Methylmercury (MeHg); CASRN 22967-92-6

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Methylmercury

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	07/27/2001
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	yes	05/01/1995

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Methylmercury (MeHg)
CASRN — 22967-92-6
Last Revised — 07/27/2001

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD 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 effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is

essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Developmental neuropsychological impairment **Human epidemiological studies (Grandjean et al., 1997; Budtz-Jørgensen et al., 1999a)**	Benchmark Dose: $BMDL_{05}$ range of 46-79 ppb in maternal blood for different neuropsychological effects in the offspring at 7 years of age, corresponding to a range of maternal daily intakes of 0.857-1.472 µg/kg-day	10	1	1E-4 mg/kg-day (0.0001 mg/kg-day)

*Conversion Factors and Assumptions —Maternal daily dietary intake levels were used as the dose surrogate for the observed developmental effects in the children exposed in utero. The daily dietary intake levels were calculated from blood concentrations measured in the mothers with supporting additional values based on their hair concentrations. This conversion is explained in the text below. A benchmark dose approach (BMD) was used rather than a no-observed-adverse-effect level/lowest-observed-adverse-effect level (NOAEL/LOAEL) approach to analyze the neurological effects in children as the response variable. This analysis is also explained in the text below.

This assessment updates the 1995 RfD assessment on IRIS and is the same as the RfD that was based on the study of a poisoning episode in Iraq in which developmental neurotoxicity was observed following ingestion of methylmercury-treated grain (Marsh et al., 1987).

I.A.2. Principal and Supporting Studies (Oral RfD)

Congress directed EPA, through the House Appropriations Report for Fiscal Year 1999, to contract with the National Research Council (NRC), a body of the National Academy of Sciences, to evaluate the available data on the health effects of methylmercury, with particular emphasis on new data since the publication of the Mercury Study Report to Congress (MSRC) (U.S. EPA, 1997). NRC was asked to provide recommendations regarding issues relevant to the derivation of an appropriate RfD for methylmercury. The NRC report, "Toxicological

Effects of Methylmercury," was released to the public on July 11, 2000 (NRC, 2000). This assessment reported here relied on the quantitative analyses performed by the NRC, as described in that report.

Methylmercury is a highly toxic substance; a number of adverse health effects associated with exposure to it have been identified in humans and in animal studies. Most extensive are the data on neurotoxicity, particularly in developing organisms. The nervous system is considered to be the most sensitive target organ for which there are data suitable for derivation of an RfD.

There are three epidemiological studies for which quantitative analyses have become available since EPA's derivation of an RfD in 1995 (NRC, 2000). These longitudinal, developmental studies were conducted in the Seychelles Islands, the Faroe Islands, and New Zealand. The subjects of the Seychelles longitudinal prospective study were 779 mother-infant pairs from a fish-eating population (Myers et al., 1995a-c, 1997; Davidson et al., 1995, 1998). Infants were followed from birth to 5.5 years of age, and assessed at various ages on a number of standardized neuropsychological endpoints. The independent variable was maternal-hair mercury levels. The Faroe Islands study was a longitudinal study of about 900 mother-infant pairs (Grandjean et al., 1997). The main independent variable was cord-blood mercury; maternal-hair mercury was also measured. At 7 years of age, children were tested on a variety of tasks designed to assess function in specific behavioral domains. The New Zealand study was a prospective study in which 38 children of mothers with hair mercury levels during pregnancy greater than 6 ppm were matched with children whose mothers had lower hair mercury levels (Kjellstrom et al., 1989, 1986). At 6 years of age, a total of 237 children were assessed on a number of neuropsychological endpoints similar to those used in the Seychelles study (Kjellstrom et al., 1989). The Seychelles study yielded scant evidence of impairment related to in utero methylmercury exposure, whereas the other two studies found dose-related effects on a number of neuropsychological endpoints. In the assessment described here, emphasis is placed on the results of the Faroe Islands study, the larger of the two studies that identified methylmercury-related developmental neurotoxicity. Supporting evidence from the New Zealand study provides assurance that choosing this focus is the appropriate strategy for protecting public health. In addition, of all three studies an integrative analysis is set out later in this assessment report.

EPA chose BMD analysis as the most appropriate method of quantifying the dose-effect relationship in these studies, which was also the recommendation of the NRC (2000). EPA chose the *K* power model for BMD analysis, with the constraint that $K >= 1$, such that the model precludes supralinearity. There is no identified mechanism by which methylmercury would produce a supralinear response; therefore the *K* power model was thought to have more biological plausibility compared with other models. A power of 1 provided the best fit of the Faroese data using the *K* power model (Budtz-Jørgensen et al., 1999b, 2000), so this model

was used in this RfD derivation. A value of $P_0 = 0.05$ was used: that is, the cutoff for abnormal response was set at the lowest 5% (5^{th} percentile) of children. Most human characteristics, including children's neurodevelopmental abilities, have an approximately bell-shaped or "normal" distribution. Generally speaking, children who function at or below approximately the 5^{th} percentile are considered significantly developmentally compromised for the ability that is being measured (e.g., IQ < 75, or comparable standard scores for more specific abilities such as attention, language, or memory). A BMR of 0.05 was chosen for this assessment, which would result in a doubling of the number of children with a response at the 5^{th} percentile of the population. This choice was particularly appropriate, because effects were identified on a number of neuropsychological endpoints in the offspring at approximately the same body burden in the mother. A benchmark dose lower limit ($BMDL_{05}$) (the lower 95% confidence limit of the BMD_{05}) was calculated for each endpoint described above from the three studies.

DOSE CONVERSION

The biomarker of choice for the Faroese data was cord blood, and the BMDLs were reported 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. EPA chose 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).

The model is described by the formula below:

$$d = (c \times b \times V)/(A \times f \times bw)\ \mu g/kg/day$$

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 absorbed dose taken up by blood (unitless)
- **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.

Concentration in blood (c)

The concentration in blood corresponds to the $BMDL_{05}$.

