

Response to questions posed by Andy Smith

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1. Benchmark Dose Calculation

In this section it is explained why the BMD of the logarithmic dose-response model has wide confidence bands at high BMRs.

Let $Y(d, c_1, \dots, c_k)$ denote the response of a child with exposure d and confounder values: c_1, \dots, c_k . In our benchmark calculations we considered dose-response models on the following form:

$$Y(d, c_1, \dots, c_k) = \beta_0 + \beta \cdot g(d) + \beta_1 \cdot c_1 + \dots + \beta_k \cdot c_k + \epsilon,$$

where $\epsilon \sim N(0, \sigma^2)$. The function g (which is assumed known and thus does not depend on any parameters) is increasing and $g(0) = 0$. For the logarithmic model $g(d) = \log(d + 1)$.

The expected excess response at exposure d ($EER(d)$) is the expected difference between the response of a child at exposure d and an unexposed child i.e.

$$EER(d) = E[Y(d, c_1, \dots, c_k)] - E[Y(0, c_1, \dots, c_k)].$$

In Budtz-Jørgensen et al. (2000) it is shown that the BMD satisfies:

$$EER(\text{BMD}) = \Omega_{P_0, \text{BMR}} \cdot \sigma,$$

where $\Omega_{P_0, \text{BMR}}$ is constant depending only on the prespecified values of P_0 and BMR. Thus, exposure to the BMD results in an expected excess response equal to a fraction of the standard deviation of the random response component (ϵ). The higher the BMR the higher this fraction.

On Figure 1 (Figure 3 in Budtz-Jørgensen et al. (2000)), for each model the estimated expected excess response on the Boston Naming Test due to mercury exposure is shown as a function of the mercury dose ($d \rightarrow \widehat{EER}(d)$). The BMD is the dose which causes a certain level of excess response given as a fraction of the standard deviation of the random response component. Since the estimates of σ are approximately the same in all the models, the BMDs can (approximately) be found as the intersections between the excess response curves and the same horizontal line. The curves are clearly different: the logarithmic curve is far above the linear dose-response in the low dose range. Thus, at low BMRs the logarithmic model will yield lower BMDs than the linear model. At a certain BMR the logarithmic and the linear excess response curves meet, yielding identical BMDs. However, the BMDL of the logarithmic curve will still be lower

because the this curve is not as steep as linear one when the two curves meet. Thus, the point of intersection with the horizontal line is more uncertain for the logarithmic curve, thereby giving wider BMD-confidence bands. An example of this is seen for the maternal hair concentration in Table 2: For BMR=10% the logarithmic BMD is higher than the linear BMD while the opposite relation is seen for the BMDLs. However, at low doses, where the logarithmic curve is steeper than the linear curve, the confidence bands of the logarithmic model are *narrower* than those of the linear model. Thus, the precision of the BMD estimate is dependent on the BMR. For low BMRs the confidence bands of the logarithmic model are the narrowest while this model yields the widest confidence bands at higher BMRs.

2. Benchmark calculations using different logarithmic models

In Budtz-Jørgensen et al. (1999) benchmark doses were calculated using the logarithmic model: $g(d) = \log(d + 1)$, where d is the mercury concentration. The constant of 1 was added to the concentrations to avoid dose-response functions with an infinite slope at zero dose. However, another constant could just as well have been chosen. Here the sensitivity of the benchmark results to the choice of the constant is investigated.

Table 1 gives the BMDLs for the Boston Naming Test calculated for five different values of the constant added to the concentrations before applying the logarithmic transformation. This table also gives minus twice the log of the likelihood function for each model indicating how well the models fit the data. From the table it is seen that the models fit the data almost equally well (although 1 gives a very slightly better fit than the rest), while the BMDLs are quite different. The higher the constant the higher the BMDLs, but all BMDLs are lower than the corresponding BMDLs of the linear model and the square root model reported in Budtz-Jørgensen et al. (1999) and quoted in the table.

Table 1: BMDLs using the model: $g(d) = \log(d + a)$, where d is the cord blood mercury concentration and a is a known constant, and $P_0 = 0.05$.
Response variable: Boston Naming Test with cues.

a	0.5	1	2	K -power	Linear	Square Root
$-2 \cdot \log(L)$	7790.43	7790.42	7790.43	7793.72	7793.72	7790.84
BMR=0.05	1.65	3.11	5.61	61.22	57.50	22.33
BMR=0.10	5.27	9.66	16.73	102.22	96.29	53.96

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.