

Adverse mercury effects in 7 year-old children expressed as loss in "IQ"

Esben Budtz-Jørgensen^{1,2,3}, Frodi Debes^{2,4}, Pal Weihe⁴, Philippe Grandjean^{2,5}

¹*Department of Biostatistics, University of Copenhagen
Blegdamsvej 3, DK-2200 Copenhagen N, Denmark.*

²*Institute of Public Health, University of Southern Denmark
Winsløwparken 17, DK-5000 Odense C, Denmark.*

³*Department of Biostatistics, Harvard School of Public Health,
Boston, MA 02115, USA*

⁴*Faroese Hospital System, FR-100 Tórshavn, Faroe Islands*

⁵*Department of Environmental Health, Harvard School of Public Health,
Boston, MA 02115, USA*

1 Introduction

In the Faroes studies, outcome tests were chosen to reflect nervous system functions that are known to be sensitive to methylmercury and other developmental neurotoxicants. In reporting the impact of prenatal methylmercury exposure, we have emphasized traditional regression coefficients (Grandjean et al., 1997). However, all neuropsychological tests have different means and variances, and such tables may be hard to interpret for many readers beyond mere significance testing. One possible way of illustrating the impact of methylmercury exposure is to compare with the effect of age. Each regression equation includes the child's age as covariate, and the regression coefficients for age and mercury can therefore be compared. Overall, the effect of a doubling of the methylmercury exposure corresponds to a loss in maturation of about 1.5-2 months at about age 7 years (Grandjean et al., 1997). That means that a few doublings of developmental methylmercury exposure could render a child unfit to start school.

Another means of expressing the mercury effects is to provide regression coefficients in relation to the standard deviation of each individual neuropsychological test (Grandjean et al., 1999). The major neuropsychological tests show that a doubling of the exposure is associated with a decreased performance at about 10% of the standard deviation. This result emphasizes that the exposure causes a shift in the distribution of the performance data.

Although these two ways of expressing the results may be appropriate and help in interpreting the outcomes, they may still not be sufficient for calculations of societal impacts of exposures to this neurotoxicant. Most calculations of this kind are based on measures of intelligence, because past estimates of school performance, needs for special education,

academic achievements, and economic success have utilized such measures. It is quite possible that the types of neurobehavioral tests that were used in the Faroes study are similarly linked to the outcomes considered of societal importance, but no such data exist. In addition, most of the tests used in the Faroes study can also be assumed to correlate with standard measures of intelligence. To facilitate the production of estimates of societal impact, a transformation of the test scores into the scale of measurement commonly employed in intelligence testing would therefore be both useful and appropriate.

One possibility in creating an approximation to standard measures of intelligence is to combine all verbally-mediated tests to obtain an index of verbal ability similar to a verbal IQ. In this case, a doubling of the exposure would cause a deficit of about 10% of the standard deviation. For the IQ scale, where the standard deviation is 15, this effect is about 1.5 IQ points. Such a calculation, derived from several disparate tests chosen for other purposes of course, leads to an IQ-like metric with a strong dependence upon the original choice of tests. Still, the estimated effect on such an IQ-like scale agrees with the results from the New Zealand study.

The average WISC-R full-scale IQ for the New Zealand study population ($n = 237$) was 93, and in the group with maternal hair mercury above $6 \mu\text{g/g}$ ($n = 61$) the average was 90 (Kjellstrom et al., 1989). The average exposure in the latter group was about 4-fold higher than in the study population as a whole, so that each doubling of exposure caused an IQ decrease of 1.5 points. Kjellstrom later estimated the increased number of subjects with very low IQ at increased methylmercury exposures (Kjellstrom, 2000): An IQ below 70 was twice as common (increase from 5 to 10%) in the highest hair mercury group ($> 10\mu\text{g/g}$) compared to the group with hair mercury below $6 \mu\text{g/g}$.

Although this evidence may support that a conversion of the Faroese neuropsychological test data to an IQ measure, the tests used are by no means appropriate surrogates for verbal or performance IQ tests, and they are known not to correlate well in other populations. This lack of correlation is not surprising, given the criteria for test selection. However, three of the tests used were in fact sub-tests of the WISC-R. In American and Norwegian standardizations of the WISC-R, the correlations of these tests with the full-scale IQ for the appropriate age groups are provided. Furthermore information has been collated by Sattler from studies of American children that will allow estimation of full-scale IQ from performance on a few WISC-R tests.