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 involving human volunteers conducted by Miettinen et al. (1971). It is generally believed that absorption of ingested methylmercury is high and not likely to vary a great deal. An absorption factor of 0.95 was used as in the Mercury Study Report to Congress (U.S. EPA, 1997).

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

Currently, four published reports address 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 amount 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; WHO, 1990).

EPA chose 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 as gleaned from the five publications are 45 to 70 days. The MSRC (U.S. EPA, 1997) 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 $days^{-1}$ also was 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 noted that the distribution was highly skewed and that the median was 53 days; the corresponding elimination constant was 0.013 $days^{-1}$.

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 were larger than those observed in the other studies. Stern offers the opinion that this difference may result from relatively large size of the Al-Shahristani data set as compared with 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 reported a mean elimination constant of 0.011 $days^{-1}$ for the Al-Shahristani data alone; the combined data set mean elimination constant was 0.014 $days^{-1}$.

The decision to select point estimates for dose conversion parameters was done in this assessment with the acknowledgment that some of the variability around these parameters would be truncated. This loss was compensated for by using a pharmacokinetic uncertainty factor. Nevertheless, it did not seem prudent to select a point estimate, which is meant to reflect a population's central tendency, from one data set only. The two central tendency estimates of Swartout and Rice (2000) and Stern (1997) were very close in value (0.013 versus 0.014); the differences presumably resulted from the application of different distribution types. In this assessment the value of 0.014 $days^{-1}$ was used for *b* in the dose conversion.

Volume of blood in the body (V)

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)

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 (NCHS, 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, 2000) 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 value was used for body weight in the dose conversion.

Dose conversion using the one-compartment model

$$d = (c \times b \times V)/(A \times f \times bw)$$

$$d = (BMDL_{05}\ \mu g/L \times 0.014 days^{-1} \times 5L)/(0.95 \times 0.059 \times 67\ kg)$$

BMD ANALYSIS OF THE FAROE ISLANDS STUDY

The Faroe cohort was exposed to polychlorinated biphenyls (PCBs) as well as to methylmercury. An association was identified between PCB levels in cord tissue and four measures for which an effect of methylmercury also was identified (Grandjean et al., 1997). Analyses performed by the Faroe investigators indicate that the effects of methylmercury and PCBs are independent of each other (Budtz-Jørgensen et al., 1999a). Further, NRC presented an analysis of benchmark analyses designed to explore the influence of PCBs (Table 1). PCB measurements were made on cord tissue taken from about one-half of the Faroese cohort (about 450 children) and the "adjusted for PCBs" values are based on those children for whom PCB cord tissue levels and cord-blood mercury levels were available. PCB-adjusted analyses also were conducted of children in the lowest tertile with respect to PCB levels, which reduced the number of children studied to about 150. No clear pattern arose from a comparison of the PCB-adjusted analyses and the original results. The observed variability probably was no more than that which would be expected to exist by chance alone. This analysis provides compelling evidence that the effects of methylmercury identified in this study are not the consequence of exposure to PCBs.

BMD ANALYSIS OF ALL THREE EPIDEMIOLOGICAL STUDIES

Benchmark dose analyses were performed for a number of endpoints from all three studies (Faroe Islands, Seychelles, New Zealand) (NRC, 2000, Chapter 7). NRC estimated a central tendency measure, equivalent to a BMD, across all three studies for all endpoints that were identified as significant in the Faroe Islands and New Zealand studies, and for all endpoints at 5.5 years of age in the Seychelles study. They also determined a lower limit based on a theoretical distribution of BMDs, which is the logical equivalent of a BMDL.

NRC also used a hierarchical random-effect model to reduce random variation in the estimate for these same endpoints from all three studies (NRC, 2000, Table 7-5, pp. 290-294). Additionally, this analysis was used in calculating BMD and BMDLs for the most sensitive and median endpoints from both the Faroe Islands and New Zealand studies (NRC, 2000, Table 7-6, p. 294). This approach also allowed an integrative analysis of data from all three studies.

Table 1. BMD (BMDL) Estimates from the Faroe Islands Study with and without Adjustment for PCBs and in the Subset of Children Whose PCB Exposure Was Low (calculated using the K-power model)

Exposure	Endpoint[a]	Full Cohort	Adjusted for PCBs	Low-PCB Tertile

Exposure	Endpoint[a]	Full Cohort		Adjusted for PCBs		Low-PCB Tertile	
		BMD_{05}	$(BMDL_{05})$[b]	BMD_{05}	$(BMDL_{05})$	BMD_{05}	$(BMDL_{05})$
Maternal-hair (ppm)	Finger tapping	20	(12)	17	(9)	7	(4)
	CPT reaction time	18	(10)	27	(11)	13	(5)
	BNT	15	(10)	24	(10)	21	(6)
	CVLT: delayed recall	27	(14)	39	(12)	32	(7)
Cord blood (ppb)	Finger tapping	140	(79)	149	(66)	41	(24)
	CPT reaction time	72	(46)	83	(49)	53	(28)
	BNT	85	(58)	184	(71)	127	(40)
	CVLT: delayed recall	246	(103)	224	(78)	393	(52)

[a]CPT = Continuous Performance Test; BNT = Boston Naming Test; CVLT = California Verbal Learning Test.
[b]BMDs are calculated under the assumption that 5% of the responses will be abnormal in unexposed subjects ($P_0 = 0.05$), assuming a doubling of the 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.

