# Response to questions posed on 17 April, 2000, by the NAS mercury committee

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## 1. Calculation of BMDLs in the $K$-power model

The parameters of the $K$-power model were estimated using the SAS procedure NLIN. From these estimates the BMDs were calculated. The lower confidence bands (the BMDLs) were obtained using the so-called parametric bootstrap method (Efron and Tibshirani, 1993). Using the estimated distribution of the original data 2000 new data sets were simulated. After each simulation, the BMD was estimated (again using the SAS procedure NLIN), and the BMDL was then determined as the 5th percentile in the empirical distribution of the estimates. For more details we refer to our recent article (Budtz-Jørgensen et al., 2000).

## 2. Results of the $K$-power model with unrestricted $K$

In our original calculations (Budtz-Jørgensen et al., 1999) the power parameter in the $K$-power model was restricted to values equal to or above 1 (in agreement with the suggestion by Crump, 1999). Below BMDs and BMDLs are calculated using the $K$-power model without this restriction. So far these calculations have only been performed for the Boston Naming Test after cues.

**Boston Naming**

*BMDs and BMDLs ($\mu g/g$) calculated for the maternal hair mercury concentration for different BMRs and $P_0 = 5\%$ using the $K$-power model with and without restriction on the power parameter. Further, $-2{\cdot}log(L)$ indicates minus twice the log of the likelihood function.*

| DR-model | $K$-power | | $K$-power ($K \geq 1$) | |
|---|---|---|---|---|
| $-2{\cdot}\log(L)$ | 8021.56 | | 8021.66 | |
| $K$ | 0.8158 | | 1 | |
| | BMD | BMDL | BMD | BMDL |
| BMR=0.05 | 13.80 | <0.10 | 15.22 | 10.02 |
| BMR=0.10 | 25.96 | <0.40 | 25.49 | 16.69 |

**Comments on the results**

For 53 of the 2000 simulated data sets (2.65%) NLIN did not converge. This is the reason why a point estimate of the BMDL is not given. However, from the 1947 BMD estimates obtained, we were able to conclude that the BMDLs are below the given limits.

Without the power parameter restriction it is seen that the BMDLs are very small. The simulations show that in the unrestricted $K$-power model there is a high risk of estimating dose-response functions that are clearly biologically implausible in the very low dose range (below the observed exposures). For example, in one simulation the estimated dose-response function predicted that an unexposed child would score more than 60 points better on the Boston Naming Test than a child with a maternal hair mercury concentration of 0.1 $\mu$g/g (the observed range in the scores on the Boston Naming Test is 40). Thus, this investigation indicates that the unrestricted $K$-power model is not suited for benchmark dose calculations from epidemiological data.

For the cord blood concentrations $K$ was estimated to 0.20 in the unrestricted $K$-power model. The estimated BMDs were 0.22 $\mu$g/l and 3.19 $\mu$g/l for a BMR of 5% and 10%, respectively. BMDLs were not calculated but these will be even lower than the ones obtained for the maternal hair mercury.

## 3. Sensitivity of benchmark results to exclusion of highly exposed children

In this section it is investigated how sensitive the benchmark results are to exclusion of the most highly exposed children. These investigations are performed for the Boston Naming Test and for both exposure parameters. Using the cord blood concentrations two sets of children were excluded:

1. The most exposed child
2. The 5 most exposed children

For the maternal hair concentration we excluded:

1. The most exposed child
2. Children with a maternal hair concentration above 20 $\mu$g/g

The last set corresponds to the 7 most highly exposed children. This restriction was preferred to the requested set of the 5 most highly exposed children because it has been used in some of our own earlier sensitivity analyses.

## 3a. Blood Mercury Results

**Boston Naming**

*BMDs and BMDLs ($\mu g/l$) calculated using all observations for different BMRs and $P_0 = 5\%$. Further, $-2 \cdot log(L)$ indicates minus twice the log of the likelihood function.*

| DR-model | $K$-power | | Linear | | Square root | | Logarithmic | |
|---|---|---|---|---|---|---|---|---|
| $-2 \cdot \log(L)$ | 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 | 142.32 | 96.29 | 102.03 | 53.96 | 27.94 | 9.66 |

Estimate of $K$ in the (restricted) $K$-power model = 1.

**Boston Naming**

*BMDs and BMDLs ($\mu g/l$) calculated after exclusion of the most highly exposed child for different BMRs and $P_0 = 5\%$. Further, $-2 \cdot log(L)$ indicates minus twice the log of the likelihood function.*

| DR-model | $K$-power | | Linear | | Square root | | Logarithmic | |
|---|---|---|---|---|---|---|---|---|
| $-2 \cdot \log(L)$ | 7781.95 | | 7781.95 | | 7780.32 | | 7780.43 | |
| | BMD | BMDL | BMD | BMDL | BMD | BMDL | BMD | BMDL |
| BMR=0.05 | 72.97 | 52.76 | 72.97 | 50.61 | 37.64 | 20.87 | 6.31 | 3.06 |
| BMR=0.10 | 122.22 | 87.37 | 122.22 | 84.75 | 93.79 | 50.24 | 26.95 | 9.44 |

Estimate of $K$ in the (restricted) $K$-power model = 1.

