Fact Sheet Date: March 12, 1998

NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE: Mercury **CAS REGISTRY NUMBER:** 7439-97-6

AMBIENT WATER QUALITY VALUE: 0.7 ug/L

BASIS: Non-oncogenic, Chronic

I INTRODUCTION

The ambient water quality value applies to the water column and is designed to protect humans from the effects of contaminants in sources of drinking water; it is referred to as a Health (Water Source) or H(WS) value.

Regulations (6 NYCRR 702.2) require that the water quality value be based on the procedures in sections 702.3 through 702.7. Potential water quality values are derived below, and the value of 0.7 ug/L is selected for mercury as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

Mercury has a Specific MCL of 2 ug/L as defined in 700.1. This is a maximum contaminant level for drinking water established by the New York State Department of Health under the State Sanitary Code (10 NYCRR Part 5, Public Water Supplies).

Mercury is not in a principal organic contaminant class as defined in 700.1.

The U.S. Environmental Protection Agency has established a maximum contaminant level goal (MCLG) of 2 ug/L and a MCL of 2 ug/L for drinking water for mercury.

B. Derivation of Water Quality Value

Regulations require that the water quality value for mercury not exceed the Specific MCL of 2 ug/L.

III ONCOGENIC EFFECTS (702.4)

Mercury is not considered carcinogenic (U.S. EPA, 1995a).

IV NON-ONCOGENIC EFFECTS (702.5)

U.S. EPA (1995a) conducted a comprehensive review of toxicological data on non-oncogenic effects for mercury as part of criteria development under the Great Lakes Water Quality Initiative (GLI) (attached as Exhibit I). The GLI was a joint undertaking by U.S. EPA and the Great Lakes States and included representatives of interest groups. Its final regulations and the criteria document for this substance received extensive public review in a formal rule making process.

However, U.S. EPA (1995b) strongly encourages the use of the toxicity determinations on U.S. EPA's Integrated Risk Information System (IRIS) when deriving water quality values. Subsequent to the publication of the GLI mercury criteria, U.S. EPA presented on IRIS a reference dose (RfD) for mercury of 1×10^{-4} mg/(kg · day) (U.S. EPA, 1995c). This is attached as Exhibit II. This RfD, less stringent than the value of 6×10^{-5} mg/(kg · day) used for deriving the GLI criteria, is based on a benchmark dose analysis of continuous data for occurrence of clinical effects in children (Marsh, 1987). The Department believes this new RfD to be more appropriate than the GLI criteria as the basis for a statewide water quality value.

This RfD, equivalent to an acceptable daily intake (ADI), is used to derive a water quality value for protection from non-oncogenic effects using New York State procedures as described below.

A potential water quality value is calculated from the ADI, above, based on a 70 kg adult consuming 2 liters of water per day and allocating 20% of the ADI to drinking water, as follows:

Water Quality Value = $\underline{[1 \times 10^{-4} \text{ mg/(kg} \cdot \text{day)}] [1000 \text{ ug/mg}] [70 \text{ kg}] [0.2]}$ = 0.7 ug/L

[2 L/day]

V CHEMICAL CORRELATION (702.7)

A value based on chemical correlation is not applicable because data are sufficient to evaluate non-oncogenic effects, and mercury is not considered to be oncogenic.

VI SELECTION OF VALUE

The H(WS) value is designed to protect humans from oncogenic and non-oncogenic effects from contaminants in sources of drinking water. To protect for these effects, regulations (6 NYCRR 702.2(b)) require that the value be the most stringent of the values derived using the procedures found in sections 702.3 through 702.7. The non-oncogenic value of 0.7 ug/L (6 NYCRR 702.5) is the most stringent value derived by these procedures and is the ambient water quality value for mercury.

VII REFERENCES

6 NYCRR (New York State Codes, Rules and Regulations). Water Quality Regulations, Surface Water and Groundwater Classifications and Standards: Title 6 NYCRR, Chapter X, Parts 700-705. Albany, NY: New York State Department of Environmental Conservation.

10 NYCRR (New York State Codes, Rules and Regulations). Public Water Systems: Title 10 NYCRR, Chapter 1, State Sanitary Code, Subpart 5-1. Albany, NY: New York State Department of Health, Bureau of Public Water Supply Protection.

