A NOVEL APPROACH TO DESCRIBING U-SHAPED DOSE-RESPONSE CURVES FOR MANGANESE USING CATEGORICAL REGRESSION

BRITTANY MILTON, MSC
IMNI SYMPOSIUM
OCTOBER 14, 2015

BACKGROUND INFORMATION

- Establishing the daily recommended intake and allowable range of oral intake for an essential nutrient requires determination of
  1) the minimum intake that will satisfy nutritional requirements and;
  2) the maximum tolerable intake that will not result in toxicity (FNB, 2001)
- The challenge is to define an allowable range of oral intakes that will not result in adverse health outcomes due to either excess or deficiency
- Dose-response assessment can assist health scientists in meeting this challenge

<table>
<thead>
<tr>
<th>Traditional Approaches for Dose-response Assessment</th>
<th>Limitations of Traditional Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Reference dose (RfD)</td>
<td>Based on one critical study and health effect; no way to quantify error</td>
</tr>
<tr>
<td>2) Benchmark Dose (BMD)</td>
<td>Based on one critical study; several mathematical models may indicate a ‘good’ fit</td>
</tr>
</tbody>
</table>

Categorical regression has found application in dose-response modeling for risk assessment purposes (Allen et al. 2005; Gift et al. 2008). The US EPA has developed a software package called CatReg to perform these analyses.
AN INTRODUCTION TO THE Mn PROBLEM: IDENTIFYING A DAILY INTAKE LEVEL

- Mn is a chemical element required by humans and animals for normal growth, development and function of different organs and systems
- Mn imposes a risk on human health for both deficient and excess oral intake.

To find a balance between excess and deficiency, there is a need to develop an approach where excess and deficiency are modeled simultaneously (Chambers et al. 2010).

CATEGORICAL REGRESSION

Hertzberg and Miller (1985) proposed categorical regression to empirically evaluate differences in sensitivity for toxicity data with ordered responses.

Categorical regression has found application in nutrient risk assessment because of its ability to:
- Include multiple studies, incorporating different designs, species, dose levels, etc. into dose-response assessment by standardizing multiple health endpoints on a common severity scale
- Combine multiple studies to increase statistical power; account for uncertainty

Categorical regression is a statistical tool for estimating the probability of an adverse health effect associated with health risks from exposure to toxic substances (CatReg User Manual, US EPA 2006).

Limitations of Categorical Regression
- Toxicological judgment is needed to rate the severity of the observed effects, introducing subjectivity
- Statistically driven; no information on biological processes underlying the induction of adverse health outcomes is used in model fitting
Chambers et al. (2010) used CatReg to model excess and deficiency probability curves separately and identified 2.6 mg/day as the optimal intake level of dietary Cu.

CatReg and its Limitations

- CatReg was designed to model acute inhalation exposure; problematic for deficiency.
- To model deficiency, must impose an increasing relationship.

*DECREASING* deficiency relationship: as dose increases, probability of *adverse* health decreases

*INCREASING* deficiency relationship: as dose increases, probability of *non-adverse* health increases

How to model excess and deficiency simultaneously?
DEVELOPMENT OF Mn DATABASE

This database was created to support both qualitative traditional approaches to dose-response assessment, as well as emerging quantitative approaches such as categorical regression.

A total of 181 eligible studies described in 228 articles were identified.

18-POINT SEVERITY SCORING MATRIX

Table 1: 18-point severity scoring matrix developed during January 2013 workshop at RSI.

Table 2: Distribution of individual level data in the Manganese database.
**CHARACTERISTICS OF THE Mn-CATREG DATABASE**

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>Number of Experiments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPECIES</td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>251</td>
</tr>
<tr>
<td>Mouse</td>
<td>73</td>
</tr>
<tr>
<td>Human</td>
<td>15</td>
</tr>
<tr>
<td>Pig</td>
<td>22</td>
</tr>
<tr>
<td>Rabbit</td>
<td>4</td>
</tr>
<tr>
<td>Hamster</td>
<td>10</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>12</td>
</tr>
<tr>
<td>SEX</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>254</td>
</tr>
<tr>
<td>Female</td>
<td>72</td>
</tr>
<tr>
<td>Both sexes</td>
<td>30</td>
</tr>
<tr>
<td>Unknown</td>
<td>22</td>
</tr>
<tr>
<td>EXPOSURE ROUTE</td>
<td></td>
</tr>
<tr>
<td>Oral</td>
<td>323</td>
</tr>
<tr>
<td>- Drinking water</td>
<td>87</td>
</tr>
<tr>
<td>- Food</td>
<td>138</td>
</tr>
<tr>
<td>- Gastric tube</td>
<td>91</td>
</tr>
<tr>
<td>- Tablet/capsule</td>
<td>4</td>
</tr>
<tr>
<td>TYPE OF STUDY</td>
<td></td>
</tr>
<tr>
<td>Experimental</td>
<td>307</td>
</tr>
<tr>
<td>Observational</td>
<td>11</td>
</tr>
</tbody>
</table>

How can we synthesize this information on excess and deficiency into one dose-response model?

