

Odense and Copenhagen, Denmark, 6 July, 1999

## **FINAL REPORT to U.S.EPA**

# **Benchmark Modeling of the Faroese Methylmercury Data**

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Methylmercury is a common contaminant of seafood and freshwater fish (1). While adverse effects have been unequivocally demonstrated in poisoning incidents, the implications of lower-level exposures in fish-eating populations have been controversial (2,3). A birth cohort was generated in the Faroe Islands during 1986-1987 and is being studied prospectively to examine the possible adverse effects of prenatal exposure to methylmercury (4).

Deficits in several domains of brain function were associated with increased prenatal exposures to methylmercury, while postnatal exposures appeared less important (4,5). Regression analyses have been used to estimate these associations, but such data are of limited use when considering approximate thresholds of effects and safe levels of exposure. An attractive approach in this regard is to calculate so-called benchmark doses and their lower confidence limits (6). The present report therefore presents benchmark calculations for indicative findings of this study.

### **Study population**

A cohort of 1022 singleton births was assembled during 1986-1987, and mercury concentrations were measured in maternal hair at parturition (: g/g) and in cord blood (: g/l) as biomarkers of the prenatal methylmercury exposure (4). The latter was thought to be the best indicator of the amount of this neurotoxicant that had reached the fetal circulation and the fetal brain during susceptible periods of development.

Because the effects of fetal childhood exposure to methylmercury are persistent (1), detailed examination of the children was carried out at school age, i.e., in 1993-1994. Seven children had died, and a total of 917 of the surviving children (90.3%) completed the examinations, 443 of them in 1993.

## Neuropsychological tests

Neuropsychological tests were chosen to include tasks that would be affected by the neuropathological abnormalities described in congenital methylmercury poisoning and the functional deficits seen in children with early-life exposure to neurotoxicants (4,7). Tests with advantageous psychometric properties, i.e., with a wide range of scores possible without floor or ceiling effects, and acceptable test-retest reliability, were preferred, including computer-assisted tests. Based on the scores obtained, one test was selected for detailed study for each of five domains of brain function (4):

1. Motor speed: Neurobehavioral Evaluation System (NES2) Finger Tapping Test, maximum number in 15 s with the preferred hand. This task is a measure of manual motor ability that focuses specifically on speed.
2. Attention: NES2 Continuous Performance Test, average reaction time during the last three of the four minutes of testing. This test measures vigilance/attention.
3. Visuospatial performance: Bender Visual Motor Gestalt Test, number of errors in copying the 9 figures as scored by the Göttingen system. This visuospatial test has been used extensively as a non-specific measure of brain damage but may also be informative in regard to the functioning of the non-dominant cerebral hemisphere.
4. Language: Boston Naming Test, total number of correct responses, including semantic and phonemic cues. This test of lexical knowledge measures dominant cerebral hemisphere function.
5. Short-term memory: California Verbal Learning Test (Children), number correct for spontaneous long-delay recall of 12 words. This test assesses short-term verbal memory.

## Benchmark Calculations

In examining dose-response relationships, we have used the approach suggested by Crump (6). Thus, the benchmark dose (BMD) is the dose of a substance that results in an increased probability of an abnormal test performance by a benchmark response (BMR), i.e., from  $P_0$  for an unexposed child to  $P_0 + \text{BMR}$  for a child exposed to the BMD.

In accordance with previous applications of this method (1,6), a  $P_0$  of 5% has been chosen as the default value. Thus, the level ( $x_0$ ) of abnormal test performance is defined by a probability of 5% in an unexposed population. An abnormal test performance is therefore defined in purely statistical terms and may have little to do with actual limits for 'abnormal' performance in a neuropsychological sense. It should also be noted that, as the Faroese cohort does not include an unexposed control group, the performance level for an unexposed child is obtained by fitting a dose-response curve to all data points followed by extrapolation to zero exposure.

In general, larger values of  $P_0$  are likely to result in lower BMD values. As an alternative to a  $P_0$  of 5%, we have therefore also conducted calculations with  $P_0$  corresponding to one standard deviation, i.e., a cut-off level of about 16%. These calculations have been performed with the sole objective of exploring the dependence of the benchmark

calculations on the choice of  $P_0$ .

The BMDL, which is intended to be used as an alternative to the NOAEL, is calculated as the statistical 95% lower confidence bound of the BMD (6). This makes the BMDL dependent on the number of observations. Thus, an increased number of observations will diminish the uncertainty of the BMD estimates, i.e., narrower confidence bands and thereby higher BMDLs.