**Boston Naming**

*BMDs and BMDLs ($\mu g/l$) calculated after exclusion of the 5 most highly exposed children for different BMRs and $P_0 = 5\%$. Further, $-2 \cdot log(L)$ indicates minus twice the log of the likelihood function.*

| DR-model | $K$-power | | Linear | | Square root | | Logarithmic | |
|---|---|---|---|---|---|---|---|---|
| $-2 \cdot \log(L)$ | 7736.50 | | 7736.50 | | 7734.88 | | 7734.17 | |
| | BMD | BMDL | BMD | BMDL | BMD | BMDL | BMD | BMDL |
| BMR=0.05 | 71.13 | 49.95 | 71.13 | 47.39 | 41.36 | 21.59 | 7.29 | 3.28 |
| BMR=0.10 | 119.12 | 82.25 | 119.12 | 79.36 | 103.54 | 52.06 | 33.51 | 10.40 |

Estimate of $K$ in the (restricted) $K$-power model = 1.

**Comments on the blood results**

The results of the $K$-power model and the linear model are sensitive to the exclusion of the most highly exposed child. After this exclusion the BMDLs (for BMR=5% and BMR=10%) decreased more than 11% compared to the result for the full data set. The results of the square root model and (especially) the logarithmic model exhibit only minor changes as a result of the exclusions.

## 3b. Hair Mercury Results

**Boston Naming**

*BMDs and BMDLs ($\mu g/g$) calculated using all observations for different BMRs and $P_0 = 5\%$. Further, $-2{\cdot}log(L)$ indicates minus twice the log of the likelihood function.*

| DR-model | $K$-power | | Linear | | Square root | | Logarithmic | |
|---|---|---|---|---|---|---|---|---|
| $-2{\cdot}\log(L)$ | 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 |

Estimate of $K$ in the (restricted) $K$-power model = 1.

**Boston Naming**

*BMDs and BMDLs ($\mu g/g$) calculated after exclusion of the most highly exposed child for different BMRs and $P_0 = 5\%$. Further, $-2{\cdot}log(L)$ indicates minus twice the log of the likelihood function.*

| DR-model | $K$-power | | Linear | | Square root | | Logarithmic | |
|---|---|---|---|---|---|---|---|---|
| $-2{\cdot}\log(L)$ | 8011.25 | | 8011.25 | | 8011.64 | | 8012.66 | |
| | BMD | BMDL | BMD | BMDL | BMD | BMDL | BMD | BMDL |
| BMR=0.05 | 14.23 | 9.66 | 14.23 | 9.15 | 11.98 | 6.08 | 8.18 | 2.98 |
| BMR=0.10 | 23.83 | 15.65 | 23.83 | 15.33 | 27.73 | 13.30 | 39.98 | 9.12 |

Estimate of $K$ in the (restricted) $K$-power model = 1.

**Boston Naming**

*BMDs and BMDLs ($\mu g/g$) calculated after exclusion of the 7 children with maternal hair concentration above 20 $\mu g/g$ for different BMRs and $P_0 = 5\%$. Further, $-2 \cdot log(L)$ indicates minus twice the log of the likelihood function.*

| DR-model | $K$-power | | Linear | | Square root | | Logarithmic | |
|---|---|---|---|---|---|---|---|---|
| $-2 \cdot \log(L)$ | 7948.53 | | 7948.80 | | 7949.49 | | 7950.45 | |
| | BMD | BMDL | BMD | BMDL | BMD | BMDL | BMD | BMDL |
| BMR=0.05 | 14.11 | 9.20 | 13.27 | 8.45 | 11.92 | 5.90 | 8.73 | 3.02 |
| BMR=0.10 | 19.95 | 14.43 | 22.22 | 14.15 | 27.56 | 12.87 | 44.12 | 9.27 |

Estimate of $K$ in the (restricted) $K$-power model = 1.49.

**Comments on the hair results**

All results are very robust to the exclusions.

**References**

Budtz-Jørgensen E., Keiding N. and Grandjean P. (1999). *Benchmark modeling of the Faroese methylmercury data.* Final Report to U.S.EPA.

Budtz-Jørgensen E., Keiding N. and Grandjean P. (2000). *Benchmark Dose Calculation from Epidemiological Data.* Research Report. Submitted for publication.

Crump K. (1995). *Calculations of Benchmark Doses from Continuous Data.* Risk Analysis 15, 79-89.

Efron B. and Tibshirani R.J. (1993). *An Introduction to the Bootstrap.* Chapman & Hall.