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Citation	Grandjean, Philippe, Roberta F. White, Pal Weihe, and Poul J. Jørgensen. 2003. "Neurotoxic risk caused by stable and variable exposure to methylmercury from seafood." <i>Ambulatory Pediatrics</i> 3, no. 1 (2003): 18-23.
Published Version	10.1367/1539-4409(2003)003<0018:NRCBSA>2.0.CO;2
Citable link	<a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:34787262">http://nrs.harvard.edu/urn-3:HUL.InstRepos:34787262</a>
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Manuscript to be published in Ambulatory Pediatrics

# Neurotoxic Risk Caused by Stable and Variable Exposure to Methylmercury from Seafood

Grandjean, Philippe MD, PhD\*‡; White, Roberta F. PhD\*‡; Weihe, Pal MD\*§; Jørgensen, Poul  
J. MScII

From the \*Institute of Public Health, University of Southern Denmark, Odense, Denmark;  
‡Departments of Environmental Health and Neurology, Boston University Schools of Medicine  
and Public Health, Boston, Massachusetts; §Department of Occupational and Public Health,  
Faroese Hospital System, Torshavn, Faroe Islands; and ||Odense University Hospital, Odense,  
Denmark.

Reprint requests to (P.G.) Department of Environmental Medicine, University of Southern  
Denmark, Winslowparken 17, DK-5000 Odense, Denmark.

E-mail: pgrand@health.sdu.dk

Supported by the U.S. National Institute of Environmental Health Sciences (ES06112 and ES  
09797), the European Commission (Environment Research Programme), and the Danish Medical  
Research Council. The contents of this paper are solely the responsibility of the authors and do  
not represent the official views of the NIEHS, NIH or any other funding agency.

## ABSTRACT

*Objectives.* To examine whether the dose-effect relationship for developmental mercury neurotoxicity is affected by variable mercury exposure during pregnancy.

*Methods.* The study was based on a birth cohort of 1022 children born in the Faroe Islands from March 1986 to December 1987. Neurobehavioral performance of 917 children (90%) was assessed at age 7. Intrauterine methylmercury exposure was determined from mercury concentrations in cord blood and two sets of maternal hair. Complete exposure information was available for 614 (67%) children.

*Results.* In children with complete exposure data, eight of sixteen neuropsychological tests showed deficits significantly associated with the cord-blood mercury concentration after confounder adjustment. Variable intrauterine exposure was suggested by disagreement between mercury concentrations in the two maternal hair samples. Removal of the 61 (10%) of the children with the greatest degree of variable exposure had a minimal effect on most exposure-effect relationships. However, the effect of the cord-blood concentration on verbal learning and memory was greater after this exclusion.

*Conclusion.* The study supports previous findings from this cohort study that maternal mercury exposure during pregnancy is associated with neuropsychological deficits detectable at age 7 years and that this association is evident in women with stable exposures throughout pregnancy and thus not due to variable exposures.

**ABBREVIATIONS.** Hg, mercury; MeHg, methyl mercury

Methylmercury (MeHg) is a neurotoxicant which accumulates in seafood and freshwater fish.<sup>1</sup>

Because of the worldwide occurrence of this pollutant, concerns about the health implications

have spurred detailed risk assessments.<sup>1,2</sup> The risks to human health were demonstrated in a poisoning incident in Iraq, where MeHg-treated grain was inadvertently used for bread-making.<sup>3</sup> The most serious neurological deficits were observed in children whose mothers were pregnant during the exposure.<sup>3</sup> In developing the dose-response relationship for this incident, researchers used as the exposure indicator the peak mercury (Hg) concentration observed in 1-cm segments of maternal hair grown during the pregnancy period.<sup>4</sup>

While analysis of a hair sample for Hg is an easy way of obtaining an exposure estimate,<sup>5</sup> segmental analysis of hair strands to determine short-term exposure variations would not be practical in large-scale studies. Such detailed exposure assessment may not be necessary for dietary exposures in fishing communities, where exposures would vary much less than during a poisoning incident. Still, theoretical calculations show that a large meal of contaminated seafood could cause a relative change in the hair-Hg concentration that may not be negligible.<sup>6</sup> The impact of such meals is smoothed by the sustained retention of MeHg in the body (the biological half-life of MeHg is thought to be approximately 1.5 months<sup>7</sup>). In addition, any short-term peak absorption levels resulting from variations in maternal diet may be moderated by placental passage so that they become less marked in the fetal circulation.

