

b. Derivation of an AEL for nPB.

Benchmark Dose Modeling

Background. EPA considered two methods to derive a recommended acceptable exposure level for workplace exposure: (1) The use of the no-observed-adverse-effect level (NOAEL) to define the starting point of departure (POD) for the computation of a reference value, and (2) the use of benchmark dose-response (BMD) modeling to define the POD. Both methods are essentially a two-step process, the first step defining a POD, and then the second extrapolating from the POD to a lower, environmentally relevant exposure level. EPA's in-depth analysis uses the BMD modeling approach, for reasons explained below; however, under either approach, one arrives at a similar value.

The traditional approach to derive safe exposure limits for numerous chemicals regulated in a variety of programs, including the SNAP program, has been to first determine the NOAEL (or LOAEL if a NOAEL cannot be identified), use the NOAEL as the POD, and then apply uncertainty factors based on EPA's guidelines to determine an appropriate reference value. Using the NOAEL to determine a reference value has long been recognized as having limitations in that it: (1) Is limited to one of the doses in the study; (2) does not account for variability in the estimate of the dose-response, which is due to the characteristics of the study design; (3) does not account for the slope of the dose-response curve; and (4) cannot be applied when there is no NOAEL, except through the application of an additional uncertainty factor (Crump, 1984; Kimmel and Gaylor, 1988).

A newer analytic approach is to use benchmark dose modeling to define a point of departure for deriving a reference value or slope factor that is more independent of study design. For risk assessment of nPB, EPA followed the BMD guidelines to develop an AEL. The EPA Risk Assessment Forum has written guidelines for the use of the BMD approach in the assessment of non-cancer health risk (USEPA, 1995b), and the EPA Benchmark Dose Workgroup is in the process of drafting technical guidance for the application of the BMD approach in cancer and non-cancer dose-response assessments. Use of BMD methods involve fitting mathematical models to dose-response data and using the results to select a BMD that is associated with a predetermined benchmark response (BMR) at the low end of the observed range in the studies used, such as a 10% increase in the incidence of a particular

lesion or a 10% decrease in body weight gain. The BMD derived from mathematical modeling is the central estimate of the dose/exposure associated with the BMR. The point of departure derived from BMD modeling, however, is the Benchmark Dose Lowerbound (BMDL), or the lower 95% bound on the dose/exposure associated with the BMR. Using the lower bound accounts for the uncertainty inherent in a given study (e.g., small sample size), and assures (with 95% statistical confidence) that the desired BMR is not exceeded.

The advantage of the benchmark dose approach is that it considers response data across all exposure groups. For example, a benchmark dose can be calculated even in studies where a NOAEL could not be identified, *i.e.*, in studies where responses even in the lowest exposure group tested were considered adverse. Unlike the NOAEL/LOAEL, the benchmark dose does not have to be one of the exposure levels (dose groups) chosen in the experimental design. In a hypothetical experiment where groups of rats are exposed to a chemical at 0 ppm, 100 ppm, 500 ppm and 1,000 ppm, the NOAEL or LOAEL must be either 100 ppm, 500 ppm, or 1,000 ppm simply because those were the only levels tested in the experiment. However, the benchmark dose derived from the data in the same experiment could be 200 ppm, 750 ppm, or even 997 ppm depending on the shape of the dose response curve described by the data. EPA uses the BMD approach whenever possible because it provides a more quantitative alternative to identification of a point of departure than the traditional NOAEL/LOAEL approach (US EPA 1995b).

Dosimetric adjustments and application of uncertainty factors.

Under either approach—NOAEL/LOAEL or BMD modeling—an adjustment to the point of departure for the calculation of a reference value may be necessary to calculate a "human equivalent concentration" (HEC) if there are differences between the exposure regime used in the toxicity studies and a typical workweek of 8 hours per day and 5 days per week. Once a POD and the corresponding HEC is identified, uncertainty factors (UFs) are applied to account for extrapolation uncertainties that could underestimate the chemical's toxicity potential for exposed humans (in this case, workers using nPB). According to standard risk assessment methods as delineated in Agency guidance (US EPA, 1994), UFs of up to 10 may be applied for each of the following conditions:

(1) Data from animal studies are used to estimate effects on humans;

(2) Data on healthy people or animals are adjusted to account for variations in sensitivity among members of the human population (e.g., interindividual variability);

(3) Data from subchronic studies are used to provide estimates for chronic exposure;

(4) Studies that only provide a lowest observed adverse effect level (LOAEL) rather than a no observed adverse effect level (NOAEL) or benchmark dose; or

(5) An incomplete data base of toxicity information exists for the chemical (US EPA, 1995b).

Finally, a modifying factor (MF), which is an additional uncertainty factor that is greater than zero and less than or equal to 10, may be used. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

It is important to note that EPA does not have specific guidelines for occupational studies. As such, EPA is applying its general risk assessment principles and adapting its methodologies, as appropriate to consider risk in an occupational setting. For example, as mentioned above, EPA is adjusting its exposure scenario to derive a human equivalent concentration (HEC) that is representative of workplace exposure, rather than continuous lifetime exposure.

Selection of Endpoints for Benchmark Dose Modeling. Based on EPA guidance, endpoints were selected for BMD analysis and for potential use as a point of departure using the following principles:

- Toxicological significance of the endpoint
- Relevance to humans
- Quality of study and dose-response data
- Reproducibility of effects across multiple studies.

EPA selected reduced sperm motility and increased liver vacuolation for BMD analysis because they met the above criteria, and because these effects were seen consistently throughout the toxicological database at low exposures. EPA guidance states that endpoints selected as appropriate for risk assessment should be modeled if their LOAEL is up to 10-fold above the lowest LOAEL. This ensures that no endpoints with the potential to have the lowest BMDL are excluded from the analysis. The selection of the most appropriate