The Benchmark Dose (BMD) approach for health effects of PCB exposure

Toxicity studies are conducted to both identify and characterize the potential adverse effects of a test material. Analysis of the data obtained in these studies is structured to identify a dose that can be used as a starting point for human health risk assessment. The dose used for this purpose, however derived, is referred to as the Reference Point (RP).

The No-Observed-Adverse-Effect-Level (NOAEL) is a RP that has been commonly used in risk assessment of non-genotoxic substances. The NOAEL has a long history of use in the regulatory process of human risk assessment, and is the usual RP for estimating health-based guidance values such as acceptable daily intakes (ADIs) for food additives and pesticide residues, and tolerable daily intakes (TDIs) or tolerable weekly intakes (TWIs) for contaminants. The Benchmark Dose (BMD) approach is an alternative way of defining the RP.

The NOAEL approach

The NOAEL approach is applicable to all toxicological effects considered to have a threshold. The study NOAEL is derived as follows:
- For each adverse effect/endpoint, identify the highest experimental dose level where effects were not detected, using expert opinion and statistical tests to compare each treatment level with the control group.
- The study NOAEL is the lowest relevant NOAEL obtained for any of the adverse effects detected in the study.

In this connection, in risk assessment, a very important issue is the Point of Departure. It is defined as the dose-response point that marks the beginning of a low-dose extrapolation. This point is most often the upper bound on an observed incidence or on an estimated incidence from a dose-response model. Chemical risk assessment provides threshold doses or concentrations of regulatory concern such as acceptable daily intakes (ADI) or predicted no effect concentrations (PNECs) for individual chemicals which are based on so-called points of departure (No Observed Adverse Effect Levels, NOAELs, No Observed Effect Concentrations, NOECs, or benchmark doses). Exposures below these levels are usually considered safe. Hence, the NOAEL is the highest dose tested without observation of an adverse effect in the particular experiment. The numerical value of the NOAEL is thus dependent upon the selection of dose levels when the study was designed and on the ability of the study to detect adverse effects. Since studies with low power (e.g. small group sizes) and/or insensitive methods are able to detect only relatively large effects, these tend to result in higher NOAELs. If there is a significant effect at all dose levels, the lowest dose used in the study may be set as the lowest-observed-adverse-effect-level (LOAEL).

The BMD approach

The BMD approach is applicable to all toxicological effects. It makes use of all of the dose-response data to estimate the shape of the overall dose-response relationship for a particular endpoint. The BMD is a dose level, derived from the estimated dose-response

curve, associated with a specified change in response, the benchmark response (BMR). The BMD has been defined as the dose of a toxic compound that increases the probability of an abnormal response by a BMR, i.e. from P_0 for an unexposed subject to P_0 + BMR for a subject at the BMD (Crump 1984;Crump 1995). The BMDL is the BMD's lower confidence bound, and this value is normally used as the reference point. Figure 1 gives a graphical illustration of the BMD definition (Budtz-Jorgensen et al. 2001). The key concepts in the BMD approach are illustrated in figure 2 (EFSA).
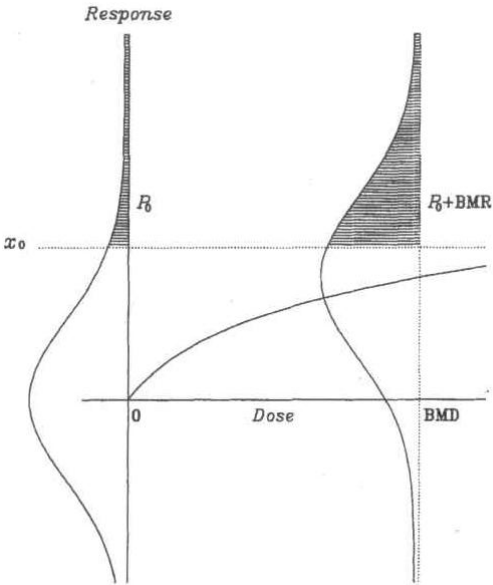

