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Mercury in the Umbilical Cord: Implications for Risk Assessment for Minamata Disease

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Umbilical cord tissue was obtained from 50 births in the Faroe Islands, where high mercury intake is due to ingestion of pilot whale meat. The mercury concentration correlated significantly with the frequency of maternal whale meat dinners during pregnancy and with mercury concentrations in umbilical cord blood and in maternal hair. The results were compared with published values for mercury in umbilical cord tissue from 12 infants diagnosed with congenital methylmercury poisoning in Minamata, Japan. From the regression coefficients obtained in the Faroese samples, the median umbilical cord mercury concentration of 4.95 nmol/g dry weight in Minamata would correspond to 668 nmol/l cord blood and 114 nmol/g maternal hair. These levels agree well with other evidence of susceptibility of the fetus to increased exposure to methylmercury. *Key words:* blood analysis, hair, mercury, methylmercury, Minamata disease, pregnancy, seafood. *Environ Health Perspect* 102:548–550 (1994)

When Minamata disease was recognized in the 1950s, the cause was unknown. Later, when methylmercury was finally identified as the causative chemical, data on individual exposures were difficult to obtain retrospectively. However, knowing the local tradition of keeping dried umbilical cords, Harada et al. (1) collected cord tissue from 12 patients who had been born with congenital Minamata disease. For comparison, similar cord specimens were obtained from 16 children with other mental disturbances and 64 other children who served as controls. The analyses documented much higher mercury concentrations in the Minamata patients compared to the control groups, but the distributions overlapped considerably, particularly between Minamata disease and other mental disturbances. As the diagnostic criteria were not described in the published paper (1), the extent of possible misclassification is difficult to assess today.

Although these data support the notion that Minamata disease was due to methylmercury poisoning, they are difficult to translate into useful dose-response relationships. The most frequently used measures of methylmercury exposures are mercury concentrations in hair and in blood. No such data were available from the Minamata incident.

We have therefore examined the relation between the mercury concentrations in umbilical cord tissue (UC-Hg) with that in maternal hair and in umbilical cord blood. The samples were obtained in connection with a cohort study in the Faroe Islands where mercury exposures from seafood may approach those that occurred in Minamata (2).

Materials and Methods

Umbilical cords were collected at consecutive births from 1 March 1986 until the end of 1987 at the three Faroese hospitals (2). Maternal hair and umbilical cord blood were also obtained for mercury analysis. A questionnaire was administered by the midwife to obtain basic information on the general course of the pregnancy and nutritional habits, including frequencies of dinners based on pilot whale meat or fish, use of alcohol, and tobacco smoking. A total of 1023 births were included in the cohort, representing 75% of all births during the sampling period (2). Obstetric data indicate that limited selection bias took place (3).

About 10 cm of the umbilical cord was collected close to the umbilicus and kept frozen at -20°C until analysis. On the basis of the mercury concentrations in maternal hair and umbilical cord blood (2), a selection of 50 samples was made to obtain a maximal range and a relatively even distribution of expected mercury concentrations, i.e., with an overrepresentation of high levels of mercury.

From each cord sample, a specimen of 0.5–1 cm was excised. The specimen was freeze-dried for at least 24 hr and then stored in a desiccator. To determine mercury concentrations in umbilical cord, we placed an accurately weighed, freeze-dried sample of at least 0.05 g with 3 ml of 8 M ultrapure HNO₃ (Merck, Darmstadt, Germany) in a PTFE-lined digestion vessel (CEM, Indian Trail, North Carolina). The closed vessel was heated for 10 min in a microwave oven (CEM 80) at 100% power. Under these digestion conditions, all organic compounds except for aromatics are decomposed (4), thereby removing all major sources of interference with the detection method. The digest was transferred to a Minisorp tube (NUNC, Roskilde, Denmark) and kept closed until

analysis within 48 hr. As documented by Pineau et al. (5), storage of the digested sample for a maximum of 1 week does not cause any change in the mercury concentration. A volume of 250 µl of digested sample was transferred to another Minisorp tube, and 2 ml of saturated KMnO₄ (Merck) in 3% H₂SO₄ (Merck) was added. The tubes were sealed with perforated parafilm (American Can Company, Greenwich, Connecticut) and agitated before incubation in a 75°C warm water bath for 30 min. After cooling, we reduced excess potassium permanganate by carefully adding 250 µl saturated hydroxylamine hydrochloride (Merck). The solution was agitated carefully until clear. Each digested sample was prepared and analyzed in duplicate.