The WISC-R has been standardized in several languages, including Norwegian, but not Faroese. Thus, tables for conversion of raw scores into scaled scores are not available. Given the fact that mercury is likely to affect the scores, such tables would ideally have to be developed for Faroese children with negligible methylmercury exposure. Still, conversion to an estimated scaled score could be achieved by means of adjustment in a regression analysis. We have chosen to use regression analysis with adjustment for age as a continuous variable (and other covariates) and to express the mercury regression coefficient in terms of the standard deviation of the test. This metric should allow the desired conversions.

The present document has therefore been developed as a supplement to published papers, and at the request of research groups that are calculating societal impacts of mercury exposures. In relying on the Faroes data, we would like to stress some important features of this study. First of all, the Faroese society is rather homogeneous, with a stable, traditional family structure, and with strong social support systems in the communities. The mercury exposure mainly originates from the consumption of whale meat, and this, again, depends on personal dietary preferences and the availability of whale (which varies between the islands, seasonally, and from year to year). The mercury exposures therefore include elements of a natural experiment, which would support the likelihood that the mercury exposure would be relatively independent of important covariates, such as socioeconomic confounders. The statistical analyses have supported this anticipation. The whale meat is very lean, but pilot whales accumulate other potential neurotoxicants, such as PCBs, in their blubber, and blubber consumption could be an important confounder or interaction parameter. Fortunately, whale meat and blubber consumption are not strongly related, and a subject's exposure to PCBs depends on the life-time accumulation of these substances, while mercury levels in the body are due to exposures during the recent several months. Accordingly, PCB has been found to cause limited confounding of these data (Budtz-Jørgensen et al., 2002; Steuerwald et al., 2000). Possible confounding due to PCB is therefore not further addressed in this report.

With few exceptions, all neuropsychological tests were administered by specialized academic colleagues, who each examined all children using the same battery of tests. The WISC(R) Similarities subtest was first administered by the neuropsychologist, but this particular examination station was found to have too little time to conduct the complete battery. As a result this test was then transferred to an assistant at another station. This assistant received detailed instruction and supervision to ensure comparability. Nonetheless, the data from the two examiners differed. While we originally reported no mercury effect on this subtest (Grandjean et al., 1997), a statistically significant effect was apparent from the results obtained by the neuropsychologist only (Grandjean and White, 2001). We therefore provide the separate data for the two examiners. In regard to the reaction time on the NES2 Continuous Performance Test, a similar problem occurred, and the results from the second year were excluded (Grandjean et al., 1997). This data selection is maintained here. In regard to the Digits Spans test, we administered only the forward condition, because the backward condition (which is necessary to generate the WISC-R score) was too difficult and was thought not to be a sensitive measure of potential neurotoxicant-related dysfunctions in these children. In contrast, the Block Designs subtest was easier than anticipated for the Faroese children, as compared to reference data from other countries. These caveats must be taken into regard, when interpreting intelligence measures based on these subtests. In regard to the data analysis, some transformations were used to increase the fit of the regression models (Grandjean et al., 1997), and the present tables provide both transformed and non-transformed data.

The National Research Council has recommended the use of a linear exposure scale due to its biological plausibility. The Faroes data showed that a logarithmic exposure scale, in general, provided a better fit to the data; although this difference was only of borderline

statistical significance. However, in the linear model, the small number of observations at very high exposure levels acted as highly influential points. This problem is avoided after a logarithmic transformation of the mercury concentrations. In a previous publication (Grandjean et al., 1997), we presented the results for the logarithmic exposure scale for the full cohort and also after exclusion of children with a maternal hair-mercury concentration above $10 \mu\text{g/g}$ (a level that at the time was thought to represent an increased risk of neurotoxic effects). We have chosen to address the problem of influential points in two different ways. First, the linear model was fitted to the whole data set using a robust estimation procedure. Secondly, we performed an ordinary regression analysis restricted to children with a maternal hair-mercury concentration below $10 \mu\text{g/g}$.