Figure 1: Hypothetical dose-response relation illustrating the concepts of benchmark approach. The dose-response curve indicates that when the dose increases, so does the expected response. The distribution of responses in unexposed subjects is shown on the y-axis. Responses above the prespecified x_0 are considered abnormal. The risk of an abnormal response in unexposed subjects is P_0, indicated by the shaded area. At the BMD, the response distribution has been translated upward and the risk of an abnormal response has increased to P_0 + BMR. The BMDL is placed somewhere between zero and the estimated BMD, depending on the amount of information in the study.
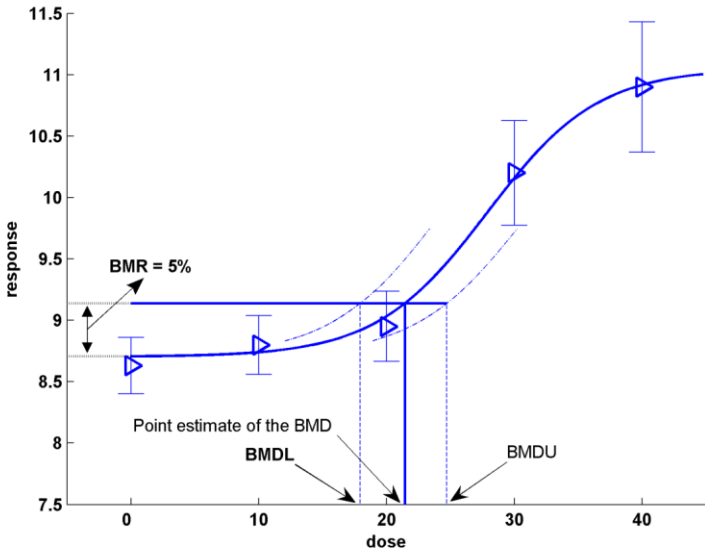
Figure 2: The solid curve is a fitted dose-response model. This curve determines the BMD (point estimate), which is generally defined as a dose that corresponds to a low but measurable change in response, denoted the benchmark response (BMR). The dashed curves represent respectively the upper and lower 95% confidence bounds (one sided) for the effect size as a function of dose. Their intersections with the horizontal line are at the lower and upper bounds of the BMD, denoted BMDL and BMDU, respectively.

It should be noted that the BMR is not defined as a change with regard to the observed mean background response, but with regard to the background predicted by the fitted model. This distinction is important because, in general, the fitted curve does not hit the observed background response exactly. In the figure, the BMD corresponds to a 5% change in response relative to background (BMR = 5%). The fitted curve yields an estimated background response of 8.7, and a 5% increase of that equals 9.14 (8.7 + 0.05*8.7 = 9.14). Thus, the BMD of 21.5 is obtained from the intersection of the horizontal line at a response of 9.14 with the fitted dose-response model. In this example, the BMDL has a value of 18.

The essential steps involved in identifying the BMDL for a particular study are:
- Specification of a low but measurable response level; e.g. a 5% or 10% increase or decrease in response compared with the background response. This is called the BMR.
- Fitting a set of dose-response models, and calculation of the BMD and the BMDL for those models that describe the data according to statistical criteria, resulting in a range of BMDL values for each adverse effect/endpoint.
- Selection of a BMDL for each potentially critical endpoint.
- An overall study BMDL, i.e. the critical BMDL of the study, is obtained from the range of BMDL values for the different potentially critical endpoints.

The BMD approach itself provides a formal quantitative evaluation of data quality, by taking into account all aspects of the specific data. When data are relatively poor or uninformative, the resulting BMDL for that dataset will tend to be low. But the meaning of that BMDL remains as it was defined: it reflects a dose level where the associated effect size is unlikely to be larger than the BMR used. Nonetheless, it might happen that the data are so poor that using the associated BMDL as a potential RP appears unwarranted, and the dataset may need to be discarded. This might be decided when the confidence intervals around the BMD are wide or when different models result in widely different BMDL values.

The most well known BMD software is the benchmark dose software (BMDS) developed by the U.S. EPA (www.epa.gov/ncea/bmds) and the PROAST software developed by RIVM (www.rivm.nl/proast).

Specific issues of human dose-response data

Dose-response data from observational epidemiological studies may differ from typical animal toxicity data in several aspects. The main differences relevant to BMD calculations are briefly discussed below.

- Exposure data often do not fall into a small number of well defined dosage groups. The BMD approach can be readily used with individual exposure data.

- Unlike most experimental studies, observational studies may not include an unexposed control group, because all individuals may be exposed to some extent, e.g. an atmospheric pollutant, a food contaminant. In this case, the BMD approach still applies, since fitting a dose-response curve does not necessarily require observations at zero exposure. However the response at zero exposure would then need to be estimated by low-dose extrapolation. Hence the BMD derived from epidemiological data can be strongly model-dependent (Budtz-Jorgensen et al. 2001).

- It should also be noted that the estimation of human exposure is often imprecise, and ignoring the imprecision may lead to a biased assessment of the dose-response relationship.

