McCarthy Motor Test	Gross and fine motor skills	Motor system integration

Abbreviations: WJ, Woodcock-Johnson Tests of Achievement; CBCL, Child Behavior Check List; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; TOLD, Test of Language Development; WISC-R:PIQ, Wechsler Intelligence Scale for Children-Revised Performance IQ; WISC-R:FSIQ, Wechsler Intelligence Scale for Children-Revised Full-Scale IQ.

Table 4-4. Benchmark dose calculations (ppm MeHg in maternal hair) from various studies and for various endpoints (NRC, 2000)

Study	Endpoint	BMD[a]	BMDL
Seychelles[b]	Bender Copying Errors	***[c]	25
	Child Behavior Checklist	21	17
	McCarthy General Cognitive	***	23
	Preschool Language Scale	***	23
	WJ Applied Problems	***	22
	WJ Letter/Word Recognition	***	22
Faroe Islands[d]	Finger Tapping	20	12
	CPT Reaction Time	17	10
	Bender Copying Errors	28	15
	Boston Naming Test	15	10
	CVLT: Delayed Recall	27	14
New Zealand[e]	TOLD Language Development	12	6
	WISC-R:PIQ	12	6
	WISC-R:FSIQ	13	6
	McCarthy Perceptual Performance	8	4
	McCarthy Motor Test	13	6

[a]BMDs are calculated from the K-power model under the assumption that 5% of the responses will be abnormal in unexposed subjects ($P_0 = 0.05$), assuming a 5% excess risk (BMR = 0.05).
[b]Data from Crump et al. (1998, 2000). "Extended" covariates.
[c] *** indicates value exceeds 100.
[d]Data from Budtz-Jørgensen et al. (1999).
[e]Data from Crump et al. (1998, 2000).

Abbreviations: WJ, Woodcock-Johnson Tests of Achievement; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; TOLD, Test of Language Development; WISC-R:PIQ, Wechsler Intelligence Scale for Children-Revised Performance IQ; WISC-R:FSIQ, Wechsler Intelligence Scale for Children-Revised Full-Scale IQ.

- California Verbal Learning Test
  - – short-term reproduction ($p = 0.02$)
  - – long-term reproduction ($p = 0.05$)

When an alternative approach to adjusting for covariates was used (Peters-Belson method) was used, two more measures showed significant associations:

- WISC-R Block Design ($p = 0.05$)
- Bender Gestalt Test errors ($p = 0.05$)

More endpoints were significantly associated with cord-blood mercury than with maternal hair mercury. Table 7-3 from the NRC report is reproduced below as Table 4-5; this presents calculations, in terms of cord-blood mercury concentrations, of BMDs and BMDLs for five Faroese endpoints.

4.2.3.2 Comparison of Endpoints

Boston Naming Test (BNT)

The BNT was the endpoint of choice of the NRC panel (NRC, 2000, p. 327). This test assesses word retrieval and formulation abilities in children, adults, and brain-injured patients. In the test, 60 line drawings are shown to the subject one at a time, and the subject is asked to name each of them. Familiarity (frequency of occurrence of the target names) decreases as the test progresses. Responses of the patient are scored for latency and correctness. When the subject misses an item, two kinds of cues may be given. A "stimulus cue" is a short phrase that gives additional information about the target item (e.g., something to eat). A "phonetic cue" is the first sound of the target word. Scores are summarized according to the number of spontaneously given correct responses, the number of correct responses following stimulus cues, and the number of correct responses following phonetic cues. The number of stimulus cues and the number of phonetic cues given by the examiner also is recorded. The peer-review panel noted that there is not much normative data on the BNT but that it is often used by child clinical neuropsychologists because of its documented validity in various child studies (EPA, 2000e). The BNT

Table 4-5. Benchmark dose calculations (ppb methylmercury in cord blood) from the Faroe Islands Study for various endpoints

Endpoint	BMD[a]	BMDL
Finger Tapping	140	79
CPT Reaction Time	72	46
Bender Copying Errors	242	104
Boston Naming Test	85	58
CVLT: Delayed Recall	246	103

[a]BMDs are calculated from the K-power model under the assumption that 5% of the responses will be abnormal in unexposed subjects ($P_0 = 0.05$), assuming a 5% excess risk (BMR = 0.05).
CPT, Continuous Performance Test; CVLT, California Verbal Learning Test.
Source: NRC (2000); data from Budtz-Jørgensen et al. (1999).

has been useful as a measure of confrontation naming and word retrieval skills and can be used to differentiate between children with and without language-based learning disabilities; moreover, it is a predictor of related cognitive and academic skills, especially reading achievement (Yeates, 1994, as quoted in U.S. EPA 2000e).

Continuous Performance Test (CPT)

The endpoint from the Faroe Islands study that yielded the lowest BMDL in the NRC analysis was the CPT reaction time. This test was modified from the Neurobehavioral Evaluation System (NES) version, which is a standardized battery used mainly in occupational settings in adults. In the Faroe Islands study, the child was required to respond as quickly as possible when a silhouette of a cat appeared on a computer screen, but not when the silhouettes of other animals (number not specified) appeared (Grandjean et al., 1997). Dependent variables included number of missed responses (omission errors) and average reaction time for the last 3 minutes of a 4-minute task. False positives (errors of commission) apparently were not analyzed. Reaction time in a task that includes decision making (respond to cat, don't respond to others) is a measure of the speed of information processing. The investigators found an increase in reaction time correlated with cord blood using all data; this correlation was still seen when only data were used from children whose mothers had hair concentrations below 10 ppm (low-level exposure). In addition, there was an association between cord blood mercury levels and an increase in omission errors in the full group and low-level exposure group. This finding indicates poorer attention to the task as a function of methylmercury exposure.

Speed of information processing as measured by reaction time is highly correlated with IQ in humans (Jensen and Munro, 1979; Matthews and Dorn, 1989; Vernon, 1983; Vernon et al., 1985; Western and Long, 1996). It has been argued that speed of information processing is a measure of *g*, the highest order common factor in all tests of cognitive ability (Jensen, 1993b). Reaction time in complex reaction time tasks is consistently observed to be correlated with psychometric *g* in studies in several cultural groups (Buckhalt and Jensen, 1989; Ja-Song and Lynn, 1992; Lynn et al., 1991; Lynn and Wilson, 1990; Shigehisa and Lynn, 1991). Generally, the association between *g* and decision reaction time increases with increasing task complexity (Beh et al., 1994; Jensen, 1987). It is estimated that the correlation between reaction time and *g*-loaded psychometric tasks is 0.3-0.5, whereas the correlation based on several reaction time and psychometric tasks approaches 0.7 (Jensen, 1993a; Vernon, 1989), which is similar to the correlation among different IQ tests (Jensen, 1993a). Reaction time tasks also discriminate between brain-injured and other individuals (Western and Long, 1996) and identify children with attention deficits (Zahn et al., 1991).

The NRC chose not to rely on CPT reaction time as the critical endpoint because results were from only half the cohort. The Faroe investigators reported that effects on CPT reaction time were significant for the first year of testing but not the second, with combined effects for the 2 years significant at p = 0.01. The authors stated that "[b]ecause supervision was stringent only during the first year, these data were chosen for development of the final regression model" (Grandjean et al., 1997, pp. 422-423). The NRC felt that measures from the full cohort would be more reliable than those based on half the cohort; their report did not state any concerns regarding elimination of the second year data per se (NRC, 2000, p.286).

Advantages of the choice of the CPT reaction time as the critical endpoint would be that there was no evidence of an effect of PCBs on this measure, and the correlation of complex reaction time with measures of intelligence such as IQ. The disadvantage is that the analysis is based on half the cohort. However, this limitation also holds true for the BNT corrected for PCB exposure. Therefore, there is little or no reason to choose one over the other in this regard.

California Verbal Learning Test for Children (CVLT)

The California Verbal Learning Test for Children is a word-list-learning task that measures acquisition of information following repeated exposure to verbal stimuli. Of principal interest are the variables of learning, delayed recall, and perseveration. The test has good test-retest reliability as well as internal consistency. The theoretical foundations of the CVLT are based upon several decades of cognitive science research in brain/behavior relationships. The test discriminates clinical groups such as those with hyperactivity/attention deficit disorders, children with learning disabilities, and children suffering prenatal insults such as fetal alcohol syndrome.

4.2.3.3 Consideration of Potential PCB effect

EPA agrees with NRC that analyses of the Faroese test results show that there are real mercury-related adverse effects that cannot be attributed to concomitant PCB exposure. This was noted in Section 4.2.2.2. The external peer review panel for the methylmercury RfD agreed with that conclusion. However, they disagreed with the NRC choice of the BNT results from the full cohort because of the potential effect of PCB exposure. They thought that the BNT results were the most sensitive to PCB influence of any evaluated in the Faroe Islands. The peer review panel pointed to the analyses presented by NRC (reproduced in this document as Table 4-6) as presenting an opportunity to consider the use of benchmark estimates corrected for any potential PCB influence. The Faroes investigators calculated a

PCB-adjusted BMD and BMDL for the BNT using cord blood as the exposure biomarker; these were considerably greater than the BMD/BMDL for either the full cohort without PCB adjustment or that from the low-PCB tertile. Similar increases after adjusting for PCBs were not seen for Finger Tapping, CPT reaction time, or CVLT delayed recall tests, when cord blood was the exposure metric. NRC noted that the PCB measurements were done on cords from only about one-half of the Faroese cohort (about 450 children) and that the use of data from only the low-PCB tertile further reduces *n* to about 150 children. NRC reported that the reduced sample sizes in these analyses increased the variability in the results. They saw no clear pattern as to how the PCB-adjusted analyses differed from the original results. The NRC concentrated its focus on the low-PCB subset BMDs and BMDLs. They compared results from two tests with no PCB effect (CPT and Finger Tapping) with those with potential for PCB influence (BNT and CVLT). They reported that the BMDs for the low-PCB subset for the BNT and CVLT did not differ from the BMDs for the whole cohort any more than did the BMDs for the two tests with no influence of PCBs. The NRC authors felt that the variability seen in Table 4-6 is no more than that which would be expected by chance alone (NRC, 2000, p. 288).

Table 4-6. BMD (BMDL) Estimates from the Faroe Islands Study With and Without Adjustment for PCBs and in the Subset of Low PCB-Exposed Children (calculated using the K-power model)

		Full Cohort	Adjusted for PCBs	Low-PCB subset
Exposure	Endpoint	BMD (BMDL)[a]	BMD (BMDL)	BMD (BMDL)
Hair	Finger Tapping	20 (12)	17 (9)	7 (4)
	CPT Reaction Time	18 (10)	27 (11)	13 (5)
	Boston Naming Test	15 (10)	24 (10)	21 (6)
	CVLT: Delayed Recall	27 (14)	39 (12)	32 (7)
Cord Blood	Finger Tapping	140 (79)	149 (66)	41 (24)
	CPT Reaction Time	72 (46)	83 (49)	53 (28)
	Boston Naming Test	85 (58)	184 (71)	127 (40)
	CVLT: Delayed Recall	246 (103)	224 (78)	393 (52)

[a] BMDs are calculated under the assumption that 5% of the responses will be abnormal in unexposed subjects (P_0 = 0.05), assuming a 5% excess risk (BMR = 0.05).
Source: E. Budtz-Jørgensen, Copenhagen University, N. Keiding, Copenhagen University, and P. Grandjean, University of Southern Denmark, unpublished material, April 28, 2000, in Table 7-4, p. 289, NRC 2000.

4.2.3.4 Supporting Studies

A second Faroese cohort was recruited from children born between 1994 and 1995. In the study reported by Steurwald et al. (2000), decreases in neurologic optimality score (NOS) were associated with increasing cord blood mercury. This association remained statistically significant after adjustment for confounders (including cord and maternal serum PCB levels). Inspection of data plotted in the paper indicate that a decrease in NOS was observed in the two highest quartiles; that is, at cord blood mercury levels greater than 20 ppb. This indicates a dose-dependent effect at levels as low as (or lower than) those for which neuropsychological deficits were reported in the main study of 7-year-old children (Grandjean et al, 1997). The size of this study is rather small (N = 182) and involves subtle changes at a very early developmental period, the clinical implications of which are less clear than the changes found in the main study of 7-year-olds.

NRC conducted an analysis that combined results from the SCDS, New Zealand, and Faroes studies (NRC, 2000, pp. 290-294). Their approach was to use a hierarchical random-effects model that followed a method proposed by Dominici et al. (in press). To inform their analyses, NRC plotted BMDs and BMDLs (as ppm mercury in maternal hair) for measures from all three studies. For outcomes in the SCDS for which there were no BMDs, the analysis used an arbitrary value of 150. They concluded from the plot (Figure 7-3, NRC, 2000, p. 285) that study-to-study variability was large relative to outcome-to-outcome variability. NRC felt that use of a hierarchical model would allow one to borrow strength from the different studies to achieve greater precision in BMD and BMDL estimates. The NRC results are seen in their Table 7-5 (NRC, 2000, p. 291). They present what they refer to as smoothed results, which reflect reduced random variability. For the Faroes data, the BMDL estimates are not much changed from the original values; the unsmoothed range of BMDLs is 10 to 15 ppm mercury in maternal hair, while the smoothed results range from 12 to 15 ppm. The NRC notes that all smoothed BMDLs are closer to their BMDs; they also concluded that the hierarchical modeling reduced much variability among outcomes but not among studies.

NRC estimated a central tendency measure, equivalent to a BMD, across all three studies and all endpoints. They also determined a lower limit based on a theoretical distribution of BMDs, which is the logical equivalent of a BMDL. These values as well as other estimates derived from the Faroes and New Zealand studies are in Table 4-7.

Table 4-7. Central tendency estimates, ppm mercury in maternal hair[a]

Approach	Original values		Smoothed values	
	BMD	(BMDL)	BMD	(BMDL)
Most sensitive endpoint from New Zealand	8	(4)	12	(7)
Median endpoint from New Zealand	12	(6)	13	(8)
Mean of endpoints from New Zealand	12	(6)	13	(8)
Most sensitive endpoint from Faroes	15	(10)	17	(12)
Median endpoint from Faroes	20	(12)	20	(13)
Mean of endpoints from Faroes	22	(12)	21	(13)
Mean of all endpoints		(14)		(15)
Integrative analysis			21[b]	(8[c])

[a] Source: Table 7-6, NRC 2000, p. 294.

[b] Logically equivalent to a BMD.

[c] Logically equivalent to a BMDL.

The external review panel for the methylmercury RfD suggested that a reasonable alternative to using a single test result as the basis for the RfD would be to develop a composite index from several test outcomes. Their recommendation was to evaluate mercury-associated endpoints for any potential PCB effect. The next step would be to use either PCB-adjusted results or only those results with no PCB effect in some compositing approach to provide a multiendpoint BMDL. The most appropriate compositing approach would be one with a weighting scheme to account for different sample sizes for the individual tests.

A second way to proceed would be to use factor analysis to create a composite factor that accounts for the majority of the variance among the individual test results. The resulting estimate would serve as the basis for RfD calculation. The peer review panel that suggested this approach noted that it is novel and would require substantial effort to reanalyze the data (U.S. EPA, 2000f).

EPA has decided that the two suggestions have a great deal of merit. We will pursue some of these analyses for the extant Faroes and New Zealand data and for the SCDS data on 7-year-old children as they become available. We felt, however, that the integrative analysis reported by NRC serves as substantial support for the choice of an endpoint from the Faroese test data. We felt that at this time the use of NRC's integrated BMD /BMDL or one derived form the suggested alternatives as the sole basis for an RfD would introduce an unacceptable degree of model uncertainty into the RfD.

4.2.3.5 Choice of Endpoint

The lowest of the BMDLs from the Faroese tests is 46 μg/L mercury in cord blood for the CPT reaction time scores. NRC recommended a different choice. They remarked that in a neuropsychological test battery, the reliability of the individual endpoints can be highly variable, so the most sensitive endpoint may not be the most appropriate choice. The Faroes investigators reported difficulties in administering the CPT. The data from the second half of the cohort were discarded for the analysis of this endpoint; thus the *n* was about half that for the other tests. The NRC panel suggested that a more appropriate choice would be to select the second most sensitive endpoint, the BNT BMDL of 58 ppb mercury in cord blood (NRC, 2000, p. 300). Interestingly, the BNT had the lowest BMDL in the analyses based on maternal hair mercury.

The external peer reviewers of the methylmercury RfD disagreed with the NRC choice. The felt that the use of a single neuropsychological endpoint to form the basis for making a risk assessment is problematic. They felt that the use of the BNT data from the whole Faroese cohort was not warranted, as the BMDL thus derived could reflect an effect of PCB exposure. The peer reviewers preferred the BNT BMDL adjusted for PCB exposure of 71 ppb mercury in cord blood. In their report they noted that the adverse effect of methylmercury reflected in the BNT scores is not isolated, but rather occurs at levels not far removed from effects on other neuropsychological tests, providing some assurance of its credibility. A difficulty with the use of the PCB-adjusted BMDL is that this BMDL is based on scores from only about one-half of the total cohort. As noted in Section 4.2.3.3, NRC felt it was more appropriate to use the BMDL from analyses with the larger *n*.

The peer review panel described three other options for RfD derivation. One option would be to use the BMDL from the CVLT. The panel noted the clinical relevance and predictive value of this test as the well as likelihood that there is no influence of PCB exposure on this measure. The major drawback to this choice is that the BMDL from this test for the full cohort is the highest (103 ppb mercury in cord blood or 14 ppm mercury in maternal hair) of those listed in Table 4-6. One could easily argue that the RfD based on this measure is not public health protective. In the light of analyses that indicate that mercury correlations with test measures remain when the highest exposure subset is eliminated (10 ppm or more mercury in maternal hair), this would seem a poor choice.

A third option would be to develop a composite index across several measures in the Faroes study. The peer reviewers suggested that the BMDLs from the statistically significant tests could be developed, evaluated for effects of PCBs, and composited in some way, such as a geometric mean. The compositing

method should consider a weighting scheme to deal with varying sample sizes for the different tests. NRC essentially did a composite measure with the integrative analysis; for all endpoints in all three large studies, the BMDL is 8 ppm mercury maternal hair, or 32 ppb cord blood mercury (Table 4-7). Geometric means for the Faroese measures are in Table 4-8 below. These were calculated separately for the whole cohort, PCB-adjusted BMDLs, and lowest PCB subset. EPA will pursue the suggestion of a weighted composite index at a future time.

A final longer term option of the peer review panel was to devise a within-study integrative multivariate approach using factor analysis for analytical derivation of a composite factor that combines results across tests with overlapping functional domains. The panel acknowledged that this would require some statistical methodology development.

EPA prepared a comparison of the NRC and peer-reviewer-recommended approaches, which also includes the BMDLs from the NRC integrative analysis and geometric means of four scores from the Faroes. Table 4-8 presents BMDLs in terms of cord blood mercury. These are converted (using a one-compartment model as in Section 4.4.2) to an ingested dose of methylmercury that would result in the cord blood level. The last column of Table 4-8 shows the corresponding RfD from application of a UF of 10 (see Section 4.5.6). The calculated RfD values converge at the same point: 0.1 μg/kg/day. Among all the endpoints listed, there are few deviations from 0.1 μg/kg/day: 0.2 μg/kg/day for the CVLT entire cohort and 0.05 μg/kg/day for CPT and Finger Tapping, lowest PCB subset. For comparative purposes several measures from the New Zealand data analyses were also included in Table 4-8; the median BMDL from the New Zealand study would give an RfD of 0.05 μg/kg/day. If one were to use the NRC integrative analysis BMDL equivalent value, the resulting RfD would be 0.05 μg/kg/day.

Rather than choosing a single measure for the RfD critical endpoint, EPA considers that this RfD is based on several scores from the Faroes measures. These test scores are all indications of neuropsychological processes involved with a child's ability of a child to learn and process information. The BMDLs for these scores are all within a relatively close range. In subsequent sections, one endpoint is carried through the dose conversion and application of the UF to calculation of the RfD; namely, the NRC-recommended BMDL of 58 ppb mercury in cord blood from the BNT.

Table 4-8. Comparison of BMDLs–endpoint from Faroes, New Zealand and NRC Integrative Analysis[a]

Test[b]	BMDL ppb mercury cord blood	Ingested dose μg/kg bw /day[c]	RfD μg/kg bw /day[d]
BNT Faroes			
Whole cohort	58	1.081	0.1
PCB adjusted	71	1.323	0.1
Lowest PCB	40	0.745	0.1
CPT Faroes			
Whole cohort	46	0.857	0.1
PCB adjusted	49	0.913	0.1
Lowest PCB	28	0.522	0.05
CVLT Faroes			
Whole cohort	103	1.920	0.2
PCB adjusted	78	1.454	0.1
Lowest PCB	52	0.969	0.1
Finger Tap Faroes			
Whole cohort	79	1.472	0.1
PCB adjusted	66	1.230	0.1
Lowest PCB	24	0.447	0.05
Geometric mean			
Whole cohort	68	1.268	0.1
PCB adjusted	65	1.212	0.1
Lowest PCB	34	0.634	0.1
Median values			
Faroes	48	0.895	0.1
New Zealand	24	0.447	0.05
Smoothed values			
BNT Faroes	48	0.895	0.1
CPT Faroes	48	0.895	0.1
CVLT Faroes	60	1.118	0.1
Finger Tap Faroes	52	0.969	0.1
MCCPP New	28	0.522	0.05
MCMT New	32	0.596	0.1
Integrative			
All endpoints	32	0.596	0.1

[a]BMDLs from NRC (2000), Tables 7-4, 7-5, 7-6. Hair mercury was converted to blood mercury using a 250:1 ratio and an assumption of equivalent maternal and cord levels.
[b]Abbreviations: BNT, Boston Naming Test; CPT, Continuous Performance Test; CVLT, California Verbal Learning Test; MCCPP, McCarthy Perceived Performance; MCMT, McCarthy Motor Test.
[c] Calculated using a one-compartment model as in Section 4.4.2.4.
[d] Calculated using an UF of 10 as in Section 4.5.6.

4.3 CHOICE OF DOSE-RESPONSE APPROACH

4.3.1 Benchmark Versus NOAEL

In recent years, EPA has been moving to use of BMDs versus experimental NOAELs as the departure point for calculation of RfDs. The Agency is preparing guidance for application of this methodology. Guidance has been published in the Technical Support Document on Risk Assessment, Human Health Methodology for Ambient Water Quality Criteria (U.S. EPA, 2000g).

NRC also made comments on the applicability or preference for BMDs over NOAELs (NRC, 2000, pp. 272-273). They cite comments by several risk assessment scientists on statistical drawbacks to NOAELs. The NOAEL, for example, must correspond to one of the experimental doses; it can vary considerably across different experiments. In calculating an RfD, there is no statistical or other treatment of the data to adjust for the choice of dose groups by different experimenters. NRC notes that the identification of a no-effect dose group is based on statistical comparisons between exposed and controls; thus, larger studies have higher power to detect small changes and tend to produce lower NOAELs. Furthermore, because NOAELs are identified as a consequence of pairwise comparisons, there is no widely accepted procedure for calculating a NOAEL in settings where exposure is measured on a relatively continuous scale.

In its guidance documents EPA lists some other advantages of BMD over the LOAEL/NOAEL approach. The traditional method does not incorporate information on the shape of the dose-response curve, but rather uses only a single point (NOAEL or LOAEL). This point depends on the number of doses and spacing of those doses in the experiment. The possible LOAEL/NOAELs are limited to the discrete values of the experimental doses, whereas the “real” value of the NOAEL could be any value between the experimental NOAEL and the LOAEL.

The determination of a NOAEL is dependent on the background incidence of the effect in controls. Statistically significant differences between treatment groups and controls are more difficult to detect if background incidence is relatively high, even if biologically significant effects are noted.