The mercury analysis was performed by flow-injection cold-vapor atomic absorption spectrometry (Perkin-Elmer model 5100 with FIAS-200 and AS-90; Perkin-Elmer, Norwalk, Connecticut). The mercury results were read against a standard curve prepared from a mercury stock solution of 1 g/l by dilution 10-fold the first time and thereafter two times at 100-fold with 1% HCl (Merck), containing a few drops of 5% KMnO₄ per 50 ml of solution, until a 10 µg Hg/l solution was obtained. From this standard solution, dilutions to 1, 2, and 4 µg Hg/l were made and used for a standard curve, including a blank consisting of 1% HCl with 5% KMnO₄. The total analytical imprecision was estimated to be 8.7% at a mercury concentration of 72.3 nmol/l. The accuracy of the mercury determination was assessed by the use of Seronorm Trace Element batch 906 (Nycomed, Oslo, Norway) as quality control material. The average mercury concentration measured in seven determinations was 72.3 nmol/l (assigned value 73 nmol/l). The detection limit estimated from a blank solution (mean + 3 SD) was 0.75 nmol/l. All analyses were conducted without any information available on mercury concentrations previously found in cord blood and maternal hair.

Results

Determination of the mercury concentrations in duplicate samples of umbilical cord showed a variation that averaged 3.65% (coefficient of variation; CV). This variation is similar to the average imprecision (CV) of 4.03% seen in split samples from the 50 individuals. The overall medi-

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an UC-Hg concentration was 1.53 nmol/g, with a maximum of 6.38 nmol/g.

High mercury concentrations in the cord tissue were clearly related to the frequency of whale meat dinners during pregnancy, although considerable individual variation occurred. The mercury concentrations in the umbilical cord correlated well with those in cord blood ($r_s = 0.85$; $p < 0.001$) and almost as well with mercury in maternal hair ($r_s = 0.77$; $p < 0.001$; Figs. 1 and 2). The regression lines can be calculated from these data (UC-Hg in nmol/g):

$$\text{Cord blood-Hg (nmol/l)} = 139.42 \times (\text{UC-Hg}) - 21.86$$

$$\text{Hair-Hg (nmol/g)} = 19.49 \times (\text{UC-Hg}) + 17.86$$

Using these equations, the results from Harada et al. (1) can be translated into more commonly used indicators of mercury exposure (Table 1). In addition, the approximate daily intake under chronic exposure conditions can be estimated. This calculation is based on the finding that the steady-state concentration in blood (in micrograms per liter) is approximately 0.8 times the daily methylmercury intake (in micrograms) (6), and that the fetal cord blood mercury concentration is about 20% higher than that of maternal blood (7) (Table 1).

Discussion

The high mercury exposures that occur in the Faroe Islands are a result of frequent intake of marine food items, and pilot whale meat is the main source (2). The mercury concentrations in whale meat vary, depending on age and catch, for example, but averages (8) are usually several-fold above a limit of 0.5 mg/kg applied in many countries for mercury in seafood. As expected, the highest mercury concentrations in the cord tissue were associated with frequent whale meat dinners.

Although we determined total mercury only, we observed a highly significant correlation between mercury concentrations in umbilical cord versus blood and maternal hair. The ratio of mercury concentrations in hair (nmol/g) versus blood (nmol/l) seen in this study is in reasonable accordance with the an overall expected average of about 250 (9). The relation to cord mercury concentrations has not been reported previously. Due to the wide range of exposures in the Faroe Islands, the regression equations for mercury concentrations in these different types of specimens are particularly useful for interpreting the data on cord mercury concentrations obtained in Minamata.

The mercury contents in umbilical

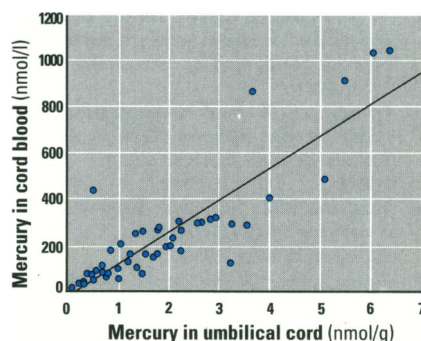


Figure 1. Total mercury concentrations in umbilical cord (nmol/g dry weight) and in cord blood (nmol/l) with the regression line.