- Response variables in human studies are often subject to confounding factors that may interfere with the dose-response of interest. Failure to take a confounding factor into account may result in either underestimation or overestimation of the BMD. Effect modification may present an additional issue that needs to be taken into account, e.g. when a greater vulnerability occurs in elderly subjects. The BMDL should then reflect the response in the most vulnerable subpopulation. Adjustment for confounding or effect modification is not possible in BMDS, and only partly in the PROAST software.

BMD compared to traditional NOAEL

Traditionally, when experimental animal data are used for risk assessment of substances in food, which are not genotoxic and carcinogenic, the No-Observed-Adverse-Effect-Level (NOAEL) and/or the Lowest-Observed-Adverse-Effect-Level (LOAEL) for the critical effect of a substance, forms the Reference Point for deriving health-based guidance values, such as an Acceptable Daily Intake (ADI). However, while this approach may utilize qualitative information, it does not use the data available in a quantitative way. In contrast, the Benchmark Dose (BMD) approach makes extended use of the dose-response data from studies in experimental animals or from observational epidemiological studies to better characterize and quantify potential risks.

An argument in favor of the BMD approach is that this approach provides a higher level of confidence in the conclusions in any individual case since the BMDL takes into account the quality of the data better than the NOAEL.

The BMD approach is applicable to all chemicals in food, irrespective of their category or origin, e.g. pesticides, additives or contaminants. The BMD approach is of particular value for i) situations where the identification of a NOAEL is uncertain, ii) providing a Reference Point for the Margin of Exposure in case of substances that are both genotoxic and carcinogenic, and iii) dose-response assessment of observational epidemiological data.

Applying the BMD approach to the dose-response relations for exposure to PCBs

The objective of this section is to contribute to a better characterization of the dose-response assessment in case of health outcomes due to environmental exposures to PCBs. Such PCB exposure-response functions for humans are rather largely unknown. This is why in risk assessment in connection to human PCB exposures the procedure relies mainly on data obtained with experimental animals. This requires introduction of various uncertainty factors when applying to human population.

We found BMD analysis particularly well suited for risk assessment based on continuous health outcome data from our human PCB exposure studies. Endpoints from four cohorts were used: the 2047 adults and 434 8-9-year old children from the EU 5thFP PCBRISK project (Kocan et al. 2004;Petrik et al. 2006), the 575 12-year old children from a recent follow-up study (Trnovec et al. 2010) and 811 adolescent (14-16.5-year old) boys from the first Flemish Environment and Health Study (2002-2006) (Schroijen et al. 2008). BMDs for PCB exposures were calculated for free thyroxine (FT4) and thyroid volume in adults, in children for: 1)pure tone audiometry at frequencies of 125, 250 and 500 Hz; 2) transient evoked otoacoustic emissions (TEOAE) responses for 1000 and 1500 Hz grouped into half octave bands; 3) amplitudes of distortion product otoacoustic emissions (DPOAE) for 1000 and 2000 Hz; 4) simple reaction time; 5) tapping test; and 6) Vienna discrimination test, and in adolescent boys for testosterone.

A software developed at the Slovak Medical University in cooperation with the Slovak University of Technology in Bratislava was used to apply the BMD approach to the dose-response relation of exposure to PCBs.

Our results show that for FT4 and thyroid volume (P_0 = 0.05 and BMR = 0.05) BMD and BMDL was around 14000 and 10000 ng PCB/g serum lipids, respectively. The cutoff value for serum FT4 was around 21 pmol/L and for thyroid volume 16 mL. For all endpoints studied in children for both P_0 = 0.05 and P_0 = 0.1 and BMR = 0.05 the BMD and BMDLs were in the interval 1013-2420 and 673-1375 ng PCB/g serum lipids, respectively. In adolescent boys, the dose-response relation of PCBs (ng/g serum lipids) versus testosterone (ng/dL) in boys was examined. The results show that for testosterone (P_0 = 0.05 and BMR = 0.05) the BMD and BMDL was around 158 and 126 ng PCB/g serum lipids, respectively. The cutoff value (x_0) for serum testosterone was around 653 ng/dL. When correcting for age and BMI, the BMD and BMDL were around 144 and 116 ng PCB/g serum lipids, respectively. The cutoff value (x_0) for serum testosterone was around 732 ng/dL.

The data we calculated show that testosterone might be a very sensitive marker of exposure compared to other outcomes (otoacoustic emissions, neurobehavioral outcomes, etc.).

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