Implications of Linear Low-Dose Extrapolation for Noncancer Risk Assessment

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TERA
This case study is a characterization of the method, and is not intended as endorsement or opposition of linear extrapolation.

**Method 1:** extend a straight line from the chosen BMDL adjusted to the human equivalent dose or concentration (HED or HEC).

**Method 2:** linearize HED(C) dose-response data using probit transformation in logarithmic space. Fit regression line to the data and extend to the low-dose
Method 1: Linear extrapolation from BMD

0.1

Dose

Response

Human Equivalent Dose

$U_F^A$

$U_F^D$

$U_F^S$

Animal BMD
Results

• Strengths:
  • simplicity
  • Provides Risk Specific Dose at any level of exposure

• Weaknesses:
  • Risk estimates produced were highly conservative compared to current RfC/RfD methods
  • No consideration of biological understanding
Panel Comments

• Possibly useful for screening level assessment or priority setting, but should not be construed as accurate estimate of risk

• Requested exploration of non-cancer linear extrapolation in log-dose, probit space
Probit Transformation

- Linearizes biological data
- Requires quantal population data
- To allow graphing in log space, response rates were converted to Excess Risk [added risk(d) = P(d) - P(0)] for each dose group
- A dataset of at least three test doses above the control

*Figure 2-4. Diagram of quantal dose–response relationship.*

From Casarett & Doull 2009
Method 2: Linear extrapolation in Log-Dose, Probit Space

- Probit Response
- Log Dose
- Human Equivalent Dose
- Animal Data
- UF_A
- UF_D
- UF_S
Acrylamide

Effect: Nerve Degeneration
Species: Rat

\[ RfD = 0.002 \text{ mg/kg-day} \quad \text{Log}(RfD) = -2.69 \quad \text{Uncertainty Factor: 30 (A-3; H-10)} \]

Probit Response Above Control v. Log(Human Equivalent Dose) (mg/kg)

Probit at RfD = 1.9 \quad \text{Risk at the RfD} = 1 \times 10^{-3}
## Summary of Results

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Method 1. Linear Extrapolation from BMD(L)</th>
<th>Method 2. Log-Dose, Probit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk at RfC/RfD From BMD(C)L (Method 1)</td>
<td>Risk at RfC/RfD From BMD(C) (Method 4)</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acrylamide</td>
<td>$1 \times 10^{-2}$</td>
<td>$3 \times 10^{-4}$</td>
</tr>
<tr>
<td>Chlordecone</td>
<td>$1 \times 10^{-2}$</td>
<td>$1 \times 10^{-5}$</td>
</tr>
<tr>
<td>Inhalation</td>
<td></td>
<td></td>
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<tr>
<td>1,3-Dichloropropene</td>
<td>$8 \times 10^{-3}$</td>
<td>$6 \times 10^{-4}$</td>
</tr>
<tr>
<td>Nitrobenzene</td>
<td>$1 \times 10^{-2}$</td>
<td>$4 \times 10^{-3}$</td>
</tr>
</tbody>
</table>
Conclusions

• Simple
• Provides estimate of risk at any level of exposure
But,
• Limited Applicability:
  – Restrictive data requirements permitted the use of four of the 25 chemicals considered
• Inconsistent Results:
  – Risk estimates at the RfD/RfC ranged from $1 \times 10^{-12}$ (1,3-dichloropropene) to 0.5 (nitrobenzene).
Extra Slides
Areas of Uncertainty to Consider in Noncancer Dose Response Assessment

Chronic Human

Chronic Animal

Reproductive

Sub-chronic Animal

Response

Dose

0.1

$UF_H$

$UF_A$

$UF_L$

$UF_S$

$UF_D$
Calculation of Human Equivalence Dose or Concentration

- **Method 1**
  *Benchmark Dose 95% Lower-bound confidence limit (BMDL)*
  Uncertainty Factors: $UF_S$, $UF_A$, and $UF_D$

- **Method 2**
  *Benchmark Dose (BMD)*
  Uncertainty Factors: $UF_S$, $UF_A$, and $UF_D$

- **Method 3.**
  *Benchmark Dose (BMD)*
  Uncertainty Factors: *geometric means* of the $UF_S$, $UF_A$, and $UF_D$

- **Method 4.**
  *Benchmark Dose (BMD)*
  Uncertainty Factors: *geometric mean* of the $UF_A$