U.S. EPA (Environmental Protection Agency). 1995a. Great Lakes Water Quality Initiative Criteria Documents for the Protection of Human Health. Washington, D.C.: Office of Water. EPA-820-B-95-006.

U.S. EPA (Environmental Protection Agency). 1995b. Great lakes Water Quality Initiative Technical Support Document for Human Health Criteria and Values. Washington, D.C.: Office of Water EPA-820-1395-007.

U.S. EPA (Environmental Protection Agency). 1995c. Mercury. On-line. Integrated Risk Information System (IRIS). Cincinnati, OH: Office of Research and Development, Environmental Criteria and Assessment Office.

New York State Department of Environmental Conservation
Division of Water
March 28, 1997

EXHIBIT I
(From U.S. EPA, 1995a)

GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR MERCURY
CAS NO. 7439-97-6
(INCLUDING METHYLMERCURY, CAS NO. 22967-92-6)

Tier 1 Human Noncancer Criterion

A review of the available literature on the environmental cycling, fate, and toxicity of mercury and mercury compounds indicates that HNC derivation is most appropriately based upon the human dose-response to methylmercury. Numerous reviews on mercury toxicity (e.g., WHO, 1976; 1990; EPA, 1980; 1984a; 1984b; 1985a) describe the human dose-response relationship resulting from food-borne exposure to methylmercury in Iraq (1971-72), Japan (1940s thru 1960s), and elsewhere. These data are judged to be sufficient fo0r Tier 1 criterion derivation.

Studies of wi0despread human food-borne exposure to methylmercury in fish (Minamata and Niigata, Japan) and in seed grain (Iraq) have shown that neurological symptoms of mercury toxicity in adults appear with blood levels of mercury in the range of 200 to 500 ng/ml (Nordberg and Strangert, 1976; Clarkson et al., 1976; WHO, 1976; 1990; EPA, 1980; 1984a; 1984b; 1985a). However, there are a few studies of workers exposed occupationally to mercury via inhalation which suggest that blood mercury levels as low as 10-20 ng/ml may result in the development of signs of renal dysfunction (increased proteinurea and albuminurea) and abnormal psychomotor performance (Roels et al., 1982; Piikivi et al., 1984; Buchet et al., 1980). The adult LOAEL of 200 ng/ml in blood has been associated with an intake level of 200-500 ug/d (EPA, 1980; WHO, 1990), although the human adult population's variability in mercury elimination rate is significantly bimodal (Clarkson et al, 1976; Nordberg and Strangert, 1976). The human LOAEL of 200 ug/d, or 3 ug/kg/d, for the development of neurological effects forms the basis for the RfD derived by EPA (1985b) and the fish consumption criteria derived by EPA (1980). It has been estimated that less than 5% of the adult population will experience neurological effects at these levels (WHO, 1990).

Risk assessments by EPA (1980) and EPA (1985b) utilized a total uncertainty factor of 10 in conjunction with the LOAEL dose, and both stated that the LOAEL and the risk assessment addressed the sensitivity and the adequate protection of both pre- and postnatal exposures. EPA (1980) justified the 10-fold uncertainty factor as an accounting for "individual differences in habits of fish consumption and in susceptibility to the toxic effects of methylmercury, including

prenatal exposures". EPA (1985b) justified the 10-fold uncertainty factor "to adjust the LOAEL to what is expected to be a NOAEL. Since the effects are seen in sensitive individuals for chronic exposure, no additional factors are deemed necessary".

For the derivation of the Tier 1 Human Noncancer Criterion, a total uncertainty factor of 50 will be utilized. This is composed of a 10-fold factor to adjust the adult LOAEL to a presumed adult NOAEL and an additional 5-fold factor to protect CNS development during the sensitive fetal life stages. The use of a 10-fold factor for LOAEL-to-NOAEL conversion is justified by consideration of the severity and irreversibility of the effects at the LOAEL, the long latency of mercury effects, and the occupational studies which suggest that the threshold may be considerably lower than 200 ng Hg/ml blood.