The peer reviewers of the methylmercury RfD provided comment on the appropriateness of the BMD methodology for the methylmercury human data:

> Derivation of LOAELs and NOAELs from the data would require disaggregation of the data based upon artificial cutpoints (e.g., quartiles) to determine which range of exposure appears to be different from the baseline group. While this approach provides a useful profile of effect with dose (e.g. Fig. 1 of the 1997 Faroes paper), it uses a grouping of the data that makes specifying the threshold less exact than with the more statistically robust and inclusive benchmark dose approach. The LOAEL/NOAEL approach also does not factor variability into the estimation of the threshold dose in the health protective way that the BMDL concept accomplishes. In the LOAEL/NOAEL approach, the more variable the data the higher the LOAELs and NOAELs tend to become because it is more difficult to define a statistical difference from the control group. In contrast, greater variability will tend to drive down the estimate of the BMDL since it is the lower 95% confidence limit estimate on the BMD. (G. Ginzberg in U.S. EPA, 2000f)

NRC recommended and EPA concurred with the use of a BMD approach to calculate the methylmercury RfD.

4.3.2 Choice of Exposure Metric

NRC discussed at length in its Chapter 4 the suitability of both hair and blood mercury as biomarkers of exposure. The measurement of mercury exposure in the study population serves two purposes when applied to risk assessment. The biomarker serves as the surrogate for the methylmercury dose to the target tissue, in this case fetal brain. As such, the biomarker is one of the coordinates of inputs to the dose-response models. From this perspective, the ideal biomarker is one that is closest pharmacokinetically to the target. Of the measurements available, cord blood represents a compartment closer to fetal brain than does hair, which is an excretion compartment.

The other use of biomarker in this risk assessment is as a surrogate for ingested dose, the unit in which an RfD is expressed. The ideal biomarker for this stage is closest pharmacokinetically or has the best correlation with ingested dose. Maternal hair or blood may be more suitable from this point of view.

Another point to consider in biomarker choice is temporality: is the biomarker an adequate indicator of exposure during critical developmental windows? NRC noted that cord-blood mercury tends to reflect exposure in the later stages of pregnancy, whereas hair mercury can be used to determine exposure at any point in pregnancy, given the appropriate sample. The NRC panel noted that for most assessment of hair mercury there will be significant uncertainty when attempting to relate a particular

hair level to a time-specific dose to the fetal brain. In addition, there is no information on differential effects of methylmercury at different periods of gestation; it is in no way certain when critical developmental windows occur. Considering the information (or lack thereof) on time of exposure offered by each biomarker, there is no compelling reason to consider one more appropriate than the other.

NRC provided a table (Table 6-1, NRC, 2000, p. 253) that compares test performance associated with mercury concentration as a function of either cord-blood or maternal hair measurement. This comparison suggests that the cord-blood measure explains more of the variability in more of the outcomes than does maternal hair mercury.

In selecting the exposure metric, the above factors were considered. Cord blood is the biomarker most closely linked (at least conceptually) to the target organ. Cord blood is the marker for which there are the most associated adverse effects in the Faroes study. Neither cord-blood nor maternal hair mercury (as generally measured) provides a clear advantage in assessing exposure during putative critical developmental windows. Maternal hair mercury is conceptually closer to maternal ingested dose than is the cord-blood compartment. However, sensitivity analyses indicate that the maternal hair:maternal blood ratio is a key contributor to variability in calculations of ingested dose (Stern,1997; Clewell et al., 1999). On balance, the best choice for exposure metric for RfD calculation is cord-blood mercury.

4.3.3 Choice of BMD

In applying a BMD approach to data that are continuous in effect, there are several interdependent steps as defined by Gaylor and Slikker (1992). The first is to fit a regression model that characterizes the mean of the set of outcome measurements as a function of dose; the assumption of a normal distribution is made. (Choice of model is described in Section 4.3.4). The second step is to define the cutoff for normal versus abnormal response. This cutoff point (x_0) is defined statistically. In the third step, the dose-specific probability of falling into the abnormal category is determined (P_0). One chooses a specific increase in the frequency of abnormal responses by comparison to background probability; this specific risk above background risk is the benchmark response, or BMR. The dose at which the BMR is reached is the BMD. In other words, the BMD is the dose that results in an increased probability of an abnormal test performance by a benchmark response; that is, from P_0 for an unexposed person to P_0 + BMR for a person exposed to the BMD. The last step is to calculate the BMDL or 95% lower limit on the BMD. Choices for P_0 and BMR are described below.

One could set P_0 based on clinical definitions of adverse response or other information. For example, long experience with birth weight in a population could prompt a choice of 2500 g as a cutoff for normal. Alternatively P_0 can be set as a fixed percentile of performance in the unexposed population. For a linear model and random error normally distributed with variance, this has the effect of setting P_0 at a specified number of standard deviations below the mean for the unexposed group. Generally the larger the P_0, the lower the BMD. For the analysis of the behavioral data, including the Faroe study, the NRC panel (NRC, 2000, p. 298) recommended that $P_0 = 0.05$: that is, that the cutoff for abnormal response be set at the lowest 5% (5^{th} percentile) of children. This means that the cutoff point (x_0) is defined by a probability of 5% in an unexposed population. It should be noted that specification of P_0 for the Faroese data (or the other human methylmercury studies) is somewhat problematic because there are no subjects with true zero exposure. The mean response rate at zero is not actually based on observed data but is extrapolated from the fitted model (Budtz-Jørgensen et al., 1999). Support for P_0 of 0.05 is found in Crump et al. (2000); the authors note that this choice is "suggested by the convention of considering 95% of the clinical responses in healthy individuals to define the normal range." EPA agrees that $P_0 = 0.05$ is a reasonable choice.

BMR is the benchmark response, the specific risk above background risk. In other risk assessments (mostly on quantal data) it has been set at 0.1, 0.05, or 0.01. In the MSRC, BMDs and BMDLs were calculated for BMRs of 0.1, 0.05, or 0.01. EPA chose to apply a BMR of 0.1 to the Iraqi data (MSRC volume V, pp. 6-27-6-28; U.S. EPA, 1997e). This was based on publications by Allen et al. (1994) that indicated that a 10% risk level roughly correlated with a NOAEL for developmental toxicity data from controlled animal studies. For a methylmercury RfD based on the Faroese data, NRC recommended that the BMR be set to 0.05, which would result in a doubling of the number of children with a response at the 5^{th} percentile of an unexposed population (NRC, 2000, pp. 283, 298).

The NRC panel felt that their choice of a P_0 of 0.05 and a BMR of 0.05 was justifiable in terms of being sufficiently protective of public health. The committee recognized, however, that the choice of P_0 and BMR is at the interface of science and policy and should be a science-informed policy judgment. EPA at this time has no established policy on an acceptable risk level for the effects reported in the Faroese children. EPA is in the process of publishing guidance on benchmark dose methodology and processes. Most of the experience that supports this guidance comes from assessment of toxicological

(animal) data. The guidance acknowledges that choices of model, and inputs such as P_0 and BMR, should be informed by a consideration of the type of data and the ancillary information on which the assessment is based. Our decision in the specific case of methylmercury is influenced by the public health conclusions that NRC articulated: the measured effects in the human studies are sentinels of adverse outcomes in children, related to their ability to learn and achieve success in educational settings. Thus, EPA accepts the NRC recommendation to set $P_0 = 0.05$ and BMR = 0.05 in this instance.

4.3.4 Choice of Model

A report prepared for EPA and subsequently published by Budtz-Jørgensen (1999) provided calculations of BMD and BMDL using square root and log transformations as well as calculations for K-power models. NRC used these results and similar calculations for the New Zealand and Seychelles studies to make some assessments of model suitability. They noted great variability in calculated BMDs and BMDLs as a function of model. This was so despite the inability of standard statistical assessments of model adequacy to distinguish between models. In response to NRC, Budtz-Jørgensen and colleagues provided some additional analyses. These were sensitivity analyses that repeated the regression models after omitting some of the highest observations (E. Budtz-Jørgensen, Copenhagen University, N. Keiding, Copenhagen University, and P. Grandjean, University of Southern Denmark, unpublished material, April 28, 2000, quoted in NRC, 2000, p. 293). Their results suggested that the influence of the extreme observations did not explain the model-to-model variability (NRC, 2000, p. 293).

NRC concluded that the most reliable and defensible results for the purpose of risk assessment are those based on the K-power model. (NRC, 2000, pp. 293-298). This model takes the following form, as presented in Budtz-Jørgensen et al. (2000):

$$\mu(d) = \beta \cdot d^K$$

where d is the child's mercury dose and K and β are parameters to be estimated. The K-power model was fit under the constraint that $K \geq 1$, so that supralinear models were ruled out. A power of 1 generally provided the best fit to the Faroese data (Budtz-Jørgensen et al., 2000). With K = 1, the above model is linear.

NRC observed that in situations where there are no internal controls (i.e., no unexposed individuals) and where the dose response is relatively flat, the data will often be fit equally well by

linear, square-root, and log models. The models can yield very different results for BMD calculations, however, because these calculations necessitate extrapolating to estimate the mean response at zero exposure level. Both the square-root and the log models take on a supralinear shape at low doses, leading to lower estimates of the BMD than do linear or K-power models. The mechanisms by which methylmercury exerts its neurotoxic effects in developing systems are speculative. However, no likely mode of action for methylmercury leads one to expect a supralinear dose-response at low dose. Thus, from a toxicological perspective, the K-power model has greater biological plausibility, because it allows for the dose-response to take on a sublinear form, if appropriate.

NRC pointed out that the model sensitivity for BMD from the Faroes data appears in conflict with the concept, put forward by Crump and others, that by estimating risks at moderate levels, such as 5% or 10%, the BMD should be relatively robust to model specification. Budtz-Jørgensen et al. (2000) responded that this model dependence is a consequence of the lack of true controls (subjects with zero exposure). The majority of exposures in the Faroes resulted in hair mercury concentrations exceeding 5 ppm (or 24 ppb cord blood). The interquartile range for hair mercury was 3 to 8 ppm (13 to 40 ppb for cord blood) (Grandjean et al., 1992). Models fit to the Faroese data are in effect capturing the shape of the dose-response in this middle range of exposure. The NRC report Figure 7-5, taken from Budtz-Jørgensen et al. (1999), shows dose-response curves fitted to hair mercury data for the linear, square-root, and log transformations. Budtz-Jørgensen et al. (2000) provided some information on model fit. They did not present goodness-of-fit statistics *per se*, but rather tested each model against an expanded model that included both the linear and logarithmic term. The authors observed that for $P_0 = 0.05$, and with cord blood as the exposure metric, the logarithmic transformation tended to show a better fit than the linear model for the following tests: CPT, BNT, and CVLT. There was no difference in fit for the Finger Tapping and Bender Gestalt test or for any of the five tests when maternal hair mercury was the biomarker. The NRC notes that variations in estimated BMDs are not explained by differences in how well the models fit the bulk of the data, but rather by what the models predict for the mean response for unexposed individuals.

In reaching its conclusion on model choice, NRC concluded that biologically based arguments were needed. The argument was as follows:

> One useful way to think of differences between the various models is that the linear model implicitly assumes an additive effect of Hg exposure, the log model assumes a multiplicative effect, and the square root lies somewhere in between. All three models fit essentially equally well to data that for the most part correspond to concentrations between 2 and 20 ppm in hair. However, the models differ fairly dramatically with regard to

how they extrapolate to values below those levels. The linear model would predict that the change in mean outcome as MeHg concentration goes from 0 to 10 ppm in hair should be the same as the change observed in the mean outcome as concentration increases from 10 to 20 ppm. In contrast, the log model would predict that the change in mean outcome associated with any doubling of MeHg concentration should be the same as the change observed in the mean outcome as concentration increases from 10 to 20 ppm. Thus, the log model would predict that the same magnitude change in outcome would be expected as the concentration goes from 1 to 2 ppm or from 4 to 8 ppm as that observed for the concentration going from 10 to 20 ppm—that is, the extrapolation down to zero exposure will predict a very steep slope at low doses. Given the relative absence of exposures at very low levels, a decision should be made on biological grounds regarding which model makes the most sense for risk assessment. The committee believes that an additive (linear) or perhaps sublinear model is the most justifiable from a biological perspective, thus ruling out square-root and log-transformed models. For MeHg, the committee believes that a good argument can be made for the use of a K-power model with K constrained to be greater than or equal to 1 (NRC, 2000 p. 297).

4.3.6 Selection of the Point of Departure for the RfD

Based on all considerations in the preceding sections, the following is selected as the basis for the RfD. Our choice is a benchmark approach using the results of the Faroese tests with significant associations with cord-blood mercury. As an example, the BNT results for the whole cohort are used. The K-power model ($K \geq 1$ to eliminate supralinearity) is the model choice, with $P_0 = 0.05$ and BMR = 0.05. Consistent with other uses of BMD, the 95% lower limit or BMDL is used as the point of departure for the RfD.

The result for the example calculation is a BMD of 85 ppb and a BMDL of 58 ppb; other BMDs and BMDLs are given in Table 4-8.

4.4 DOSE CONVERSION

The biomarker of choice for the Faroes data was cord blood and the BMDLs were presented in units of ppb mercury in cord blood. In order to calculate an RfD, it is necessary to convert this figure to an ingested daily amount that would result in exposure to the developing fetus at the BMDL level in terms of ppb mercury in blood. NRC (2000) offered advice on the use of these dose-conversion procedures.

4.4.1 PBPK Models Versus One-Compartment Model

In estimating the 1995 RfD, EPA used a one-compartment model. Since publication of the MSRC, there have been evaluations of the use of this model and the parameter inputs as well as the discussion of PBPK models for methylmercury. None of the existing models deal specifically with young children, nor are there data on methylmercury pharmacokinetics in children.

NRC briefly discussed the PBPK model published by Clewell et al. (1999). This model includes several fetal compartments that could be considered fetal submodels. NRC noted that this model is conceptually more accurate and flexible than the one-compartment model. The report also notes that the complexity of the model makes evaluation of it more problematic (NRC, 2000, p. 84). Moreover, given the state of the data on methylmercury exposure, it would be necessary to use default values for some model inputs. These factors add to the overall uncertainty in the use of this or any of the other available PBPK models for methylmercury. EPA has chosen to use the one-compartment model for dose conversion for this RfD. This model has shown reasonably good fit to data on mercury blood level changes in human subjects during and after consumption of methylmercury-contaminated fish (Ginsberg and Toal, 2000). It has been used by other public health agencies such as WHO and ATSDR (1999).

4.4.2 One-Compartment Model for Methylmercury

4.4.2.1 Description of Model

The model is described by the formula below:

$$d\ \mu g/day = \frac{c \times b \times V}{A \times f}$$

where

d = daily dietary intake (expressed as μg of methylmercury)
c = concentration in blood (expressed as μg/L)
b = elimination constant (expressed as $days^{-1}$)
V = volume of blood in the body (expressed as liters)
A = absorption factor (expressed as a unitless decimal fraction)
f = fraction of daily intake taken up by blood (unitless).

The following form of the equation expresses d in units of μg/kg body weight/day.

$$d = \frac{c \times b \times V}{A \times f \times bw}$$

where

bw = body weight (expressed in kg).

In this one-compartment model, all maternal compartments are compressed to one: namely, blood. It is assumed that the blood methylmercury concentration is at steady state. This assumption constitutes an area of uncertainty with the use of this model. One could either assume that the methylmercury concentrations of fetal blood and maternal blood are the same or adjust the cord-blood concentration to maternal levels using an empirically derived factor. There are some published indications that mercury in cord blood is higher than in maternal blood (for example, Dennis and Fehr, 1975: Pitkin et al., 1976; Kuhnert et al., 1981). Other publications show that there is no difference in concentration (for example, Fujita and Takabatake, 1977; Sikorski et al., 1989). EPA has chosen to assume that maternal blood mercury is at the same level as fetal or cord blood and acknowledges that this is an additional area of uncertainty in the dose conversion. This is discussed in Section 4.5.4.1.

4.4.2.2 Choice of Parameter Inputs—Distributions Versus Point Estimates

NRC presents an analysis of uncertainty and variability in the values to be used in the equation above (NRC, 2000, pp. 83-95). Although there are data from human studies that form the basis of the parameter estimates, it is clear that there is variability (and uncertainty) in these estimates. NRC notes that each of the model parameters is a random variable best described by a probability distribution. The ingested methylmercury concentration that leads to the benchmark cord-blood concentration is also a probability distribution determined by the combination of the distributions of the individual parameters. NRC cited two analyses of the variability and uncertainty in the ingested dose estimates based on the one-compartment model applied to maternal hair (Stern, 1997; Swartout and Rice, 2000) as well as similar analysis of a PBPK model (Clewell et al., 1999). Table 4-9 reproduces NRC's compilation of those analyses. In this table NRC also presented results of analyses that took maternal blood as the starting point, rather than maternal hair as was done in the published papers.

In 1995, EPA used central tendency estimates (or point estimates intended to reflect central tendency estimates) for all parameter inputs in the RfD dose conversion. Although this is a reasonable approach, it does not encompass the range of likely parameter values or the range of estimated ingestion values. The RfD is not intended to protect only the mid-part of a population, but the whole population including sensitive subgroups. Thus, if one chooses to use central tendency or point estimates in the dose

Table 4-9. Comparison of Results from Three Analyses of the Interindividual Variability in the Ingested Dose of MeHg Corresponding to a Given Maternal-Hair or Blood Hg Concentration

Study	Maternal medium	50th percentile[a] (μg/kg-d)	50th percentile/ 5th[b] percentile	50th percentile/ 1st percentile[c]
Stern (1997)	Hair	0.03-0.05[d] (mean = 0.04)	1.8-2.4 (mean = 2.1)	2.3-3.3 (mean = 2.7)
	Blood	0.01	1.5-2.2 (mean = 1.8)	1.7-3.0 (mean = 2.4)
Swartout and Rice (2000)	Hair	0.08	2.2	Data not reported
	Blood[e]	0.02	2.1	2.8
Clewell et al. (1999)	Hair	0.08	1.5	1.8
	Blood[f]	0.07	1.4	1.7

[a]Predicted 50th percentile of the ingested dose of methylmercury that corresponds to 1 ppm Hg in hair or 1 ppb in blood.
[b]Ratio of 50th percentile of ingested dose of methylmercury that corresponds to 1 ppm Hg in hair or 1 ppb in blood to the 5th percentile.
[c]Ratio of 50th percentile of ingested dose of methylmercury that corresponds to 1 ppm Hg in hair or 1 ppb in blood to the 1st percentile.
[d]Range reflects minimum and maximum values among eight alternative analyses.
[e]Data from J. Swartout, U.S. Environmental Protection Agency, personal commun.; June 9, 2000.
[f]Data from H.J. Clewell, ICF Consulting, personal commun.; April 19, 2000.

conversion, it is necessary to include a UF in the final RfD calculation to ensure that pharmacokinetic variability is appropriately factored into the consideration of sensitive subgroups.

The choice of UF can be informed by the analyses of variability presented by NRC. In general, all three analyses found similar ranges of variability due to pharmacokinetic factors. The ratios of estimated ingested doses at the 50th percentile/99th percentile ranged from 1.7 to 3.3. If one considers only the estimates using maternal blood as the starting point, then the range for all three studies is 1.7 to 3.0. NRC noted that variability was higher when maternal hair, rather than blood mercury was the biomarker used. In 1997, EPA identified the hair-to-blood ratio as a major contributor to the variability (and thus uncertainty) in estimating the ingested dose and in the RfD based on it. This provides an additional rationale for use of the cord-blood-based BMD.

In determining the methylmercury RfD, EPA chooses to use point estimates, rather than distributions, in the dose conversion and to account for uncertainty by application of a numerical UF. This UF considers the probability distribution that relates biomarker concentration and ingested dose (see Section 4.5). This approach was recommended in the NRC report. NRC notes that use of parameter distributions and an ingested dose distribution (the "direct approach") does not eliminate uncertainty. In the direct approach, one would select an ingested dose corresponding to a BMD blood mercury concentration for the percentile of the population variability that is to be accounted for; that is, one would select the 95th or 99th (or some other suitable) percentile. The choice must be made among probability distributions predicted by analyses such as those done by Stern (1997) and Swartout and Rice (2000). NRC said that "the differences in the analyses are due to the use of different data sets for parameter estimates, and there is no clear basis for choosing one data set over another. Even when central-tendency estimates and uncertainty factors are used, the most appropriate value for each model parameter must be selected. Selection of different values for model parameters could underlie differences in the modeling results" (NRC, 2000, pp. 94-95).

EPA chooses to make explicit choices for each dose-conversion parameter and to deal with both the uncertainty and variability implicit in those choices by the application of a UF in the calculation of the RfD.

4.4.2.3 Choice of Parameter Inputs—Values for One-Compartment Model Terms

NRC recommended (NRC, 2000, p. 95), that in choices of point estimates EPA should consider the information and analyses in three publications: Stern (1997), Swartout and Rice (2000), and Clewell et al. (1999). All are recent contributions to the peer-reviewed literature. In addition, Swartout and Rice (2000) largely comprises analyses that received extensive scientific review as part of the MSRC (U.S. EPA, 1997e). EPA found little in Clewell et al. (1999) that could be used directly to make parameter estimates, but rather used data and analyses from the other two papers. The rationales for use of specific values for equation parameters follow.

Concentration in blood (c)

The concentration in blood is that corresponding to the BMDL (58 ppb in the example). As noted above, no numerical change is made to account for any potential differences between maternal blood mercury level and cord-blood concentration.

Fraction of mercury in diet that is absorbed (A)

After administration of radiolabeled methylmercuric nitrate in water to three healthy volunteers, uptake was reported to be >95% (Aberg et al., 1969). This value is supported by experiments in human volunteers conducted by Miettinen et al. (1971). These researchers incubated fish liver homogenate with radiolabeled methylmercury nitrate to produce methylmercury proteinate. The proteinate was then fed to fish for a week; the fish were killed, cooked, and fed to volunteers after confirmation of methylmercury concentration. The authors reported that the fraction of the administered dose not excreted in the feces within 3 to 4 days ranged from 91.2% to 97.0% with a mean of 94%. This fraction was assumed to be the amount absorbed; it probably includes some inorganic mercury formed from the ingested methylmercury and subsequently excreted. Stern (1997) noted that this method is most likely to result in an underestimate. It is generally felt that absorption of ingested methylmercury is high and not likely to vary a great deal. Use of an absorption factor of 0.95 as was done in the MSRC is reasonable.

Fraction of the absorbed dose that is found in the blood (f)

The MSRC notes that in 1995 EPA used data from Kershaw et al. (1980), Miettinen et al. (1971), and Sherlock et al. (1984) as the basis for the choice of a value of 0.05 (U.S. EPA, 1997e).

There are currently four published reports of the fraction of absorbed methylmercury dose distributed to blood volume in humans. Kershaw et al. (1980) reported an average fraction of 5.9% of absorbed dose in total blood volume, based on a study of five adult male subjects who ingested methylmercury-contaminated tuna. In a group of nine male and six female volunteers who had received ^{203}Hg-methylmercury in fish, approximately 10% of the total mercury body burden was present in 1 L of blood in the first few days after exposure; this dropped to approximately 5% over the first 100 days (Miettinen et al., 1971). In another study, an average value of 1.14% for the percentage of absorbed dose per kg of blood was derived from data on subjects who consumed a known amount of methylmercury in fish over a 3-month period (Sherlock et al., 1984). Average daily intake in the study ranged from 43 to 233 μg/day, and there was a dose-related effect on percentage of absorbed dose that ranged from 1.03% to 1.26% in 1 L of blood. Smith et al. (1994) administered radiolabeled methylmercury to seven subjects. The paper presented published modeled data rather than observations; the mean fraction of absorbed dose in blood was 7.7% (SD, 0.88%).

Stern (1997) noted that although the Smith et al. (1994) and Kershaw et al. (1980) data could be fit by a log-normal distribution, the data sets were too small for a reasonable determination of the

underlying distributions. Stern used the mean and standard deviation of those two data sets for average parameter values as inputs to the log-normal distribution; the average of the means is 0.067. Swartout and Rice (2000) used the observations published by Kershaw et al. (1980), Miettinen et al. (1971), and Sherlock et al. (1984) as adjusted for 5 L of blood as inputs with a log-triangular distribution. The median value was 5.9% or 0.059, close to the values of 0.05 used in the MSRC and by other groups (e.g., Berglund et al., 1971, and WHO, 1990).