Evaluation of this issue is complicated because the time of a peak exposure must be considered in relation to vulnerable periods of brain development.<sup>8</sup> At the same time, the implications of temporal differences in susceptibility must be considered in light of the persistence of MeHg in the body. The cord-blood Hg concentration has been found to be the best available predictor of deficits on several neurobehavioral outcome parameters.<sup>9-11</sup> This biomarker appears to be advantageous, because it reflects the amount of MeHg that has penetrated into the

fetal circulation, and it also indicates exposures occurring late in gestation, when most cognitive functions appear to be particularly vulnerable.<sup>8</sup> However, for outcome variables sensitive to exposures during the early part of the gestation, the Hg concentration present in cord blood at the time of parturition could be a poor risk indicator if the exposure has been variable.

Several biomarkers of exposure are available from a prospective study of developmental MeHg neurotoxicity carried out in the Faroe Islands.<sup>12</sup> In addition to the Hg concentration in cord blood, we also analyzed two sets of maternal hair samples. One full-length sample collected at the time of parturition reflected the average MeHg exposure during the pregnancy period.<sup>13</sup> In addition, a segment close to the scalp has now been analyzed to document the exposures closer in time to the parturition.<sup>14</sup> Although differences in hair growth rates, certain types of hair treatment, and other factors may affect Hg deposition in hair,<sup>15</sup> concordance between the Hg concentrations in the two samples would suggest a rather stable exposure during the pregnancy period. Thus, these results may be used to determine the neurobehavioral implications of stable versus variable intrauterine MeHg exposure levels.

## METHODS

### **Participants**

A birth cohort was generated in 1986-1987 at the three hospitals in the Faroe Islands. MeHg exposure in this population originates from pilot whale meat and certain kinds of fish and seabirds. As the major source of exposure, the whale meat contains a relatively high MeHg concentration.<sup>16</sup> It is most often eaten as thin slices of cured meat, but a large steak of uncured whale meat could possibly cause a substantial peak exposure. Because the crude dietary

questionnaire on maternal food habits during pregnancy<sup>13</sup> did not allow a detailed assessment on dietary exposure patterns, biomarkers were used to characterize individual levels and changes in exposure during pregnancy. For this purpose, both cord blood and maternal hair were sampled at parturition and subsequently analyzed for Hg.

### **Methylmercury exposure assessment**

Prenatal exposure to MeHg was determined from analysis of the total Hg concentration in cord blood by cold-vapor atomic absorption.<sup>13</sup> Hair samples corresponding to the full duration of pregnancy were analyzed to obtain a measure of the average exposure.<sup>13</sup> In addition, remaining hair samples have now been reanalyzed to obtain the Hg concentration in the proximal 2 cm.<sup>14</sup> Assuming that a lag time of 5-6 weeks is not covered by the hair sample when cut close to the scalp and also assuming a hair growth rate of 1 cm per month,<sup>2</sup> the proximal 2-cm segment will have been formed and will have incorporated circulating mercury during weeks 27-35 of a term pregnancy. Using a biological half-life of 45 days for MeHg in the body,<sup>7</sup> the relative contribution of dietary MeHg intakes to the Hg concentration in this segment can then be estimated (Fig. 1). For the full-length hair samples, more than two-thirds were 8-9 cm and only 5% were less than 5 cm long. In this case, MeHg intakes during the early part of the pregnancy would contribute relatively more to the Hg concentration measured (Fig. 2). All results are given in  $\mu\text{g/g}$  and can be converted to  $\text{nmol/g}$  by multiplying by a conversion factor of 5.0.