Table 2 presents $BMDL_{05}$s from a number of endpoints in terms of cord-blood mercury. These tests are all indications of neuropsychological processes involved in a child's ability to learn and process information. The BMDLs for these scores are all within a relatively close range. They were converted using a one-compartment model to an ingested dose of methylmercury that would result in the cord-blood level. The last column shows the corresponding RfD from application of a UF of 10 (see next section). The calculated RfD values converge at the same point: 0.1 µg/kg/day. Among the endpoints from the Faroe Islands study were three 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, the lowest PCB tertile. EPA also calculated geometric means from the four endpoints from the Faroe Islands study; RfDs were 0.1 µg/kg/day based on these calculations. For the New Zealand study smoothed values, both the median value and the results of the McCarthy Perceived Performance test yielded RfDs of 0.05 µg/kg/day, and the McCarthy Motor Test yields an RfD of 0.1 µg/kg/day. Based on the integrative analysis of all three studies, the RfD would be 0.1 µg/kg/day

Table 2. Comparison of $BMDL_{05}$s and Corresponding RfDs from Faroes, New Zealand, and NRC Integrative Analysis[a]

Test[b]	$BMDL_{05}$ ppb mercury cord	Ingested dose µg;/kg/day[c]	RfD µg/kg/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			

Test[b]	$BMDL_{05}$ ppb mercury cord	Ingested dose µg;/kg/day[c]	RfD µg/kg/day[d]
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 Faroes			
Whole cohort	68	1.268	0.1
PCB-adjusted	65	1.212	0.1

Test[b]	$BMDL_{05}$ ppb mercury cord	Ingested dose µg;/kg/day[c]	RfD µg/kg/day[d]
Lowest PCB	34	0.634	0.1
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 Zealand	28	0.522	0.05
MCMT New Zealand	32	0.596	0.1
Median values			
Faroes	48	0.895	0.1
New Zealand	24	0.447	0.05
Integrative			
All endpoints	32	0.596	0.1

[a]$BMDL_{05}$s from NRC (2000), Tables 7-4, 7-5, 7-6. Hair mercury was converted to blood mercury using a250:1 ratio (WHO, 1990) and an assumption of equivalent maternal and cord levels.
[b]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.
[d] Calculated using an UF of 10.

Rather than choose a single measure for the RfD critical endpoint, EPA based this RfD for thisassessment on several scores from the Faroes measures, with supporting analyses from the New Zealandstudy, and the integrative analysis of all three studies.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF = 10.

MF = 1.

In its report, NRC presented an analysis of the interindividual variability in the ingested dose of methylmercury corresponding to a given maternal-blood or hair-mercury concentration (NRC, 2000, pp.83-95). NRC cited two analyses of the variability and uncertainty in the ingested dose estimates based on the one-compartment model (Stern, 1997; Swartout and Rice, 2000) as well as similar analysis of a PBPKmodel (Clewell et al., 1999). In general, all three analyses found similar ranges of variability due to pharmacokinetic factors. The ratios of estimated ingested doses at the 50^{th} percentile/99^{th} percentile ranged from 1.7 to 3.3. Using maternal blood as the starting point, the consolidated range from the three analyses is 1.7 to 3.0.

Investigators have found that the placenta is not a barrier to the transfer of methylmercury from the mother to the developing fetus. Typically, a strong correlation exists between maternal-blood mercury concentrations and fetal-blood mercury concentrations, as shown by cord-blood. A 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). Overall, data from these studies 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.

EPA has chosen not to make a numerical adjustment between cord-blood and maternal-blood mercury. At this time the relationship between cord-blood and maternal-blood mercury is considered subject to variability and uncertainty, and is to be included in the determination of the uncertainty factor (UF).

CHOICE OF UNCERTAINTY FACTOR

An RfD is based on human data, so an interspecies UF was not needed. The points of departure were the BMDL for a number of endpoints from the Faroe Islands study, with supporting analyses from the New Zealand study, and an integrative analysis of all three recent large epidemiological studies. RfDs derived from these BMDLs all converged on the same value; this convergence provides reassurance that additional UFs, other than for intraspecies variability, are not needed. Further, no issues were identified that indicated the need for a modifying factor (i.e., MF = 1).

The two major phenomena included in the intraspecies UF for methylmercury were 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. EPA chose not to make a numerical adjustment in the dose conversion for the potential differences between cord- and maternal-blood mercury levels, but rather toconsider them additional aspects of toxicokinetic variability and uncertainty.

A quantitative uncertainty analysis of toxicodynamics was not possible. However, the population of the Faroe Islands is descended from Scandinavian stock that settled many generations ago, and is extremely homogeneous. The average toxicodynamic response of this population compared with that of the United States, which is genetically much more diverse, is unknown. Similarly, the relative variability of different populations also is unknown. A threefold UF for toxicodynamic variability and uncertainty was applied.

In calculating the methylmercury RfD for this assessment, a composite UF of 10 was used. This choice was made to account for the following factors:

1. Pharmacokinetic variability and uncertainty in estimating an ingested mercury dose from cord-blood mercury concentration: a factor of 3 was applied.

2. Pharmacodynamic variability and uncertainty: a factor of 3 was applied.

Choosing an overall UF of 10 is supported by additional analyses of the Faroese neuropsychological data, wherein the observations made of the most highly exposed subgroup were excluded from the model (Grandjean et al., 1997). Associations remained significant when the part of the cohort with maternal-hair mercury concentrations greater than 10 ppm was excluded from the analyses. This finding 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.

It is also important to note that no evidence of a threshold arose for methylmercury-related neurotoxicity within the range of exposures in the Faroe Islands study. This lack is indicated by the fact that, of the *K* power models, $K = 1$ provided a better fit for the endpoint models than did highervalues of K.

ADDITIONAL IDENTIFIED DATA GAPS

Areas were identified that require additional research and/or analysis.

Cardiovascular effects

There are two recently published studies 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.