The BMR is often set at 10%, so that the corresponding BMD will triple the risk of an abnormal response, given that  $P_0$  is 5%. Because a tripling in risk would seem a large effect, we have also calculated BMDs and BMDLs for a BMR of 5%, which corresponds to a doubling of the risk. To explore further the dependence of the benchmark results on the BMR, we also conducted calculations with a BMR of 2%.

The benchmark concept was originally developed in the context of highly standardized carcinogenesis trials. In the present application, the response is influenced by confounders in addition to the exposure of interest (mercury). The preferable adaptation of the benchmark concept to this situation is to use the same unexposed risk ( $P_0$ ) for each child and a linear multivariate model for the dependence on the confounders. Accordingly, for each child, the calculated limit ( $x_0$ ) for an abnormal test performance will depend on the individual values of the confounders for that child. By this approach (as will be documented in detail elsewhere), the dependence of the BMD and BMDL on the confounders will be avoided. The benchmark results can therefore be interpreted without considering the covariates.

Values of BMD and BMDL have been calculated by a statistical dose-response model. In analyzing similar data from other mercury studies, Crump has modeled the dependence of the mean test score of a child on the maternal hair mercury level ( $d$ ) using a

a)  $K$ -power model (a family of power functions):

$$: (d) = \$ @ d^K$$

The power parameter  $K$  was restricted to values equal to or above 1 and was included in the model to allow the dose-response curve to be nonlinear. To make the BMDLs comparable between studies we have analyzed the Faroese data using the same dose-response model. However, preliminary analyses suggested that the proposed power functions do not fit the Faroese data very well. Therefore, the benchmark calculations were repeated using three additional models:

b) Linear dose-response model:

$$: (d) = \$ @ d$$

c) Square root dose-response model:

$$\mu(d) = \beta \cdot \sqrt{(d+1)}$$

d) Logarithmic dose-response model:

$$: (d) = \$ @ \log(d+1)$$

If  $K$  is fixed at  $K=1$  in the model proposed by Crump, the linear dose-response model is

obtained. Notice also that before the square root and the logarithmic transformation were applied a constant of 1 was added to the concentrations to avoid dose-response models with an infinite slope at zero dose (supralinear dose-response models).

The (lack of) fit of the four models considered is compared after calculation of minus twice the log of the likelihood function ( $-2\log(L)$ ) for each model. The lower the  $-2\log(L)$ -value the better the fit.

Furthermore, the fit of the linear, the square root and the logarithmic dose-response model have been compared in pairs. Each model in a given pair was tested against an expanded model including both models. A high p-value in this goodness of fit test indicates that the model at hand does not fit the data significantly worse than the expanded model which also includes the other curve function in the pair.

The distribution of both exposure biomarkers is skewed with a few highly exposed children. These highly exposed children might influence the dose-response estimation disproportionately. Therefore, the benchmark calculations were performed both with and without these children.

Confounder adjustment was carried out as indicated above. As in previous analyses (4), obligatory confounders were: age, sex and the maternal Raven score (as a measure of maternal intelligence). When relevant, the child's computer experience was included as well. The following additional covariates were included for confounder adjustment because they were significantly associated with at least three of the 20 neuropsychological response variables: medical risks, daycare, maternal and paternal education, paternal employment (4). This uniform group of confounders was used to adjust all responses in the benchmark calculations.

## Results

The number of children completing the tests varied between 837 and 901 for four of the tests (4). For the Continuous Performance Test reaction time, the results differed between the first and the second year, and a joint regression equation could not be generated. Since supervision was stringent only during the first year, the results from the 428 children examined during the first year were used for the purpose of detailed statistical analyses (4). The numbers available for analyses were slightly reduced because of missing information on some of the covariates. As illustration of the associations explored, cumulated distributions for approximate quartile exposure groups (based on cord-blood concentrations) are provided for the two outcome tests showing the closest association with the exposure after confounder adjustment.

In the absence of detailed a priori knowledge on the shape of the dose-response curves, four different models have been used. When the maternal hair-mercury concentration is used as the exposure variable, no certain difference in fit between the different curve functions appears, and the BMDLs of the four models are in general in accordance with each other, especially for BMR=10% (Table 1). It should be noted that two digits after the decimal point are provided only for the sake of uniform presentation, not as an indication of the precision. For example, it is seen that the  $K$  power model and the linear model may have slightly different BMDLs, although  $K = 1$ . Such small differences will occur as a result of differences in the two procedures.