### **Neuropsychological assessment**

At age 7 years, 917 (90%) of the cohort members participated in a thorough clinical examination

with focus on nervous system function.<sup>9</sup> Neuropsychological tests were chosen to include tasks that would be affected by the neuropathological abnormalities described in congenital MeHg poisoning and the functional deficits seen in children with early-life exposure to other neurotoxicants.<sup>17</sup> Paper-and-pencil tests were administered by a Faroese clinical psychologist who had translated the tests into Faroese and verified their feasibility through pilot testing of Faroese children. Three computer-assisted tests were given at a separate session using the same portable computer with the recommended joy-stick. Each child was asked about familiarity with computer games, and the answer was scored as none, some and much. The individual tests are shown in Table 1.

### **Statistical analysis**

Regression equations were calculated for the 614 children (67%) who had both hair-Hg assessments available. If maternal MeHg intake had been rather constant during the pregnancy period, the two hair samples would show identical Hg concentrations. Indeed, the results were rather similar for most of the children.<sup>14</sup> To determine the effect of removing subjects with a variable exposures during pregnancy, we excluded the children with the greatest relative difference in Hg concentrations in the two analyses of maternal hair. The cord-blood Hg concentration was used as the independent exposure variable in all analyses, as previously described.<sup>9</sup> Because of skewed distributions, logarithmic transformation of the mercury concentrations was used. A standard set of eight confounders (age, sex, medical risk factors, maternal intelligence, maternal and education, paternal employment, and day care) were included for adjustment of all outcome variables, and computer experience was added for the computer-

assisted tests.

## RESULTS

The three exposure biomarkers correlated well (Table 2). As expected, the result from the proximal hair segment correlated slightly better with the cord blood concentration than did the full-length hair sample. The two hair Hg results were in good agreement in most cases (Fig.3). However, in 10% of the cases (N=59), the smaller concentration of the two was less than 60% of the higher one, a difference substantially exceeding the analytical imprecision. These subjects were therefore considered to have had a variable exposure.

Exclusion of children with the two hair-Hg parameters suggesting variable exposure improved the correlation between the two hair concentrations ( $r = 0.96$ ), but barely affected their associations with the cord-blood concentration (0.82 and 0.79, respectively, after exclusion).

Table 3 shows the test performance in children from whom two maternal hair-Hg analyses were available. These results and the association with the cord-blood Hg concentration are quite similar to those obtained from the cohort as a whole,<sup>9</sup> i.e., before exclusion of children with only one hair-Hg assessment. All regression coefficients indicate a poorer performance at higher prenatal MeHg exposure levels, and eight of them are statistically significant at a two-sided 5% limit.

In general, exclusion of the children with variable exposure did not materially affect the regression coefficients for Hg (Table 3). However, almost all verbal tests suggest a stronger Hg effect after the exclusion. In a previous report,<sup>9</sup> a single test with the best psychometric properties had previously been selected to reflect each of five modalities of brain function (motor speed,



attention, visuospatial, language and verbal memory). For all of these tests, i.e., Finger Tapping with preferred hand, CPT reaction time, copying errors on Bender test, Boston Naming score after cues, and short-term recall on CVLT, the numerical size of the regression coefficient increased, by 3% to 43%.

Similar calculations were carried out with the proximal hair-Hg concentration as the independent variable (data not shown). In general, the regression coefficients were lower for this exposure biomarker than for the cord-blood Hg concentration in accordance with previous findings.<sup>12</sup>

## DISCUSSION

Dose-effect relationships for developmental neurotoxicity in children must consider the validity of the biomarkers of exposure.<sup>23</sup> In observational studies, intakes of food contaminants are bound to vary somewhat, even in subjects who stick to a regular diet. Such temporal variations will affect the exposure biomarker result as well as the dose that reaches the target tissue, though not necessarily the same way. Thus, when the exposure is variable, the imprecision of the exposure measure will tend to increase, thereby also decreasing the likelihood of detecting a true exposure-association. This bias toward the null hypothesis will result in lower regression coefficients and higher p values.