Persistent and delayed neurotoxicity

Another area of concern is the onset or exacerbation of neurological deficits in aging populations previously exposed to methylmercury. In a follow-up study of the Minamata population, Kinjo et al. (1993) reported a high prevalence of sensory disturbance in people with Minamata disease (MD). Also evaluated were "acts of daily living" (ADL) that included

the abilities to independently eat, bathe, wash, dress, and use the toilet. The prevalence of deficits was relatively greater in persons with MD 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. Fukuda et al. (1999) evaluated adults who lived in a methylmercury-polluted area near Minamata City in Japan's Kumamoto Prefecture but who were not designated MD patients; the authors then compared them with age-matched adults. Complaints that were significantly more frequent 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) identified neurological and immune impairment in mice exposed prenatally to methylmercury as they approached 1 year of age. 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 (Newland and Rasmussen, 2000). Rice and colleagues (Rice, 1998, 1989; Rice and Hayward, 1999) identified accelerated aging of sensory system function in a series of studies in monkeys exposed during development to methylmercury. All of these observations are consistent with a hypothesis that either developmental or adult exposure to methylmercury can have adverse long-term sequelae that may not be detected for years or decades following cessation of exposure. However, these effects cannot be quantified based on available data.

Reproductive effects

Short-term, high-dose studies in rodents and guinea pigs have reported low sperm counts, testicular tubule atrophy, reduced litter size, decreased fetal survival, resorptions, and fetal malformations following exposure to methylmercury (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; Suter, 1975). No studies have been done of reproductive deficits in humans exposed to low-dose methylmercury, nor have there been any standard, two-generation reproductive studies. Bakir et al. (1973) noted a small number of pregnant women in the Iraqi population exposed to methylmercury in treated grain. Burbacher et al. (1988) reported decreased conception rates, early abortions, and stillbirths in monkeys treated with methylmercury, but at higher doses than those at which behavioral deficits were identified in the offspring. Rice (1996) also found no effect on time to pregnancy or viability of offspring at doses that produced neurotoxicity in the offspring. The available evidence therefore suggests that the developing nervous system is more sensitive to methylmercury than is reproductive competence.

The database upon which this RfD is based is considered to be of high quality and extensive. The effects of methylmercury on other organ systems, such as the kidney and liver, are well documented and occur at higher exposures than the effects on the nervous system. Further, data from the most sensitive subpopulation for nervous system effects, the fetus, is the basis for this RfD. It is therefore considered that no additional UF(s) is warranted at this time. However, as additional data become available, they may be used in future RfD derivation.

I.A.4. Additional Studies/Comments (Oral RfD)

In a second Faroese cohort recruited from children born between 1994 and 1995 (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). There was an exposure-related decrease in NOS as cord-blood levels increased from less than 10 µg/L to greater than 40 µg/L. This finding indicates a dose-dependent effect at levels as low as (or lower than) those for which neuropsychological deficits were reported in the study of 7-year-old children (Grandjean et al., 1997). The size of this study was relatively small (N = 182) and identified subtle changes at a very early developmental period, the clinical implications of which are less clear than the changes found in the study of 7-year-olds.

The Marsh et al. (1987) study, chosen as the most appropriate one for determining the RfD derived by EPA for methylmercury in 1995 (U.S. EPA, 1995), reported clinical neurologic signs in 81 mother-and-child pairs. Maternal-hair mercury concentrations were 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 for developmental effects was determined by application of a BMD approach. The analysts considered the combined incidence of all neurological effects in children exposed in utero. A Weibull model for extra risk was used to determine the BMD; in current terminology, this was a $BMDL_{10}$ (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). 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, 1997, pp. 6-22-6-23).

It is informative to compare RfDs derived from animal studies with 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). 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, 1989). Research in a cohort of monkeys dosed beginning *in utero* and continuing until 4 years of age revealed similar sensory system impairment (Rice and Hayward, 1999; 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. Reference doses derived from these data 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). The doses would be based on an UF of 10 to extrapolate from a LOAEL to a NOAEL and an UF of 10 to extrapolate from animals to humans. Gilbert and Grant-Webster (1995) suggested an RfD of 0.025 µg/kg/day based on the same data.

I.A.5. Confidence in the Oral RfD

Study — High
Database — High
RfD — High

The overall confidence in this RfD assessment is high. Three high-quality epidemiological studies have been published since the last derivation of the oral RfD in 1995. Two of the studies (Faroe Islands, New Zealand) reported effects on a number of neuropsychological endpoints, whereas the third (Seychelles Islands) reported no effects related to in utero exposure to methylmercury. Benchmark dose analysis of a number of endpoints from both the New Zealand and Faroe Islands study converged on an RfD of 0.1 µg/kg-day, as did the integrative analysis combining all three studies. Although there was coexposure to PCBs in the Faroe Islands study, statistical analysis indicated that the effects of PCBs and methylmercury were independent. Moreover, benchmark dose analysis of the endpoints that were significantly associated with methylmercury yielded RfDs that were approximately the same when corrected for PCBs. The same was true when the analysis was or based on the subset of the cohort in the lowest tertile with respect to PCB levels, as compared with the full cohort. These findings provide further evidence that the identified effects are in fact the result of methylmercury exposure.

The RfD used in this assessment report is the same as that derived in 1995 based on a study of a poisoning episode in Iraq. Experimental studies in monkeys also support the quantitative estimate of the RfD based on a NOAEL/LOAEL approach. Thus, there is a wealth of data from both epidemiological and experimental studies that converges on the derived RfD of 0.1 µg/kg/day.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — U.S. EPA, 2001

All reviewers' comments have been carefully evaluated and considered in the revision and finalization of this IRIS Summary. A record of these comments is summarized in the IRIS documentation files. ***To review, exit to the Summary and Response to the Peer Review for Methylmercury document (PDF)***.

Other EPA Documentation — U.S. EPA, 1980, 1984, 1987, 1988, 1995

Consensus Date - 06/19/2001

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Methylmercury conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Methylmercury (MeHg)
CASRN — 22967-92-6

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Methylmercury (MeHg)
CASRN — 22967-92-6
Last Revised — 05/01/1995

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. Evidence for Human Carcinogenicity

II.A.1. Weight-of-Evidence Characterization

Classification — C; possible human carcinogen

Basis — Based on inadequate data in humans and limited evidence of carcinogenicity in animals. Male ICR and B6C3F1 mice exposed to methylmercuric chloride in the diet had an increased incidence of renal adenomas, adenocarcinomas and carcinomas. The tumors were observed at a single site and in a single species and single sex. The renal epithelial cell hyperplasia and tumors were observed only in the presence of profound nephrotoxicity and were suggested to be a consequence of reparative changes in the cells. Several nonpositive cancer bioassays were also reported. Although genotoxicity test data suggest that methylmercury is capable of producing chromosomal and nuclear damage, there are also nonpositive genotoxicity data.