ATSDR (1999) used a factor of 0.05. They noted that estimates of f for the 6 women from the study by Sherlock et al. (1984) had an average value of 0.048, as compared with the value of 0.059 for the 14 men in the same study. ATSDR offered the opinion that these data suggest f may be lower for women than men. Apparently the study by Miettinen et al. (1971) included six female volunteers (in addition to nine males), though ATSDR did not comment on whether these data similarly provided any indication that the fraction daily intake taken up by blood was lower for females. It is not likely that any of the female subjects were pregnant. Sherlock et al. (1984) published a negative correlation between f and body weight; thus, if this is generalizable, one would expect f to decrease (as V increases) throughout pregnancy.

EPA chooses to use the median value of 0.059 published by Swartout and Rice (2000) for f in the dose conversion.

Elimination constant (b)

Currently, five studies report clearance half-times for methylmercury from blood or hair: Miettinen et al. (1971), Kershaw et al. (1980), Al-Shahristani et al. (1974), Sherlock et al. (1984), and Smith et al. (1994). The clearance half-lives for blood in these reports are quite variable, ranging from 32 to 189 days. In the Al-Shahristani et al. (1974) study, 10% of the sample population had mercury half-lives of 110 to 120 days. Average mercury half-lives from the five publications are 45 to 70 days. The MSRC (U.S. EPA, 1997e) used an average elimination constant from four of the studies (data from Smith et al. [1994] were not used). The corresponding elimination constant of 0.014 was also noted to be the average of individual values reported for 20 volunteers ingesting from 42 to 233 μg mercury/day in fish for 3 months (Sherlock et al., 1982).

Swartout and Rice (2000) applied a log-triangular distribution to the data from the five extant studies. They note that the distribution is highly skewed and that the median is 53 days; the corresponding elimination constant is 0.013.

Stern (1997) discussed the variability in the data sets. His analysis of variance indicated significant differences among the sets, which were eliminated when the Al-Shahristani data were removed. The author observed that the half-lives reported by Al-Shahristani are larger than those observed in the other studies. Stern offers the opinion that this may be due to the relatively large size of the Al-Shahristani data set by comparison to the others. Stern says that an alternative explanation is that the Al-Shahristani data reflect a genetic polymorphism in the metabolism occurring with higher frequency in the Iraqi population, which was the subject of this study. In his analyses, Stern (1997) treated the Al-Shahristani data both separately and in combination with the data from the other four studies. He reports a mean elimination constant of 0.011 for Al-Shahristani data alone; the combined data set mean elimination constant is 0.014.

The decision to select point estimates for dose conversion parameters was done with the acknowledgment that some of the variability around these parameters would be truncated. This is being compensated for by the use of a pharmacokinetic uncertainty factor. Nevertheless, it does not seem prudent to select a point estimate, which is meant to be reflective of population central tendency, from one data set only. The two central tendency estimates of Swartout and Rice (2000) and Stern (1997) are very close in value (0.013 versus 0.014); the differences are presumably due to the application of different distribution types. The value of 0.014 is used for *b* in the dose conversion.

Volume of blood in the body (V)

In the MSRC (U.S. EPA, 1997e), blood volume was estimated, as there were no data from the study population (the 81 pregnant women exposed in the poisoning episode in Iraq). It was noted then that blood volume is 7% of body weight, as determined by various experimental methods. MSRC assumed an increase of 20% to 30% (to about 8.5% to 9%) during pregnancy on the basis of the publication by Best (1961). Specific data for the body weight of Iraqi women were not found. Assuming an average body weight of 58 kg and a blood volume increase of 9% during pregnancy, a blood volume of 5.22 L was derived and was rounded to 5 L for the dose conversion.

Stern (1997) cited three studies (Brown et al., 1962; Retzlaff et al., 1969; Huff and Feller, 1956) wherein correlation of body weight and blood volume were demonstrated. All studies were of U.S. women, presumably not pregnant at the time of the study. The mean blood volumes for each study were 3.58 L, 3.76 L, and 3.49 L, respectively; the mean of the combined data set is 3.61 L. If one assumes a 30% increase in blood volume with pregnancy, this would be 4.67 L.

In their analysis, Swartout and Rice (2000) used data from a cohort of 20 pregnant Nigerian women (Harrison, 1966). Whole-blood volumes in the third trimester ranged from 4 to 6 L; the mean and median were both 5 L. Although 5 L is somewhat higher than the blood volume estimated from three studies of U.S. women, it is a reasonable value to use for *V*.

Body weight (bw)

The MSRC found no data on body weight for the study population and used a default value of 60 kg (rounded from 58) for an adult female (U.S. EPA, 1997e). Swartout and Rice (2000) in their distributional analysis used the body weight data collected on the cohort of 20 pregnant Nigerian women (Harrison, 1966); this was the data set that they used for blood volume. Body weight during the third trimester of pregnancy ranged from 49.5 kg to 73.9 kg, with a geometric mean of 55 kg. Stern (1997) used the Third National Health and Nutritional Survey (NHANES III) data for women 18 to 40 years old (National Center for Health Statistics, 1995). The mean weight was 66.6 kg and the 50th percentile value was 62.8 kg. The EPA Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (U.S. EPA, 2000a) also cites NHANES III data; in the Agency document, women of childbearing age were considered to be between the ages of 15 and 44 years old. The median body weight in this group was 63.2 kg and the mean was 67.3 kg. EPA also cites the earlier analyses of Ershow and Canter (1989); they do not state the age range but give a median of 64.4 kg and a mean of 65.8 kg. The recommendation in the EPA Methodology was to use a body weight value of 67 kg for a pregnant woman on the basis of the relatively current data from NHANES III. This is the value used for body weight in the dose conversion.

4.4.2.4 Dose Conversion Using the One-Compartment Model

The parameter values are as follows:

c = concentration in blood (expressed as 58 μg/L)
b = elimination constant (expressed as 0.014 $days^{-1}$)
V = volume of blood in the body (expressed as 5 L)
A = absorption factor (expressed as 0.95, unitless decimal fraction)
f = fraction of daily intake taken up by blood (0.059, unitless)
bw = body weight (expressed as 67 kg)

$$d = \frac{c \times b \times V}{A \times f \times bw}$$

$$d = \frac{58\ \mu g/L \times 0.014\ days^{-1} \times 5L}{0.95 \times 0.059 \times 67\ kg}$$

$$d = 1.081\ \mu g/kg\text{-}day$$

rounded to 1.0 μg/kg/day. Other BMDLs expressed as ingested maternal dose can be found in Table 4-8.

4.5 CHOICE OF UNCERTAINTY FACTOR

4.5.1 Background

The RfD can be considered a threshold for a population at which it is unlikely that adverse effects will be observed. In estimating this level from either a NOAEL or a BMD, the risk assessor applies uncertainty factors; these are used to deal with both experimental and population variability and with lack of information that results in uncertainty in the risk estimate. For a discussion of uncertainty factors, refer to the Technical Support Document for Risk Assessment, Human Health Methodology for Ambient Water Quality Criteria (U.S. EPA, 2000g).

In the MSRC, EPA published qualitative discussions and quantitative analyses of uncertainty and variability in the RfD based on the Iraqi data (U.S. EPA, 1997e,g). Major sources of uncertainty identified were these: variability in susceptibility within the study cohort, variability in pharmacokinetic parameters for methylmercury (particularly biological half-life of methylmercury and the hair-to-blood ratio for mercury), response classification error, and lack of data on long term sequelae of *in utero* exposure. At that time a composite UF of 10 was applied to account for these factors and the EPA policy choice to use a UF in the absence of a two-generation reproductive bioassay.

NRC considered areas of uncertainty and variability relevant to the generation of an RfD based on data from the Faroes population and given the current state of the databases on both pharmacokinetics and effects of methylmercury. The panel concluded that not all sources of uncertainty or variability require addition of numerical UFs. NRC (NRC, 2000, p. 319) suggests that given the state of the human data on methylmercury, UFs be considered for two reasons:

- If the uncertainty could result in underestimation of the adverse effects of methylmercury exposure on human health.

- If there is reason to suspect that the U.S. population is more sensitive than the study populations to the adverse effects of methylmercury.

NRC's recommendation was that a UF of at least 10 be applied to a BMD calculated from the BNT results from the Faroe Islands study (NRC, 2000, pp. 321-322). EPA is in general agreement with NRC's conclusions and recommendations and considered them in the choice of the numerical UF. EPA's choice is to consider the RfD to be based on the group of Faroese neuropsychological measures associated with cord-blood mercury; the areas of uncertainty and variability are the same for the choice of one test result (e.g., BNT whole cohort) or the group of test results. Descriptions of areas of uncertainty and variability and choice of UF are in the following sections.

4.5.2 Toxicodynamics

Individual response to methylmercury can vary as a function of many factors: age, gender, genetic makeup, health status, nutritional influences (including interaction among dietary components), and general individual toxicodynamic variability. Individual sensitivity has been noted in the published human studies; NRC cited the example of members of the Iraqi population who seemed insensitive to high levels of mercury exposure. EPA believes there are insufficient data to conclude that the U.S. population is more or less sensitive than the reported human study populations. The U.S. population is extraordinarily diverse by any measures listed above, certainly by comparison to the Faroese population. The Faroese population is northern Caucasian, has been relatively isolated, and is thought to be descended from a small number of so-called founders who settled the islands many generations ago. In the heterogeneous U.S. population, it is entirely likely that there are individuals both more and less sensitive to methylmercury toxicity than the cohort studied in the Faroes. As the RfD must be calculated to include sensitive subpopulations, variability in response to mercury is a consideration. EPA believes there are insufficient data to support a quantitative analysis of this area of variability and uncertainty for methylmercury, but that toxicodynamic variability must be considered in the determination of the overall uncertainty factor.

4.5.3 Exposure Estimation as an Area of Uncertainty

Limitations in evaluation of exposure can be an additional source of uncertainty. As the RfD is based on a developmental outcome, there is particular concern for uncertainty in the linkage between time and intensity of exposure and critical periods of brain development. As noted before, cord-blood mercury generally reflects mercury exposure during late pregnancy and does not reflect temporal variability in exposure level. Use of any biomarker of methylmercury exposure can result in misclassification of exposure. Generally, exposure misclassification presents a bias to the null; that is, this source of error leads to decreased ability to detect a real effect. To the degree that there is exposure misclassification in the critical study, it would be expected to result in underestimation of the methylmercury effect. At this time there are not data to support a quantitative determination of this area of uncertainty.

4.5.4 Pharmacokinetic Variability

4.5.4.1 Cord:Maternal Blood Ratios

In its use of the one-compartment model for dose conversion, EPA chose to make no adjustment for potential differences between fetal and maternal blood mercury levels. Investigators have found that the placenta is not a barrier to the transfer of methylmercury from the mother to the developing fetus. Typically, there is a strong correlation between maternal blood mercury concentrations and fetal blood mercury concentrations, as shown by cord blood.

Review of the literature identified 21 studies that reported cord blood mercury and maternal blood mercury data (Amin-Zaki et al., 1974; Baglan et al., 1974; Dennis and Fehr, 1975; Pitkin et al., 1976; Kuhnert et al., 1981; Nishima et al., 1977; Lauwerys et al., 1978; Fujita and Takabatake, 1977; Kuntz et al., 1982; Tsuchiya et al., 1984; Truska et al., 1989; Sikorski et al., 1989; Hansen et al., 1990; Soong et al., 1991; Soria et al., 1992; Ong et al., 1993; Akagi et al., 1997; Yang et al 1997; Ramirez et al., 2000; Bjerregaard and Hansen, 2000; Vahter et al., 2000). Twenty of the studies provided data in a format that could be compared with one another. The exception is Truska et al. (1989), whose published data were based on erythrocyte mercury concentrations without reported hematocrit values. Absence of these values precluded expressing mercury concentration on a μg/L or ppb whole-blood basis.

Data from 18 of the 20 studies (with a combined total of 2,676 maternal and 2,522 cord-blood samples) indicated that cord-blood mercury concentration exceeded maternal-blood mercury

concentration. Mean values ranged from a ratio of 1.04 (Fujita and Takabatake, 1977) to 2.63 (Amin-Zaki et al., 1974); the average of mean ratios was 1.55. Two studies reported cord:maternal blood ratios equal to or less than 1. Kuntz et al. (1982) (based on 57 maternal-cord blood pairs) and Sikorski et al. (1989) (based on 56 maternal-cord blood pairs) reported cord/maternal blood mercury concentration of 1.0 and 0.83, respectively.

Speciated mercury measurements were performed in 9 studies that included 550 maternal and 526 cord-blood samples. This permitted calculation of the ratios of cord blood methylmercury:maternal blood methylmercury that are presented in Table 4-10. In all nine studies, the mean values for methylmercury concentration was higher for cord blood than maternal blood. The number of subjects in these 9 studies ranged from 9 to 226 pregnant woman-fetal pairs. To deal with this variation in *n*, Table 4-10 reports both a simple average of mean ratios (cord methylmercury:maternal methylmercury = 1.68) and the mean ratio weighted by the number of subjects in the study (ratio =1.73).

Overall, these data indicate that cord-blood mercury is higher than maternal-blood mercury. The composite ratio from the studies reporting methylmercury concentrations indicates that the cord blood:maternal blood ratio is around 1.7. These values are ratios of means and do not reflect the full range of variability in the individual mother-fetal pairs. Vahter et al. (2000 reported the 5^{th} and 95^{th} percentiles of cord:maternal Hg to be 0.88 and 3.1. Individual data were available from Fujita and Takabatake (1997); ratios calculated from these data ranged from 0.78 to 4.36.

As indicated in Section 4.4.2.1, EPA chooses not to make a numerical adjustment between cord-blood and maternal-blood mercury. Such an adjustment factor would best be calculated after evaluation of data quality and variability within and between studies. EPA feels that this analysis would be an important contribution to reducing uncertainty in the RfD. At this time the relationship between cord blood and maternal-blood mercury is considered an area of uncertainty to be included in the determination of the UF.

Table 4-10. Ratio of Cord to Maternal Blood Methylmercury

Investigator	Number of Subjects	Ratio of Cord:Maternal Blood
Nishima et al., 1977	49 maternal, 49 fetal	2.17
Kuhnert et al., 1981	29 maternal, 29 fetal	1.34
Tsuchiya et al., 1984	226 maternal, 226 fetal	1.60
Hansen et al., 1990	37 maternal, 37 fetal	2.11
Soria et al., 1992	19 maternal, 19 fetal	1.08
Ong et al., 1993	29 maternal, 29 fetal	1.65
Akagi et al., 1997	21 maternal, 21 fetal	1.75
Yang et al., 1997	9 maternal controls, 9 fetal controls; 9 occupationally exposed mothers, 9 occupationally exposed fetuses.	1.67 - controls 1.39 - occupationally exposed
Vahter et al., 2000	112 maternal (gestation week 36), 98 fetal	1.92
Arithmetic mean of average ratios of cord:maternal methylmercury		1.68
Mean weighted by number of subjects for cord:maternal blood methylmercury		1.73

4.5.4.2 Other Areas of Pharmacokinetic Variability

There is no specific evidence of genetic polymorphisms that affect methylmercury metabolism or excretion. Human studies have established, however, that there is great variability in some of the factors affecting the delivery of ingested methylmercury to target organs. The MSRC sensitivity analysis and the publication by Swartout and Rice (2000) noted that the greatest variability resided in the hair:blood ratio (not a factor in the current dose conversion), the fraction of absorbed methylmercury found in blood (*f*), and the half-life of methylmercury in blood (the reciprocal, *b*, in the current dose conversion).

NRC presented an analysis of methods of ingested dose reconstruction from biomarker measurements. NRC noted that cord-blood mercury is closely linked kinetically to the fetal brain compartment but less closely linked to ingested dose. As described in Section 4.4.2 of this document, EPA chose a one-compartment model and measures of cord-blood mercury for back-calculation of the ingested dose of mercury. EPA also chose to use central tendency estimates for the parameters of the one-compartment model, rather than introduce an additional degree of uncertainty inherent in making choices of distribution shapes and the portion of the distribution that represents a sensitive population.

NRC presented analyses of uncertainty around dose-conversion estimates, which are summarized in Table 4-9 in Section 4.5.2.2. NRC discussed three independent analyses to characterize toxicokinetic variability in estimates of ingested dose corresponding to a BMD level in a particular biomarker, whether maternal hair or cord blood (NRC, 2000, pp. 91-95). These analyses were published by Stern (1997), Swartout and Rice (2000, after their work on EPA 1997), and Clewell et al. (1999). Each analysis used Monte Carlo simulation to combine probability distributions for each parameter of the model. For Stern (1997) and Swartout and Rice (2000), this was the one-compartment model shown in Section 4.4.2.1. Clewell et al. (1999) used a PBPK model with a fetal submodel. The analyses of the one-compartment model were done in a similar fashion; distributions for model parameters were determined from the published literature, and shapes of the distributions were set by the authors. Both analyses assumed correlations between some model parameters. Stern (1997) assumed that blood volume and body weight were correlated. Swartout and Rice (2000) made that assumption, as well as these correlations: hair-to-blood ratio and elimination rate constant, and fraction of absorbed dose in blood and body weight. The analysis based on the PBPK model also used parameter distribution values from the literature but included many more parameters than the one-compartment model (and more default distributions for model parameters).

The three published analyses all took maternal hair mercury as their starting point. NRC asked all three sets of authors to provide analyses of variability that used maternal blood as the starting point (as a surrogate for cord blood). These analyses were done by removing the hair:blood ratio from the model and running the Monte Carlo simulations.

Table 4-9 presents median estimates of ingested dose corresponding to 1 ppm maternal hair or 1 ppb maternal blood. Useful points of comparison are the ratios between the 50th percentile estimates and those at the end of the distribution (5th and 1st percentiles). Table 4-9 shows that using maternal blood as a starting point, the ratios of 50th percentile:1st percentile estimates ranges from 1.7 to 3.0. EPA's interpretation is that a factor of 3 will cover the toxicokinetic variability of 99% of the population. The uncertainty introduced by assuming cord-blood mercury is equivalent to maternal mercury provides additional justification for a toxicokinetic UF of 3. The choice of a factor of 3 is consistent with the standard EPA practice of a using a half-log to account for toxicokinetic variability.

4.5.5 Uncertainty in Choice of Critical Effect

Another critical area discussed by NRC is uncertainty around choice of a critical effect. NRC notes that developmental neurotoxicity is a sensitive indicator of methylmercury toxicity but that there is some

uncertainty as to the likelihood of other effects occurring at even lower levels of exposure. They cite indications of cardiovascular effects as well as neurotoxic effects uncovered later in life.

EPA agrees that there is a degree of uncertainty in our choice of critical effect; EPA believes this is not currently amenable to quantitative estimation but must be considered in the setting of the uncertainty factor. Summarized below are observations that support a concern that developmental neurotoxicity may not be the most sensitive indicator of methylmercury effects.

4.5.5.1 Cardiovascular Effects

There are some human data linking cardiovascular effects with exposure to elemental, inorganic, and organic forms of mercury. In addition, there are two recently published studies that show an association between low-level methylmercury exposure and cardiovascular effects. Sørensen et al. (1999) reported that in a study of 1,000 7-year-old Faroese children, diastolic and systolic blood pressures increased by 13.9 and 14.6 mm Hg, respectively, as the cord-blood mercury increased from 1 to 10 μg/L. They also reported a 47% decrease in heart rate variability (an indication of cardiac autonomic control) for the same increase in cord-blood mercury. Salonen et al. (1995) reported effects in adults from a study of 1,833 Finnish men. Over the 7-year observation period, men with hair mercury in the highest tertile (2 ppm or higher) had a 2.0 times greater risk of acute myocardial infarction than the rest of the study population.

As indicated by the Salonen (1995) study, the relatively subtle effects of methylmercury on cardiovascular indices can have public health implications. There is an analogous situation with lead exposure. Pirkle et al. (1985) reported on analyses of NHANES II data comparing the relationship between systolic and diastolic blood pressure to blood lead levels. They included in their model the 37% decrease in mean blood lead levels that was observed in white adult males between 1976 and 1980. Their calculation predicted a 4.7% decrease in the incidence of fatal and nonfatal myocardial infarction over 10 years, a 6.7% decrease in the incidence of fatal and nonfatal strokes over 10 years, and a 5.5% decrease in the incidence of death from all causes over 11.5 years.

4.5.5.2 Persistent and Delayed Neurotoxicity

Another area of concern is the onset or exacerbation of neurological deficits in aging populations exposed *in utero* or as children. There are indications of this in the followup studies of the Minamata population. These present evidence that neurological dysfunction among people who have been exposed

to methylmercury becomes more pronounced with aging. This heightened diminution of function is greater than that attributable to either age or methylmercury exposure alone. Specifically, Kinjo et al. (1993) surveyed 1,144 current patients with Minamata disease (MD) aged 40 or over and an equal number of neighbor controls matched by age and sex. MD patients have symptoms of sensory disturbance at a high prevalence rate (e.g., hypoesthesia of mouth, ~20% to 29% of subjects; hypoesthesia of limbs, ~66% to 90% of subjects; dysesthesia of limbs, ~83% to 93%; weakness, ~75% to 84%), but these problems did not systematically increase with age. However, the MD patients did show, as a function of age, increased difficulties in speaking, tremor, stumbling, and difficulties with buttoning, clothing, or hearing. Although such changes also occurred among controls, evaluation of odds ratios showed that the MD patients had higher prevalence rates than the controls for 18 separate problems including those specifically listed above. Also evaluated were "acts of daily living" (ADL) that included the abilities to independently eat, bathe, wash, dress, and use the toilet. Among subjects under age 60 there were no significant differences in ADL abilities between MD patients and controls. However, among patients aged 60 or greater there were significantly lower ADL abilities among MD patients than among age-matched controls. A conclusion of the Kinjo et al. study is that the prevalence of deficits was relatively greater in cases compared with controls as a function of increasing age. In other words, exposure to methylmercury three decades earlier accelerated the aging process in aged individuals relative to younger ones.

There has also been evaluation of the health status of people living in methylmercury-polluted areas who were not designated as MD patients. Later followup by Fukuda et al. (1999) evaluated 1,304 adults who lived in a methylmercury-polluted area near Minamata City in Kumamoto Prefecture in Japan (but were not designated MD patients) and 446 age-matched adults in a non-mercury-polluted area of Japan. All subjects were older than 40 years of age. A questionnaire survey evaluated 64 complaints that could be grouped as nonspecific, sensory, arthritic, and muscular. Complaints identified among male and female subjects that were significantly higher in methylmercury-contaminated areas included heart palpitation, dysesthesia, staggering when standing, resting and intention tremor in the hands, dizziness (especially when standing), low-tone tinnitus, low pain sensation in hands and legs, and (among women only) loss of touch sensations in hands and legs.

Animal studies lend support to the conclusion that methylmercury can have delayed effects that are uncovered with age. Spyker (1975) exposed mice during gestation and lactation to methylmercury. Offspring noted to be normal at birth developed deficits in exploratory behavior and swimming ability at 1 month; neuromuscular and immune effects were noted as the animals reached 1 year of age. Rice (1989a) exposed monkeys to 50 μg/kg/day methylmercury for the first 7 years of life. The animals were

observed with motor incoordination only when they reached the age of 14; subsequent testing showed effects on somatosensory functioning (Rice and Gilbert, 1995). Rice (1998) also exposed monkeys *in utero* and for the first 4 years. Exposure to 10 to 50 μg/kg/day was observed to result in decreased auditory function compared with controls when the animals were tested at 11 and 19 years. The deficit at 19 years was relatively greater than at 11 years, providing evidence for an interaction of aging and methylmercury exposure on auditory impairment. Rats exposed to methylmercury *in utero* through 16 days of age exhibited a decline in performance in a task that required a substantial motor output at an earlier age than did control rats; high-dose rats exhibited a decline in performance at about 500 days of age compared with 950 days for controls (Newland and Rasmussen, 2000), with no differences between groups in survival time. All of these observations are consistent with a hypothesis that early life or *in utero* exposure to methylmercury can have adverse long-term sequelae that may not be detected in childhood.