With MeHg neurotoxicity, concerns have also been raised regarding the role that peaks and troughs in exposure may play in the appearance of neurotoxic damage. Accordingly, the average exposure level may not be a precise risk indicator; under acute exposure conditions, the peak exposure level seems to provide a meaningful risk estimate.<sup>4</sup> Although peaks early and late

in gestation are unlikely to have the same impact on brain development, risk assessment efforts have not taken this factor into consideration.<sup>1,24</sup> Exposures in fishing communities with a steady supply of seafood would probably be rather stable, but segmental hair analyses of Faroese samples have shown that some variation occurs, sometimes with coefficients of variation above 20%, i.e., clearly exceeding the laboratory imprecision.<sup>14</sup> The significance of exposure variations for neurotoxic risks may therefore also apply to such settings, although clearly to a much lesser extent than in the previously described poisoning incident.<sup>3,4</sup>

Temporal patterns of exposure variations may be important because of changes in vulnerability at different stages of prenatal brain development.<sup>8</sup> Thus, Fig. 3 shows that some mothers had an increased Hg concentration in the proximal hair segment corresponding to exposures late in pregnancy, while others had a greater exposure earlier on, as indicated by a higher average concentration in the full-length hair sample. However, due to limited number of such divergent cases, the present study is not informative with regard to the timing of vulnerability. Also, the smoothing effect of the MeHg persistence in the body would tend to decrease the impact of exposure variations.

The exclusion of children with the greatest variation in exposure resulted in minor changes in mercury regression coefficients (Table 3), thus suggesting only a limited impact of peaks and troughs that were large enough to be identified this way. However, the main direction of the changes suggested a stronger mercury effect after exclusion of the children with the greatest variations in exposure. This finding is in accordance with the expectation of a bias toward the null hypothesis cause by exposure misclassification.

Some morphologic features of the brain are well developed by the end of the second

trimester. However, processes such as neuronal migration and synapse continue during the third trimester and are crucial to functional development.<sup>8</sup> Thus, as a biomarker dependent on neurotoxicant doses received during recent weeks, the Hg concentration in cord blood at the time of parturition is probably the best available risk indicator.<sup>14</sup> The fact that exposure variations earlier in pregnancy, as documented by the hair analyses, only slightly affected the cord-blood Hg regression coefficients for relevant outcomes supports the validity of this biomarker. Still, different brain functions may well differ in their temporal profile of vulnerability to a neurotoxicant such as MeHg and it is possible that the functional domains examined are subsisted by brain structures with differing vulnerability periods.

While studies in other communities have also shown Hg-associated neurotoxicity in children,<sup>25-29</sup> a prospective study in the Seychelles<sup>30</sup> has not so far shown any definite signs of adverse health effects. Although the outcome variables examined in the latter study may not have been sufficiently sensitive,<sup>31</sup> another important difference between the studies was that the exposure assessment in the Seychelles was based on Hg concentrations in maternal hair samples obtained up to 6 months after delivery.<sup>32</sup>

The Reference Dose defined by the U.S.EPA<sup>1</sup> corresponds to a hair-Hg concentration of about 1  $\mu\text{g/g}$ , i.e., a level substantially below the average seen in the Faroese birth cohort. Based on the most recent estimates from US studies, the National Research Council committee estimated that over 60,000 births may be occurring annually in which the limit is exceeded.<sup>2</sup> Hair analyses may therefore be indicated in population groups with a high intake of freshwater fish and marine food, whether or not peak exposures from species with high Hg concentrations are likely.

## CONCLUSION

The study supports previous findings from the Faroese cohort that maternal MeHg exposure during pregnancy is associated with neuropsychological deficits detectable at age 7 years.

Exclusion of children with variable intrauterine exposure levels between early and late pregnancy caused only a slight change, mainly an increase, in the mercury-association of the deficits. The reported associations with adverse effects therefore seem not to be due to peak exposures.

