

## Dose-Response Analysis of Noncancer Health Effects

- Standard: Estimate minimum dose not to be exceeded by multiplying least dose where effect observed by “uncertainty factor”
- More recently: Benchmark doses - similar to default technique for cancer effects

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## Standard Method: NOAEL

- No Observed Adverse Effect Level (NOAEL or NOEL): highest dose at which no adverse effects have been detected.
- Adjust downward by uncertainty factors to account for uncertainties and limitations in available data. (See Problem 5-3.)
- Result: Reference Dose (RfD) or Reference Concentration (RfC): Exposure that is unlikely to have harmful effects in humans
- Variability in observed responses not addressed.

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## Alternative Standard Approach: LOAEL

- If no NOAEL is available, identify a Lowest Observed Adverse Effect Level (LOAEL or LOEL): the lowest dose of the substance at which adverse effects have been observed.
- Proceed as with NOAEL, but use additional uncertainty factor of 10.

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## Problems with Standard Approach

- NOAEL is a “practical threshold” and may be an artifact of the limitations of the study; it cannot be (but often is) taken to imply the existence of a true threshold.
- Does not account for uncertainty in estimation
- NOAELs do not correspond to specific responses so are not useful for comparison across studies/substances/species/endpoints
- Shape of dose/response curve usually not considered.

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## Effects of Study Design on NOAEL/LOAEL

- NOAEL/LOAEL must be one of doses used in study.
- Small sample size reduces ability to distinguish treatment response from control (statistical power), so may result in inflated NOAEL

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## Default Point of Departure

- POD = BMDL: lower 95% bound on the dose associated with the benchmark response
- Benchmark dose (BMD): Expected value of dose to give benchmark response level
- Benchmark response level (BMR): Various possibilities

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## Benchmark Dose (BMD) Method

Dose-response extrapolation Parallels 1996 Proposed Guidelines for Carcinogen Risk Assessment:

- Response data modeled in range of observation
- Extrapolation below range of observation may be by modeling if appropriate, or by default: Straight-line extrapolation to background response level from point of departure (POD)

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## Benchmark Response Levels for Dichotomous Variables

- 10% excess risk (so BMD =  $ED_{10}$  and BMDL =  $LED_{10}$ )
- Lower if possible (minimizes amount of low-dose extrapolation)
  - Some reproductive and developmental studies are sensitive enough to use 5%
  - Some epidemiological studies are sensitive enough to use 1%
- Higher if necessary

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## Benchmark Response Levels for Continuous Variables

- Any minimal level of change in endpoint generally considered to be biologically significant (e.g., change in human body weight of 10%)
- In some cases, data can be “dichotomized” as adverse or not adverse.
- One control standard deviation from the control mean. (For normal effects, gives excess risk of  $\approx$  10% for being in 2% tails of control distribution.)

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## Advantages of BMD Approach

- BMD not restricted to an experimental dose. In particular, can be estimated even when all doses in a study have significant adverse response (no NOAEL)
- Takes uncertainty and variability into account
- Uses all the data in the study
- Can also be used to establish reference dose/concentration (RfD or RfC) or to compare different substances (by comparing BMD or BMDL for same BMR)

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## Advantages of NOAEL/LOAEL

- Available data may not allow modeling (e.g., all exposed individuals respond)
- Rare effects that are not statistically significantly different from control group, but are biologically meaningful (e.g., increase in a rare malformation)

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