However, for the cord blood concentration the results are clearly different for the different curves (Table 2). The likelihood calculations show that, especially for the attention

test, the logarithmic transformation seems to give a better fit than the linear model. Also, a low p-value in Table 3 indicates an inferior fit of the individual model when compared to the combined linear-logarithmic model. The logarithmic model always fits as well as the combination, while the linear model does not for the attention response and, to some extent, for the language and memory tests. For the cord-blood mercury parameter, the power parameter in the  $K$ -power model is estimated to 1 (yielding the linear model) as the best fit for all response variables. Thus, the logarithmic model also provides a better fit than the  $K$ -power model. This finding therefore suggests that the power functions used by Crump (6) may not necessarily provide the best fit.

Although the difference in fit between the logarithmic and the square root function is far from significant, the BMDLs of the logarithmic model are considerably lower. This finding further supports the notion that the benchmark method may be highly sensitive to assumptions about the dose-response curve.

A serious disadvantage of the  $K$ -power model and the linear model is that the BMDLs for the cord-blood parameter are very sensitive to a few observations at high dose levels. Thus, when the child with highest exposure (351 : g/l) was excluded, the BMDLs decreased by 10-20%. The influence of this subject on the results obtained by the logarithmic dose-response function was negligible.

The results obtained with the two sets of exposure biomarkers may be compared when taking into account that an approximate ratio between them suggests that 1 : g/g hair corresponds to about 5 : g/l cord blood. Taking this factor into account, the BMDs and the BMDLs differ in most cases between the two exposure biomarkers. Overall, the results for the blood concentrations are lower when the logarithmic or the square root dose-response functions are used. When log transformed, this biomarker mostly showed a stronger association with the response variables than did the hair-mercury concentration (4). However, several of the BMDLs obtained with the linear dose-response model are lower for the hair mercury parameter than for the cord blood concentration.

Using the logarithmic dose-response model under the default conditions, where BMR is 10%, the lowest BMDLs are obtained for the attention measure (6.13 : g/g hair and 3.96 : g/l cord blood). The results for the language test are somewhat higher, i.e., 9.14 : g/g hair and 9.66 : g/l cord blood. As indicated above, the results for other curve functions are higher. For both sets of dose indicators and for all four dose-response models, lower BMDLs are obtained if BMR is set at 5%, rather than 10%. Again, the results for the attention measure are the lowest. Supplementary calculations using a BMR of 2% showed the same tendency, but at even lower levels.

Using both the linear and the logarithmic dose-response models for the two most sensitive outcome variables, BMDLs were also calculated using  $P_0 = 0.16$ , i.e., corresponding to one standard deviation. As could be expected, these BMDLs are lower than the corresponding values for  $P_0 = 0.05$ . Furthermore, the strongest dependence on  $P_0$  is seen for the logarithmic model.

## Discussion

Benchmark dose calculations have been used previously for determination of Reference Doses. As also seen with the Iraqi data used by the U.S. EPA for benchmark calculations (1), the results depend on the choice of the dose-response function. The magnitude of both  $P_0$  and BMR may also affect the results. Little biological information is available to allow any a

priori judgment concerning default settings for these parameters. Thus, four dose-response models have been applied. Further, in addition to  $P_0$  and BMR values that allow comparison with previous calculations, the present study has also included alternative settings to provide evidence on their impact on the benchmark calculations.

The results obtained show that BMDs and BMDLs vary substantially. In choosing the most reliable or appropriate results, some guidance is available. Thus, at least for the present data, it would seem appropriate to include the logarithmic dose-response model in the consideration of benchmark doses. This model appears to provide a better fit for some of the outcome variables, notably those that show the closest association with the cord-blood mercury concentration.

The magnitude of  $P_0$  and BMR is also of obvious importance. Although a  $P_0$  of 5% and a BMR of 10% have been used in some previous calculations, lower BMDs and BMDLs may be obtained with a  $P_0$  of 16% and a BMR of 5% (and even lower at 2%). No clear guidance is available at this point how to choose the most appropriate magnitude of  $P_0$  and BMR. Thus, given the uncertainties associated with these choices, the different sets of BMDL results should be considered only as indicators of orders of magnitude.

The current Reference Dose for methylmercury corresponds to a hair mercury concentration of 1.1 : g/g. With an approximate ratio of 1 : 200 between mercury concentrations in cord blood and maternal hair in the present material, this level corresponds to about 5.5 : g/l cord blood. This concentration is quite similar to the 10% BMDLs obtained for the attention and language tests in the present study, i.e., the most sensitive responses that were associated with the lowest BMDLs. While the comparable BMDLs obtained for the hair concentration measure are somewhat higher, the results for a BMR of 5% are of the same order of magnitude as the cord blood results at BMR = 10%.