Rather, if some outcome variables are affected by peak exposures early in pregnancy, exposure variability may have resulted in an underestimation of MeHg effects sensitive to exposures early in pregnancy. Accordingly, the cord-blood Hg concentration remains the most valid risk indicator.

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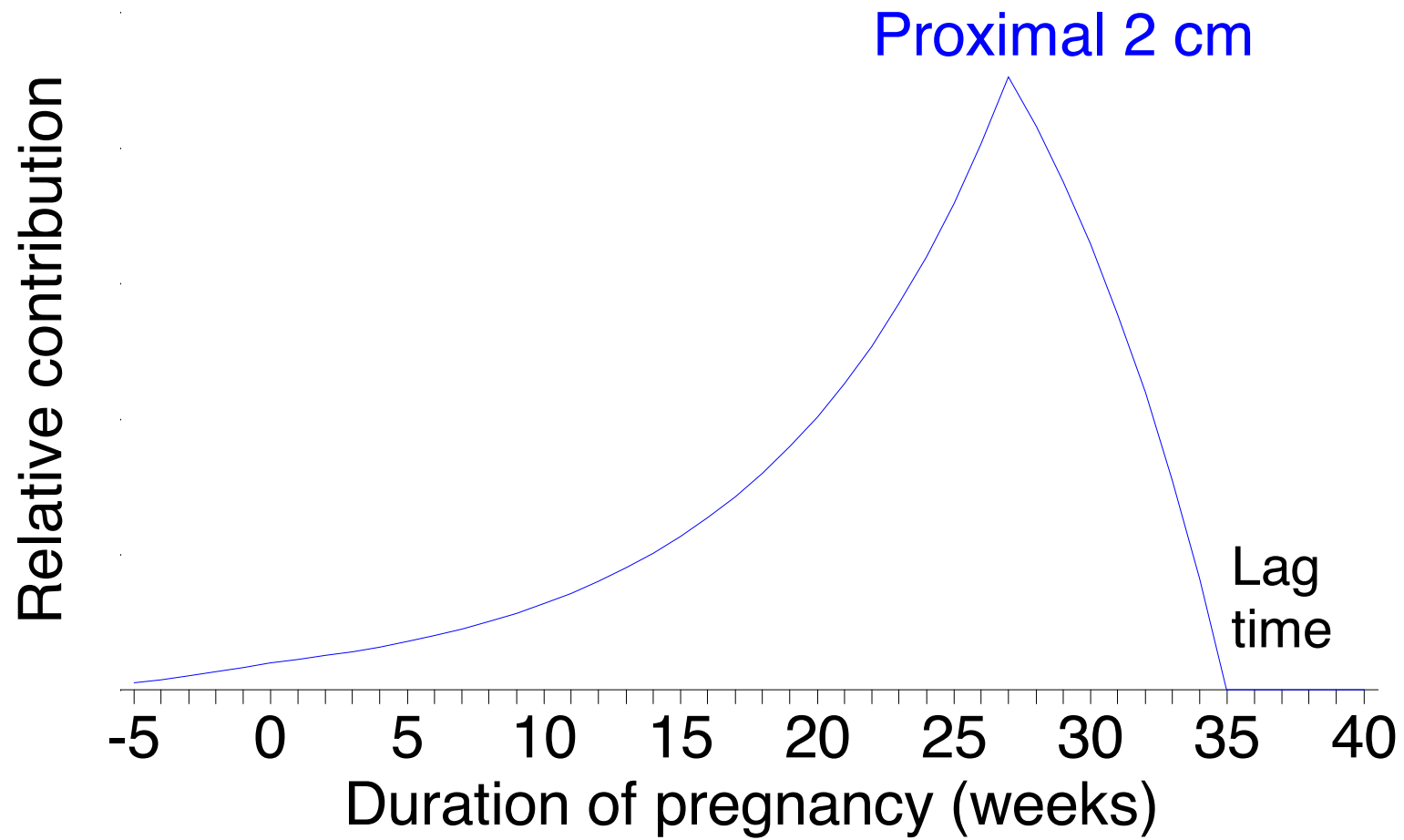
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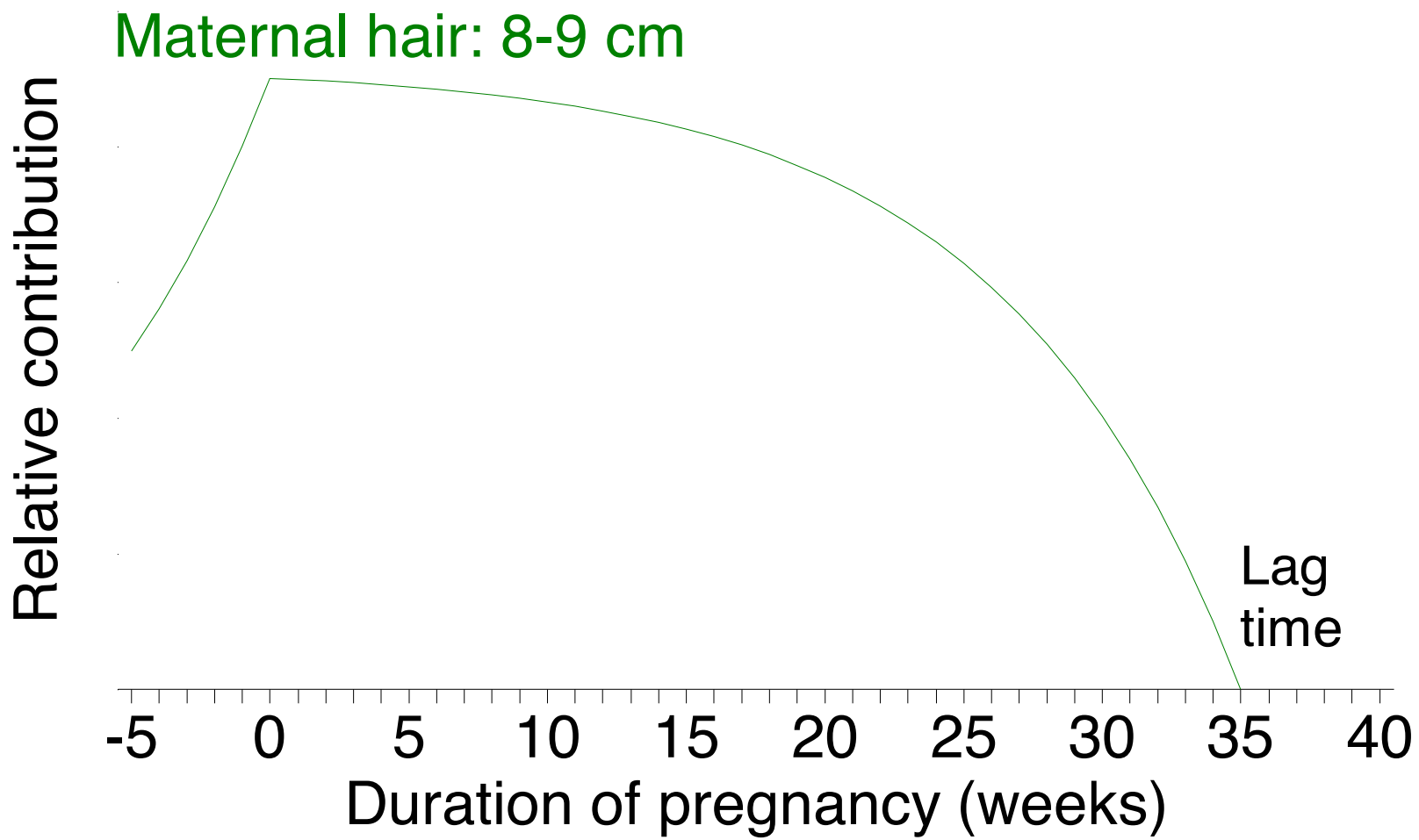
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