II.A.2. Human Carcinogenicity Data

Inadequate. Three studies were identified that examined the relationship between methylmercury exposure and cancer. No persuasive evidence of increased carcinogenicity attributable to methylmercury exposure was observed in any of the studies. Interpretation of these studies, however, was limited by poor study design and incomplete descriptions of methodology and/or results.

Tamashiro et al. (1984) evaluated the causes of death in 334 subjects from the Kumamoto Prefecture who had been diagnosed with Minamata disease (methylmercury poisoning) and died between 1970 and 1980. The subjects involved fishermen and their families who had been diagnosed with the disease; thus, Minamata disease was used as a surrogate for methylmercury exposure. The controls were selected from all deaths that had occurred in the same city or town as the cases and were matched on the basis of sex, age at death (within 3 years) and year of death; two controls were matched to each subject. Malignant neoplasms were designated as the underlying cause of death in 14.7% (49/334) of the subjects and 20.1% (134/668) of the controls. For 47 subjects in which Minamata disease was listed as the underlying cause of death, the investigators reanalyzed the mortality data and selected one of the secondary causes to be the underlying cause of death in order to allow examination of the subjects and controls under similar conditions and parameters. The three subjects for which Minamata disease was listed as the only cause of death were excluded from further analysis. Using the Mantel-Haenzel method to estimate odds ratios, no significant differences were observed between the subjects and controls with respect to the proportion of deaths due to malignant neoplasms among males, females or both sexes combined. The estimated odds ratios and 95% confidence intervals were 0.84 (0.49-1.43), 0.58 (0.28-1.21) and 0.75 (0.50-1.11) for males, females and both sexes combined. Similarly, no increases in odds ratio were observed among the subjects relative to the controls when malignant neoplasms were identified as a secondary cause of death or were listed on death certificates as one of the multiple causes of death. These data suggest that cancer incidence was not increased in persons with overt signs of methylmercury poisoning when compared with persons for whom no diagnosis of methylmercury poisoning had been made. Interpretation is limited by potential bias in designating the cause of death among patients with known Minamata disease and by the uncertainty regarding the extent of methylmercury exposure and undiagnosed Minamata disease among the controls. In a subsequent study, Tamashiro et al. (1986) compared the mortality patterns (between 1970 and 1981) among residents of the Fukuro and Tsukinoura districts in the Kumamoto Prefecture (inhabited mainly by fishermen and their families) with that of age-matched residents of Minamata City (also in the Kumamoto Prefecture) who died between 1972 and 1978. In this study, high exposure to methylmercury was inferred from residence in a district believed to have higher intake of local seafood. By contrast, in the 1984 study described above, high methylmercury exposure was inferred from a diagnosis of

Minamata disease. A total of 416 deaths were recorded in the Fukuro and Tsukinoura districts in 1970-1981, and 2325 deaths were recorded in Minamata City in 1972-1978. No statistically significant increase in the overall cancer mortality rate was observed; however, an increase in the mortality rate due to liver cancer was observed (SMR, 207.3; 95% CI, 116.0-341.9). Analysis of mortality by sex showed a statistically significant increase in the rate of liver cancer only among males (SMR, 250.5; 95% CI, 133.4-428.4). Males also had statistically significant higher mortality due to chronic liver disease and cirrhosis. The authors note that these results should be interpreted with caution because the population of the Fukuro and Tsukinoura districts had higher alcohol consumption and a higher prevalence of hepatitis B (a predisposing factor for hepatocellular cancer). Interpretation of these results is also limited by an incomplete description of the methodology used to calculate the SMRs; it is unclear whether the study authors used appropriate methods to compare mortality data collected over disparate time frames (12 years for exposed and 7 years for controls).

In a study from Poland, Janicki et al. (1987) reported a statistically significant increase in mercury content of hair in leukemia patients (0.92 +/- 1.44 ppm [sic]; n=47) relative to that in healthy unrelated patients (0.49 +/- 0.41 ppm; n=79). Similarly, the mercury content in the hair of a subgroup of leukemia patients (0.69 +/- 0.75; n=19) was significantly greater than that in healthy relatives who had shared the same residence for at least 3 years preceding the onset of the disease (0.43 +/- 0.24 ppm; n=52). When patients with specific types of leukemia were compared with the healthy unrelated subjects (0.49 +/- 0.41 ppm; n=79), only those with acute leukemia (type not specified; 1.24 +/- 1.93 ppm; n=23) had a significantly increased hair mercury content. No significant differences in hair mercury content were observed in 9 patients with chronic granulocytic leukemia or 15 patients with chronic lymphocytic leukemia when compared with the unrelated, healthy controls. The authors inferred that acute leukemia was associated with increased level of mercury in hair. This study is of limited use for cancer risk assessment because of the following: uncertainty regarding the correlation between the chronology of incorporation of mercury in the hair and onset of the disease; the small population studied; the failure to describe adequately the characteristics of the leukemia patients or healthy controls (age distribution, length of residence in the region, criteria for inclusion in the study); uncertainty regarding the source of mercury exposure (the authors presumed that exposure was the result of use of methylmercury-containing fungicides); and the failure to address exposure to other chemicals or adjust for other leukemia risk factors. Furthermore, the variability of hair mercury content was large, and the mean hair mercury levels were within normal limits for all groups. Thus, the statistical significance may have been due to chance.