These calculations, although only indicative, may suggest that the current Reference Dose corresponds to an approximate NOAEL derived from the Faroese data. Accordingly, the Reference Dose would seem not to include any uncertainty factor. Although at least one uncertainty factor of up to 10 is usually used to take into account individual susceptibility differences, the inclusion of such considerations would result in a lower Reference Dose.

The outcome of these calculations should not be considered without a critical assessment of the cohort study as such. Thus, a detailed review was recently conducted at a workshop convened by NIEHS in Raleigh, NC, in November, 1998. Also, the relevance of the Faroese cohort study for risk assessment purposes must be considered. The culture is Scandinavian, i.e., western European, with a traditional and stable family structure, and a highly efficient societal system of health care, education and social support. Dietary deficiencies are nonexistent, and the intake of essential fatty acids and selenium is high because of their occurrence in seafood. The median birth weight in the Faroes is 3700 g, i.e., among the highest in the world, only 14 cohort children having a birth weight below 2500 g. Breastfeeding in the Faroes is mostly continued for at least six months, with more than 97% of the cohort children being breastfed for at least one month. Alcohol intake during pregnancy is minimal, with more than 75% of the mothers being total abstainers. Accordingly, this homogeneous population has substantial epidemiological advantages but is unlikely to provide information on hypersusceptible subpopulations.

Most of the methylmercury exposure in the Faroes originates from pilot whale, a traditional food item which is eaten as thin slices of cured meat or larger steaks. If large amounts of whale meat are consumed within a short time period, an episodic exposure situation may occur. A small number of long hair strands from cohort mothers has been analyzed in segments of 1-1.5 cm, i.e., representing 30-45 days of hair growth. Results so far

(unpublished data) have shown a few instances of definite variation, where the peak level was about twice the lowest concentration along the strands. Taking into account the biological half-life of about 45 days for methylmercury in the body, these analyses provide evidence of only limited variation in exposure levels. Also, if the exposure is variable, the exposure biomarkers will be more imprecise. Increased imprecision will result in an underestimation of the true mercury effect on the outcome variables.

Many Faroese also eat whale blubber which contains polychlorinated biphenyls (PCBs) (8). These substances have been linked to neurobehavioral dysfunctions (9), although the specific causative congeners have not been identified, and confounding from methylmercury has not been excluded. Nonetheless, we determined the PCB concentrations in cord tissue for half of the cohort (4). Detailed statistical analyses showed that confounding is limited, and interaction is unlikely with the methylmercury-associated effects (10).

Another cohort is being followed in the Seychelles, but results have only been published from examinations up to 5.5 years of age (3). In this study, a variety of developmental tests have been used, and the prenatal methylmercury exposure was determined from the maternal hair concentration only. With a population from a mid-income developing country, where the family structure is different, it is perhaps not surprising that subtle mercury neurotoxicity has not been demonstrated (11). Although the Seychelles study may offer some confidence that methylmercury effects may be of limited, or perhaps even negligible, extent in some fish-eating populations, the Faroese data provide information on subtle effects in a homogeneous population as determined with highly sensitive methods. Support for this notion has now emerged from studies of newborns in the Faroe Islands (12), and school-age children from Madeira (13) and the Brazilian Amazon (14).

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**Table 1. Results of benchmark calculations using the maternal hair-mercury concentration (: g/g) as the dose parameter.**

**1. Motor speed (finger tapping)**

Model	a) <i>K</i> power		b) Linear		c) Square root		d) Logarithmic	
$-2\hat{A}\log(L)$	8539.77		8539.83		8540.17		8540.57	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	19.92	12.07	19.70	11.33	20.05	8.23	18.74	4.27
BMR=0.10	30.09	19.07	33.00	18.98	48.13	18.47	146.69	15.17

$P_o = 0.05$

**2. Attention (CPT reaction time)**

Model	a) <i>K</i> power		b) Linear		c) Square root		d) Logarithmic	
$-2\hat{A}\log(L)$	5777.49		5777.49		5777.17		5776.84	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	17.66	10.25	17.66	9.35	13.99	5.48	7.43	2.23
BMR=0.10	29.58	16.60	29.58	15.66	32.75	11.86	34.49	6.13

$P_o = 0.05$

**3. Visuospatial performance (Bender)**

Model	a) <i>K</i> power		b) Linear		c) Square root		d) Logarithmic	
$-2\hat{A}\log(L)$	8309.41		8309.41		8309.56		8309.89	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	28.36	14.78	29.03	14.03	38.29	11.27	91.57	6.82
BMR=0.10	45.66	22.45	48.62	23.50	95.47	25.95	1963.47	30.32