An uncertainty factor of 5 is utilized to ensure that the criterion will be protective of the fetal effects of mercury exposure via maternal ingestion of mercury-contaminated fish. The particular sensitivity of the fetus has been recognized in reviews of mercury toxicity (WHO, 1976; 1990; D'Itri, 1978; EPA, 1980; 1984a; 1984b; 1985a). The earliest of these assessments (WHO, 1976) developed a dose-response relationship for the adult which was not presented as being accurate for the more sensitive fetal effects. It was noted that many infant victims reported from Minamata had severe cerebral involvement (palsy and retardation) whereas their mothers had mild or no manifestations of poisoning. Although these observations were qualitatively confirmed by animal studies, quantification of the difference in the degree of sensitivity between human fetuses and adults has been elusive. EPA (1980; 1985b) utilized a total uncertainty factor of 10 and assumed that the resulting risk assessments were adequately protective of fetal effects. However, WHO (1990) reviewed the database on oral methylmercury ingestion, including more recent studies, and made significant advances in delineating quantitatively the greater sensitivity of prenatal exposure relative to adult exposure. Although WHO (1990) did not recommend a particular numeric sensitivity factor for the fetus, their assessment sufficiently demonstrates that an additional uncertainty factor is reasonable and prudent to help ensure adequate protection. They concluded that adult effects occur at a LOAEL (for 5% increased occurrence rate) of 200 ng/ml blood, or at 50 ug/g in hair. Fetal effects on CNS development occur at a LOAEL (5% increased occurrence rate) of 10-20 ug/g as a peak level in maternal hair. Since the level of mercury in maternal blood correlates to the simultaneous level in new hair growth, the hair serves as a fairly reliable indicator of maternal blood mercury levels during pregnancy. The data suggest that the fetal effects LOAEL may be 2.5 to 5 times lower than the adult effects LOAEL.

The HNC is derived from the adult LOAEL dose of 3 ug/kg/d which is associated with the LOAEL in blood of 200 ng/ml, and an uncertainty factor of 50. The methylmercury form is the most significant of the

mercury compounds from the standpoint of ambient environmental mercury and human exposures and health impacts. Aqueous concentrations of mercury, and especially methylmercury, may be very low in ambient waters. Other forms of mercury, such as elemental mercury or mercury (I), may be reasonably anticipated to be transformed predominantly to methylmercury in the aquatic environment via oxidation to mercury (II) and biomethylation. The biomethylation of inorganic mercury and the very high propensity for methylmercury to bioaccumulate in aquatic organisms result in a high and significant human exposure potential (EPA, 1980; D'Itri, 1990; Annett et al., 1975). The various forms of mercury released to and found in the ambient aquatic environment may be assumed to be converted primarily to methylmercury. Therefore, the HNC is expressed as the total recoverable mercury concentration. Finally, a body weight of 65 kg was used instead of a body weight of 70 kg because of the potential fetal effects of mercury exposure via maternal ingestion of mercury-contaminated fish.

$$ADE = \frac{NOAEL}{UF} = \frac{3.0 \times 10^{-3}\ mg/kg/d}{50} = 6.0 \times 10^{-5}\ mg/kg/day$$

Where: Uncertainty Factor = 50, composed of:
10x for use of LOAEL instead of NOAEL
5x for intraspecies differences
(protection of fetal CNS development)

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EXHIBIT II
(From U.S. EPA, 1995c, printed 1997)

1 - IRIS
NAME - Methylmercury (MeHg)
RN - 22967-92-6

RDO -
o ORAL RFD SUMMARY:

Critical Effect	Experimental Doses*	UF	MF	RfD
----Developmental neurologic abnormalities in human infants Human epidemiologic studies	Benchmark Dose: 11 ppm in hair; equivalent to maternal blood levels 44 ug/L and body burdens of 69 ug or daily intake of 1.1 ug/kg-day	10	1	1E-4 mg/kg-day

Marsh et al., 1987;
Seafood Safety, 1991
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*Conversion Factors and Assumptions -- Maternal daily dietary intake levels were used as the dose surrogate for the observed developmental effects in the infants. The daily dietary intake levels were calculated from hair concentrations measured in the mothers. This conversion is explained in the text below. A benchmark dose approach was used rather than a NOAEL/LOAEL approach to analyze the neurological effects in infants as the response variable. This analysis is also explained in the text below.
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o ORAL RFD STUDIES:

Marsh, D.O., T.W. Clarkson, C. Cox, L. Amin-Zaki and S. Al-Trkiriti. 1987. Fetal methylmercury poisoning: Relationship between concentration in a single strand of maternal hair and child effects. Arch. Neurol. 44: 1017-1022.