4.5.5.3 Reproductive Effects

EPA has a concern for potential reproductive effects of methylmercury. There are no studies of reproductive deficits in humans exposed to low-dose methylmercury. Bakir et al. (1973) did comment on the low number of pregnant women in the Iraqi population exposed to methylmercury in treated grain. They noted that among the 6,350 cases admitted to the hospital for toxicity, they would have expected 150 pregnancies; only 31 were reported. There are no two-generation reproductive assays for methylmercury. Shorter term studies in rodents and guinea pigs have reported effects including low sperm counts, testicular tubule atrophy, reduced litter size, decreased fetal survival, resorptions, and fetal malformations (Khera, 1973; Lee and Han, 1995; Hughes and Annau, 1976; Fuyuta et al., 1978, 1979; Hirano et al., 1986; Mitsumori et al., 1990; Inouye and Kajiwara, 1988). Burbacher et al. (1988) reported decreased conception rates, early abortions, and stillbirths in *Macaca fascicularis* monkeys treated with methylmercury hydroxide; the NOAEL for this study was 0.05 mg/kg/day. In a study of male *Macaca fascicularis* (Mohamed et al., 1987), a LOAEL for sperm abnormalities was 0.05 mg/kg/day.

The MSRC did an evaluation of the potential for methylmercury to be a germ-cell mutagen. Methylmercury is clastogenic but does not appear to cause point mutations. Methylmercury is widely distributed in the body, crossing both blood–brain and placental barriers in humans. Data indicate that methylmercury administered intraperitoneally. reaches germ cells and may produce adverse effects. When Suter (1975) mated female mice to treated males, he observed a slight reduction in both numbers of implantations and viable embryos; this was true for one mouse strain but not for another tested at the

same time. When Syrian hamsters were treated intraperitoneally with methylmercury, aneuploidy but not chromosomal aberrations was seen in oocytes (Mailhes, 1983). Sex-linked recessive lethal mutations were increased in *Drosophila melanogaster* given dietary methylmercury (Ramel, 1972). Watanabe et al. (1982) noted some decrease in ovulation in hamsters treated subcutaneously with methylmercury, further indication that methylmercury is distributed to female gonadal tissue. Studies have reported increased incidence of chromosome aberrations (Skerfving et al., 1970, 1974) or sister chromatid exchange (Wulf et al., 1986) in lymphocytes of humans ingesting mercury-contaminated fish or meat. Chromosome aberrations have been reported in cats treated in vivo and in cultured human lymphocytes in vitro. Evidence of DNA damage has been shown in a number of in vitro systems. The MSRC (U.S. EPA 1997e) concluded that because there are data for mammalian germ-cell chromosome aberrations and limited data from a heritable mutation study, methylmercury is placed in a group of high concern for potential human germ-cell mutagenicity. The only factor keeping methylmercury from the highest level of concern is lack of positive results in a heritable mutation assay.

In summary, there is increasing weight of evidence for effects other than neurodevelopmental that may be associated with low-dose methylmercury exposure.

4.5.6 Choice of Uncertainty Factor

For this methylmercury RfD the two major areas of uncertainty that can be addressed with a UF are interindividual toxicokinetic variability in ingested dose estimation and pharmacodynamic variability and uncertainty. For the former, EPA relied in part on the NRC analyses of variability in the pharmacokinetic factors underlying the conversion of a biomarker level of methylmercury to an ingested daily dose of methylmercury that corresponds to that level. We chose not to make a numerical adjustment in the dose conversion for the potential differences in cord vs. maternal blood mercury level, but rather consider this an additional area of toxicokinetic uncertainty. A quantitative uncertainty analysis was not feasible for toxicodynamics. A common practice is to apply a threefold UF for toxicodynamic variability and uncertainty.

In the calculation of this methylmercury RfD, a composite UF of 10 is used. This is to account for the following factors:

- Pharmacokinetic variability and uncertainty in estimating an ingested mercury dose from cord blood. A factor of 3 is applied for this area.

- Pharmacodynamic variability and uncertainty. A factor of 3 is applied for this area.

There are additional areas of concern in this risk estimate that lend support to an overall factor of 10. These include the following: inability to quantify long-term sequelae, lack of a two-generation reproductive effects assay, and issues on selection of critical effect (concern that there may be observable methylmercury effects at exposures below the BMDL). Section 4.5.5 discusses some of the concerns on selection of the critical effect. In this context one must also consider the analyses of the Faroese neuropsychological data wherein the observations in the most highly exposed subgroup were excluded from the model. Associations remained significant when the part of the cohort with maternal hair mercury concentrations greater than 10 ppm was excluded from the analyses. This indicates that it would be reasonable to expect some percentage of the population to show effects at or below 10 ppm hair mercury or at levels at or below 40 ppb cord blood. Given the overall robustness of the methylmercury database, but in consideration of the above areas of uncertainty, a composite factor of 10 is warranted.

4.6 CALCULATION OF THE RfD

The critical endpoint is drawn from the series of neuropsychological test results reported from the Faroese cohort. The BMDLs calculated on these endpoints are in Table 4-8. The ingested doses in μg/kg bw/day that correspond to the BMDLs range from 0.447 to 1.92. The ingested dose for the BNT whole-cohort BMDL is 1.081 μg/kg bw/day, rounded to 1.0 μg/kg bw/day.

For methylmercury, the RfD is calculated as follows:

$$RfD = \frac{BMD}{UF \times MF}$$

$$= \frac{1.0\ \mu g/kg-day}{10}$$

$$= 1 \times 10^{-4}\ mg/kg-day$$

= 0.1 $\mu g/kg/day$.

As shown in Table 4-5, an RfD of 0.1 μg/kg bw/day reflects the range of neuropsychological test results in the Faroese children exposed *in utero*. These test scores are all indications of neuropsychological processes that are involved with the ability of a child to learn and process information. In the studies so far published on subtle neuropsychological effects in children, there has been no definitive separation of prenatal and postnatal exposure that would permit dose-response modeling. That is, there are currently no data that would support the derivation of a child (vs. general population) RfD. This RfD is applicable to lifetime daily exposure for all populations including sensitive subgroups. It is not a developmental RfD per se, and its use is not restricted to pregnancy or developmental periods.

5.0 EXPOSURE ASSESSMENT

5.1 OVERVIEW OF RELATIVE SOURCE CONTRIBUTION ANALYSIS

When a water quality criterion is based on noncarcinogenic effects, anticipated exposures from sources other than drinking water and fish ingestion are taken into account so that the entire RfD is not attributed to drinking water and freshwater/estuarine fish consumption alone. The amount of exposure attributed to each source compared with total exposure is called the relative source contribution (RSC) analysis. The RfD used in calculating the criterion incorporates the RSC to ensure that the criterion is protective enough, given the other anticipated sources of exposure. The method of accounting for nonwater exposure sources is described in more detail in the revised 2000 Human Health Methodology (U.S. EPA, 2000a).

The method of determining the RSC differs depending on several factors, including (1) the magnitude of total exposure compared with the RfD, (2) the adequacy of the exposure data available, (3) whether more than one guidance or criterion is to be set for a contaminant, and (4) whether there is more than one significant exposure source for the chemical and population of concern. The population of concern for methylmercury is discussed in Section 5.2. The sources of exposure to methylmercury and estimates of exposure used to determine the RSC for the identified population are discussed in Sections 5.3 through 5.4. Section 5.5 summarizes the exposure uncertainties based on data adequacy. Finally, Section 5.6 provides the RSC estimates for methylmercury.

5.2 POPULATION OF CONCERN

Methylmercury is a highly toxic contaminant that can cause a variety of adverse health effects. Toxicity has been observed in adults exposed through consumption of contaminated food. Toxic effects and subtle neuropsychological effects have been seen in children exposed *in utero* when their mothers consumed contaminated food while pregnant. The RfD (see section 4) is based on changes in neuropsychological measures in children exposed *in utero*. The choice was made to use a developmental endpoint, as this appeared to be the most sensitive indicator of a methylmercury effect. As discussed in section 4, there is concern that other less-studied effects may occur at lower doses. There is also concern (based on recent reports on the Minamata, Japan, population) that exposure *in utero* or in childhood could result in subtle impairments that would not be detectable until middle age or older.

The RfD for methylmercury was not calculated to be a developmental RfD only. It is intended to serve as a level of exposure without expectation of adverse effects when that exposure is encountered on a daily basis for a lifetime.

In the studies on subtle neuropsychological effects in children published so far, there has been no definitive separation of prenatal and postnatal exposure that would permit dose-response modeling. That is, there are currently no data that would support the derivation of a child RfD versus a general population RfD.

Therefore, the population at risk evaluated for the methylmercury criterion is adults in the general population, not only the developing fetus or child.

5.3 OVERVIEW OF POTENTIAL FOR EXPOSURE

The sources and fate of methylmercury are discussed in detail in Volume III of the *Mercury Study Report to Congress* (MSRC) (U.S. EPA, 1997b). The MSRC exposure assessment is in Volume IV (U.S. EPA, 1997c). A brief summary of the information in that document is presented here. Methylmercury occurs naturally in the environment. It is readily produced from inorganic mercury in fresh and marine surface waters and sediments through the methylating action of certain microorganisms. Bacterial methylation rates appear to increase under anaerobic conditions, elevated temperatures, and low pH. Methylmercury generally constitutes no more than 25% of the total mercury in surface water; typically, less than 10% is observed (U.S. EPA, 1997b). According to the MSRC, mercury cycles in the environment as a result of natural and anthropogenic activities. Most of the mercury in the atmosphere is elemental mercury vapor, which can remain there for as much as 1 year and, due to atmospheric mobilization, can be widely dispersed and transported thousands of miles from likely sources of emission (U.S. EPA, 1997b). However, the MSRC also clearly states that methylmercury is the chemical species of concern due to its fate and transport to waterbodies and sediments, and its subsequent bioaccumulation in the aquatic food web.

Because the source of most mercury is deposition from atmospheric mercury emissions, ingestion is an indirect route of exposure. The MSRC included numerous computer-simulated estimates of mercury exposure for selected population scenarios, based on fate and transport models (see U.S. EPA, 1997b,c). These are summarized throughout this chapter in the *Predicted Concentrations* subsections. Further exposure assessment information is presented in Volumes III and IV of the MSRC (U.S. EPA, 1997b,c)

and a characterization of human health from methylmercury exposure is discussed in detail in Volume VII (U.S. EPA, 1997g). That exposure assessment information is summarized throughout this chapter. The primary source of human exposure to methylmercury is through consumption of contaminated fish and seafood. This reflects the tendency of aquatic organisms to rapidly absorb methylmercury and to store it for long periods of time in their muscle tissue, thus accumulating it to levels that are potentially toxic to humans who eat fish and shellfish. The concentrations of methylmercury in fish tissue are highly variable across water bodies. Within a water body, methylmercury concentration generally increases with fish size and trophic level.

Derivation of the water quality criterion requires that intake of methylmercury from other sources of exposure be evaluated for comparison with intake from water and/or freshwater and estuarine fish. In addition to its occurrence in water and freshwater and estuarine fish, methylmercury occurs in soil, air, marine fish and other seafood, and nonfish foods. Intake of these media thus represent potential pathways for exposure. Other potential routes include occupational exposure and erosion of dental amalgams. Estimates of intake from these sources are presented in Section 5.4 below. Assessment of these sources of methylmercury clearly indicates that substantially all exposure to methylmercury occurs from the ingestion of contaminated fish. The other sources of exposure (water, nonfish foods, air, and soil) are all several orders of magnitude less than exposures from fish consumption.

5.4 ESTIMATES OF OCCURRENCE AND EXPOSURE FROM ENVIRONMENTAL MEDIA

This section reports data available for the estimation of methylmercury intake from relevant exposure sources. Exposure may occur from several environmental sources including soil, sediment, ambient surface water, drinking water, food products, and air. Human exposures are estimated by combining information on the occurrence of methylmercury in environmental media with intake rates for these media. Information on intake assumptions, environmental concentrations, and estimated exposure are reported by medium below.

Table 5-1. Exposure parameters used in derivation of the water quality criterion

Parameter	Population			Source
	Children (0-14 years)	Women of Childbearing Age (15-44 years)	Adults in the General Population	
Body Weight, kg	30	67	70	U.S. EPA (2000a)
Drinking Water Intake, L/day	1.0	2.0	2.0	U.S. EPA (2000a)
Freshwater/Estuarine Fish Intake, gm/day	156.3[b]	165.5[b]	17.5[c]	U.S. EPA (2000a)
Inhalation, m^3/day	10.4	11	20	U.S. EPA (1994, 1997h)[d]
Soil Ingestion, g/day	0.0001, 0.01[a]	0.00005	0.00005	U.S. EPA (1997h)
Mean Marine Fish Intake, kg/day	74.9[b]	91.04[b]	12.46[c]	U.S. EPA (2000b)
Median Marine Fish Intake, kg/day	59.71[b]	75.48[b]	0[c]	U.S. EPA (2000b)
90^{th} Percentile Marine Fish Intake, g/day	152.29[b]	188.35[b]	49.16[c]	U.S. EPA (2000b)

[a]Pica child soil ingestion
[b]For children and women of childbearing age, intake rates are estimates of "consumers only" data (as described in U.S. EPA, 2000b).
[c]For adults in the general population, intake rates are estimates of all survey respondents to derive an estimate of long-term consumption (U.S. EPA).
[d]Inhalation rates for children and women of childbearing age from U.S. EPA, 1997h. Inhalation rates for adults in the general population from U.S. EPA (1994).

5.4.1 Exposure Intake Parameters

Exposure parameters selected for derivation of the water quality criterion should reflect the population to be protected. Default values for most exposure parameters are provided in the 2000 Human Health Methodology (U.S. EPA, 2000a). Where necessary, values for parameters not specified in the Methodology were obtained from the Exposure Factors Handbook (U.S. EPA, 1997h). Parameter values used to estimate intake of methylmercury by children aged 0-14 years, women of childbearing age, and adults in the general population are summarized in Table 5-1.

5.4.2 Intake from Drinking Water/Ambient Water

In cases where the water quality criterion is based on fish intake only, drinking water intake is accounted for as a separate exposure. In these instances, information on treated drinking water, if available, is the relevant information to use when accounting for other sources of exposure. Measured concentrations for methylmercury in drinking water and raw surface and ground source waters have been reported in the MSRC (U.S. EPA, 1997c). Predicted concentrations and ingestion rates summarized in this section are based on computer simulation models described in Volume IV of the MSRC (U.S. EPA, 1997c).

5.4.2.1 Measured Concentrations in Water

Raw Surface Water. Studies in the United States and Europe suggest that the concentrations of methylmercury in raw surface water are highly variable (U.S. EPA, 1997b). Properties reported to influence the levels of methylmercury in water bodies include proximity to a point source of mercury, pH, anoxia, dissolved organic carbon, and the presence of wetlands (U.S. EPA, 1997b). Estimates of the percent of total mercury in surface waters that exists as methylmercury are available from a number of studies. The available data suggest that methylmercury generally constitutes less than 20% of the total mercury in the water column (Kudo et al., 1982; Parks et al., 1989; Bloom and Effler, 1990; Watras et al., 1995a). In lakes without point source discharges, methylmercury frequently constitutes 10% or less of total mercury in the water column (Lee and Hultberg, 1990; Bloom et al., 1991; Lindqvist, 1991; Porcella et al., 1991; Watras and Bloom, 1992; Driscoll et al., 1994, 1995; Watras et al., 1995b). U.S. EPA (1997b) reported the use of Monte Carlo simulation to derive a point estimate of 0.078 for the fraction of total mercury present as methylmercury in the epilimnion (water column above the thermocline) of lakes for the purpose of estimating a bioaccumulation factor (BAF) for trophic level 4. Speciation data used as input for the simulation are shown in Table 5-2.

Data for measured concentrations of methylmercury and total mercury in ambient water as presented in the MSRC (U.S. EPA, 1997b) are summarized in Table 5-3. Since publication of the MSRC, Krabbenhoft et al. (1999) reported concentrations of total mercury and methylmercury in surface water samples collected as part of a U.S. Geological Survey (USGS) national scale pilot study to examine relations for total mercury and methylmercury in water, sediment, and fish. Water samples were collected in the summer and fall of 1998 at 106 sites from 21 basins across the United States, including Alaska and Hawaii. The sampling sites spanned the dominant east-to-west mercury deposition gradient

Table 5-2. Data Used in the Monte Carlo Simulation to Estimate the Fraction of Total Dissolved Mercury in the Epilimnion Present as Methylmercury

Fraction of Total Mercury Present as Methylmercury	Location	Reference
0.046	Pallette Lake, WI	Bloom et al. (1991)
0.054	Oregon Pond, NY	Driscoll et al. (1995)
0.059	Lake Michigan	Mason and Sullivan (1997)
0.089	Clear Lake, CA	Suchanek et al. (1993)
0.089	Onondaga Lake, NY	Henry et al. (1995)
0.092	Iso Valkjarvi, Finland	Rask and Verta (1995)
0.15	22 lake aggregate, WI	Watras et al. (1995a,b)

Source: U.S. EPA (1997c, Appendix D)

and represented a wide range of environmental settings. The study authors reported that most (number not reported) samples were collected from streams. Total mercury was measured using U.S. EPA Method 1631 with detection by cold vapor atomic fluorescence spectroscopy (CVAFS). Methylmercury was analyzed by distillation and aqueous phase ethylation, with detection by CVAFS. The detection limits for total mercury and methylmercury were 0.04 ng/L and 0.025 ng/L, respectively (Olson and DeWild, 1999). Of the 106 total sites, 21 were classified as background or reference sites. The mean concentration for methylmercury at background sites was 0.13 ng/L, which represented 3.4% of the mean total mercury concentration. When all sites were considered, the mean methylmercury concentration (104 sites) was 0.15 $\pm$ 0.26 ng/L (range 0.01 to 1.481 ng/L). The median value was 0.06 ng/L. The difference in mean and median values was attributed to high mercury concentrations at sites impacted by mining activities, which resulted in a skewed distribution. Methylmercury constituted 1% to 11% of total mercury concentration in the 21 study basins.

Other measured concentrations of total mercury and methylmercury in fresh water as reported in the MSRC (U.S. EPA, 1997b) are summarized in Table 5-3. Reported values for methylmercury measured at two sites in the United States ranged from less than 0.004 ng/L to 0.06 ng/L. The New Jersey Department of Environmental Protection and Energy (NJDEPE) (1993) reported total mercury concentrations for lakes of 0.04 to 74 ng/L and values of 1 to 7 ng/L for rivers and streams. Based on the

Table 5-3. Measured Methylmercury Concentrations in Surface Fresh Water

Study Description	Total Mercury (ng/L)	Methylmercury (ng/L)	Methylmercury % of Total	Reference
Lake Crescent, WA	0.163	<0.004	<2.5	Bloom and Watras (1989)[a]
Little Rock Lake (reference basin)	1.0-1.2	0.045-0.06	mean of 5	Watras and Bloom (1992)[a]
Lake Michigan (total)	7.2 microlayer 8.0 at 0.3m 6.3 at 10m	NA	NA	Cleckner et al. (1995)[a]
Lake Champlain	(filtered) 3.4 microlayer 3.2 at 0.3m 2.2 at 15m	NA	NA	Cleckner et al. (1995)[a]
Lakes Rivers and Streams	0.04 - 74 1 - 7	NA	NA	NJDEPE (1993)[a]
USGS National Mercury Pilot Study (predominately streams)	3.43 Background 16.6 All sites	0.13 Background 0.15 All sites	3.4 1 - 11	Krabbenhoft et al. (1999)

[a] As reported in U.S. EPA (1997c)
NA Not available

U.S. EPA (1997b) Monte Carlo estimate for speciation (0.078), these values would correspond to approximate methylmercury concentrations of 0.003 to 6 ng/L for lakes and 0.078 to 0.55 ng/L for rivers and streams. The MSRC did not indicate whether the NJDEPE (1993) data represented measures of central tendency.

Ground Water. Nationally aggregated data for mercury or methylmercury concentrations in ground water were not reported in the MSRC (U.S. EPA, 1997b). Local estimates of concentration are available from three studies. Krabbenhoft and Babiarz (1992) reported mercury levels of 2 to 4 ng/L in near-surface ground water in remote areas of Wisconsin, with a maximum of 0.3 ng/L (roughly 7.5% to 15% of total mercury concentration) occurring as methylmercury. Bloom et al. (1989) reported a value of 0.3 ng/L for total mercury in a Washington state well. In contrast to these comparatively low concentrations, Dooley (1992) reported total mercury levels up to and exceeding 2,000 ng/L in southern New Jersey domestic wells.

Drinking Water. Much of the data reported for total mercury concentration in drinking water is below the detection limit of 100 ng/L associated with older methods of analysis (U.S. EPA, 1997b). Lindqvist and Rodhe (1985) estimated that the concentration range of mercury in drinking water is the same as rain, with an average level of total mercury in drinking water of 25 ng/L. NJDEPE (1993) reported a range of 0.3 to 25 ng/L for total mercury in U.S. drinking and tap water. Speciation data for mercury in drinking water are not available, but may be similar to those observed for rain water (U.S. EPA, 1997c). The percentage of total mercury that is methylmercury in rain water ranged from 0.1% to 6.3% in two studies reported by Lee and Iverfeldt (1991) and Fitzgerald et al. (1991). The high end of this range approaches the point estimate of 7.8% derived for the fraction of methylmercury in the water column of lakes using Monte Carlo simulation (U.S. EPA, 1997b). Assuming that 7.8% of the total mercury is methylmercury (U.S. EPA, 1997b), these data suggest a crude estimate of methylmercury concentration in drinking and tap water ranging from 0.023 ng/L to 1.95 ng/L.

5.4.2.2 Predicted Concentrations in Water

U.S. EPA (1997b) reported the results of watershed fate and transport modeling conducted to predict the background concentration of mercury in water bodies. Atmospheric concentrations and deposition rates were used as inputs to the IEM-2M model. The IEM-2M model is composed of two integrated models that simulate mercury fate using mass balance equations that describe processes in watershed soils and a shallow lake. Using this approach, background levels of total dissolved mercury concentrations in the water column of 0.9 and 0.2 ng/L were predicted for hypothetical Eastern and Western U.S. sites, respectively. More than 80% of the total mercury in the water column was predicted to occur as the inorganic divalent species. As indicated above, the fraction of the predicted background concentration occurring as methylmercury was 7.8% (U.S. EPA, 1997b).

In the MSRC, the background values reported above were used as inputs to a localized model analysis that examined the impact of a variety of anthropogenic emission sources (municipal waste combustors, hospital medical waste incinerators, utility boilers, chlor-alkali plant) on methylmercury concentrations in the water column at distances of 2.5, 10, or 25 km from the source. This effort was undertaken because some monitoring studies suggest that measured mercury concentrations may be higher in areas adjacent to stationary industrial and combustion sources known to emit mercury (U.S. EPA, 1997b). Results of this analysis are of relevance to derivation of the water quality criterion because they include data specifically for predicted methylmercury concentrations, and thus permit comparison with measured concentrations.

The Industrial Source Code air dispersion model (ISC3) was used for simulation. Hypothetical facilities were defined to represent actual emissions from existing industrial processes and combustion sources; these were situated in hypothetical locations intended to simulate a site in either the Western or Eastern United States (U.S. EPA, 1997b). Input values for air concentrations consisted of simulated concentration results (50th and 90th percentile values) obtained using the regional Lagrangian model of air pollution (RELMAP). The assumptions and inputs utilized in this modeling effort are described in detail in Volume III of the MSRC (U.S. EPA, 1997b).

Results for predicted methylmercury concentrations in water are illustrated in Table 5-4. Predicted concentrations for dissolved methylmercury in water across all scenarios ranged from 0.014 to 1.0 ng/L. The highest predicted concentrations occurred at a location 2.5 km from a chlor-alkali plant. The predicted contribution of the hypothetical emission sources to methylmercury concentration ranged from 0 to 99% across all modeling scenarios. Although these results are meant to describe events on a local (adjacent to emission source) rather than nationwide scale, they provide a general frame of reference for comparison with measured values. The predicted range compares to the measured concentration range of 0.01 to 1.481 ng/L reported by Krabbenhoft et al. (1999) for 104 surface water samples collected at sites across the United States. The range of predicted concentrations overlapped the methylmercury concentrations in ground water (less than or equal to 0.3 ng/L, based on one study) and drinking water (0.023 to 1.95 ng/L) estimated from measurement data presented in Section 5.4.2.1.