2 Methods

2.1 Multiple regression analysis

Mercury effects were estimated in multiple regression analyses with confounder correction. We used a uniform set of confounders determined by Grandjean et al. (1997). For each response, the mercury regression coefficient were expressed in percent of the total response variation. Thus, the relation between outcome (Y), exposure (X) and confounders (Z) was described using the model $Y = \beta_0 + \beta_x g(X) + \beta_z^t Z + \epsilon$, where g is a known dose-response function and ϵ is a random error. The scale of the exposure regression coefficient β_x depends on the scale of the outcome, so we instead estimated a standardized coefficient $\beta_x / \sqrt{\text{var}(Y)}$. For the logarithmic model [$g(x) = \log(x)$], these standardized coefficients were calculated by Grandjean et al. (1999). Here these results are supplemented by also assuming a linear dose-response relation [$g(x) = x$].

The distribution of mercury concentrations is skewed. Therefore, in the linear model, a few highly exposed children become overly influential in the estimation of the mercury effect. This problem was addressed using robust regression methods. Hocking (2003, section 6.7.3) proposed to down weigh observations with a high value of Cook's distance (D). For each observation, D measures how much the parameters change when the observation is excluded. In the linear model, the most influential 10% of the observations were down-weighted when estimating the mercury effect. This approach is robust to outliers as well as to observations with unusual covariate values (e.g., a very high mercury concentration). Furthermore, the mercury effect was re-estimated in children with a maternal hair mercury concentration below $10 \mu\text{g/g}$.

The WISC-R has a standard deviation of 15. Thus, by multiplying the standardized coefficients by this number the mercury effect on each test can be expressed metrically in terms of points on an "IQ" scale. An estimate of the mercury effect on estimated "IQ" may then be obtained by averaging the effects of appropriate outcomes.

2.2 Structural equation analysis

Standardized regression coefficients from different outcomes must somehow be combined to obtain a conversion of the individual test results to points on an IQ-like scale. However, it may not be clear how much weight each outcome should be given in this calculation. Furthermore, the standard analysis fails to take measurement error in observed variables into account. It is well known that imprecisions in the exposure will generally lead to underestimation of the exposure effect. Errors in the response will not introduce bias in estimated regression coefficients, but the standardized coefficients are sensitive also to this type of error. To illustrate this point, consider an additive error model for the observed response (Y) and the true response (η), i.e. $Y = \eta + U$, where U is a random error. Based on regression analysis, the standard coefficient estimator will converge to $\beta_x / [\text{var}(\eta) + \text{var}(U)]$. Thus, for imprecise outcomes (like those considered here), the estimator may be considerably attenuated compared to the true coefficient $\beta_x / \text{var}(\eta)$.

Structural equation models allow combination of outcome information without specification of individual outcome weights. Instead, neurobehavioral test scores are viewed as manifestations of underlying latent variables. For the Faroese data, Budtz-Jørgensen et al. (2002) considered the scores on the California Verbal Learning Test, Boston Naming Test and the WIS Digit Span test to be reflections of a verbally mediated function, while the scores on NES2 Finger Tapping and NES2 Hand-Eye Coordination were considered indicators of the child's motor ability. This analysis showed that a strong mercury effect was present for the verbally mediated function, while the effect on the motor function was weaker, but still statistically significant.

In the measurement part of the model, each outcome (Y_j) was assumed to be linearly related to the underlying cognitive function (η_o), and a random measurement error (U), i.e. $Y_j = \nu_j + \lambda_j \eta_o + U$. The λ_j 's are known as factor loadings and account for the possibility that different outcomes may have different scales. Similarly, on the exposure side, (log-transformed) mercury concentrations in maternal hair and cord blood were viewed as error prone indicators of the true exposure (η_e).

The structural part of the model assumed that the latent exposure and the confounders affected the latent outcome linearly $\eta_o = \alpha + \beta \eta_e + \gamma^t Z + \zeta$, where γ is a vector of confounder regression coefficients and ζ is a normally distributed residual. The original analysis focused on drawing inference about the mercury effect parameter β , but here the main aim is to estimate the standardized effect of the true exposure on the true response: $\beta / \sqrt{\text{var}(\eta_o)}$. Contrary to the simple regression results, this parameter takes into account measurement error both in the exposure and in the response.

Finally, a structural equation model was developed for the three (untransformed) WISC-R subscores. This model assumed that the WISC-R outcomes reflect the same underlying response. This latent response was assumed to be affected by the mercury exposure and the potential confounders. Thus, the predictors are assumed to affect the observed test scores indirectly through the latent response. To take into account the examiner effect

on the similarities score, a direct effect from the covariate 'examiner' to the similarities outcome was included. In this way, we assume that the identity of the examiner affects only the similarity score.