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In 1971-1972 many citizens in rural Iraq were exposed to MeHg-treated seed grain that was mistakenly used in home-baked bread. Latent toxicity was observed in many adults and children who had consumed bread over a 2- to 3-month period. Infants born to mothers who ate

contaminated bread during gestation were the most sensitive group. Often infants exhibited neurologic abnormalities while their mothers showed no signs of toxicity. Some information indicates that male infants are more sensitive than females. Among the signs noted in the infants exposed during fetal development were cerebral palsy, altered muscle tone and deep tendon reflexes as well as delayed developmental milestones, i.e., walking by 18 months and talking by 24 months. The neurologic signs noted in adults included paresthesia, ataxia, reduced visual fields and hearing impairment. Some mothers experienced paresthesia and other sensory disturbances but these symptoms were not necessarily correlated with neurologic effects in their children. Unique analytic features of mercury (Hg), that is, analysis of segments of hair correlated to specific time periods in the past permitted approximation of maternal blood levels that the fetuses were exposed to in utero. The data collected by Marsh et al. (1987) summarizes clinical neurologic signs of 81 mother and child pairs. From x-ray fluorescent spectrometric analysis of selected regions of maternal scalp hair, concentrations ranging from 1 to 674 ppm were determined and correlated with clinical signs observed in the affected members of the mother-child pairs. Among the exposed population were affected and unaffected individuals throughout the dose-exposure range.

While the purpose of the Seafood Safety publication was to critique the quantitative risk assessment that FDA had performed for MeHg, this material is included in the EPA risk assessment because the Tables of Incidence of various clinical effects in children that were provided in the FDA assessment readily lend themselves to a benchmark dose approach. Specifically the continuous data for the Iraqi population that was reported in Marsh et al. (1987) are placed in five dose groups and incidence rates are provided for delayed onset of walking, delayed onset of talking, mental symptoms, seizures, neurological scores above 3 and neurological scores above 4 for affected children. Neurologic scores were determined by clinical evaluation for cranial nerve signs, speech, involuntary movement, limb tone strength, deep tendon reflexes, plantar responses, coordination, dexterity, primitive reflexes, sensation, posture, and ability to sit, stand and run. This paper provided groupings of the 81 mother-infant pairs for various effects, and the authors present the data in Tables 6-11 through 6-16B.

EQUATION USED FOR CALCULATION OF DAILY DOSE: From the concentration of Hg present in maternal hair, a corresponding blood concentration value is determined. A hair concentration of 11 ppm converts to a blood concentration of 44 ug/L; the following equation can then be used to determine the daily dose that corresponds to that blood concentration of Hg. Use of this equation is based on the assumption that steady-state conditions exist and that first-order kinetics for Hg are being followed.

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

d (ug/day) = 44 ug/L multiplied by 0.014 multiplied by 5 liters divided by 0.95 then divided by 0.05 yields 65 ug/day

where:

d = daily dietary intake (expressed as ug of MeHg)

C = concentration in blood (expressed as ug/L)

b = elimination constant (expressed as days-1)

V = volume of blood in the body (expressed as liters)

A = absorption factor (unitless)

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

The following sections provide the data and rationale supporting the choice of parameter values used in the conversion equation. It should be noted that even if the upper or lower ranges of the parameter values were used, the conversion factor precision remains the same due to rounding error. The Agency realizes that new pharmacokinetic data may become available that warrant a change to some o hair levels for a group of individuals with moderate to high fish consumption rates, with yearly highs occurring in the fall and early winter (Phelps et al., 1980; Suzuki et al., 1993). The high slope reported by Tsubaki and Irukayama (1977) may have reflected the fact that Hg levels were declining at the time of sampling so that the hair levels reflect earlier, higher blood levels. Phelps et al. (1980) obtained multiple blood samples and sequentially analyzed lengths of hair from individuals. Both hair and blood samples were taken for 339 individuals in Northwestern Ontario. After reviewing the various reports for converting hair concentrations to blood concentrations, the Phelps paper was selected because of the large sample size and the attention to sampling and analysis. The ratio Phelps observed between the total Hg concentration in hair taken close to the scalp and simultaneous blood sampling for this group was 296. To estimate the actual ratio, the authors assumed that blood and hair samples were taken following complete cessation of MeHg intake. They also assumed a half-life of MeHg in blood of 52 days and a lag of 4 weeks for appearance of the relevant level in hair at the scalp. Phelps also determined that 94% of the Hg in hair was MeHg. Based on these assumptions, they calculated that if the actual hair:blood ratio was 200, they would have observed a ratio of 290. Based on these and other considerations, Phelps states that the actual ratio is "probably higher than 200, but less than the observed value of 296." As the authors point out, 2/3 of the study population were sampled during the falling phase of the seasonal variation (and 1/3 or less in the rising phase). This methodology would tend to result in a lower observed ratio;

therefore, the actual average is likely to be greater than 200.