5.4.2.3 Intake Estimates for Drinking Water and Ambient Water

Using the methylmercury concentration data in treated drinking water, and in ambient water it is possible to estimate exposure from water ingestion. For methylmercury, data on measured concentrations in ground and treated drinking water are limited. The database for surface water is somewhat more extensive. Estimates of intake based on ingestion of drinking water and ambient water are provided below.

Ambient Surface Water

A central tendency value for methylmercury in ambient surface water based on national data is available from a pilot study conducted by the U.S. Geological Survey (Krabbenhoft et al., 1999). Concentrations of methylmercury in ambient surface water ranged from a mean background level of 0.13 ng/L (or 1.3×10^{-7} mg/L) to a mean concentration for all sites of 0.15 ng/L (or 1.5×10^{-7} mg/L).

Combining the mean for methylmercury concentrations at all sites with default exposure assumptions of a 30 kg child aged 0 to 14 years who consumes 1 L/day of ambient surface water yields an estimated exposure of 5.0×10^{-9} mg/kg-day. Combining the mean value for methylmercury concentrations at all sites with default exposure assumptions of 2 L/day for water ingestion rate and 67 kg for body weight yields an exposure estimate of 4.5×10^{-9} mg/kg-day for a woman of childbearing age (15-44 years old). Adults in the general population have an estimated exposure value of 4.3×10^{-9} mg/kg-day, based on a default body weight and water intake rate of 70 kg and 2 L/day, respectively. These values are summarized in Table 5-5.

Table 5-4. Range of Predicted Dissolved Methylmercury Concentrations in Water for Hypothetical Emissions Scenarios

Site	RELMAP Percentile	Methylmercury (ng/L)		Scenario	
		Min	Max	Min	Max
Eastern	50	0.077	1.0	Large hospital incinerator, 25 km	Chlor-alkali plant, 2.5 km
Eastern	90	0.11	1.0	Multiple scenarios	Chlor-alkali plant, 2.5 km
Western	50	0.014	1.0	Multiple scenarios	Chlor-alkali plant, 2.5 km
Western	90	0.034	1.0	Multiple scenarios	Chlor-alkali plant, 2.5 km

Source: U.S. EPA (1997c)

Table 5-5. Ambient Surface Water Intake Assumptions and Estimates

Population of Concern	**Methylmercury in Ambient Surface Water[a] (mg/L)**	**Ingestion Rate[b] (L/day)**	**Body Weight[b] (kg)**	**Daily Exposure Estimate (mg/kg-day)**
Children (0-14 yr)	1.5×10^{-7}	1.0	30	5.0×10^{-9}
Childbearing Women	1.5×10^{-7}	2.0	67	4.5×10^{-9}
Adults in the General Population	1.5×10^{-7}	2.0	70	4.3×10^{-9}

[a] Methylmercury concentration is the mean for all sites in the national pilot study as reported in Krabbenhoft et al. (1999)

[b] U.S. EPA (2000a)

Drinking Water

Although drinking water concentrations can be calculated based on surface water and ground-water concentrations (U.S. EPA, 2000a), the available ground-water data were not adequate for this purpose. Therefore, exposure from drinking water was roughly estimated for women of childbearing age, children aged 0-14 years, and adults in the general population based on existing drinking and tapwater concentration data (NJDEPE, 1993). For the purpose of this estimate, it was assumed that the reported data reflected contributions from both ground water and surface water. Combining the estimated range for methylmercury concentrations in drinking water (0.0234 to 1.95 ng/L, or 2.34×10^{-8} to 1.95×10^{-6} mg/L) with default values for a 30 kg child aged 0 to 14 years consuming 1 L/day of drinking water yields an exposure estimate ranging from 7.8×10^{-10} to 6.5×10^{-8} mg/kg-day. Combining the estimated range for methylmercury concentrations in drinking water with default values of 2 L/day for drinking water intake and 67 kg for body weight yields an exposure estimate that ranges from 7.0×10^{-10} to 5.8×10^{-8} mg/kg-day for a woman of childbearing age (15-44 years old). Exposure estimates from ingesting drinking water by adults in the general population range from 6.7×10^{-10} to 5.6×10^{-8} mg/kg-day, based on a default body weight and water intake rate of 70 kg and 2 L/day, respectively. These values and intake assumptions are summarized below in Table 5-6.

Table 5-6. Drinking Water Intake Assumptions and Estimates

Population of Concern	**Methylmercury in Drinking Water (mg/L)**	**Ingestion Rate[a] (L/day)**	**Body Weight[a] (kg)**	**Daily Exposure Estimate (mg/kg-day)**
Children (0-14 yr)	2.3×10^{-8} to 1.9×10^{-6}	1.0	30	7.8×10^{-10} to 6.5×10^{-8}
Childbearing Women	2.3×10^{-8} to 1.9×10^{-6}	2.0	67	7.0×10^{-10} to 5.8×10^{-8}
Adults in the General Population	2.3×10^{-8} to 1.9×10^{-6}	2.0	70	6.7×10^{-10} to 5.6×10^{-8}

[a] U.S. EPA (2000a)

5.4.3 Nonfish Dietary Exposures

5.4.3.1 Measured Concentrations in Food Other Than Fish

Historically, measurements of mercury have not been speciated in food items other than fish, primarily because of the lack of adequate methodology (Madson and Thompson, 1998). However, the limited data available suggest that nonfish foods such as dairy products, fruits, and vegetables may potentially contribute to intake of methylmercury. Furthermore, it is possible that the agricultural practice of using fishmeal in animal feeds may result in increased levels of methylmercury in nonfish foods (ATSDR, 1999). This section examines the available data on mercury and methylmercury concentrations in nonfish human food items.

Information on the concentration of total mercury in dietary items is available from the *Total Diet Study* (TDS) conducted by the U.S. Food and Drug Administration (U.S. FDA). The TDS is an on-going nationwide program that determines the levels of nutrients and selected contaminants in foods for the purpose of estimating intakes of these substances by the U.S. population. A total of 839 samples for 47 food items were collected and analyzed for total mercury during the period from 1991 to 1996 (U.S. FDA, 1999). Of the reported results, 756 (90%) were below the detection limit for mercury (0.01 to 0.02 mg/kg depending on food item) and 30 (3.6%) were considered to contain trace amounts of mercury. These trace values represent the best estimates of those who analyzed the data, but in all cases are below the nominal limit of quantitation.

Examination of the data for the 41 nonfish dietary items analyzed (6 items were fish) indicates that the total mercury concentration was below the detection limit for most samples. These samples were assigned a concentration of zero for statistical analysis (U.S. FDA, 1999). Trace amounts of total mercury were found in one sample each (out of 18 total samples for each item) of fried beef liver, cooked oatmeal, and boiled spinach. The maximum detected concentration of mercury in nonfish dietary items was 0.03 mg/kg in fried beef liver. The reported median concentrations for total mercury in all individual nonfish dietary categories were zero. Based on these data, the central tendency estimate for methylmercury intake from nonfish dietary items is zero. For comparison, the mean mercury concentration from all 47 food categories (containing both fish and nonfish dietary items) was 0.006 mg/kg (U.S. FDA, 1999).

The MSRC (U.S. EPA, 1997b) also summarized data for methylmercury concentrations reported in local studies. Measured concentrations of methylmercury in garden produce and crops are summarized in Table 5-7. Because the database for methylmercury content in these foods is limited, information is also presented from studies that report total mercury concentrations. In general, the level of methylmercury in agricultural produce is low, with the highest concentration (30 ng/g dry weight) observed in leafy vegetables. Plants grown in the presence of elevated soil or atmospheric concentrations of mercury are reported to contain elevated concentrations of total mercury (U.S. EPA, 1997b). Temple and Linzon (1977) sampled the mercury content of fresh fruits and vegetables around a large chlor-alkali plant in an urban-residential neighborhood. Among garden produce, leafy crops accumulated the highest levels of mercury. One lettuce sample contained 99 ng/g wet weight of mercury (background: <0.6 ng/g), and a sample of beet greens contained 37 ng/g wet weight (background: 3 ng/g). Tomatoes and cucumbers within 400 m of the chlor-alkali plant averaged 2 and 4.5 ng/g wet weight of mercury, respectively, compared with measured background levels of 1 ng/g.

Because the mercury content in plants tends to be low, livestock typically accumulate little mercury from forage or silage (U.S. EPA, 1997b). However, use of fishmeal as food for poultry and other livestock may result in increased mercury levels in these animals (ATSDR, 1999). Measured concentrations of mercury and methylmercury in meat products are summarized in Table 5-8. Although the database is limited, the available data suggest that methylmercury concentrations in meats are generally low in comparison with levels observed in fish (U.S. EPA, 1997b).

Pedersen et al. (1994) monitored the level of mercury in wine, beer, soft drinks, and various juices. Total mercury levels in these beverages were at or below the detection limit of 6 μg/L in all samples tested.

Infant postnatal exposure to methylmercury through ingestion of breast milk is a pathway of potential concern. As noted in Section 3.4, methylmercury is excreted in breast milk (Bakir et al., 1973; Sundberg and Oskarsson, 1992). The ratio of mercury in breast milk to mercury in whole blood was approximately 1:20 in women exposed to methylmercury via contaminated grain in Iraq between 1971 and 1972 (Bakir et al., 1973). Skerfving (1988) found that 16% of mercury in human breast milk is methylmercury. Note that the MSRC found the data on breast milk to be insufficient to support estimation of exposure by this route.

Table 5-7. Measured Mercury Concentrations in Garden Produce and Crops

Study Description	Total Mercury (ng/g dry wt)	Methylmercury (ng/g dry wt)	Methylmercury (mg/kg dry wt)	% Methylmercury	Reference
NY Garden Conditions: Leafy Vegetables	64-139	9.5-30	9.5×10^{-3} - 30×10^{-3}	15-23	Cappon (1987)
NY Garden Conditions: Tuberous Plants	11-36	0.3-6.6	0.3×10^{-3} - 6.6×10^{-3}	11-36	
NY Garden Conditions: Cole[a]	50-64	8.8-12	8.8×10^{-3}- 12×10^{-3}	18	
NY Garden Conditions: Fruiting vegetables	2.9-27	0-2.4	0 - 2.4×10^{-3}	0-9.1	
NY Garden Conditions: Beans	4.3	0	0	0	
Maize	1.7 - 7.3	NA	NA	NA	Szymaczak and Grajeta (1992)

NA Not available
[a] Members of the plant genus *Brassica* including cabbage, broccoli, and cauliflower.
Source: U.S. EPA (1997c)

Table 5-8. Measured Mercury Concentration in Meats

Study Description	Total Mercury (ng/g wet weight)	Approx. Total Mercury (ng/g mercury dry weight)[1]	Approx. Total Mercury (mg/kg mercury dry weight)	% Methyl-mercury	Reference
Saginaw River, MI "Roaster" Ducks (n=6)	48	124.7	124.7×10^{-3}	NA	U.S. EPA (1992a)
Wild Deer (Northern Wisconsin)	5-14	13-36	13×10^{-3} - 36×10^{-3}	11-57 %	Bloom and Kuhn (1994)
Beef: Raw	< 1	< 2.6	$<2.6 \times 10^{-3}$	> 10%	
Beef: Lunch Meat	21	54.5	54.5×10^{-3}	4%	
Beef: Frank	<1	< 2.6	$<2.6 \times 10^{-3}$	> 60%	
Beef Muscle: Control Group	2-3	5.2 - 7.8	5.2×10^{-3} - 7.8×10^{-3}	NA	Vreman et al. (1986)*
Beef Muscle: Exposed Group	1-4	2.6 - 10.4	2.6×10^{-3} - 10.4×10^{-3}	NA	
Beef Liver: Control Group	3000 - 7000	7800 - 18000	7.8 - 18.0	NA	
Beef Liver: Exposed Group	9000 - 26000	23400- 67000	23.4 - 67.0	NA	
Pork: Raw and Sausage	< 1	< 2.6	$<2.6 \times 10^{-3}$	0-70%	Bloom and Kuhn (1994)
Chicken: Raw and Lunch Meat	< 1 to 29	< 2.6 to 75.4	$<2.6 \times 10^{-3}$ - 75.4×10^{-3}	20-67%	
Turkey: Lunch Meat	< 1	< 2.6	$<2.6 \times 10^{-3}$	>20%	

* Exposed animals received 1.7 mg mercury/day as mercury acetate; intake for controls was approximately 0.2 mg mercury/day.
[1] Based on an assumed water content of 0.615, which is average for beef (Baes et al., 1984).
Source: U.S. EPA (1997c)

5.4.3.2 Predicted Concentrations in Foods Other than Fish

U.S. EPA (1997d) reported predicted concentrations in fruits, vegetables, beef, pork, poultry, dairy products, and eggs. As described in previous sections on predicted concentrations in various media, this effort was undertaken because some monitoring studies suggest that measured mercury concentrations may be higher in areas adjacent to stationary industrial and combustion sources known to emit mercury (U.S. EPA, 1997b). Results of this local study are of relevance to derivation of the water quality criterion because they include data specifically for predicted methylmercury concentrations, and thus permit comparison with measured concentrations.

The Industrial Source Code air dispersion model (ISC3) was used for the computer simulation to estimate nonfish dietary exposure. Model plants (defined as hypothetical facilities which were developed to represent actual emissions from existing industrial processes and combustion sources), were situated in hypothetical locations intended to simulate a site in either the Western or Eastern United States (U.S. EPA, 1997b). Input values for air concentrations consisted of simulated concentration results (50^{th} and 90^{th} percentile values) obtained using the regional Lagrangian model of air pollution (RELMAP). The assumptions and inputs utilized in this modeling effort are described in detail in Volume III of the MSRC (U.S. EPA, 1997b).

Predicted concentrations in a variety of nonfish foods are reported in Table 5-9. Because the computer models used to generate these concentrations incorporated a point source for mercury emissions, these predictions likely approach a worst-case scenario for methylmercury levels in foods. Based on a large hospital waste incinerator scenario in the Eastern United States (50th percentile), concentrations of methylmercury (expressed on a dry-weight basis) ranged from 0.095 ng/g to 7.1 ng/g in fruits and vegetables, with the highest concentration observed in leafy vegetables. Concentrations of methylmercury animal products ranged from 0.0013 ng/g to 4.2 ng/g, with the highest concentrations observed in beef and dairy products. The hypothetical facility was considered to contribute less than 10% to the total plant mercury concentration (U.S. EPA, 1997b). The local source was considered to contribute 7% to 11% of the total mercury in beef, dairy products, and pork and 41% of total mercury in poultry and eggs (U.S. EPA, 1997b).

5.4.3.3 Intake Estimates for Food Other Than Fish

Data from the U.S. FDA TDS (described in Section 5.4.3.1) suggest that nonfish dietary items generally account for a very small fraction of total mercury intake. For the purpose of estimating methylmercury intake from nonfish foods, the central tendency estimate of methylmercury concentration is assumed to be zero. Thus, the average daily intake is zero mg/kg-day for adults in the general

Table 5-9. Predicted Methylmercury Concentrations in Produce and Animal Products Based on a Large Hospital Waste Incinerator Scenario

Item	Total Mercury (ng/g dry wt.)	% Methylmercury	Methylmercury (ng/g dry wt.)
Produce			
Root vegetables	1.9	5	0.095
Fruits	35	5	1.7
Fruiting vegetables	35	5	1.7
Leafy vegetables	34	21	7.1
Animal Products			
Beef	8.6	19	1.6
Beef liver	22	19	4.2
Dairy	11	19	2.1
Pork	0.007	18	0.0013
Poultry	0.12	3	0.0036
Eggs	0.12	3	0.0036
Lamb	3.9	19	0.74

[a]Data based on ISC simulation for receptors at a humid site 2.5 km from a large hospital hazardous materials incinerator (HMI) and input from RELMAP (East 50th Percentile).
Source: U.S. EPA (1997b)

population, children, and women of childbearing age. This estimate is in agreement with WHO (1990), which reported that nonfish foods accounted for 0% of average daily intake of methylmercury.

Methylmercury intake from animal products and produce has been estimated by computer model simulation for four hypothetical high-end exposure scenarios: rural subsistence farmer (adult and child), rural home gardener (adult and child), urban high-end adult, and high-end fisher (adult and child) (U.S. EPA, 1997c). These predicted methylmercury intakes are presented in Table 5-10. Methylmercury intake from animal products was estimated only for the rural subsistence farmer. Intake from animal products and produce was not considered in the remaining scenarios. The subsistence farmer was anticipated to represent a very high-end exposure scenario. Simulation of intake for these scenarios employed a body-weight exposure assumption for children (i.e., 17 kg) that differs from the currently recommended value (i.e., 30 kg) for derivation of water quality criterion values (see Table 5-1). Estimated exposure from produce for several high-end scenarios ranged from 2.3×10^{-7} mg/kg-day for the

high-end urban adult to 5.8 x 10^{-5} mg/kg-day for the adult high-end fisher. Estimated exposures from animal products for the rural subsistence farmer scenario were 2.1 x 10^{-6} mg/kg-day and 5.3 x 10^{-6} mg/kg-day for an adult and child, respectively. These model-predicted estimates support the finding of generally low methylmercury intake from nonfish foods indicated by measurement data from the TDS (U.S. FDA, 1999) and the conclusion in the MSRC that substantially all exposure to methylmercury is from fish consumption.

5.4.4 Fish Consumption Estimates

The MSRC concluded that most human exposure to methylmercury is from food and that it is primarily from fish consumption (U.S. EPA, 1997g). Ingestion of contaminated fish is also reported by many other authors to be the only significant source of methylmercury exposure to the general human population (Stern, 1993; Swedish EPA, 1991; WHO, 1990). This conclusion is based on the observation that in many nonfish foods, the mercury content is typically near detection limits and is comprised mainly of inorganic species (WHO, 1990). In contrast, most of the mercury in fish is methylated.

This section provides information on measured and predicted tissue concentrations of methylmercury in freshwater fish and marine fish, and estimates of intake for several target populations. The MSRC presented data for freshwater fish and marine fish. The MSRC did not include a separate evaluation of estuarine fish, although the data on marine species presented in the MSRC (from the National Marine Fisheries Service) include some estuarine species. Sections 5.4.4.1 and 5.4.4.2, below, summarize the major studies presented in the MSRC for freshwater fish. Section 5.4.4.3 presents an estimate of intake for both freshwater and estuarine species. Although the intake estimate is based on the freshwater fish methylmercury concentrations only, EPA believes that the freshwater fish concentrations are similar to the concentrations in these estuarine species presented in the MSRC. EPA, therefore, believes that calculating an intake estimate using the freshwater/estuarine default consumption rates provides a reasonable approximation of combined freshwater/estuarine fish methylmercury exposure. A more accurate estimate of marine fish methylmercury intake has been made (Section 5.4.4.7) since this source of exposure is included in the RSC estimate that is factored into the final water quality criterion calculation.

Table 5-10. Predicted Methylmercury Intake from Dietary Items Based on Five Hypothetical High-End Exposure Scenarios

Parameter	Exposure Scenario[a]										
	Rural Subsistence Farmer		Rural Home Gardener		Urban				High End Fisher		Recreational Angler
	Adult	Child	Adult	Child	Adult Average	Adult High-end	Child Average	Child High-end	Adult	Child	Adult
Body Weight (kg)	70	17	70	17	70	70	17	17	70	17	70
Fraction of Total Mercury From All Sources[b] That Is Methylmercury[c] (%)	10	13	6	6	2	6	2	2	99	99	100
Total Methylmercury Ingestion-All Modeled Sources[b] (mg/kg-day)	4.1E-06	6.9E-06	5.9E-07	7.8E-07	4.0E-09	2.4E-07	3.2E-08	1.2E-06	1.1E-03	1.6E-03	5.6E-04
Fraction of Total Mercury in Produce That Is Methylmercury[d] (%)	6	6	6	6	NA	6	NA	NA	6	6	NA
Methylmercury Intake From Produce (mg/kg-day)	1.7E-06	1.4E-06	5.8E-07	6.6E-07	NA	2.3E-07	NA	NA	5.8E-05	6.6E-07	NA
Fraction of Total Mercury in Animal Products that is Methylmercury[e] (%)	19	19	NA	NA	NA	NA	NA	NA	NA	NA	NA
Methylmercury Intake From Animal Products (mg/kg-day)	2.1E-06	5.3E-06	0	0	NA	NA	NA	NA	0	NA	NA

[a]Data based on ISC simulation for receptors at a humid site 2.5 km from a large hospital medical waste incinerator (HMI) and input from RELMAP (East 50th Percentile)
[b]All sources includes intake from fish, water, soil, produce, and animal products.
[c]Predicted fraction of total mercury that is ingested from all sources as methylmercury.
[d]Predicted fraction of total mercury that is ingested from produce as methylmercury.
[e]Predicted fraction of total mercury that is ingested from animal products as methylmercury.
NA Not available
Source: U.S. EPA (1997c)

5.4.4.1 Measured Concentrations in Freshwater Fish

Data for mercury concentrations in freshwater fish have been previously compiled and evaluated by EPA in Volume IV of the MSRC (U.S. EPA, 1997c). The discussion below provides information on the national studies considered and the database selected by U.S. EPA after careful consideration of data quality issues to provide concentration data for estimating human exposure to methylmercury (U.S. EPA, 1997c).

Two national studies were considered by U.S. EPA (1997c) for estimation of mercury concentrations in freshwater finfish populations. Lowe et al. (1985) reported mercury concentrations in fish from the National Contaminant Biomonitoring Program. The freshwater fish data were collected between 1978-1981 at 112 stations located across the United States. Mercury was measured by a flameless cold vapor technique, with a detection limit of 0.01 μg/g wet weight. Most of the sampled fish were taken from rivers (93 of the 112 sample sites were rivers); the other 19 sites included larger lakes, canals, and streams. Fish weights and lengths were consistently recorded. The mercury concentrations measured in this study are shown in Table 5-11. Several varieties of fish were sampled. Carp, large mouth bass, and white sucker were most common. The geometric mean mercury concentration of all sampled fish was 0.11 μg/g wet weight; the minimum and maximum concentrations reported were 0.01 and 0.77 μg/g wet weight, respectively. The highest reported mercury concentrations (0.77 μg/g wet weight) occurred in a northern squawfish collected from the Columbia River. Mean mercury concentrations (whether geometric or arithmetic mean not specified) by species are reported in the MSRC (U.S. EPA, 1997c).

A national study of chemical residues in freshwater fish was conducted by U.S. EPA (1992b) and also reported by Bahnick et al. (1994). As reported in the MSRC (U.S. EPA, 1997c), five bottom-feeding species (e.g., carp) and five game fish species (e.g., bass) were sampled at each of the 314 sampling sites in the United States. These sites were selected based on proximity to either point or nonpoint pollution sources. Thirty-five "remote" sites among the 314 total sites were included to provide nonimpacted background pollutant concentrations. The study primarily targeted sites that were expected to be impacted by increased dioxin levels. The point sources proximate to sites of fish collection included the following: pulp and paper mills, Superfund sites, publicly owned treatment works (POTWs), and other industrial sites. Data describing fish age, weight, and sex were not consistently collected. Whole body mercury concentrations were determined for bottom feeders, and mercury concentrations in fillets were analyzed for the game fish. Total mercury levels were analyzed using flameless atomic absorption,

with reported detection limits of 0.05 μg/g early in the study (465 samples analyzed prior to 1990) and 0.0013 μg/g later in the study (195 samples), as the analytical technique improved. Nondetects were reported as a zero value and averaged as zeros. The estimated standard deviation for replicate samples was 0.047 μg/g in the concentration range of 0.08 to 1.79 μg/g. Mercury was detected in fish collected from 92% of the sample sites. Concentration data are provided in Table 5-12. The maximum mercury level detected was 1.8 μg/g, and the mean concentration in 669 fish samples across all sites was 0.26 μg/g. The highest measurements occurred in walleye, largemouth bass, and carp. The mercury concentrations in measured in fish around POTWs were the highest among all point source data; the median value for mercury concentration was 0.61 μg/g.