3 Results

3.1 Regression analysis

3.1.1 Logarithmic dose-response model

For each outcome, the effect of a doubling of the cord blood mercury concentration was estimated. This effect was then expressed in percent of the standard deviation of the response. Results are given in Table 1. Here the results of Grandjean et al. (1999) have been supplemented as explained in the introduction. The scores of WISC(R) Similarities test have now been analyzed after stratification on the examiner (i.e., neuropsychologist or specially trained assistant). Furthermore, in the original analysis, the scores on NES2 Continuous Performance Test Total missed and Wechsler Intelligence Scale Block Designs were transformed to achieve normally distributed residuals. Table 1 also provides the results obtained without transformation of the outcomes.

The strongest standardized coefficients are seen for the reaction time score on NES2 Continuous Performance Test and for the Boston Naming scores, indicating that a doubling in the mercury concentration corresponds to a reduction in test performance of about 10-15% of the outcome standard deviation. In agreement with the results of Grandjean and White (2001), the mercury effect on the Similarities score is seen to be highly dependent on the type of examiner. Based on the scores of the neuropsychologist, a 15% loss is estimated per doubling in exposure, while a weak positive effect of mercury exposure is seen for the score of the assistant.

Response	β	s.e.	p	β in % of resp. std.	Residual std
NES2 Finger tapping					
Preferred hand	-0.33	0.17	0.049	-5.37	5.71
Non preferred hand	-0.12	0.16	0.46	-1.97	5.49
Both hands	-0.50	0.34	0.14	-4.11	11.5
NES2 Hand-Eye Coordination					
Error score*	0.010	0.0078	0.19	3.70	0.26
NES2 Continuous Performance Test					
Ln total missed*	0.081	0.036	0.024	10.08	0.78
Total missed*	0.71	0.28	0.012	11.11	6.12
Reaction time*	12.1	3.26	<0.001	15.93	70.3
Wechsler Intelligence Scale					
Digit Spans	-0.082	0.042	0.05	-5.62	1.42
Similarities					
All children ¹	-0.014	0.12	0.91	-0.35	3.70
Examiner A ²	-0.47	0.22	0.039	-15.05	3.02
Examiner B ³	0.087	0.14	0.52	2.13	3.86
Sqrt. Block Designs	-0.050	0.031	0.11	-4.36	1.06
Block Designs	-0.41	0.24	0.090	-4.63	8.24
Bender Visual Gestalt Test					
Errors on copying*	0.20	0.14	0.15	3.83	4.90
Reproduction	-0.076	0.046	0.10	-4.64	1.56
Boston Naming Test					
No cues	-0.53	0.15	<0.001	-10.47	5.01
With cues	-0.57	0.15	<0.001	-9.75	4.92
California Verbal Learning Test					
Learning	-0.38	0.24	0.12	-4.33	8.32
Short-term repro.	-0.57	0.073	0.019	-6.64	2.49
Long-term repro.	-0.16	0.083	0.047	-5.69	2.78
Recognition	-0.087	0.061	0.15	-4.24	2.02

¹ Adjusted for examiner, ² Neuropsychologist, ³ Assistant, * Higher scores indicate an adverse effect

Table 1: Estimated effects of a doubling in the cord blood mercury concentration.

3.1.2 Linear dose-response model

For each outcome, the effect of 10 $\mu\text{g}/\text{l}$ increase in the cord blood mercury concentration was estimated. To reduce the influence of a few highly exposed children, a robust estimation procedure was used. Then, the analysis was restricted to children with a maternal hair concentration below 10 $\mu\text{g}/\text{g}$.