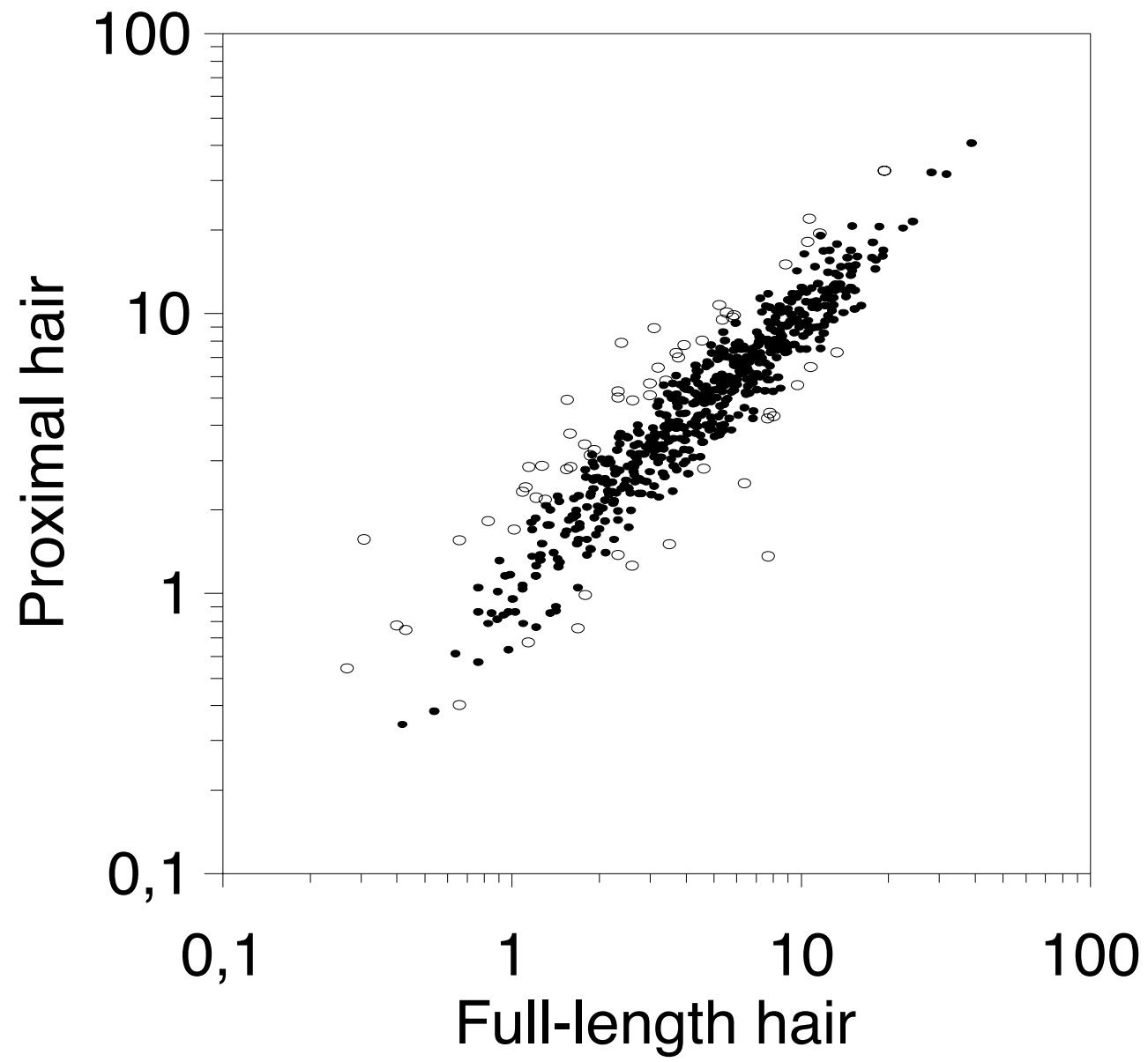
**Fig. 1.** Relative contribution by MeHg exposures during pregnancy to the Hg concentration in a 2-cm proximal hair segment sampled at the time of parturition and assuming a biological half-life for MeHg of 45 days.