The intake estimates presented in this document, similar to the MSRC, are based on the mean concentration values from the studies described above; that is, the fish mercury concentration data based on the Bahnick et al. (1994) and Lowe et al. (1985) studies were used for the estimates. However, the MSRC also includes summary data from numerous other studies that indicate significantly higher levels of methylmercury in freshwater fish. For example, concentrations of methylmercury in bass, crappie, northern pike, and trout of 2.0, 1.39, 1.71, and 1.19 μg/g, respectively, represent a few of the higher species concentrations reported (see U.S. EPA, 1997d, Table 4-48).

Measurements of elevated levels of mercury in fish have been reported elsewhere. For example, the North East States Coordinated Air Use Management (NESCAUM) summarized data from New England's freshwater fish in the "Mercury Study: A Framework for Action" by the Northeast States and Eastern Canadian Provinces (1998) (see Table 5-11).

Additional data are available for New York State (Simonin and Meyer, 1998). In New York State, maximum mercury concentrations over 2 ppm were seen for the following species: walleye (3.2 ppm), striped bass (5.4 ppm), white perch (3.2 ppm) Northern pike (2.1 ppm), smallmouth bass (3.34 ppm), largemouth bass (2.39 ppm), rock bass (2.7 ppm), drum (1.4 ppm), channel catfish (2.0 ppm), sunfish (1.2 ppm), American eel (1.6 ppm), Lake trout (2.7 ppm), white sucker (1.2 ppm), black crappie (1.4 ppm), and carp (5.8 ppm).

5.4.4.2 Predicted Concentrations in Freshwater Fish

As previously indicated, the MSRC included numerous computer-simulated estimates of mercury exposure for selected population scenarios (U.S. EPA, 1997c). These included predicted concentrations

in Tier 4 (predatory) fish based on exposure modeling. The Industrial Source Code air dispersion model (ISC3) was used for simulation of methylmercury concentrations in water and biota near mercury emissions sources. Model plants (large and small municipal waste combustors, large and small hazardous materials incinerators, coal and oil-fired utility boilers, chlor-alkali plant), defined as hypothetical facilities which were developed to represent actual emissions from existing industrial processes and combustion sources, were situated in hypothetical locations intended to simulate a site in either the Western or Eastern United States (U.S. EPA, 1997b). Input values for air concentrations consisted of simulated concentration results (50^{th} and 90^{th} percentile values) obtained using the regional Lagrangian model of air pollution (RELMAP). The assumptions and inputs utilized in this modeling effort are described in detail in Volume III of the MSRC (U.S. EPA, 1997b).

Fish tissue methylmercury concentrations of 5.3×10^{-1} μg/g and 9.7×10^{-2} μg/g were predicted for the simulated Eastern and Western sites, respectively, in scenarios where the hypothetical emission sources had zero percent impact on local mercury levels (i.e., the predicted concentration resulted only from background levels of mercury in the environment and regional anthropogenic sources). These levels are of the same order of magnitude as the mean measured values of 0.11 and 0.26 μg/g (1.1×10^{-1} and 2.6×10^{-1} μg/g) reported by Lowe et al. (1985) and Bahnick et al. (1994) respectively. The maximum predicted tissue concentration of 68 μg/g was associated with the Eastern site chlor-alkali plant scenario.

5.4.4.3 Intake Estimates from Freshwater/Estuarine Fish

The mercury concentration data reported in U.S. EPA (1992b) and Bahnick et al. (1994) were selected to determine a rough estimate of methylmercury intake from freshwater and estuarine fish. In contrast to the data reported by Lowe et al. (1985), the selected study provides an arithmetic mean as a measure of central tendency. These data have previously been used by U.S. EPA (1997d) to calculate methylmercury intake estimates under different fish ingestion scenarios. In this section, new estimates of methylmercury intake are calculated in accordance with technical guidance provided in the 2000 Human Health Methodology (U.S. EPA, 2000a). Using the mean mercury concentration of 0.26 μg mercury/g fish wet weight (or mg/kg) reported by U.S. EPA (1992b) and Bahnick et al. (1994), and assuming that approximately 100 percent is methylmercury (U.S. EPA, 1997d), the average estimated methylmercury concentration in freshwater/estuarine fish is 0.26 mg/kg.

Table 5-11. Freshwater Fish Mercury Concentrations from Lowe et al. (1985) and Northeast States and Eastern Canadian Provinces (1998)

Lowe et al. (1985)	
Fish Species	***Mean Mercury Concentration (μg/g Wet Wt)***
Bass	0.157
Bloater	0.093
Bluegill	0.033
Smallmouth Buffalo	0.096
Carp, Common	0.093
Catfish (channel, largemouth, rock, striped, white)	0.088
Crappie (black, white)	0.114
Freshwater Drum	0.117
Northern Squawfish	0.33
Northern Pike	0.127
Perch (white and yellow)	0.11
Sauger	0.23
Sucker (bridgelip, carpsucker, klamath, largescale, longnose, rivercarpsucker, tahoe)	0.114
Trout (brown, lake, rainbow)	0.149
Walleye	0.1
Mean of Measured Fish	0.11[a]
Northeast States and Eastern Canadian Provinces (1998)	
Fish Species	***Maximum Mercury Concentration in ppm***
Largemouth bass	8.94
Smallmouth bass	5.0
Yellow perch	3.15
Chain pickerel	2.81
Lake trout	2.70
Walleye	2.04
Brown bullhead	1.10
Brook trout	0.98

[a] Geometric mean; U.S. EPA (1997c) did not specify whether means for individual species or species categories were geometric or arithmetic means.

Source: U.S. EPA (1997c), Northeast States and Eastern Canadian Provinces (1998).

To estimate daily exposure from methylmercury in freshwater/estuarine fish, average body weights and high-end fish ingestion rates (90th percentile) for the populations of concern are estimated, as recommended in the 2000 Human Health Methodology. Default intake values for fish intake by children, women of child-bearing age, and adults in the general population are provided in U.S. EPA (2000a). These intake values were estimated from the on-going, nationally based Continuing Survey of Food Intake for Individuals (CSFII) conducted by the U.S. Department of Agriculture. The CSFII is conducted annually, and dietary data from all 50 States are collected (U.S. EPA, 2000a). The estimates of intake based on CSFII incorporated data for both consumers and nonconsumers of fish, and represent intake of all fish whether store-bought or sport-caught (U.S. EPA, 2000a). The freshwater/estuarine fish ingestion rates for children, women of child-bearing age, and adults in the general population are estimated to be 156.3 g/day, 165.5 g/day, and 17.5 g/day, respectively (U.S. EPA, 2000a). Note that the estimates for both children and women of childbearing age are based on short-term consumption, whereas the estimate for adults in the general population is based on average long-term consumption.

Table 5-12. Freshwater Fish Mercury Concentrations from Bahnick et al. (1994).

Species	**Mean Mercury Concentration (μg/g Wet Wt)**
Carp	0.11
Sucker (white, redhorse, spotter)	0.167
Catfish (channel and flathead)	0.16
Bass (white, largemouth, smallmouth)	0.38
Walleye	0.52
Northern Pike	0.31
Crappie	0.22
Brown Trout	0.14
Mean of Measured Fish	0.26

Source: U.S. EPA (1997c)

The recommended body weights for children 0 to 14 years, women of childbearing age, and adults in the general population are 30 kg, 67 kg, and 70 kg, respectively (U.S. EPA, 2000a). Based on these exposure assumptions, the daily exposure estimates of methylmercury intake from ingestion of freshwater/estuarine fish for children, women of childbearing age, and adults in the general population are 1.4×10^{-3} mg/kg-day, 6.4×10^{-4} mg/kg-day, and 6.5×10^{-5} mg/kg-day, respectively. Input assumptions and calculated daily exposure estimates for freshwater/estuarine fish are summarized in Table 5-13.

5.4.4.4 Measured Concentrations in Marine Fish and Shellfish

The MSRC (U.S. EPA, 1997b,c) has summarized data on concentrations of total mercury and methylmercury in marine fish and shellfish. Analyses of total mercury concentrations in marine fish and shellfish have been carried out over the past two to three decades. Data describing methylmercury concentrations in marine fish are predominantly based on the National Marine Fisheries Service (NMFS) database, the largest publicly available database on mercury

Table 5-13. Freshwater/Estuarine Fish Intake Assumptions and Estimates

Population of Concern	Mercury in Fish[a] (mg/kg)	Methyl-mercury/ Mercury in Fish[b] (%)	Methyl-mercury in Fish (mg/kg)	Ingestion Rate[c] (kg/day)	Body Weight[c] (kg)	Daily Exposure Estimate (mg/kg-day)
Children	0.26	100	0.26	0.1563	30	1.4×10^{-3}
Women of Childbearing Age	0.26	100	0.26	0.1655	67	6.4×10^{-4}
Adults in the General Population	0.26	100	0.26	0.0175	70	6.5×10^{-5}

[a] U.S. EPA (1992b) and Bahnick et al. (1994)
[b] U.S. EPA (1997c)
[c] U.S. EPA (2000a)

concentrations in marine fish. In the early 1970s, the NMFS conducted testing for total mercury in more than 200 seafood species of commercial and recreational interest (Hall et al., 1978). The determination of mercury in fish was based on flameless (cold vapor) atomic absorption spectrophotometry following chemical digestion of the fish sample. These analytical methods are described in Hall et al. (1978).

The NMFS Report provides data on number of samples, the number of samples where mercury was not detected ("nondetects"), and mean, standard deviation, minimum, and maximum detected mercury levels (in parts per million wet weight) for 1,333 combinations of fish/shellfish species, variety, location caught, and tissue (Hall et al., 1978). This database consists of 777 fish/shellfish species for which mercury concentration data are provided. This represents 5,707 analyses of fish and shellfish tissues for total mercury, of which 1,467 or 26%, were reported at nondetectable levels. A discussion of the issues associated with evaluation and use of nondetect data for methylmercury in the NMFS database is provided in the MSRC (U.S. EPA, 1997c). A summary of NMFS concentration data is provided in Table 5-14.

Two additional databases for mercury concentration in marine fish and shellfish are cited in the MSRC (U.S. EPA, 1997d). These are the *Report on the Chance of U.S. Seafood Consumers Exceeding "The Current Daily Intake for Mercury and Recommended Controls"* (U.S. FDA, 1978) and a report by Stern et al. (1996) that examined exposure of New Jersey residents to mercury via fish consumption. Although concentration data from these databases are reported in the MSRC (U.S. EPA, 1997c), detailed descriptions and evaluations of study quality are not provided.

The intake estimates presented in this document, similar to the MSRC, are based on the mean concentration values from the studies described above; that is, the fish mercury concentration data based on the NMFS, Stern et al., and U.S. FDA studies were used for the estimates. However, the MSRC also includes summary data from numerous other studies that indicate significantly higher levels of methylmercury in marine fish. For example, concentrations of methylmercury in mackerel, pompano, shark, snapper, and swordfish of 2.9, 8.42, 4.53, 2.17, and 2.72 μg/g, respectively, represent a few of the higher species concentrations reported (see U.S. EPA, 1997c).

5.4.4.5 Other Measured Concentration Data for Marine Fish and Shellfish

Additional national-scope information on methylmercury in marine biota is available from Project Mussel Watch. Project Mussel Watch measures concentrations of organic and trace metal contaminants

in fresh, whole soft-parts of bivalve mollusks (i.e., mussels and oysters) at more than 240 coastal and estuarine sites. Data are currently available from 1986 through 1993 and are summarized in the MSRC (U.S. EPA, 1997b). Average concentrations along the North Atlantic, Eastern Gulf, and Pacific coasts (0.15, 0.14, and 0.11 μg/g dry weight, respectively) are higher than those collected along the Middle Atlantic, South Atlantic, and Western Gulf coasts (0.06, 0.09, and 0.08 μg/g dry weight, respectively). The highest concentrations exceeded 1.0 μg/g dry weight and were collected along the Western Gulf and Pacific coasts (1.80 and 1.01 μg/g dry weight, respectively).

Annual Mussel Watch data on mercury concentrations in bivalve mollusks at specific sites have been aggregated to national geometric means for the purpose of analyzing temporal trends (O'Conner and Beliaeff, 1995). The national means do not show any temporal trend in mercury concentrations in mussels and oysters for the period 1986-1993. Temporal trend analysis was also conducted on a site-by-site basis for 154 Mussel Watch sites for which there were data for at least 6 years during the period of 1986-1993 (O'Conner and Beliaeff, 1995). Seven sites exhibited an increasing trend in mercury concentrations, and eight sites exhibited a decreasing trend in mercury concentrations, with 95% statistical confidence.

5.4.4.6 Predicted Concentrations in Marine Fish and Shellfish

The computer simulations conducted by EPA and reported in the MSRC (U.S. EPA, 1997c) did not provide predictions for methylmercury concentrations in marine fish or shellfish.

5.4.4.7 Intake Estimates from Marine Fish and Shellfish

In accord with technical guidance provided in U.S. EPA (2000a), mean, median, and 90th percentile concentrations of methylmercury in marine fish were used to estimate daily exposure from methylmercury in marine fish. Species-specific mean concentrations of mercury in marine fish from the National Marine Fisheries Service (NMFS, 1978) are presented in EPA's MSRC (U.S. EPA, 1997c). These data are summarized in Table 5-14. For species where concentration was not reported in NMFS (1978), concentrations were estimated from data reported by Stern et al. (1996), U.S. FDA Compliance Testing data, or U.S. FDA (1978) as cited in U.S. EPA (1997c).

Table 5-14. Average Mercury Concentrations in Marine Fish and Shellfish

Species	Concentration[a] (μg Hg/g Wet Wt.)	Species	Concentration (μg Hg/g Wet Wt.)
Finfish			
Anchovy	0.047	Pompano*	0.104
Barracuda, Pacific	0.177	Porgy*	0.522[b]
Cod*	0.121	Ray	0.176
Croaker, Atlantic	0.125	Salmon*	0.035
Eel, American	0.213	Sardines*	0.1
Flounder*[,e]	0.092	Sea Bass*	0.135
Haddock*	0.089	Shark*	1.327
Hake	0.145	Skate	0.176
Halibut*	0.25	Smelt, Rainbow*	0.1
Herring	0.013	Snapper*	0.25
Kingfish	0.10	Sturgeon	0.235
Mackerel*	0.081	Swordfish*	0.95[c]
Mullet	0.009	Tuna*	0.206
Ocean Perch*	0.116	Whiting (silver hake)*	0.041
Pollock*	0.15	Whitefish*	0.054[d]
Shellfish			
Abalone	0.016	Oysters	0.023
Clam*	0.023	Scallop*	0.042
Crab*	0.117	Shrimp	0.047
Lobster*	0.232	Other shellfish*	0.012[b]
Molluscan Cephalopods			
Octopus*	0.029	Squid*	0.026

Source: U.S. EPA (1997c).

*Denotes species used in calculation of methylmercury intake from marine fish for one or more populations of concern, based on existence of data for consumption in the CSFII (U.S. EPA, 2000b).

[a] Mercury concentrations are from NMFS (1978) as reported in U.S. EPA (1997d) unless otherwise noted, measured as μg of total mercury per gram wet weight of fish tissue.

[b] Mercury concentration data are from Stern et al. (1996) as cited in U.S. EPA (1997c).

[c] Mercury concentration data are from U.S. FDA Compliance Testing as cited in U.S. EPA (1997c).

[d] Mercury concentration data are from U.S. FDA (1978) as cited in U.S. EPA (1997c).

[e] Mercury data for flounder were used as an estimate of mercury concentration in marine flatfish in marine intake calculations

A consumption-weighted mean concentration of mercury for all marine fish was calculated as follows. Each of the marine species selected for inclusion in the analysis was weighted based on species-specific U.S. population intake rates among the three populations of concern (U.S. EPA, 2000b). This weighting system accounts for variability of consumption among different species and across different populations of concern. The consumption weighting factor for each of the selected marine species was calculated as follows. The consumption rates for individual marine species were summed to give a total consumption rate for a particular population of concern. The weighting factor was then calculated as the quotient of the species-specific consumption rate divided by the total consumption rate:

$$\text{Weighting factor for species A} = \frac{\text{Species A consumption rate (g/day)}}{\text{Sum of consumption rates for all selected species (g/day)}}$$

For each population of concern, the average mercury concentration for each species was multiplied by its consumption weighting factor. This product was then summed across all selected marine species to estimate the mean concentration of mercury in all marine fish for that particular population of concern:

$$\text{Mean conc}(\mu g/g) = \sum [\text{species-specific conc}(\mu g/g) \times \text{species-specific weighting factor}]$$

Assuming that approximately 100% of the mercury in marine fish is present as methylmercury (U.S. EPA, 1997c), the weighted-average methylmercury concentrations in marine fish consumed by each of the populations of concern are 0.167 mg/kg, 0.147 mg/kg, and 0.157 mg/kg for children (aged 0-14 years), women of childbearing age, and adults in the general population, respectively.

Specific body weights and several fish ingestion rates (arithmetic mean, median and 90th percentile) for the populations of concern were used to estimate daily exposure from methylmercury in marine fish. Marine fish intake values for children, women of childbearing age, and adults in the general population are provided in U.S. EPA (2000b). For children and women of childbearing age, these intake values were estimated using 3 years of "consumers only" data (1994-1996) from the on-going, nationally based Continuing Survey of Food Intake for Individuals (CSFII) conducted by the U.S. Department of Agriculture. Intake values for adults in the general population were obtained using all survey respondents to derive an estimate of long-term consumption. The marine fish ingestion rates for children, women of childbearing age, and adults in the general population are presented in Table 5-15.

The current default body weights for children 0 to 14 years, women of childbearing age, and adults in the general population are 30 kg, 67 kg, and 70 kg, respectively (U.S. EPA, 2000a). Based on these exposure assumptions, the mean daily exposure estimates of methylmercury intake from ingestion of marine fish for children, women of childbearing age, and adults in the general population are 4.1×10^{-4} mg/kg-day, 2.0×10^{-4} mg/kg-day, and 2.7×10^{-5} mg/kg-day, respectively. The median daily exposure estimates of methylmercury intake from ingestion of marine fish for children, women of childbearing age, and adults in the general population are 3.2×10^{-4} mg/kg-day, 1.6×10^{-4} mg/kg-day, and 0 mg/kg-day, respectively. In addition, the 90th percentile daily exposure estimates of methylmercury intake from ingestion of marine fish for children, women of childbearing age, and adults in the general population are 8.5×10^{-4} mg/kg-day, 4.1×10^{-4} mg/kg-day, and 1.1×10^{-4} mg/kg-day, respectively. Input assumptions and calculated daily exposure estimates for marine fish are summarized in Table 5-16.

5.4.5 Respiratory Exposures

5.4.5.1 Measured Concentrations in Air

Outdoor Air. Vapor-phase elemental mercury is the predominant form of mercury in the atmosphere and constitutes up to 98% of the total mercury concentration (U.S. EPA, 1997b). Increased

Table 5-15. Marine Fish Ingestion Rates

Population of Concern	Mean Intake (kg/day)	Median Intake (kg/day)	90th Percentile Intake (kg/day)
Children	0.07490	0.05971	0.15229
Women of Childbearing Age	0.09104	0.07548	0.18835
Adults in the General Population	0.01246	0	0.04916

Source: U.S. EPA (2000b)

concentrations of the divalent form of mercury may be present near emission sources. Small fractions of particulate mercury and methylmercury may also be present. Atmospheric mercury concentrations in the United States are generally very low (U.S. EPA, 1997b). U.S. EPA (1993a) as cited in the MSRC summarized information on total mercury concentrations in outdoor air and reported ranges of 1 to 4 ng/m^3 for rural areas and 10 to 170 ng/m^3 for urban areas. Methylmercury concentrations from these samples constituted 0% to 21% of the total mercury concentration, with percentage values reported to generally be on the low end of this range. A measure of central tendency was not provided with this estimate. Particulate mercury typically constituted less than 4% of total atmospheric mercury in rural areas, although this fraction was increased in urban areas. The current background mercury concentration over the Northern Hemisphere is considered to be between 1.5 and 2.0 ng/m^3 (Expert Panel on Mercury Atmospheric Processes, 1994). A background concentration of 1.6 ng/m^3 was reported by Fitzgerald (1994). This value was subsequently used by U.S. EPA (1997b) to model mercury fate in watershed soils and surface waters.

Bloom and Fitzgerald (1988) measured vapor-phase mercury concentrations in outdoor air samples collected from Long Island Sound, CT. Total mercury concentrations ranged from 1.4 to 5.3 ng/m^3. The fraction of total mercury present as methylmercury was estimated to be 0% to 1%. During the month of October, the mean methylmercury concentration was 12 pg/m^3 (range 4 to 38 pg/m^3). This concentration represented 0.7% of the total gaseous mercury concentration. During the month of November, the measured methylmercury concentration was less than 10 pg/m^3 and from December through August, the concentration was below the detection limit of 5 pg/m^3.

Indoor Air. No data were identified for indoor air concentrations of methylmercury.

5.4.5.2 Predicted Concentrations in Air

EPA has modeled mercury air concentrations for the continental United States using RELMAP simulation, meteorological data for the year 1989, and current mercury emission data. The background level of mercury in the atmosphere was assumed to be 1.6 ng/m^3. The results of this simulation are reported in (U.S. EPA, 1997b). Predicted concentrations for total mercury are given in Table 5-17. The predicted total mercury concentrations ranged from approximately 1.6 to 1.9 ng/m^3, with the highest concentrations predicted for the Eastern United States. The tabulated results indicate that total

Table 5-16. Intake Assumptions and Estimates for Marine Fish

Population of Concern[a]	Mercury in Marine Fish (mg/kg)	Methylmercury/ Mercury in Marine Fish %	Methylmercury in Marine Fish (mg/kg)	Body Wt. (kg)	Mean Daily Exposure Estimate (mg-kg-day)	Median Daily Exposure Estimate (mg-kg-day)	90th%Daily Exposure Estimate (mg-kg-day)
Children	1.67E-01	100%	1.67E-01	30	4.1E-04	3.2E-04	8.3E-04
Women of Childbearing Age	1.47E-01	100%	1.47E-01	67	2.0E-04	1.6E-04	4.1E-04
Adults in the General Population	1.57E-01	100%	1.57E-01	70	2.7E-05	0.0E+00	1.1E-04

[a] Marine fish intake assumptions for the populations of concern from U.S. EPA (2000b) are summarized in Table 5-15.

Table 5-17. Percentile Analysis of RELMAP Predicted Total Mercury Concentration Results (ng/m^3) for the Continental United States

Region	Min	10th	50th	90th	Max
Continental U.S.	1.602	1.607	1.624	1.685	1.995
East of 90˚ W longitude	1.616	1.640	1.668	1.720	1.995
West of 90˚ W longitude	1.602	1.606	1.616	1.642	1.743

Source: U.S. EPA (1997b)

mercury concentration never exceeded the background level by a large percentage (25% maximum) under the conditions of this simulation. Methylmercury concentration estimates were not provided in the model output as reported in the MSRC (U.S. EPA, 1997b) but, again, is presumed to be present predominantly as elemental mercury.

5.4.5.3 Intake Estimates for Air

The primary species of mercury to which humans are exposed through inhalation is vapor-phase elemental mercury (U.S. EPA, 1997g). Thus, inhalation exposure to methylmercury is not expected to be a significant route of concern when compared to intake via fish consumption.

Assuming the background mercury concentration of 0.0016 $\mu g/m^3$ (or 1.6 ng/m^3) reported by Fitzgerald (1994), of which approximately one percent is methylmercury (Bloom and Fitzgerald, 1988), the average methylmercury concentration in air is 0.000016 $\mu g/m^3$ (or 1.6×10^{-8} mg/m^3). Estimates of daily exposure from methylmercury in air were calculated using inhalation rates and body weights specific to the populations of concern. The long-term inhalation rate based on a time-weighted average for children 0 to 14 years is estimated to be 10.4 m^3/day (U.S. EPA, 1997h). The average, long-term inhalation rates for women of childbearing age and adults in the general population are estimated to be 11 m^3/day and 20 m^3/day, respectively (U.S. EPA, 1994, 1997h). The recommended body weights for children 0 to 14 years, women of childbearing age, and adults in the general population are 30 kg, 67 kg, and 70 kg, respectively (U.S. EPA, 2000a). Based on these exposure input assumptions, the daily exposure estimates from methylmercury in air for children 0 to 14 years, women of childbearing age, and adults in the general population are 5.5×10^{-9} mg/kg-day, 2.6×10^{-9} mg/kg-day, and 4.6×10^{-9} mg/kg-day, respectively. These input assumptions and calculated daily exposure estimates for air are presented in Table 5-18.