The carcinogenic effects of organomercury seed dressing exposure were investigated in a series of case-control studies for incidence of soft-tissue sarcomas (Eriksson et al., 1981, 1990; Hardell and Eriksson, 1988) or malignant lymphomas (Hardell et al., 1981). These studies

were conducted in Swedish populations exposed to phenoxyacetic acid herbicides or chlorophenols (the exposures of primary interest in the studies), organomercury seed dressings, or other pesticides. Exposure frequencies were derived from questionnaires and/or interviews. Control groups from the same region of the country were matched to cases based on vital status. A total of 402 cases of soft-tissue sarcoma and (among persons not exposed to phenoxyacetic acid herbicides) 128 cases of malignant lymphoma were reported. In each study, the odds ratio for exposure to organomercury in seed dressings and the incidence of sarcoma or lymphoma was either <1.0 or the range of the 95% confidence interval for the odds ratio included 1.0; therefore, no association was indicated for organomercury exposure and soft-tissue sarcoma or malignant lymphoma. The study subjects were likely to have experienced exposures to the other pesticides and chemicals.

II.A.3. Animal Carcinogenicity Data

Limited. Three dietary studies in two strains of mice indicate that methylmercury is carcinogenic. Interpretation of two of the positive studies was complicated by observation of tumors only at doses that exceeded the MTD. A fourth dietary study in mice and four dietary studies in rats failed to indicate carcinogenicity associated with methylmercury exposure. Interpretation of four of the nonpositive studies was limited because of deficiencies in study design or failure to achieve an MTD.

Methylmercuric chloride (>99% pure) was administered in the diet at levels of 0, 0.4, 2 or 10 ppm (0, 0.03, 0.15 and 0.73 (mg/kg)/day in males and 0, 0.02, 0.11 and 0.6 (mg/kg)/day in females) to 60 ICR mice/sex/group for 104 weeks (Hirano et al., 1986). Interim sacrifices (6/sex/group) were conducted at 26, 52 and 78 weeks. Complete histopathological examinations were performed on all animals found dead, killed in extremis or killed by design. Mortality, group mean body weights and food consumption were comparable to controls. The first renal tumor was observed at 58 weeks in a high-dose male, and the incidence of renal epithelial tumors (adenomas or adenocarcinomas) was significantly increased in high-dose males (1/32, 0/25, 0/29 and 13/26 in the control, low-, mid- and high-dose groups, respectively). Ten of the 13 tumors in high-dose males were adenocarcinomas. These tumors were described as solid type or cystic papillary types of adenocarcinomas. No invading proliferation into the surrounding tissues was observed. The incidence of renal epithelial adenomas was not significantly increased in males, and no renal adenomas or adenocarcinomas were observed in any females studied. Focal hyperplasia of the tubular epithelium was reported to be increased in high-dose males (13/59; other incidences not reported). Increases in non-neoplastic lesions in high- dose animals provided evidence that an MTD was exceeded. Non-neoplastic lesions reported as increased in treated males included the following: epithelial degeneration of the renal proximal tubules; cystic kidney; urinary cast and pelvic dilatation; and decreased spermatogenesis. Epithelial degeneration of the renal

proximal tubules and degeneration or fibrosis of the sciatic nerve was reported in high-dose females.

Methylmercuric chloride (>99% pure) was administered in the diet at levels of 0, 0.4, 2 or 10 ppm (0, 0.3, 0.14 and 0.69 (mg/kg)/day in males and 0, 0.03, 0.13 and 0.60 (mg/kg)/day in females) to 60 B6C3F1 mice/sex/group for 104 weeks (Mitsumori et al., 1990). In high-dose males, a marked increase in mortality was observed after week 60 (data presented graphically; statistical analyses not performed by authors). Survival at study termination was approximately 50, 60, 60 and 20% in control, low-, mid- and high-dose males, respectively, and 58, 68, 60 and 60% in control, low-, mid- and high-dose females, respectively. The cause of the high mortality was not reported. At study termination, the mean body weight in high-dose males was approximately 67% of controls and in high-dose females was approximately 90% of controls (data presented graphically; statistical analyses not performed by study authors). The incidence of focal hyperplasia of the renal tubules was significantly increased in high-dose males (14/60; the incidence was 0/60 in all other groups). The incidence of renal epithelial carcinomas (classified as solid or cystic papillary type) was also significantly increased in high- dose males (13/60; the incidence was 0/60 in all other groups). The incidence of renal adenomas (classified as solid or tubular type) was also significantly increased in high-dose males; the incidence was 0/60, 0/60, 1/60 and 5/60 in control, low-, mid- and high-dose males, respectively, and 0/60, 0/60, 0/60 and 1/60 in control low-, mid- and high-dose females, respectively. No metastases were seen in the animals. The incidences of a variety of non- neoplastic lesions were increased in the high-dose mice including the following: sensory neuropathy; neuronal necrosis in the cerebrum; neuronal degeneration in the cerebellum; and chronic nephropathy of the kidney. Males exhibited tubular atrophy of the testis (1/60, 5/60, 2/60 and 54/60 in control, low-, mid- and high-dose, respectively) and ulceration of the glandular stomach (1/60, 1/60, 0/60 and 7/60 in control, low-, mid- and high-dose males, respectively). An MTD was achieved in mid-dose males and high- dose females. High mortality in high-dose males indicated that the MTD was exceeded in this group.

Mitsumori et al. (1981) administered 0, 15 or 30 ppm of methylmercuric chloride (>99% pure) in the diet (0, 1.6 and 3.1 (mg/kg)/day) to 60 ICR mice/sex/group for 78 weeks. Interim sacrifices of up to 6/sex/group were conducted at weeks 26 and 52. Kidneys were microscopically examined from all animals that died or became moribund after week 53 or were killed at study termination. Lungs from mice with renal masses and renal lymph nodes showing gross abnormalities were also examined. Survival was decreased in a dose- related manner; at week 78 survival was 40, 10 and 0% in control, low- and high-dose males, respectively, and 55, 30 and 0%, in control, low- and high- dose females, respectively (statistical analyses not performed). The majority of high-dose mice (85% males and 98% females) died by week 26 of the study. Examination of the kidneys of mice that died or were sacrificed after 53 weeks showed a significant increase in renal tumors in low-dose males

(13/16 versus 1/37 in controls). The incidence of renal epithelial adenocarcinomas in control and low-dose males was 0/37 and 11/16, respectively. The incidence of renal epithelial adenomas in control and low-dose males was 1/37 and 5/16, respectively. No renal tumors were observed in females in any group. No metastases to the lung or renal lymph nodes were observed. Evidence of neurotoxicity and renal pathology were observed in the treated mice at both dose levels. The high mortality in both groups of treated males and in high- dose females indicated that the MTD was exceeded in these groups. (Note: Hirano et al. (1986) was a followup to this study.)