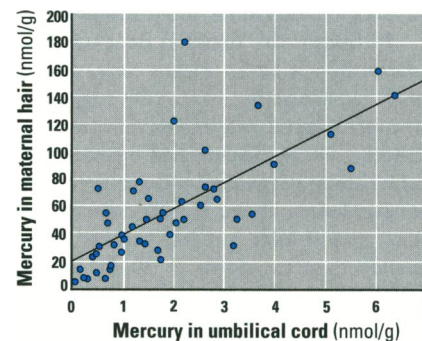


Figure 2. Total mercury concentrations in umbilical cord (nmol/g dry weight) and in maternal hair (nmol/g) with the regression line.

Table 1. Calculated maternal hair and blood mercury concentrations for children diagnosed with congenital Minamata disease

Mercury in umbilical cord (nmol/g) ^a	Calculated mercury in maternal hair (nmol/g)	Calculated mercury in cord blood (μmol/l)	Calculated daily mercury intake (μg/day)
0.2	21.9	0.007	1.4
1.8	53.6	0.23	49
3.3	81.5	0.43	90
3.5	85.5	0.46	96
3.9	93.5	0.52	108
4.5	105.4	0.60	125
5.2	119.3	0.70	146
5.4	123.3	0.73	153
8.2	177.0	1.12	233
11.3	238.6	1.56	324
12.4	258.5	1.70	354
23.3	471.0	3.22	671

^aThe intake is calculated from a ratio between steady-state maternal blood mercury concentration (20% less than that of cord blood, μg/l) and daily intake (μg) of 0.8 (see text).

^bFrom Harada (1).

cord tissue from Minamata may have changed during desiccation and storage at room temperature. Quite conceivably, the mercury concentrations could decrease with time, for example, due to reduction by microorganisms and subsequent evaporation. The rate of this change is obviously difficult to ascertain *a posteriori*. Also, the desiccation process and prolonged storage may have led to a final dry weight that is lower than the one obtained in the laboratory by drying a tissue sample that has been preserved by freezing. A loss in dry weight would result in higher mercury concentrations. Whether this process might counterbalance a potential loss in mercury from the tissue is unclear. In this regard, the considerable variation in cord mercury concentrations from Minamata patients is noteworthy; some of the patients had very low concentrations of mercury that were similar to those seen in the control groups. However, misclassification of Minamata disease in patients with spastic paresis of other etiology, for example, may have played a role in this regard. That misclassification occurred is indicated by the fact that some mercury concentra-

tions were very high in children with mental development problems presumed different from congenital Minamata disease.

Despite these limitations, the data for Minamata disease obtained by Harada (1) are of interest to calculate at least an order of magnitude for the corresponding mercury concentrations in maternal hair and in cord blood. The data given in Table 1 illustrate the approximate levels of mercury exposure that would be associated with congenital Minamata disease. Somewhat higher intakes were calculated by Futatsuka (10), who reported a median daily mercury intake around the Minamata Bay of 3597.5 nmol (719.5 μg); this level was based on a dietary survey among 80 female members of full-time fishermen's families residing at Minamata Bay, where the highest prevalence rate for Minamata disease was found.

From data obtained in Iraq where methylmercury poisoning was due to contaminated flour, a maternal hair mercury concentration of 50–100 nmol/g seemed to imply a 5% risk of congenital Minamata disease (9,11). The data given in Table 1 suggest that all but one of the Japanese

patients had exposures above this limit.

Although the detailed dose-response relationship is by no means clear, a recent study by Kjellström et al. (12) suggested a risk of delayed mental development in children whose mothers had ingested shark meat during pregnancy and acquired a hair concentration above 65–75 nmol/g mercury, and similar but less marked effects seemed to occur down to 30–50 nmol/g. This study is of particular interest because the exposure was chronic and mediated by passage through the food chains. The Faroese cohort is now being examined in detail to disclose any neurobehavioral dysfunctions that can be attributed to prenatal methylmercury exposures.

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