U.S. EPA (1997c) reported inhalation exposure estimates based on ISC simulation for a humid site 2.5 km from a large hospital medical waste incinerator (HMI) and input from RELMAP (Eastern U.S., 50th percentile) (Table 5-19). The inhalation parameters used in the simulation for children (16 m^3/day) differed from the rate adopted from U.S. EPA (1997h) for calculation of inhalation intake from measured concentrations (see Table 15-1). Estimated intake for all five exposure scenarios was zero mg/kg-day. This prediction supports the finding of low methylmercury intake via inhalation as calculated from measured concentrations.

Table 5-18. Inhalation Exposure Intake Assumptions and Estimates

Population of Concern	Mercury in Air[a] (mg/m^3)	Methyl-mercury/ Mercury in Air[b] (%)	Methyl-mercury in Air (mg/m^3)	Inhalation Rate[c] (m^3/day)	Body Weight[d] (kg)	Daily Exposure Estimate (mg/kg-day)
Children (0-14 yr)	1.6×10^{-6}	1	1.6×10^{-8}	10.4	30	5.5×10^{-9}
Women of Childbearing Age	1.6×10^{-6}	1	1.6×10^{-8}	11	67	2.6×10^{-9}
Adults in the General Population	1.6×10^{-6}	1	1.6×10^{-8}	20	70	4.6×10^{-9}

[a] Fitzgerald (1994) as cited in U.S. EPA (1997b).
[b] Bloom and Fitzgerald (1988) as cited in U.S. EPA (1997b).
[c] Inhalation rates from U.S. EPA (1994, 1997h).
[d] Current default body weight values from U.S. EPA (2000a).

Table 5-19. Predicted Methylmercury Intake from Air for Five Hypothetical High-End Exposure Scenarios

Parameter	Exposure Scenario[a]										
	Rural Subsistence Farmer		Rural Home Gardener		Urban				High End Fisher		Recrea-tional Angler
	Adult	Child	Adult	Child	Adult Aver-age	Adult High-end	Child Aver-age	Child High-end	Adult	Child	Adult
Inhalation Rate (m^3/day)	20	16	20	16	20	20	16	16	20	16	20
Contact Rate for Inhalation (hr/day)	24	24	24	24	24	16	24	24	24	24	24
Body Weight (kg)	70	17	70	17	70	70	17	17	70	17	70
Methylmercury Intake (mg/kg-day)	0	0	0	0	0	0	0	0	0	0	0

[a]Data based on ISC simulation for a receptors at a humid site 2.5 km from a large Hospital medical waste incinerator (HMI) and input from RELMAP (East 50th Percentile).
Source: U.S. EPA (1997c)

5.4.6 Soil/Sediment Exposures

5.4.6.1 Measured Concentrations in Soil/Sediment

The available data for measured methylmercury and total mercury concentrations in soils and sediments are summarized in Table 5-20, including a small number of studies that provide some data that are national in scope. In general, soil mercury levels are usually less than 200 ng/g in the top soil layer, but values exceeding this level are not uncommon, especially in areas affected by anthropogenic activities (U.S. EPA, 1997b). Soil mercury levels vary greatly with depth, with nearly all the mercury found in the top 20 cm of soil. Mercury levels are positively correlated with the percentage of organic matter in soil (Nriagu, 1979).

Some information is available on estimated typical or background levels of total mercury in U.S. soils and may be used with speciation data to estimate soil methylmercury concentrations. The MSRC (U.S. EPA, 1997b) states that approximately 1 to 3% of the total mercury in surface soil is methylmercury. The other 97% to 99% of total soil mercury can be considered to be largely Hg(II) complexes, although a small fraction of mercury in typical soil will be Hg^0 (Revis et al., 1990). The methylmercury percentage has been observed to exceed 3% in garden soil with high organic content under slightly acidic conditions (Cappon, 1987). Computer simulations of mercury fate and transport predict that methylmercury constitutes 2% of the total mercury in watershed soils (U.S. EPA, 1997b).

Davis et al. (1997) reported a range of 50 to 200 ng/g for total mercury concentrations in nonmercuriferous soils and sediments in background areas not directly impacted by volcanic emissions or anthropogenic releases. The authors stated that methylmercury typically constitutes 0.01% to 2 % of the total mercury concentration. Supporting information on the derivation of this estimate was not provided by the authors. The MSRC (U.S. EPA, 1997b) cited data from NJDEPE (1993) that indicates that typical U.S. soils contain 8 to 117 ng/g of total mercury. Neither an estimate of mean mercury concentration nor speciation data were provided in the description of this study as summarized in the MSRC. Assuming that approximately 2% of the total mercury concentration is present as methylmercury, these data suggest that typical U.S. soils contain 0.16 to 2.3 ng/g as methylmercury.

Shacklette and Boerngen (1984) reported mean concentrations, geometric standard deviations, and ranges for total mercury in soils and other surficial materials based on samples collected at 1318 sites across the conterminous United States. The geometric mean concentration for the conterminous United States was 58 ± 2,520 ng/g (ppb), and the estimated arithmetic mean was 89 ng/g. Additional data

indicate that the mean concentration of mercury in soils varies by region. In soils from the Western United States (west of the 96th meridian), the geometric mean concentration was 46 ± 2,330 ng/g (range <10 to 4,600 ng/g) and the estimated arithmetic mean was 65 ng/g. In soils from the Eastern United States (east of the 96th meridian), the geometric mean concentration was 81 ± 2,520 ng/g (range 10 to 3,400 ng/g), with an estimated arithmetic mean of 120 ng/g. Speciation data were not reported by these authors. Assuming that methylmercury constitutes approximately 2% of the total mercury concentration, the geometric and arithmetic mean levels of mercury present as methylmercury in soils in the conterminous United States would be approximately 1.2 ng/g and 1.8 ng/g, respectively.

Additional data are available on soil mercury and methylmercury concentrations for sites in the United States. As reported in the MSRC (U.S. EPA, 1997b), methylmercury concentrations in soil samples at locations in New York and Washington ranged from 0.3 to 22.9 ng/g dry weight and constituted 0.5% to 5.3% of the total soil mercury content. No other information on these studies was provided.

As characterized in the MSRC (U.S. EPA, 1997b), sediment mercury levels are typically higher than soil levels, and concentrations exceeding 200 ng/g are not unusual. Sediment mercury levels follow the same trends as soil in regards to depth, humic matter, and methylmercury percentage. There is some evidence suggesting that the methylmercury percentage increases with increasing total mercury contamination (Parks et al., 1989). Concentrations of mercury and (where available) methylmercury are tabulated in Table 5-20.

Table 5-20. Concentrations of Total Mercury and Methylmercury in Soil and Freshwater Aquatic Sediments

Location	Total Mercury (ng/g dry wt)	Methylmercury (ng/g dry wt)	% Methylmercury	Reference
Soils				
Discovery Park, Seattle, WA	29-133	0.3 - 1.3	0.6 - 1.5	Lindqvist et al. (1991)[a]
Wallace Falls, Cascades, WA	155 - 244	1.0 - 2.6	0.5 - 1.2	Lindqvist et al. (1991)[a]
Control Soil New York State	117	4.9	4.2	Cappon, (1981)[a]
Compost New York State	213	7.3	3.3	Cappon, (1987)[a]
Garden Soil New York State	406	22.9	5.3	Cappon, (1987)[a]
Soil and Other Surficial Materials in Conterminous U.S.	Conterminous U.S. 58 (geo mean) 89 (arith mean) Western U.S. 46 (geo mean) 65 (arith mean) Eastern U.S. 81 (geo mean) 120 (arith mean)	NA	NA	Shacklette and Boerngen (1984)
Typical U.S. Soils	8 - 117	NA	NA	NJDEPE (1993)[a]
Typical background levels in nonmercurifer-ous soils	50 - 200	0.01 - 2	NA	Davis et al. (1997)
Freshwater Aquatic Sediments				
80 Minnesota Lakes	34 -753 mean 174	NA	NA	Glass et al. (1990)[a]
North Central Wisconsin lakes	90 -190	NA	NA	Rada et al. (1989)[a]
Little Rock Lake, Wisconsin	10 - 170	NA	NA	Wiener et al. (1990)[a]
U.S. Lake sediment mean ranges	70 - 310	NA	NA	NJDEPE (1993)[a]

Location	Total Mercury (ng/g dry wt)	Methylmercury (ng/g dry wt)	% Methylmercury	Reference
U.S. GS National Pilot Study	105 Background 211 All sites	2.1 Background 1.87 All sites	0.1 1	Krabbenhoft et al. (1999)

[a] As cited in U.S. EPA (1997b)

5.4.6.2 Predicted Concentrations in Soil

The MSRC (U.S. EPA, 1997b) reported the results of watershed fate and transport modeling conducted to predict the concentration of mercury in watershed soils. Atmospheric concentrations and deposition rates were used as inputs to the IEM-2M model. The IEM-2M model is composed of two integrated models that simulate mercury fate using mass balance equations which describe processes in watershed soils and a shallow lake. Using this approach, total mercury concentrations of 47 and 8 ng/g were predicted for soils at hypothetical Eastern and Western U.S. sites, respectively. These predicted concentrations for total mercury in soils are lower than the measured concentrations reported by Shacklette and Boergen (1984) for conterminous and regional U.S. soils. More than 90% of the total mercury in soil was predicted to occur as the inorganic divalent species. The fraction of the predicted background concentration occurring as methylmercury was 2% for the Eastern site (U.S. EPA, 1997c), suggesting a soil methylmercury concentration of 0.9 ng/g based on modeling predictions for speciation. Corresponding speciation data was not reported for the Western site.

5.4.6.3 Intake Estimates for Soil/Sediment

The primary species of mercury in soil is largely considered to be Hg(II) complexes, although a small fraction of mercury in typical soil will be Hg^0 (Revis et al., 1990). Thus, ingestion exposure to methylmercury in soil is not expected to be a significant route of concern when compared to exposure via fish ingestion.

Assuming the background mercury arithmetic mean concentration of 89 ng/g (or 0.089 mg/kg) reported by Shacklette and Boerngen (1984), of which approximately 2% is methylmercury (U.S. EPA, 1997b,c; Cappon, 1987; Davis et al., 1997), the average estimated methylmercury concentration in soil is 1.78 ng/g (or 0.00178 mg/kg). To estimate daily exposure from methylmercury in soil, ingestion rates and body weights for populations of concerns must also be estimated. The average incidental soil ingestion rate for children is estimated to be 1×10^{-4} kg/day (U.S. EPA, 1997h). In addition, the average soil ingestion rate for pica children is estimated to be 1×10^{-2} kg/day (U.S. EPA, 1997h). The average soil ingestion rates for women of child-bearing age and the general adult population are both estimated to

be 5 x 10^{-5} kg/day (U.S. EPA, 1997h). The default body weights for children 0 to 14 years, women of child-bearing age, and adults in the general population are 30 kg, 67 kg, and 70 kg, respectively (U.S. EPA, 2000a). Based on these exposure input assumptions, the daily exposure estimates from methylmercury in soil for children, pica children, women of child-bearing age, and adults in the general population are 5.9 x10^{-9} mg/kg-day, 5.9 x 10^{-7} mg/kg-day, 1.3 x10^{-9} mg/kg-day, and 1.3 x10^{-9} mg/kg-day, respectively. These input assumptions and calculated daily exposure estimates for soil are presented in Table 5-21.

Table 5-21. Summary of Soil Ingestion Intake Assumptions and Estimates

Population of Concern	**Mercury in Soil[a] (mg/kg)**	**Methyl-mercury/ Mercury in Soil[b] (%)**	**Methyl-mercury in Soil (mg/kg)**	**Ingestion Rate[c] (kg/day)**	**Body Weight[d] (kg)**	**Daily Exposure Estimate (mg/kg-day)**
Children	0.089	2	0.00178	0.0001	30	5.9 x10^{-9}
Pica Children	0.089	2	0.00178	0.01	30	5.9 x10^{-7}
Women of Childbearing Age	0.089	2	0.00178	0.00005	67	1.3 x10^{-9}
Adults in the General Population	0.089	2	0.00178	0.00005	70	1.3 x10^{-9}

[a] Shacklette and Boerngen for the conterminous U.S. (1984).
[b] U.S. EPA (1997b,c); Cappon (1987) as cited in U.S. EPA (1997b); Davis et al. (1997).
[c] U.S. EPA (1997h).
[d] U.S. EPA (2000a).

Estimates of soil ingestion based on exposure modeling reported in the MSRC (U.S. EPA, 1997c) are summarized in Table 5-22. Predicted exposures are based on an ISC model simulation for a receptors at a humid site 2.5 km from a large hospital medical waste incinerator (HMI) and input from RELMAP (East 50th Percentile). Soil intake among the hypothetical receptors was highest for the urban pica child (1.2×10^{-6} mg/kg-day). The remaining estimates ranged from 3×10^{-9} to 2.4×10^{-8} mg/kg-day. These approximations are comparable to exposure estimates based on measured concentrations of mercury in soils in Table 5-21 when the twofold difference in assumed soil ingestion rate is considered.

5.4.7 Occupational and Other Exposures

Occupational Exposure. Occupational exposures are not routinely factored into the derivation of water quality criterion but may be considered on a chemical-specific basis. Information on occupational exposure to mercury has been summarized in the MSRC (U.S. EPA, 1997c). OSHA (1975) estimated that approximately 150,000 U.S. workers are exposed to mercury in at least 56 occupations. More recently, Campbell et al. (1992) reported that about 70,000 workers are annually exposed to mercury. Occupational settings in which exposure to mercury may occur include chemical and drug synthesis, hospitals, laboratories, dental practices, instrument manufacture, and battery manufacture (NIOSH, 1977). Jobs and processes involving mercury exposure include manufacture of measuring instruments (barometers, thermometers, etc.), mercury arc lamps, mercury switches, fluorescent lamps, mercury broilers, mirrors, electric rectifiers, electrolysis cathodes, pulp and paper, zinc carbon and mercury cell batteries, dental amalgams, antifouling paints, explosives, photographs, disinfectants, and fur processing.

Inorganic mercury accounts for nearly all occupational exposures (U.S. EPA, 1997c). Airborne elemental mercury vapor is the main pathway of concern, particularly in those industries with the greatest number of mercury exposures. Occupational exposure to methylmercury appears to be insignificant or rare. Thus, occupational exposures are not considered relevant to the derivation of ambient water criteria for methylmercury.

Table 5-22. Predicted Mercury Intake from Soil for Five Hypothetical High-End Exposure Scenarios

Parameter	Exposure Scenario [a]										
	Rural Subsistence Farmer		Rural Home Gardener		Urban				High-End Fisher		Recrea-tional Angler
					Adult		Child				
	Adult	Child	Adult	Child	Average	High-end	Average	Pica	Adult	Child	Adult
Soil Ingestion Rate (g/day)	0.1	0.2	0.1	0.2*	0.1	0.1	0.2*	7.5	0.1	0.2	0.1
Body Weight (kg)	70	17	70	17	70	70	17	17	70	17	70
Total Mercury Intake (mg/kg/day)	1.5E-07	1.2E-06	1.5E-07	1.2E-06	2.0E-07	2.0E-07	1.6E-06	6.1E-05	1.5E-07	1.2E-06	1.5E-07
Fraction of Total Mercury That Is Methylmercury (%)	2	2	2	2	2	2	2	2	2	2	2
Methylmercury Intake (mg/kg/day)	3.0E-09	2.4E-08	3.0E-09	2.4E-08	4.0E-09	4.0E-09	3.2E-08	1.2E-06	3.0E-09	2.4E-08	3.0E-09

[a]Data based on ISC simulation for a receptors at a humid site 2.5 km from a large hospital medical waste incinerator (HMI) and input from RELMAP (East 50th Percentile).

*Soil ingestion rates for rural home gardener and urban child (average) were not available. An ingestion rate of 0.2 g/day was assumed based on the soil ingestion rates for the rural subsistence farmer and high-end fisher children.

Source U.S. EPA (1997c)

Exposure from Dental Amalgam. Gradual erosion of dental amalgam represents a pathway by which many people are routinely exposed to extremely small amounts of mercury. Dental amalgam fillings contain approximately 50% mercury by weight. The mercury in the amalgam is continuously released over time. Speciation data indicate that release occurs primarily as elemental mercury vapor (Begerow et al., 1994). Exposure to methylmercury via this route is thus expected to be insignificant. Therefore, exposure to methylmercury via this pathway is not considered relevant to RSC analysis for derivation of the water quality criterion.

5.5 EXPOSURE DATA ADEQUACY AND ESTIMATE UNCERTAINTIES

After identifying relevant exposure pathways and obtaining available data for quantifying exposure via each pathway, it is important to consider whether the data are adequate to describe exposure estimates for each exposure medium. The adequacy of the contaminant concentration data, in part, determines the specific method with which the RSC estimates will be determined. Important factors include sample size, accurate representation of the sample (e.g., whether sample selection was biased and whether data are current), the accuracy in the sample analysis procedures (i.e., whether errors occurred during measurement), and the sensitivity of the measurement relative to the environmental levels of concern (i.e., whether detection limits are low enough such that the concentration can be detected in most samples within a data set). Additional discussion on data adequacy is provided in the 2000 Human Health Methodology (U.S. EPA, 2000a).

5.5.1 Adequacy of Intake Estimate for Drinking Water

Ground water. Nationally distributed data for methylmercury or total mercury in ground water were not located. The MSRC (U.S. EPA, 1997b) reports data from three local studies in the United States. However, supporting information on sample size, detection limits, analytical methodology, and other information relevant to data adequacy are not provided in the MSRC. Therefore, these data (as presented in the MSRC) do not satisfy the adequacy requirements of the 2000 Human Health Methodology.

Drinking Water. The MSRC (U.S. EPA, 1997b) cited a typical level of 25 ng/L for total mercury concentration in drinking and tap water (Lindqvist and Rodhe, 1985). A range of 0.3 to 25 ng/L for total mercury in drinking water was also reported (NJDEPE, 1993). The presentation of these data in the MSRC did not provide information on the composition of this water (e.g., fraction from ground water and surface water) or treatment status. Furthermore, the presentation of data in the MSRC did not

provide information on the method of calculation or a detailed description of data quality (including source of data, sample size, detection limits, and analysis procedures) for this estimate. Thus, the data for drinking water (as presented in the MSRC) are considered sufficient only for a rough estimate of intake. Yet, using the higher-end value of 25 ng/L results in an estimate within the range estimated for surface water.

Raw surface water. National data for surface water concentrations (primarily stream data) are available from the U.S. Geological Survey National Pilot Study of Mercury Contamination (Krabbenhoft et al., 1999). Water samples were collected in the summer and fall of 1998 and thus are representative of current concentrations. Sampling occurred at 106 sites clustered in 21 basins across the United States, including Alaska and Hawaii. Data from 104 sites were used to determine values for mean, median, maximum, and minimum methylmercury concentrations. The sampling sites spanned the dominant east-to-west mercury deposition gradient and represented a wide range of environmental settings. Total mercury and methylmercury were measured using sensitive analytical methodology (U.S. EPA Method 1631). The detection limits for total mercury and methylmercury were reported in a separate document (Olson and DeWild, 1999) referenced in the report. Some samples were collected at sites impacted by mining activity. The high concentration of mercury in samples collected at those sites resulted in a positively skewed distribution, and this is reflected in the difference between the arithmetic mean and median values for samples collected at all sites (0.15 $\pm$ 0.26 ng/L vs. 0.06 ng/L, respectively). The measures of central tendency from this study compare favorably to a methylmercury concentration of 0.07 ng/L in surface water predicted by IEM-2M computer simulation (U.S. EPA, 1997b). The data reported by Krabbenhoft et al. (1999) are therefore considered to be adequate to estimate intake from surface water.

5.5.2 Intake from Nonfish Dietary Sources

Data for measured methylmercury concentrations in nonfish foods are available from several local studies and one national study. Estimates of methylmercury concentration in selected produce and animal products are also available from computer simulations (U.S. EPA, 1997c). Data from the local studies provide supporting information on methylmercury speciation and concentration in a variety of foods, but are considered too limited in scope for estimation of intakes for use in RSC analysis. Information on mercury content of fish and nonfish foods is available from the Total Diet Study (1991-1997) conducted by U.S. FDA (1999). This is an on-going, nationally based study conducted for determining intake of nutrients and contaminants by the U.S. population. Based on data adequacy requirements of the 2000 Human Health Methodology (U.S. EPA, 2000a), the sample size of the U.S.

EPA study is sufficient for calculation of central tendency and 90th percentile values. Detection limits and the number of samples with mercury concentrations below detection the limit are reported by food item. The procedure for treating these samples for statistical analysis is reported. These data are thus considered adequate to estimate central tendency and high-end intakes from nonfish food items.

5.5.3 Intake From Fish

The MSRC (U.S. EPA, 1997c) assessed data sources for estimates of both freshwater and marine fish intake. Reliable mercury concentration data are available from databases maintained for marine fish and shellfish by the National Marine Fisheries Service (NMFS, 1978) and two databases for freshwater fish (Lowe et al., 1985; Bahnick et al., 1994). These studies are national in scope, in contrast to many studies that have a local or regional focus. In addition, the studies were not initiated in response to specific incidents of mercury contamination, and thus may avoid potential bias toward high values. Results in these studies are reported as total mercury. However, the MSRC concluded, based on research conducted by Bloom (1992) and Morgan et al. (1994), that over 90% of the mercury present in fish and seafood is methylmercury. Thus, total mercury concentrations are considered appropriate for evaluation of methylmercury exposure in human populations. Detailed information on mercury concentration by species and statistical considerations in use of the available data are presented in U.S. EPA (1997c).

Issues relating to data adequacy for methylmercury concentrations in marine fish and shellfish have been addressed in the MSRC (U.S. EPA, 1997c). Although the NMFS data were initially compiled beginning in the 1970s, comparisons of the mercury concentrations identified in the NMFS database with compliance samples obtained by the U.S. FDA indicate that the NMFS data are appropriate to use in estimating intake of mercury from marine fish at the national level of data aggregation. Cramer (1994) reported on *Exposure of U.S. Consumers to Methylmercury from Fish* and noted that recent information from NMFS indicated that the fish mercury concentrations reported in the 1978 report do not appear to have changed significantly. The U.S. FDA also monitors methylmercury concentration in seafood. Cramer (1994) observed that results of recent U.S. FDA surveys indicate results parallel to earlier findings by U.S. FDA and NMFS. The National Academy of Sciences' National Research Council's Subcommittee on Seafood Safety (1991) also assessed the applicability of the NMFS 1978 database to current estimates of mercury concentrations in fish. This subcommittee similarly concluded that the mercury concentrations in the 1978 database differed little in from the U.S. FDA compliance samples estimating mercury concentrations in fish. An assessment of the NMFS database by persons with expertise in analytical chemistry and patterns of mercury contamination in the environment indicates that temporal patterns of mercury concentrations in fish do not preclude use of this database in current risk

assessment activities (EPA's Science Advisory Board's ad hoc Mercury Subcommittee; Interagency Peer Review Group, External Peer Review Group).

An issue raised by some reviewers of the MSRC (U.S. EPA, 1997c) concerned use of data in the NMFS database where mercury concentration was below the analytical detection limit. A detailed analysis of the methods for reporting and analyzing nondetect data (U.S. EPA, 1997c, Appendix C) indicated that differences among methods used to handle nondetect samples had negligible impact on the reported mean concentrations in marine fish tissue. Additional information on analytical and statistical considerations in use of the NMFS data is available in EPA's MSRC (U.S. EPA, 1997d). Overall, EPA finds that these data are adequate for estimating exposure from marine fish for derivation of the methylmercury water quality criterion.