$P_o = 0.05$

#### 4. Language (Boston Naming Test)

Model	a) $K$ power		b) Linear		c) Square root		d) Logarithmic	
$-2\hat{A}og(L)$	8021.66		8021.66		8021.71		8022.58	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	15.22	10.02	15.22	9.63	12.48	6.24	8.35	2.99
BMR=0.10	25.49	16.69	25.49	16.13	28.95	13.68	41.27	9.14

$$P_o = 0.05$$

#### 5. Short-term memory (California Verbal Learning Test)

Model	a) $K$ power		b) Linear		c) Square root		d) Logarithmic	
$-2\hat{A}og(L)$	6868.79		6868.79		6868.14		6868.07	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	27.16	14.35	27.16	13.41	26.56	9.35	27.16	4.75
BMR=0.10	45.48	22.43	45.48	22.46	64.89	21.22	266.72	17.70

$$P_o = 0.05$$

#### Results with $P_o = 0.16$

Response	2. Attention (CPT reaction time)				4. Language (Boston Naming)			
Model	b) Linear		d) Logarithmic		b) Linear		d)Logarithmic	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	9.14	4.84	2.01	0.83	7.88	5.00	2.18	1.06
BMR=0.10	17.07	9.04	6.84	2.10	14.71	9.34	7.68	2.84

**Table 2. Results of benchmark calculations using the cord-blood mercury concentration (: g/l) as the dose parameter.**

**1. Motor speed (finger tapping)**

Model	a) <i>K</i> power		b) Linear		c) Square root		d) Logarithmic	
$-2\hat{A}og(L)$	8344.41		8344.41		8344.11		8344.87	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	139.73	82.87	139.73	78.53	113.76	42.07	51.60	7.92
BMR=0.10	234.01	136.46	234.01	131.52	297.11	105.43	761.34	38.04

$P_o = 0.05$

**2) Attention (CPT reaction time)**

Model	a) <i>K</i> power		b) Linear		c) Square root		d) Logarithmic	
$-2\hat{A}og(L)$	5636.59		5636.59		5633.34		5631.38	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	71.75	48.37	71.75	45.52	26.54	13.81	3.03	1.60
BMR=0.10	120.15	80.29	120.15	76.23	64.84	32.30	9.31	3.96

$P_o = 0.05$

**3. Visuospatial performance (Bender)**

Model	a) <i>K</i> power		b) Linear		c) Square root		d) Logarithmic	
$! 2\hat{A}og(L)$	8077.48		8077.48		8076.91		8076.94	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	241.57	113.97	241.57	103.66	250.40	61.98	270.82	12.66
BMR=0.10	404.56	179.88	404.56	173.59	668.69	158.14	11930.24	78.71

$P_o = 0.05$

#### 4. Language (Boston Naming Test)

Model	a) $K$ power		b) Linear		c) Square root		d) Logarithmic	
$-2\Delta\log(L)$	7793.72		7793.72		7790.84		7790.42	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	84.98	61.22	84.98	57.50	40.78	22.33	6.46	3.11
BMR=0.10	142.32	102.22	142.3	96.29	102.03	53.96	27.94	9.66

$$P_o = 0.05$$

#### 5. Short-term memory (California Verbal Learning Test)

Model	a) $K$ power		b) Linear		c) Square root		d) Logarithmic	
$-2\Delta\log(L)$	6675.94		6675.94		6674.37		6673.32	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	246.31	110.05	246.31	103.38	172.65	51.52	49.51	7.56
BMR=0.10	412.49	176.11	412.49	173.13	456.71	130.38	711.34	35.45

$$P_o = 0.05$$

#### Results with $P_o = 0.16$

Response	2. Attention (CPT reaction time)				4. Language (Boston Naming)			
Model	b) Linear		d) Logarithmic		b) Linear		d) Logarithmic	
	BMD	BMDL	BMD	BMDL	BMD	BMDL	BMD	BMDL
BMR=0.05	37.13	23.60	1.05	0.64	43.98	29.74	1.83	1.08
BMR=0.10	69.34	44.06	2.84	1.53	82.13	55.54	5.97	2.93

**Table 3. Comparison of fit between linear and logarithmic models using the cord-blood mercury concentration (: g/l) as the dose parameter.**

Response	P-value for comparison with combined model	
	b) Linear	d) Logarithmic
1) Motor speed	0.6424	0.4151
2) Attention	0.0233	0.7314
3) Visuospatial	0.4606	0.9294
4) Language	0.0638	0.6687
5) Short-term memory	0.0718	0.4179