Response	All children					H-Hg below 10 $\mu\text{g/g}$				
	β	s.e.	p	β in % of resp. std	Residual std	β	s.e.	p	β in % of resp. std.	Residual std
NES2 Finger tapping										
Preferred hand	-0.193	0.073	0.008	-3.15	5.32	-0.125	0.117	0.29	-2.01	5.75
Non preferred hand	-0.082	0.068	0.23	-1.37	5.10	0.111	-0.054	0.62	-0.90	5.46
Both hands	-0.189	0.138	0.17	-1.55	10.8	-0.082	0.232	0.72	-0.67	11.4
NES2 Hand-Eye Coordination										
Error score*	0.0056	0.0034	0.099	2.02	0.252	0.0079	0.0055	0.15	2.82	0.269
NES2 Continuous Performance Test										
Ln total missed*	0.019	0.016	0.22	2.39	0.744	0.066	0.023	0.004	8.33	0.757
Total missed*	0.153	0.113	0.18	2.38	5.30	0.479	0.182	0.009	7.56	6.01
Reaction time*	4.40	1.30	0.0008	5.76	66.3	6.22	2.11	0.003	8.20	69.5
Wechsler Intelligence Scale										
Digit Spans	-0.025	0.018	0.16	-1.72	1.32	-0.028	0.029	0.34	-1.90	1.42
Similarities										
All children ¹	-0.039	0.050	0.43	-1.01	3.55	0.129	0.082	0.12	3.30	3.71
Examiner A ²	-0.172	0.077	0.027	-5.54	2.75	-0.084	0.154	0.59	-2.66	3.12
Examiner B ³	0.0030	0.060	0.96	0.07	3.73	0.175	0.097	0.071	4.29	3.86
Sqrt. Block Designs	-0.022	0.013	0.0860	-1.94	1.02	-0.028	0.022	0.20	-2.44	1.07
Block Designs	-0.175	0.098	0.075	-1.96	7.73	-0.217	0.168	0.20	-2.42	8.26
Bender Visual Gestalt Test										
Errors on copying*	0.073	0.059	0.22	1.38	4.65	0.118	0.100	0.24	2.23	4.92
Reproduction	0.0012	0.020	0.95	0.08	1.48	-0.053	0.033	0.11	-3.23	1.56
Boston Naming Test										
No cues	-0.190	0.063	0.003	-3.47	4.66	-0.215	0.102	0.036	-3.95	5.01
With cues	-0.213	0.061	0.0005	-3.90	4.59	-0.260	0.101	0.010	-4.73	4.94
California Verbal Learning Test										
Learning	-0.088	0.104	0.40	-1.01	7.98	-0.208	0.169	0.22	-2.39	8.34
Short-term repro.	-0.058	0.032	0.069	-2.25	2.42	-0.121	0.051	0.017	-4.70	2.49
Long-term repro.	-0.064	0.036	0.075	-2.22	2.72	-0.093	0.058	0.11	-3.19	2.80
Recognition	-0.022	0.022	0.30	-1.09	1.64	-0.062	0.041	0.13	-3.12	1.97

¹ Adjusted for examiner, ² Neuropsychologist, ³ Assistant, * Higher score indicate an adverse effect

Table 2. Estimated effects of a 10 $\mu\text{g/l}$ increase in the cord blood concentration.

It is noteworthy that on both the logarithmic and the linear exposure scales, all regression coefficients are in the direction of increasing deficits at higher exposures, except for two of the WISC Similarities and one of the Bender Reproduction results on the linear scale.

3.2 Structural equation analysis

In this analysis, log-transformed mercury concentrations in cord blood and maternal hair were assumed to be measures of the causative latent exposure. As previously described (Budtz-Jørgensen et al., 2002), four neuropsychological test scores were considered reflections of the child’s underlying motor function, while seven other scores were assumed to be representations of a verbally mediated-function. A highly significant mercury effect was seen for the verbal function, while the effect on the motor function was weaker (Table 3). The scales of the latent variables must be selected before the analysis. Here, the true mercury exposure is expressed on the scale of the log-transformed cord blood concentrations. The Finger Tapping score with preferred hand was selected as the reference indicator for motor function, while the verbally mediated function was expressed on the scale of the Boston Naming Test score with cues. With these definitions, the estimated effects parameters of Table 3 (β) have the same scale as mercury effect estimates in Table 1 for Finger Tapping with preferred hand and Boston Naming with cues, respectively. It is seen that the structural equation analysis yielded mercury effects were comparable to the most significant effects seen for the individual scores of motor and verbal function, respectively.

While the verbal effect is more statistically significant than the motor effect, the standardized coefficients are both close to 10%. This agreement may seem surprising given that the p -values differ, but it can be explained as a result of higher imprecision in the motor scores. A higher degree of imprecision will reduce the power to detect predictor effects, but in this analysis it will not reduce the standardized coefficient.

Response	β	p	β in % of resp. std
Motor function	-0.31	0.034	-9.74
Verbally mediated function	-0.49	0.002	-10.45

Table 3. Effect of a doubling in mercury exposure on two latent response functions.