In view of these limitations a value of 250 was considered acceptable for the purpose of estimating average blood levels in the Iraqi population.

CALCULATION OF DIETARY INTAKE FROM BLOOD CONCENTRATION: The first step in this process is to determine the fraction of Hg in diet that is absorbed. Radio-labeled methyl-mercuric nitrate (MeHgNO3) was administered in water to three healthy volunteers (Aberg et al., 1969). The uptake was >95%. Miettinen et al. (1971) incubated fish liver homogenate with radio-labeled MeHgNO3 to produce methylmercury proteinate. The proteinate was then fed to fish that were killed after a week and then cooked and fed to volunteers after confirmation of MeHg in the fish. Mean uptake exceeded 94%. Based on these experimental results, this derivation used an absorption factor of 0.95.

The next step involves determining the fraction of the absorbed dose that is found in the blood. There are three reports on the fraction of absorbed MeHg dose distributed to blood volume in humans. Kershaw et al. (1980) report an average fraction of 0.059 of absorbed dose in total blood volume, based on a study of five adult male subjects who ingested MeHg-contaminated t una. In a group of nine male and six female volunteers who had received 203 Hg-methylmercury in fish approximately 10% of the total body burden was present in 1 liter of blood in the first few days after exposure, dropping to approximately 5% over the first his parameter in the past (WHO, 1990).

ELIMINATION CONSTANT: Based on data taken from four studies, reported clearance half-times from blood or hair ranged from 48-65 days. Two of these studies included the Iraqi population exposed during the 1971-1972 outbreak. The value from the Cox study (Cox et al., 1989) is derived from the study group that included the mothers of the infants upon which this risk assessment is based. The average elimination constant of the four studies is 0.014; the average of individual values reported for 20 volunteers ingesting from 42-233 ug Hg/day in fish for 3 months (Sherlock et al., 1982) is also 0.014.

VOLUME OF BLOOD IN THE BODY AND BODY WEIGHT: Blood volume is 7% of body weight as has been determined by various experimental methods and there is an increase of 20 to 30% (to about 8.5 to 9%) during pregnancy (Best and Taylor, 1961). Specific data for the body weight of Iraqi women were not found. Assuming an average body weight of 60 kg. (Snyder et al., 1981) and a blood volume of 9% of body weight during pregnancy, a blood volume of 5.4 liters is derived.

DERIVATION OF A BENCHMARK DOSE: Benchmark dose estimates were made for excess risk above background based on a combination of all childhood neurologic end points. This method was chosen since the Agency felt

that any childhood neurologic abnormality is considered an adverse effect and likely to have serious sequelae lasting throughout lifetime. In addition, grouping of all neurologic endpoints provided a much better goodness of fit of the data than when any endpoint was used individually. The endpoints that were grouped delayed the onset of walking and talking, neurologic scores <3, mental symptoms, and seizures. Using these data sets taken from the Seafood Safety paper, benchmark doses at the 1, 5 and 10% incidence levels were constructed using both Weibull and polynomial models. The Weibull model places the maximum likelihood estimate with corresponding 95% confidence level at 11 ppm of MeHg in maternal hair. The Agency decided to use the lower 95% confidence level for the 10% incidence rate. Recent research by Faustman et al. (1994) and Allen et al. (1994a,b) suggests that the 10% level for the benchmark dose roughly correlates with a NOAEL for quantal developmental toxicity data. The 95% lower confidence limits on doses corresponding to the 1, 5, and 10% levels were calculated using both models and the values determined using the polynomial model always fell within 3% of the Weibull values. For final quantitative analysis the Weibull model was chosen because of goodness of fit of the data and because this model has been used in the past by the Agency for developmental effects. The experience of the Agency indicates that this model performs well when modeling for developmental effects.