**JOINT MODEL FOR EXCESS AND DEFICIENCY (JMED MODEL)**

- JMED Model is based on a special case of categorical regression called *binary logistic regression*.
- Response variable represents the presence or the absence of an adverse health effect.
- JMED Model is based on two independent variables: *dose (mg/kg bw day)* and *study type* (excess or deficiency).
- Indicator variable is used to inform whether an observation originates from an excess or deficiency study.
- The use of an indicator ultimately allows for an asymmetrical U-shaped curve, reflecting the differential behaviour observed in the deficiency and excess data sets.
- JMED model provides a representation of dose-response data where all information is contained within one model; it also affords the opportunity to express excess and deficiency curves separately.
**JMED Model: Mathematical Definition**

The probability of an adverse health effect is estimated as a function of dose ($x_1$), study type ($x_2$), and their interaction ($x_1x_2$).

<table>
<thead>
<tr>
<th>Independent Variables</th>
<th>Response Variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>$x_0 = \log_{10}$ dose of $D_{obs}$</td>
<td>$Y = \begin{cases} 1 &amp; \text{if excess} \ 0 &amp; \text{if deficiency} \end{cases}$</td>
</tr>
<tr>
<td>$x_2 = \begin{cases} 1 &amp; \text{if excess} \ 0 &amp; \text{if deficiency} \end{cases}$</td>
<td>$P = \begin{cases} 1 &amp; \text{presence of an adverse health effect} \ 0 &amp; \text{absence of an adverse health effect} \end{cases}$</td>
</tr>
</tbody>
</table>

**Independence Model (IM)**

To model the relationship between dose and overall risk attributed to excess and/or deficiency, we assume a health effect induced by a deficiency mechanism is independent of one induced by an excess mechanism. The independence model (IM) is expressed as $P_{DUE} = P_D + P_E - P_DP_E$ and emerges as a U-shaped curve.
REFERENCE POINTS FOR SAFE EXPOSURE GUIDELINES

JMED and IM models provide two benchmarks that could potentially act as safe exposure limits:

1) Equiprobable Crossover Point (EPCP)
   - dose level where the excess and deficiency curves cross
   - dose level at which probability of adverse health effects due to excess or deficiency are equal

2) XMINDUE – dose level that minimizes overall risk due to excess and deficiency

The confidence interval for XMINDUE can be interpreted as a range of intake levels that minimizes overall risk and hence, an allowable range of oral intake.

APPLICATION: MN DATABASE

<table>
<thead>
<tr>
<th>EPCP (mg/kg bw)</th>
<th>95% Confidence Limits</th>
<th>XMINDUE (mg/kg bw)</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>(1.7, 2.5)</td>
<td>2.2</td>
<td>(2.0, 2.4)</td>
</tr>
</tbody>
</table>

- Combined results for all species without adjustments for species differences
- Stratified analysis can be used to obtain species-specific results
- More data on excess than deficiency in this analysis
APPLICATION: CU DATABASE

Additional indicator variables can be incorporated in the JMED model to permit species-specific analyses, allowing for deficiency, excess, and U-shaped dose-response curves for all species with sufficient data. The data in the Mn database did not support this analysis, however, a copper database assembled by Krewski et al (2010) can be employed to demonstrate this tool.

Stratification exercises allow rich data sources to bridge the missing gaps in limited data sources.

The $X_{MINDUE}$ for humans is 2.73 mg Cu/day with confidence limits (1.4, 4.2).

WHO (1996) recommends minimal intake of 1.3 mg Cu/day, while maximum tolerable uptake has been established at 10 mg Cu/day.

CLOSING REMARKS

- This approach incorporates all available data on Mn toxicity in the world’s literature and synthesizes it into one dose-response model
- Two reference points – the EPCP and $X_{MINDUE}$ were introduced from the JMED and IM models
- The confidence intervals associated with these reference points can be interpreted as an allowable range of oral intake
- This novel approach was developed based on a two-level response variable; should data suffice, future applications could focus on a three- or four-level response variable
- This approach can be applied to any substance that is characterized by a benefit-risk relationship, such as drugs
CONTRIBUTORS

- Patrick Farrell, PhD, Carleton University
- Daniel Krewski, PhD, MHA, RSI and University of Ottawa
- Nick Birkett, MD, MSc, University of Ottawa
- Donald Mattison, MD, MSc, RSI and University of Ottawa
- Siva Ramoji, MSc, RSI
- Nataliya Karyakina, MD, PhD, RSI and University of Ottawa
- Natasha Shilnikova, MD, PhD, RSI and University of Ottawa
- Doreen McGough, PhD, International Manganese Institute

18-POINT SEVERITY SCORING MATRIX