Table 4 gives the estimated mercury effect in the structural equation model for the three WISC-R outcomes. Here, the reference indicator was the digit span score. Thus, the effect of a doubling in mercury exposure on the latent variable corresponds to a loss of 0.038 digit span points. Even though the structural equation model accounts for exposure error, this effect is somewhat weaker than the corresponding regression coefficient (see Table 1). With a standardized coefficient of about 6.5%, this mercury effect is also weaker than those estimated from verbal and motor outcomes (see Table 3). However, it should be noted that this structural equation model did not provide a close fit to the data indicating that

the assumption that the WISC-R outcomes measure the same underlying variable may not be appropriate.

Response	β	p	β in % of resp. std
WISC-R	-0.038	0.10	-6.49

Table 4. Effect of a doubling in mercury exposure on latent "IQ" as reflected by three WISC-R subtests.

4 Discussion

Important limitations of the standard regression approach must be recognized, when considering tables of regression coefficients. The result is highly dimensional, and proper evaluation of the overall statistical significant would require some adjustment for multiple comparisons. Some simple adjustment methods have been developed, but these are known to be overly conservative, especially for correlated outcomes like the Faroese. Furthermore, an adjustment for imprecisions of the individual regressions would be appropriate, since misclassification of the exposure estimate is likely to cause a bias toward the null hypothesis. In addition, each outcome parameter needs to be assessed on the basis of its likely sensitivity to small changes in performance. A test, such as the WISC(R) Digit Spans forward condition, has very few possible outcomes in children aged 7 years, and its sensitivity to subtle neurotoxicity may therefore not be sufficient to render this test valid for detection of deficits caused by methylmercury exposure. However, most of these issues can be taken into account in structural equation analyses. These calculations confirmed the results of the most sensitive individual outcomes, indicating that a doubling in mercury exposure reduces test performance by 10% response standard deviation. Still, the structural equation rewards the outcomes that are more correlated to the other variables (outcomes, exposure markers and confounders) in the model, and the final result may not necessarily be equal to an effect on true intelligence. Even if this is the case, one cannot conclude that such strongly significant deficits are without societal impact, simply because the individual tests may show only a limited association with standard measures of intelligence. This issue cannot be resolved at this time, because of the absence of data that links deficits in, say the Boston Naming Test, to school performance and other achievements that are usually included, when monetizing such adverse effects.

References

- Budtz-Jørgensen E, Keiding N, Grandjean P, Weihe P (2002). Estimation of health effects of prenatal mercury exposure using structural equation models. *Environ Health 1*: 2.
- Grandjean P, White RF (2001). Neurobehavioral dysfunction as possible sentinel. *Hum Ecol Risk Assess 7*: 1079-89.
- Hocking R.R, (2003). *Methods and Applications of Linear Models. Regression and the Analysis of Variance.* Wiley, New Jersey.

- Kjellstrom T (2000) Methyl-mercury exposure and intellectual development in vulnerable groups in New Zealand. Proceedings of the US-Japan workshop, Nov. 2000. Minamata, Japan, National Institute for Minamata Disease.
- Kjellström T, Kennedy P, Wallis S, Stewart A, Friberg L, Lind B, Wutherspoon T, Mantell C (1989). Physical and mental development of children with prenatal exposure to mercury from fish. Stage 2, interviews and psychological tests at age 6. (Report 3642) Stockholm, National Swedish Environmental Protection Board.
- Sattler JM. Assessment of Children, 3rd ed. San Diego: Sattler, 1988.
- Steuerwald U, Weihe P, Jørgensen PJ, Bjerve K, Brock J, Heinzow B, Budtz-Jørgensen E, Grandjean P (2000). Maternal seafood diet, methylmercury exposure, and neonatal neurological function. *J Pediatr* 136: 599-605.
- Grandjean, P., Budtz-Jørgensen, E., White, R.F., Jørgensen, P.J., Weihe, P., Debes, F. and Keiding, N. (1999). Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years. *American Journal of Epidemiology* **150**, 301-305.
- Grandjean, P., Weihe, P., White, R.F., Debes, F., Araki, S., Yokoyama, K., Murata, K., Sørensen, N., Dahl, R. and Jørgensen, P.J. (1997). Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicology and Teratology* **19**, 417-428.