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o ORAL RFD UNCERTAINTY:

UF -- An uncertainty factor of 3 is applied for variability in the human population, in particular the variation in the biological half-life of MeHg and the variation that occurs in the hair:blood ratio for Hg. In addition, a factor of 3 is applied for lack of a two-generation reproductive study and lack of data for the effect of exposure duration on sequelae ofe between 12 and 30 months of age. An attempt was made to account for possible confounding factors; the interviewers determined alcohol and tobacco consumption patterns among the mothers of affected children. Age of the mothers and multiparity was also taken into account in analysis of the data. The average indices of exposure were the same for boys and girls at 6 ug/g; only 6% had exposure above 20 ug/g. The prevalence of multiple abnormal neurologic findings was about 4% for children of both sexes. The most frequently observed abnormality was delayed deep tendon reflexes; this was seen in 11.4% of the boys and 12.2% of the girls. These investigators found that when there was a positive association between maternal Hg exposure and abnormal neurologic signs in boys, the incidence rate was 7.2%. The incidence rate for neurologic disorders in daughters was less and was found to be not statistically significant. Disorders of muscle tone were usually confined to the legs. Persistence of the Babinski reflex and incoordination due to delayed motor development were seen with equal frequency for both sexes. The discriminant analysis conducted for the boys to distinguish the 15 cases with abnormal muscle tone or reflexes from the 82 normal

controls was unable to separate differences between these groups based on confounding variables. The prevalence of abnormality of muscle tone or reflexes was found to increase 7 times with each increase of 10 ug/g of the prenatal exposure index. Although this study provides supportive data for the RfD, it is not included with the principal studies because it was confounded by alcoholism and smoking among mothers.

Studies performed in New Zealand investigated the mental development of children who had prenatal exposure to MeHg (Kjellstrom et al., 1986, 1989). A group of 11,000 mothers who regularly ate fish were initially screened by survey and of these about 1000 had consumed fish in three meals per week during pregnancy. Working from this large population base, 31 matched pairs were established. For proper comparison a reference child matched for ethnic group and age of mother, child's birthplace and birth date was identified for each high Hg child. Retrospective Hg concentrations were determined from the scalp hair of the mothers to match the period of gestation. The average hair concentration for high-exposure mothers was 8.8 mg/kg and for the reference group it was 1.9 mg/kg.

The children of exposed mothers were tested at 4 and 6 years of age. At 4 years of age the children were tested using the Denver Developmental Screen Test (DDST) to assess the effects of Hg. This is a standardized test of a child's mental development that can be administered in the child's home. It consists of four major function sectors: gross motor, fine motor, language, and personal-social. A developmental delay in an individual item is scored as abnormal, questionable when the child has failed in their response and at least 90% of the children can pass this item at a younger age. The results of the DDST demonstrated 2 abnormal scores and 14 questionable scores in the high Hg-exposed group and 1 abnormal and 4 questionable scores in the control group. Analysis of the DDST results by sector showed that developmental delays were most commonly noted in the fine motor and language sectors but the dif Hg concentration of the mothers in this study were lower than those associated with CNS effects in children exposed in Japan and Iraq. Results of the DDST demonstrated 2 abnormal scores and 14 questionable scores in the high Hg-exposed group and 1 abnormal and 4 questionable scores in the control group. Analysis of the DDST results by sector showed that developmental delays were most commonly noted in the fine motor and language sectors but the differences for the experimental and control groups were not significant. The data obtained from this study is too limited for detailed dose-response analysis. The differences in performance of the DDST between high Hg-exposed and referent children could be due to confounding variables. DDST results are highly dependent upon the age of the child. Infants of the Hg-exposed group more frequently had low birth weights and were more likely to be born prematurely. Use of this study is also limited by the fact that there was only a 44% participation rate.