Mitsumori et al. (1983, 1984) administered diets containing 0, 0.4, 2 or 10 ppm of methylmercuric chloride (0, 0.011, 0.05 and 0.28 (mg/kg)/day in males; 0, 0.014, 0.064 and 0.34 (mg/kg)/day in females) to 56/sex/group Sprague-Dawley rats for up to 130 weeks. Interim sacrifices of 10/group (either sex) were conducted at weeks 13 and 26 and of 6/group (either sex) at weeks 52 and 78. Mortality was increased in high-dose males and females. At week 104, survival was approximately 55, 45, 75 and 10% in control, low-, mid- and high-dose males, respectively, and 70, 75, 75 and 30% in control, low-, mid- and high-dose females, respectively (data presented graphically). All males in the high-dose group had died by week 119. Body weight gain was significantly decreased in high-dose males starting after week 44 and females after 44 weeks (approximately 10-20%, data presented graphically). No increase in tumor incidence was observed in either males or females. Noncarcinogenic lesions that were significantly increased in high-dose rats included the following: degeneration in peripheral nerves and the spinal cord (both sexes); degeneration of the proximal tubular epithelium (both sexes); severe chronic nephropathy (females); parathyroid hyperplasia (both sexes); polyarteritis nodosa and calcification of arterial wall (females); fibrosis of bone (females); bile duct hyperplasia (males); and hemosiderosis and extramedullary hematopoiesis in the spleen (males). Mid-dose males exhibited significantly increased degeneration of the proximal tubular epithelium and hyperplasia of the parathyroid. An MTD was achieved in mid-dose males and exceeded in high-dose males and high-dose females.

No tumor data were reported in a study using Wistar rats (Munro et al., 1980). Groups of 50 Wistar rats/sex/dose were fed diets containing methylmercury; doses of 2, 10, 50 and 250 (ug/kg)/day were fed for 26 months. High-dose female rats exhibited reduced body weight gains and showed minimal clinical signs of neurotoxicity; however, high-dose male rats showed overt clinical signs of neurotoxicity, decreased hemoglobin and hematocrit values, reduced weight gains and significantly increased mortality. Histopathologic examination of the high-dose rats of both sexes revealed demyelination of dorsal nerve roots and peripheral nerves. Males showed severe dose-related kidney damage, and females had minimal renal damage.

No increase in tumor incidence or decrease in tumor latency was observed in another study using rats of an unspecified strain (Verschuuren et al., 1976). Groups of 25 female and 25 male rats were administered methylmercuric chloride at dietary levels of 0, 0.1, 0.5 and 2.5 ppm (0, 0.004, 0.02 and 0.1 (mg/kg)/day) for 2 years. No significant effects were observed on growth or food intake except for a 6% decrease (statistically significant) in body weight gain at 60 weeks in high-dose females. Survival was 72, 68, 48 and 48% in control, low-, mid- and high-dose males, respectively, and 76, 60, 64 and 56% in control, low-, mid- and high-dose females, respectively (statistical significance not reported). Increases in relative kidney weights were observed in both males and females at the highest dose. No effects on the nature or incidence of pathological lesions were observed, and tumors were reported to have been observed with comparable incidence and latency among all of the groups. This study was limited by the small sample size.

No increase in tumor incidence was observed in a study using white Swiss mice (Schroeder and Mitchener, 1975). Groups of mice (54/sex/group) were exposed until death to methylmercuric acetate in the drinking water at two doses. The low-dose group received 1 ppm methylmercuric acetate (0.19 (mg/kg)/day). The high-dose group received 5 ppm methylmercuric acetate (0.95 (mg/kg)/day) for the first 70 days and then 1 ppm thereafter, due to high mortality (21/54 males and 23/54 females died prior to the dose reduction). Survival among the remaining mice was not significantly different from controls. Significant reductions in body weight were reported in high-dose males (9-15% lower than controls) and high-dose females (15-22% lower than controls) between 2 and 6 months of age. After dying, mice were weighed and dissected; gross tumors were counted, and limited histopathologic sections were made of heart, lung, liver, kidney and spleen for microscopic examination. This study is limited because complete histological examinations were not performed.

No increase in tumor incidence was observed in a multiple-generation reproduction study using Sprague-Dawley rats (Newberne et al., 1972). Groups of rats (30/sex) were given semisynthetic diets supplemented with either casein or a fish protein concentrate to yield dietary levels of 0.2 ppm methylmercury (0.008 (mg/kg)/day). Another group of controls received untreated rat chow. Rats that received diets containing methylmercury during the 2-year study had body weights and hematology comparable to controls. Detailed histopathological analyses revealed no lesions of the brain, liver, or kidney that were attributable to methylmercury exposure. Mortality data were not presented. Interpretation of these data is limited by the somewhat small group sizes and failure to achieve an MTD.

II.A.4. Supporting Data for Carcinogenicity

Blakley (1984) administered methylmercuric chloride to female Swiss mice (number/group not specified) in drinking water at concentrations of 0, 0.2, 0.5 or 2.0 mg/L for 15 weeks

(approximately 0, 0.03, 0.07 and 0.27 (mg Hg/kg)/day). At the end of week 3, a single dose of 1.5 mg/kg of urethane was administered intraperitoneally to 16-20 mice/group. No effects on weight gain or food consumption were observed. Lung tumor incidence in mice not administered urethane (number/group not specified) was less than one tumor/mouse in all groups. Statistically significant trends for increases in the number and size of lung adenomas/mouse with increasing methylmercury dose were observed; the number of tumors/mouse was 21.5, 19.4, 19.4 and 33.1 in control, low-, mid- and high-dose mice, respectively, and the tumor size/mouse was 0.70, 0.73, 0.76 and 0.76 mm in control, low-, mid- and high-dose mice, respectively. The study authors suggest that the increase in tumor number and size may have been related to the immunosuppressive activity of methylmercury. It should be noted that this study is considered a short-term bioassay, and pulmonary adenomas were the only tumor type evaluated.