**Fig. 2.** Relative contribution by MeHg exposures during pregnancy to the Hg concentration in an 8-cm (full-length) hair sample obtained at the time of parturition and assuming a biological half-life for MeHg of 45 days.



**Fig. 3.** Hg concentration in paired sets of proximal and full-length hair samples ( $\mu\text{g/g}$ ). The 10% of samples with the greatest relative discordance between the two measurements are indicated with open circles.



**TABLE 1.** Neuropsychological tests used

Test name	Scores	Functional domain
NES2* Finger Tapping Test <sup>18</sup>	Maximum number in 15s (preferred, non-preferred, and both hands)	Motor speed
NES2 Hand-Eye Coordination Test <sup>18</sup>	Average deviation	Motor coordination
NES2 Continuous Performance Test <sup>18</sup>	Number of missed responses Average reaction time in ms	Vigilance/attention
WISC-R‡ Digit Spans <sup>19</sup>	Forward (raw) score	Attention
WISC-R Block Designs <sup>19</sup>	Raw score	Visuospatial function
Bender Visual Motor Gestalt Test <sup>20</sup>	Number of errors on copying Number correct recalled	Visuospatial function Visual memory
Boston Naming Test <sup>21</sup>	Number correct before and after cues	Language
California Verbal Learning Test (Children) <sup>22</sup>	Number learned (five trials) Short-term recall Delayed recall Recognition	Verbal learning and memory

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\*Neurobehavioral Evaluation System 2

‡Wechsler Intelligence Scale for Children - Revised

**TABLE 2.** Correlation between mercury exposure biomarkers

Biomarker	<i>n</i>	Geometric mean	Correlation with hair	
			Proximal	Full-length
Cord blood (ug/l)	589	23.2	0.83	0.78
Proximal hair ( $\mu\text{g/g}$ )	602	4.61	1.00	0.93
Full-length hair ( $\mu\text{g/g}$ )	602	4.39	0.93	1.00



**TABLE 3.** Confounder-adjusted regression coefficients (betas) for the logarithmic transformation of the cord-blood mercury concentration as predictor of neuropsychological test deficits in all children with complete data as compared to those where agreement between the two hair parameters suggested relatively stable exposures

Test	Mean	All			Stable only		
		<i>n</i>	Beta	P value	<i>n</i>	Beta	P value
NES2 Finger Tapping							
Preferred hand	42.2	595	-1.32	0.049	537	-1.45	0.050
Other hand	40.5	596	-0.71	0.268	538	-0.38	0.587
Both hands	54.1	592	-2.22	0.114	534	-1.96	0.202
NES2 Hand-Eye Coordination							
Error score	2.62	591	0.070	0.026	533	0.076	0.025
NES2 Continuous Performance Test							
Missed responses (ln)	1.70	596	0.27	0.039	538	0.30	0.037
Reaction time	758	595	45.6	<0.001	537	47.0	<0.001
Wechsler Intelligence Scale for Children-Revised							
Digit Spans forward	3.8	587	-0.33	0.056	530	-0.32	0.098
Block Designs (squareroot)	3.8	586	-0.20	0.124	529	-0.28	0.058

## Bender Visual Motor Gestalt Test

Errors on copying	29.5	593	1.32	0.029	536	1.53	0.023
Reproduction	3.0	556	-0.33	0.105	501	-0.54	0.017

## Boston Naming Test

No cues	24.6	568	-1.46	0.015	511	-1.59	0.019
With cues	27.0	567	-1.70	0.005	511	-1.84	0.006

## California Verbal Learning Test (Children)

Learning	27.7	583	-0.90	0.367	527	-1.32	0.237
Short-term recall	3.9	577	-0.63	0.039	521	-0.90	0.009
Long-term recall	4.3	558	-0.52	0.139	502	-0.81	0.038
Recognition	10.5	552	-0.14	0.547	497	-0.20	0.450

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