A second stage follow-up of the original Kjellstrom study was carried out when the children were 6 years old to confirm or refute the developmental findings observed at age 4 (Kjellstrom et al., 1989). In this later study the high exposure children were compared with threecontrol groups with lower prenatal Hg exposure. The mothers of children in two of these control groups had high fish consumption and average hair Hg concentrations during pregnancy of 3-6 mg/kg and 0-3 mg/kg, respectively. For this study the high exposure group was matched for maternal ethnic group, age, smoking habits, residence, and sex of the child. For this second study, 61 of 74 high-exposure children were available for study. Each child was tested at age 6 with an array of scholastic, psychological, and behavioral tests which included the Test of Language Development (TOLD), the Wechsler Intelligence Scale for Children, and the McCarthy Scale of Children's Abilities. The results of the tests were compared between groups. Confounding was controlled for by using linear multiple regression analysis. A principal finding was that normal results of the psychological test variables were influenced by ethnic background and social class. The high prenatal MeHg exposure did decrease performance in the tests, but it contributed only a small part of the variation in test results. The investigation found that an average hair Hg level of 13-15 mg/kg during pregnancy was consistently associated with decreased test performance. Due to the small size of the actual study groups it was not possible to determine if even lower exposure levels might have had a significant effect on test results. The Kjellstrom studies are limited for assessing MeHg toxicity because the developmental and intelligence tests used are not the most appropriate tests for defining the effects of MeHg. Also, greater significance was seen in differences of cultural origins of the children than the differences in maternal hair MeHg concentrations.

The initial epidemiologic report of MeHg poisoning involved 628 human cases that occurred in Minamata Japan between 1953 and 1960 (Tsubaki and Irukayama, 1977). The overall prevalence rate for the Minamata region for neurologic and mental disorders was 59%. Among this group 78 deaths occurred and hair concentrations of Hg ranged from 50-700 ug/g. Hair Hg concentrations were determined through the use of less precise analytic methods than were available for later studies. The specific values derived from thgolgi cells and Purkinje cells. Extensive investigations of congenital Minamata disease were undertaken and 20 cases that occurred over a 4-year period were documented. In all instances the congenital cases showed a higher incidence of symptoms than did their mothers. Severe disturbances of nervous function were described and the affected offspring were very late in reaching developmental milestones. Hair concentrations of Hg in affected infants ranged from 10 to 100 ug/g. Data on hair Hg levels for the mothers during gestation were not available.

Rice (1989) dosed five cynomolgus monkeys (Macaca fascicularis) from birth to 7 years of age with 50 ug/kg-day and performed clinical and neurologic examinations during the dosing period and for an additional

6 years. As an indicator of the latent effects of MeHg, objective neurologic examinations performed at the end of the observation period revealed insensitivity to touch and loss of tactile response. In addition, monkeys dosed with MeHg were clumsier and slower to react when initially placed in an exercise cage as well as in the later stages of the observation period.

Gunderson et al. (1986) administered daily doses of 50-70 ug/kg of MeHg to 11 crab-eating macaques (Macaca fascicularis) throughout pregnancy which resulted in maternal blood levels of 1080-1330 ug/L in mothers and 1410-1840 ug/L in the offspring. When tested 35 days after birth the infants exhibited visual recognition deficits.

In another study, groups of 7 or 8 female crab-eating macaques (Macaca fascicularis) were dosed with 0.50 and 90 ug/kg-day of MeHg through four menstrual cycles (Burbacher et al., 1984). They were mated with untreated males and clinical observations were made for an additional 4 months. Two of seven high-dose females aborted and three did not conceive during the 4-month mating period; the other two females delivered live infants. Two of seven females of the 50 ug/kg-day dose group aborted; the remaining females delivered live infants. All 8 females of the control group conceived and 6 delivered live infants. These reproductive results approached but did not reach statistical significance. Reproductive failure within dose groups could be predicted by blood Hg levels. The dams did not show clinical signs of MeHg poisoning during the breeding period or gestation but when females were dosed with 90 ug/kg-day for 1 year 4/7 did show adverse neurologic signs.

Bornhausen et al. (1980) reported a decrease in operant behavior performance in 4-month-old rats whose dams had received 0.005 and 0.05 mg/kg-day of MeHg on days 6 through 9 of gestation. A statistically significant effect (<0.05) was observed in offspring whose dams had received 0.01 and 0.05 mg/kg during gestation. The authors postulated that more severe effects of in utero exposure would be seen in humans since the biological half-time of Hg in the brain of humans is 5 times longer than the rat. In addition, much longer in utero exposure to Hg would occur in humans since gestation is much longer in chronologic time.