Humans ingesting methylmercury-contaminated foods have been reported to experience chromosomal aberrations (Skerfving et al., 1970, 1974) or SCE (Wulf et al., 1986); however, interpretation of these studies is limited by methodological deficiencies.

As reviewed in WHO (1990), methylmercury is not a potent mutagen but appears to be capable of causing chromosome damage and nuclear perturbations in a variety of systems. In Bacillus subtilis, methylmercury produced DNA damage (Kanematsu et al., 1980). Methylmercury produced chromosomal aberrations and aneuploidy in human peripheral lymphocytes (Betti et al., 1992), SCE in human lymphocytes (Morimoto et al., 1982), and DNA damage in human nerve and lung cells as well as Chinese hamster V-79 cells and rat glioblastoma cells (Costa et al., 1991).

Bone marrow cells of cats treated with methylmercury in a study by Charbonneau et al. (1976) were examined by Miller et al. (1979). The methylmercury treatment resulted in an increased number of nuclear abnormalities and an inhibition of DNA repair capacity. Methylmercury induced a weak mutagenic response in Chinese hamster V-79 cells (Fiskesjo, 1979). Methylmercury also induced histone protein perturbations and influenced factors regulating nucleolus-organizing activity (WHO, 1990). Moreover, methylmercury has been reported to interfere with gene expression in cultures of glioma cells (WHO, 1990). Mailhes (1983) reported a significant increase in the number of hyperploid oocysts in Lak:LVG Syrian hamsters fed methyl mercury; however, no evidence of chromosomal damage was reported. Suter (1975) concluded that strain-specific differences exist with respect to the ability of methylmercury to produce dominant lethal effects in mice. Nondisjunction and sex-linked recessive lethal mutations were observed in Drosophila melanogaster treated with methylmercury (Ramel, 1972 as cited in U.S. EPA, 1985). Methylmercury produced single strand breaks in DNA in cultured L5178Y cells (Nakazawa et al., 1975).

Negative studies have also been reported. Methylmercury acetate was reported to be negative in a Salmonella typhimurium assay and a mouse micronucleus assay (Heddle and Bruce, 1977, as reported in Jenssen and Ramel, 1980). Methylmercury was not mutagenic and did not cause recombination in Saccharomyces cerevisiae but did slightly increase chromosomal nondisjunction (Nakai and Machida, 1973). Matsumoto and Spindle (1982) reported no significant increase in SCE in developing mouse embryos; they did report, however, that the developing mouse embryos were highly sensitive to in vitro treatment with methylmercury.

II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

None. The two studies by Mitsumori et al. (1981, 1990) were limited by high mortality in the high-dose males, the only group to exhibit a statistically significant increase in tumor incidence. Tumors were observed only in those dose groups in which the MTD had been exceeded. The study by Hirano et al. (1986) was not limited by low survival, but the tumors were observed in conjunction with nephrotoxicity and, thus, their incidence may have been a high-dose phenomenon that would not be expected to occur at low doses. The tumors appeared to originate from focal hyperplasia of the tubular epithelium induced as a reparative change. The hyperplasia was not observed in tubular epithelium that was undergoing early degenerative changes. Thus, the tumors may not occur where degenerative changes do not occur. The genotoxicity data indicate that methylmercury is not a potent mutagen but may produce chromosomal damage; these data do not support a hypothesis that methylmercury is a genotoxic carcinogen. It appears, rather, that methylmercury exerts its carcinogenic effect only at high dose, at or above an MTD. Because the linearized multistage procedure is based on the assumption of linearity at low doses, the relevance of deriving a slope factor based on data for which a threshold may exist is questionable.

It is likely that systemic non-cancer effects would be seen at methylmercury exposures lower than those required for tumor formation. Long- term administration of methylmercury to experimental animals produces overt symptoms of neurotoxicity at daily doses an order of magnitude lower than those required to induce tumors in mice.

II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

None.

II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

II.D.1. EPA Documentation

Source Documents -- U.S. EPA, 1995

This IRIS Summary is included in The Mercury Study Report to Congress which was reviewed by OHEA and EPA's Mercury Work Group in November 1994. An Interagency Review by scientists from other federal agencies took place in January 1995. The report was also reviewed by a panel of non-federal external scientists in January 1995 who met in a public meeting on January 25-26. All reviewers comments have been carefully evaluated and considered in the revision and finalization of this IRIS summary. A record of these comments is summarized in the IRIS documentation files.

II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review — 03/03/1994

Verification Date — 03/03/1994

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the cancer assessment for Methylmercury conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

III. [reserved]

IV. [reserved]

V. [reserved]

VI. Bibliography

Substance Name — Methylmercury (MeHg)
CASRN — 22967-92-6

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

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VII. Revision History

Substance Name — Methylmercury (MeHg)
CASRN — 22967-92-6

Date	Section	Description
05/01/1995	I.A.	Oral RfD summary replaced; new RfD
05/01/1995	II.	Carcinogenicity assessment on-line
07/27/2001	I.A., VI.A.	Oral RfD Summary and references replaced
12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Methylmercury (MeHg)
CASRN — 22967-92-6
Last Revised — 07/27/2001

- 22967-92-6
- MeHg
- Methylmercury
- Methylmercury II
- Mercury(1+), methyl-
- Mercury (1+), Methyl-, Ion
- Methyl Mercury
- Methylmercury (II) Cation
- Methylmercury Ion