Two compilations of data on mercury concentrations in freshwater fish were considered for use in development of the water quality criterion for methylmercury. The strengths and weaknesses of these studies have been evaluated and reported in the MSRC (U.S. EPA, 1997c). The studies reported by Lowe et al. (1985) and by Bahnick et al. (1994) appear to be systematic, national collections of fish pollutant concentration data. However, higher mercury concentrations in fish have been detected in other studies, and the values obtained in the Lowe et al. (1985) and Bahnick et al. (1994) studies should be interpreted as approximations of the mean concentrations in freshwater finfish (U.S. EPA, 1997c). The mean mercury concentrations for each study in all fish sampled vary by a factor of two. The mean mercury concentration reported by Lowe et al. (1985) was 0.11 μg/g, whereas the mean mercury concentration reported by Bahnick et al. (1994) was 0.26 μg/g. The basis for these differences in methylmercury concentrations is unknown. Differences in sampling of fish by trophic position, size, or age might have been responsible for the differences in mean mercury concentrations reported in the two studies. Older and larger fish, which occupy higher trophic positions in the aquatic food chain, would be expected to have higher mercury concentrations. The type of water body from which fish were collected may also influence fish mercury concentrations. Most of the fish collected by Lowe et al. (1985) were from rivers. The fate and transport of mercury in river systems is not as well characterized as in small lakes. In comparison, most of the data reported by Bahnick et al. (1994) were collected with a bias toward more contaminated/industrialized sites, although sampled sites were not specifically contaminated with mercury. Thus, it is possible that there is more mercury available to the aquatic food chains at the sites sampled by Bahnick et al. (1994). Another possibility is that the higher mercury concentrations reported by Bahnick et al. (1994) when compared with those reported by Lowe et al. (1985) reflect increases in mercury contamination over the time period between the studies. Trend data for methylmercury concentrations in freshwater fish over time do not exist, although there are data for fish

collected from coastal and estuarine sites (U.S. EPA, 1997c) as discussed above and in Section 5.4.4.5. Those data suggest that there are no clear temporal trends in tissue mercury concentrations in fish and shellfish over the past two decades. Overall, the data from either study were considered adequate for calculating central tendency and high-end estimates of methylmercury intake from freshwater fish.

5.5.4 Intake from Air

The MSRC (U.S. EPA, 1997b) reported concentration ranges for mercury in urban and rural air. Information on geographic location, sample sizes, and detection limits were not provided. A range of 0 to 21% for methylmercury speciation was presented without an estimate of central tendency. Thus, these data as presented in the MSRC do not satisfy the adequacy requirements of the 2000 Human Health Methodology. A value of 1.6 ng/m^3 was presented in the MSRC as representative of national background levels for total mercury. Details on the derivation of this concentration were not provided; however, this value was considered of sufficient reliability to be used as input for fate and transport modeling reported in the MSRC (U.S. EPA, 1997b,c). Concentration measurements and exposure modeling data presented in the MSRC (U.S. EPA, 1997c) were also evaluated as an alternative estimate of methylmercury concentration in air. Many factors (including selection of modeling equations, input assumptions, and source data) in the modeling analysis affect the predicted concentrations and resulting exposures. These factors are summarized and discussed in U.S. EPA (1997b,c,g). No data were located for methylmercury concentrations in indoor air. Thus, this potential source of exposure was not considered in the estimate of intake from air.

The information available on both measured and predicted air concentrations of methylmercury from the MSRC is insufficient to fully determine data adequacy for estimating central tendency and high-end exposures to methylmercury via inhalation. Estimates of inhalation exposure are presented, although they are considered to represent rough approximations of actual (or likely) intake. Yet, the available data summarized in the MSRC (including the computer-simulated estimates) indicate that exposure to methylmercury in ambient air is negligible.

5.5.5 Intake From Soil

Three studies report aggregate values for measured soil mercury concentration. Shacklette and Boerngen (1984) reported arithmetic and geometric mean concentrations, geometric standard deviations, and ranges for total mercury in soils and other surficial materials based on samples collected at 1,318 sites across the conterminous United States. Sample size for these estimates is adequate, and the data are

representative of concentrations in the United States, although detailed information on analytical methodology, detection limit, and the number and statistical treatment of samples below detection limit was not provided.

Davis et al. (1997) reported a range of 50 to 200 ng/g for total mercury concentration and an estimate of the percent present as methylmercury in nonmercuriferous soils and sediments in background areas not directly impacted by volcanic emissions or anthropogenic releases. However, supporting information on the derivation of this estimate was not provided by the authors. The MSRC (U.S. EPA, 1997b) cited data from NJDEPE (1993) which indicates that typical U.S. soils contain 8 to 117 ng/g of total mercury. Information necessary for assessment of data adequacy was not provided in the summary of this study.

Additional data are available on soil mercury and methylmercury concentrations for sites in the United States. The MSRC (U.S. EPA, 1997b) summarized two reports on methylmercury speciation in soils collected at sites in New York and Washington state. Because each of these studies addressed soil concentrations in only one state, they were not considered adequate for estimating methylmercury exposure from soil.

Computer simulation data for predicted soil concentration, methylmercury speciation, and exposure estimates are available for comparison to measured values. Predicted concentrations were calculated on a regional (Eastern and Western U.S.) basis. As noted by U.S. EPA (1997b,c,g), many factors in the simulation analysis (including modeling equations, input assumptions, and source data) potentially affect the predicted concentrations.

Overall, the currently available soil concentration data are considered adequate to obtain central tendency and high-end estimates of exposure. Although some information was not readily available from the summarized studies in the MSRC (e.g., detection limits), the estimates of exposure from soil ingestion presented in this document are considered adequate given the sampling size (especially the Shacklette and Boerngen study) and geographic representativeness. There is also a clear indication from all available studies that the amount of methylmercury in soil that is methylmercury is approximately 2%.

5.6 TOTAL EXPOSURE ESTIMATES

Total exposure (calculated as the sum of exposure from water, freshwater and estuarine fish, marine fish, nonfish foods, air, and soil) for the three population groups in comparison to the RfD is shown in

Table 5-23. To evaluate potential differences in exposure from ambient water and drinking water, total exposure was calculated using methylmercury exposure estimates for each source. Because the contribution of ambient water or drinking water intake to total exposure is negligible in comparison to the sum of intake from other sources, there is no difference in the total exposure estimated using these two alternatives.

The contribution of exposure from different media as a percentage of total exposure for three types of individuals is summarized in Tables 5-24 through 5-26. Daily exposure estimates on a mg/kg-day basis are presented in Tables 5-27 through 5-29. The information in these tables reflects use of three different intake assumptions for consumption of marine fish: mean, median and 90th percentile.

Table 5-23. Total Exposure Compared with the RfD for Methylmercury

Population of Concern	Exposure Parameters								Total Exposures with Ambient Water (mg/kg-day)			Total Exposures with Drinking Water (mg/kg-day)		
	Body Weight (kg)	Drinking Water Intake (L/day)	Fresh/ Estuarine Fish Intake (kg/day)	Inhalation (m^3/day)	Soil Ingestion (kg/day)	Mean Marine Fish Intake (kg/day)	Median Marine Fish Intake (kg/day)	90% Marine Fish Intake (kg/day)	Marine Mean[a]	Marine Median[b]	Marine 90%[c]	Marine Mean[a]	Marine Median[b]	Marine 90%[c]
Adults in the General Population	70	2.0	0.0175	20	0.00005	0.01246	0	0.04916	9.2×10^{-5}	6.5×10^{-5}	1.8×10^{-4}	9.2×10^{-5}	6.5×10^{-5}	1.8×10^{-4}
Women of Childbearing Age	67	2.0	0.1655	11	0.00005	0.09104	0.07548	0.18835	8.4×10^{-4}	8.0×10^{-3}	1.1×10^{-3}	8.4×10^{-4}	8.0×10^{-3}	1.1×10^{-3}
Children Age 0-14 Years	30	1.0	0.1563	10.4	0.0001 0.01[d]	0.0749	0.05971	0.15229	1.7×10^{-3}	1.6×10^{-3}	2.1×10^{-3}	1.7×10^{-3}	1.6×10^{-3}	2.1×10^{-3}
RfD									1.0×10^{-4} mg/kg-day			1.0×10^{-4} mg/kg-day		

[a] For adults in the general population, intake rates are estimates of all survey respondents to derive an estimate of long-term consumption.
[b] For children and women of childbearing age, intake rates are estimates of "consumers only" data (as described in U.S. EPA, 2000b).
[c] All freshwater/estuarine fish intake rates are based on the 90th percentile from the CSFII data (U.S. EPA, 2000b).
[d] Total exposure calculated using marine mean exposure estimate**.**
[e]Total exposure calculated using marine median exposure estimate.
[f] Total exposure calculated using marine 90th percentile exposure estimate.
[g] Pica child soil ingestion

Table 5-24. Percent of Total Exposures Using Marine Mean Intakes and Default Exposure Percentages for Three Types of Individuals [a]

Exposure Route	Fish and Water Criterion[b]			Fish-Only Criterion[c]		
	Exposure as a Percent of Total Exposure			Exposure as a Percent of Total Exposure		
	Adults in the General Population	Women of Childbearing Age	Children Age 0-14 Years	Adults in the General Population	Women of Childbearing Age	Children Age 0-14 Years
Freshwater/Estuarine Fish	70.6490	76.1903	76.0230	70.6047	76.1848	76.0200
Water				0.0608	0.0069	0.0038
Marine Fish	29.3446	23.8093	23.9764	29.3281	23.8078	23.9755
Diet (Nonfish foods)	0	0	0	0	0	0
Air	0.005	0.0003	0.0003	0.005	0.0003	0.0003
Soil	0.0014	0.0002	0.0003	0.0014	0.0002	0.0003

[a] Exposures are based upon default body weight values (Table 5-1) and do not include pica child soil ingestion.
[b] Ambient surface water exposure estimates used in the fish and water criterion.
[c] Drinking water exposure estimates used in the fish only criterion.

Table 5-25. Percent of Total Exposures Using Marine Median Intakes and Default Exposure Percentages for Three Types of Individuals [a]

Exposure Route	Fish and Water Criterion[b]			Fish-Only Criterion[c]		
	Exposure as a Percent of Total Exposure			Exposure as a Percent of Total Exposure		
	Adults in the General Population	Women of Childbearing Age	Children Age 0-14 Years	Adults in the General Population	Women of Childbearing Age	Children Age 0-14 Years
Freshwater/Estuarine Fish	99.9909	79.9997	80.2464	99.9047	79.9938	80.2431
Water				0.0862	0.0073	0.0040
Marine Fish	0	19.9998	19.7539	0	19.9984	19.7522
Diet (Nonfish foods)	0	0	0	0	0	0
Air	0.0071	0.0003	0.0003	0.0071	0.0003	0.0003
Soil	0.0020	0.0002	0.0004	0.0020	0.0002	0.0004

[a] Exposures are based upon default body weight values (Table 5-1) and do not include pica child soil ingestion.
[b] Ambient surface water exposure estimates used in the fish and water criterion.
[c] Drinking water exposure estimates used in the fish only criterion.

Table 5-26. Exposure from Various Routes as a Percent of Total Exposure Using Marine 90th % Intakes and Default Exposure Percentages for Three Types of Individuals [a]

Exposure Route	Fish and Water Criterion[b]			Fish-Only Criterion[c]		
	Exposure as a Percent of Total Exposure			Exposure as a Percent of Total Exposure		
	Adults in the General Population	Women of Childbearing Age	Children Age 0-14 Years	Adults in the General Population	Women of Childbearing Age	Children Age 0-14 Years
Freshwater/Estuarine Fish	37.1431	60.9523	61.0326	37.1297	60.9488	61.0307
Water				0.0319	0.0055	0.0031
Marine Fish	62.8535	39.0473	38.9668	62.8349	39.0453	38.9657
Diet (Nonfish foods)	0	0	0	0	0	0
Air	0.0026	0.0002	0.0003	0.0026	0.0002	0.0003
Soil	0.0007	0.0001	0.0003	0.0007	0.0001	0.0003

[a] Exposures are based upon default body weight values (Table 5-1) and do not include pica child soil ingestion.
[b] Ambient surface water exposure estimates used in the fish and water criterion
[c] Drinking water exposure estimates used in the fish only criterion.

Table 5-27. Daily Exposure Estimates from All Media Using Marine Mean Intakes for Individuals From Three Populations of Concern

Population of Concern	Summary of Exposure (mg/kg-day)[a]							
	Ambient Water	**Drinking Water[b]**	**Nonfish Dietary Items**	**Freshwater/ Estuarine Fish**	**Marine fish**	**Air**	**Soil**	**Total Exposure**
Children Age 0-14 Years	5.0×10^{-9}	6.5×10^{-8}	0	1.3×10^{-3}	4.2×10^{-4}	5.5×10^{-9}	5.9×10^{-9}	1.7×10^{-3}
%Total Exposure	0.0003%	0.0038%	0.0000%	76.0198%	23.9755%	0.0003%	0.0003%	
Women of Childbearing Age	4.5×10^{-9}	5.8×10^{-8}	0	6.4×10^{-4}	2.0×10^{-4}	2.6×10^{-9}	1.3×10^{-9}	8.4×10^{-4}
%Total Exposure	0.0005%	0.0069%	0.0000%	76.1844%	23.8076%	0.0003%	0.0002%	
Adults in General Population	4.3×10^{-9}	5.6×10^{-8}	0	6.5×10^{-5}	2.7×10^{-5}	4.6×10^{-9}	1.3×10^{-9}	9.2×10^{-5}
%Total Exposure	0.0047%	0.0608%	0.0000%	70.6014%	29.3267%	0.005%	0.0014%	

[a] Refer to exposure parameters listed in Table 5-1.

[b] Upper-bound concentration for methylmercury used in calculation.

Table 5-28. Daily Exposure Estimates From All Media Using Marine Median Intakes for Individuals From Three Populations of Concern

Population of Concern	Exposure (mg/kg-day)[a]							
	Ambient Water	**Drinking Water[b]**	**Nonfish Dietary Items**	**Freshwater/ Estuarine Fish**	**Marine fish**	**Air**	**Soil**	**Total Exposure**
Children Age 0-14 Years	5.0×10^{-9}	6.5×10^{-8}	0	1.3×10^{-3}	3.2×10^{-4}	5.5×10^{-9}	5.9×10^{-9}	1.6×10^{-3}
%Total Exposure	0.0003%	0.0040%	0.0000%	80.2429%	19.7521%	0.0003%	0.0004%	
Women of Childbearing Age	4.5×10^{-9}	5.8×10^{-8}	0	6.4×10^{-4}	1.6×10^{-4}	2.6×10^{-9}	1.3×10^{-9}	8.0×10^{-4}
%Total Exposure	0.0006%	0.0073%	0.0000%	79.9933%	19.9983%	0.0003%	0.0002%	
Adults in General Population	4.3×10^{-9}	5.6×10^{-8}	0	6.5×10^{-5}	0	4.6×10^{-9}	1.3×10^{-9}	6.5×10^{-5}
%Total Exposure	0.0066%	0.0861%	0.0000%	99.8983%	0.0000%	0.0071%	0.0020%	

[a] Refer to exposure parameters listed in Table 5-1.
[b] Upper-bound concentration for methylmercury in drinking used in calculation.

Table 5-29. Daily Exposure Estimates from All Media Using Marine 90th Percentile Intakes for Individuals from three Populations of Concern

Population of Concern	Exposure (mg/kg-day)[a]							
	Ambient Water	**Drinking Water[b]**	**Nonfish Dietary Items**	**Freshwater/ Estuarine Fish**	**Marine fish**	**Air**	**Soil**	**Total Exposure**
Children Age 0-14 Years	5.0×10^{-9}	6.5×10^{-8}	0	1.3×10^{-3}	8.5×10^{-4}	5.5×10^{-9}	5.9×10^{-9}	2.1×10^{-3}
%Total Exposure	0.0002%	0.0031%	0.0000%	61.0305%	38.9656%	0.0003%	0.0003%	
Women of Childbearing Age	4.5×10^{-9}	5.8×10^{-8}	0	6.4×10^{-4}	4.1×10^{-4}	2.6×10^{-9}	1.3×10^{-9}	1.1×10^{-3}
%Total Exposure	0.0004%	0.0055%	0.0000%	60.9485%	39.0451%	0.0002%	0.0001%	
Adults in General Population	4.3×10^{-9}	5.6×10^{-8}	0	6.5×10^{-5}	1.1×10^{-4}	4.6×10^{-9}	1.3×10^{-9}	1.8×10^{-4}
%Total Exposure	0.0025%	0.0319%	0.0000%	37.1288%	62.8333%	0.0026%	0.0007%	

[a] Refer to exposure parameters listed in Table 5-1.
[b] Upper-bound concentration for methylmercury used in calculation.

5.7 RELATIVE SOURCE CONTRIBUTION (RSC) ESTIMATES

5.7.1 RSC Policy Summary

As described in Section 5.1, water quality criteria for noncarcinogens account for anticipated exposures from sources other than drinking water and freshwater/estuarine fish ingestion. These exposures can include other dietary intakes, air, and soil. By accounting for other exposures, the entire RfD is not attributed to drinking water and freshwater/estuarine fish consumption alone. The relative source contribution (RSC) approach apportions the RfD to ensure that the water quality criterion is sufficiently protective, given the other anticipated sources of exposure. Thus, accounting for nonwater exposure sources results in a more stringent water quality criterion than if those sources were not considered. Details of the RSC approach (the Exposure Decision Tree) are described in more detail in the 2000 Human Health Methodology (U.S. EPA, 2000a).

The RSC determination differs from chemical to chemical depending on several factors: (a) the magnitude of total exposure compared with the RfD; (b) the adequacy of data available; (c) whether more than one guidance or criterion is to be set for the chemical in question; and (d) whether there is more than one significant exposure source for the chemical and population of concern. The target population for this methylmercury criterion is discussed in Section 5.2; the sources of methylmercury exposure, exposure estimates, and data adequacy are discussed in Sections 5.3 through 5.5.

5.7.2 Target Population for RSC/Rationale for Approach to Methylmercury

The target population for the RSC estimate is the general population. The health risk measure, the RfD, is intended to be protective of the whole population, including (but not restricted to) sensitive subpopulations. This is not a developmental RfD *per se*. Even though the critical endpoint was neurotoxic effects observed in children exposed *in utero*, application of the RfD is not restricted to pregnancy only, or to developmental periods only.

As discussed in the 2000 Human Health Methodology, the RSC policy approach allows for use of a subtraction method to account for other exposures when one health-based criterion is relevant for the chemical in question. In this circumstance, other sources of exposure can be considered "background" and can be subtracted from the RfD. Such is the case with methylmercury; that is, there are no health-based criteria, pesticide tolerances, or other regulatory activities to warrant apportionment using the alternate percentage method.

5.7.3 Data Adequacy for RSC Estimate

Section 5.4 describes information on levels of occurrence and provides estimates of exposure to methylmercury in ambient surface water, drinking water, fish, nonfish foods, air, soil, and sediment. The information in Section 5.4 indicates that, for almost all media sources, the sampling data meet the adequacy requirements (e.g., sample sizes, representativeness) for describing both central tendency and high-end concentrations for those sources (Box 3 of the Methodology Decision Tree approach [U.S. EPA, 2000a]). Thus, the data summarized for ambient surface water concentrations, nonfish dietary concentrations, marine fish concentrations, and soil concentrations are adequate to use for estimating overall exposure and RSC. Available data on methylmercury in ground water and estimates of methylmercury in drinking water are not as adequate, as defined by the data adequacy requirements in the 2000 Human Health Methodology. However, the estimates made for both ground water and drinking water in Section 5.4.2.3 indicate levels no higher in magnitude than the surface water estimates, even when using most high-end values. Information on ambient air concentrations summarized from the MSRC failed to indicate sample sizes, geographic representativeness, or detection limits and, thus, are not considered adequate in terms of the Methodology's Decision Tree (Box 3) requirements. However, 98% of mercury in ambient air occurs in the form of vapor-phase elemental mercury, according to the MSRC. Therefore, exposures to methylmercury in ambient air are probably negligible. This assumption is supported by the estimates presented in Section 5.4.5, including the MSRC model simulations predicting exposures of zero near a waste incinerator.

5.7.4 RSC Estimate/Apportionment of the RFD

Once it has been determined that the data are adequate to describe exposure intakes for relevant exposure sources and that there are no other health-based criteria to apportion, exposure intakes from sources other than the source addressed by the criterion are subtracted from the RfD (Box 12 of the Decision Tree, see U.S. EPA, 2000a). Based on the available data, human exposures to methylmercury from all media sources except freshwater/estuarine and marine fish are negligible, both in comparison to exposures from fish and compared to the RfD. Estimated exposure from ambient water, drinking water, nonfish dietary foods, air, and soil are all, on average, at least several orders of magnitude less than those from freshwater/estuarine fish intakes. Nonfish sources of intake are in the range of 10^{-5} to 10^{-9} µg methylmercury/kg body weight-day for adults in the general population. The combined methylmercury exposure intakes from water ingestion, (nonfish) diet, air, and soil represent approximately 0.07% of total estimated exposure to methylmercury (and less than 1/100 of 1% of the RfD) for adults in the general

population. Therefore, these exposures are not factored into the RSC because they will not quantitatively affect the final criterion value.

Ingestion of marine fish is a significant contributor to total methylmercury exposure. The MSRC (U.S. EPA, 1997c) indicates that in the general population of fish consumers, those that consume freshwater/estuarine species of fish are also consumers of marine species of fish. EPA has, therefore, made the assumption in the derivation of the methylmercury fish tissue criterion. In making this assumption, EPA does not believe that, by and large, the high-end consumer of freshwater/estuarine fish is also a high-end consumer of marine fish. The Agency believes that it is more appropriate, and a reasonably conservative assumption, to use the average intake rate (approximately 12.5 g/day) for the marine fish component of the RSC estimate.

The marine fish exposure source is estimated using species-specific mean methylmercury fish tissue data from NMFS (see Section 5.4.4.4) and calculating species-weighted intakes from the CSFII consumption rates (see Section 5.4.4.7). Following the MSRC (U.S. EPA, 1997c), nearly 100% of the mercury in marine fish was assumed to be present as methylmercury. The RSC estimate from marine fish has been calculated with an overall assumed average intake of 12.46 g/day of marine fish based on the CSFII, for all respondents aged 18 and over. The estimated weighted-average methylmercury concentration in marine fish is 0.157 mg methylmercury/kg fish, and the estimated average exposure to methylmercury from marine fish is 2.7×10^{-5} mg methylmercury/kg body weight-day. This exposure represents 27% of the RfD.

All exposure intake values estimated for methylmercury are presented in Table 5-30. The RSC factor in this case is determined by adding the estimated intakes that are quantitatively relevant for methylmercury; that is, only the intake from marine fish consumption of 2.7×10^{-5} mg/kg-day has any affect on the calculation. This amount is subtracted from the RfD of 0.1 µg methylmercury/kg body weight-day or 1.0×10^{-4} mg methylmercury/kg body weight-day. The remainder of the RfD is used to calculate the fish tissue residue concentration in terms of the assumed body weight and freshwater/estuarine fish ingestion. This results in an amount of methylmercury that is allowable in freshwater/estuarine fish and that will not exceed the RfD, considering the additional exposure from marine fish consumption.

Table 5-30. Exposure estimates for methylmercury and percent of total exposure based on adults in the general population

Exposure Source	Exposure Estimate (mg/kg-day)	Percent of Total Exposure	Percent of RfD
Ambient water intake	4.3×10^{-9}	0.0047	0.004
Drinking water intake[a]	5.6×10^{-8}	0.0605	0.006
Nonfish dietary intake	0	0	0
Marine fish intake	2.7×10^{-5}	29.33	27
Air intake	4.6×10^{-9}	0.005	0.005
Soil Intake	1.3×10^{-9}	0.0014	0.001
Total intake	9.2×10^{-5}	100	27.01

[a] This represents the high-end of the range of estimates. Because the contribution of ambient water or drinking water intake to total exposure is so negligible in comparison to the sum of intake from other sources, there is no difference in the total exposure estimated using either of these two alternatives.