In another investigation groups of Wistar rats (50/sex/dose) were administered daily doses of 2, 10, 50 and 250 ug/kg-day of MeHg for 26 months (Munro et al., 1980). Female rats that received 25 ug/kg-day had reduced body weight gains and showed only minimal clinical signs of neurotoxicity; however, male rats that received this dose did show overt clinical signs of neurotoxicity, had decreased hemoglobin and hematocrit values, had reduced weight gains, and showed increased mortality. Histopathologic examination of rats of both sexes receiving 25 ug/kg-day revealed demyelination of dorsal nerve roots and peripheral nerves. Males showed severe kidney damage and females had

minimal renal damage. This study showed a NOAEL of 5 ug/kg-day and a LOAEL of 25 ug/kg-day.

A 2-year feeding study of MeHg chloride was conducted in B6C3F1 mice (60 mice/sex/group) at doses of 0, 0.4, 2 and 10 ppm (0, 0.04, 0.17, and 0.83 mg/kg-day) to determine chronic toxicity and possible carcinogenic effects (Mitsumori et f 0.04 mg/kg-day and a LOAEL of 0.17 mg/kg-day was determined. These results indicated that B6C3F1 mice are more sensitive to the neurotoxic effects of MeHg than ICR mice.

KINETICS: MeHg in the diet is almost completely absorbed into the bloodstream. Animal studies indicate (Walsh, 1982) that age has no effect on the efficiency of the gastrointestinal absorption, which is usually in excess of 90%. From the bloodstream MeHg is distributed to all tissues, and distribution is complete within 4 days in humans. The time necessary to reach peak brain levels from a single oral dose is 1 or 2 days longer than other tissues and at this time the brain contains 6% of the total dose. Also at this time the brain concentration is six times that of the blood.

Methylmercury is converted to inorganic Hg in various tissues at different rates in mammals. The fraction of total Hg present as Hg++ depends on the duration of exposure and the time after cessation of exposure. The percentages of total Hg present as inorganic Hg++ in tissues of the Iraqi population exposed for 2 months were: whole blood 7%, plasma 22%, breast milk 39% and urine 73%. Measurements in the hepatic tissue of patients that had died was 16-40% of Hg++.

The fecal pathway accounts for 90% of the total elimination of Hg in mammals after exposure to MeHg. Essentially all Hg in feces is in the inorganic form. The process of fecal elimination begins with biliary excretion with extensive recycling of both MeHg and Hg++ complexed with glutathione. Inorganic Hg is poorly absorbed across the intestinal wall, but MeHg is readily reabsorbed such that a secretion-resorption cycle is established. The intestinal microflora convert MeHg to inorganic Hg.

Whole body half-times determined in human volunteers averaged 70 days with a range of 52-93 days. Observations of blood half-times is 50 days with a range of 39-70 days. Lactating women have a significantly shorter whole body half-time of 42 days compared with 79 days in nonlactating women.

Selenium is known to bioconcentrate in fish and it is thought that simultaneous ingestion of selenium may offer a protective effect for the toxicity of MeHg based upon its antioxidant properties. Selenium has been observed to correlate with Hg levels in blood (Granjean and Weihe, 1992).

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o ORAL RFD CONFIDENCE:

Study -- Medium
Data Base -- Medium
RfD -- Medium

The benchmark dose approach allowed use of the entire dose-response assessment and the calculation of a value that was consistent with thetraditional NOAEL/LOAEL approach. In addition, the results of laboratory studies with nonhuman primates support the quantitative estimate of the NOAEL/LOAEL range of the benchmark dose that was indicated by the human studies. The reported literature covers detailed studies of human exposures with quantitation of MeHg by analysis of specimens from affected mother-fetus pairs. A strength of the Marsh study is the fact that the quantitative data came directly from the affected population and quantitation is based on biological specimens obtained from affected individuals. Unfortunately, a threshold was not easily defined and extended application of modeling techniques were needed to define the lower end of the dose-response curve. This may indicate high variability of response to MeHg in the human mother-fetal pairs or misclassification in assigning pairs to the cohort. Recent concerns expressed in the research community relate to the applicability of a dose-response estimate based on a grain-consuming population when the actual application is likely to help characterize risk for fish-consuming segments of the population. Confidence in the supporting data base is medium. Confidence in the RfD is medium.

--------s IRIS summary. A record of these comments is summarized in the IRIS documentation files.

Other EPA Documentation -- U.S. EPA, 1980, 1984, 1987, 1988

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1 - IRIS
NAME - Methylmercury (MeHg)
RN - 22967-92-6

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