Dose-Response Modeling for the Assessment of Cumulative Risk Due to Exposure to *N*-Methyl Carbamate Pesticides

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Science Question

• Construct and fit dose-time-response models to data on *N*-methyl carbamate (NMC) induced brain acetylcholine esterase (AChE) inhibition for the Agency's NMC Cumulative Risk Assessment.
• Maximize the use of available data, including data on experimentally exposed humans and different rodent age groups, to calculate relative potency factors and evaluate the range of potencies across species and ages, to the extent the data allow.
•Evaluate the consistency of underlying dose-response assumptions used for the risk assessment and observed single chemical dose-response curves.

Research Goals

• Develop a dose-time-response model for AChE inhibition that allows both dose-response and recovery time-course parameters to be estimated from multiple AChE inhibition studies.
• Estimate the parameters for the dose-time-response model for both rodent and available human data in a way that maximizes the use of data and quantitates the uncertainty of the estimates.
• Use the resulting dose-time-response estimates to calculate (with confidence intervals):
  • Relative potency factors
  • For chemicals with relevant data, the relative potency in animals and humans of acute oral exposures;
  • For chemicals with relevant data, the relative sensitivity of young to adult animals.
• Evaluate the appropriateness of the RPF approach for this risk assessment, under the assumption of dose-additivity.

MODELING STRATEGY

We use a single model for all chemicals that describes AChE activity as a function of dose and time post dosing. Parameters must include:

-log(BMD) = *lBMD* for 10% inhibition.

- Recovery half-life

Fit the model to all relevant data-sets, treating some of the variation among data-sets as random (*e.g.*, *lBMD*), others as fixed effects with specific values for each data-set and sex (*e.g.*, background levels of AChE activity). This gives a nonlinear mixed-effects model.

DATA

Some critical features of the available data sets:

Designs:

- Time-course: measures of AChE activity at one or a few dose levels at several time points following a single gavage exposure.
- Repeated gavage exposures on a sub-chronic time scale; some datasets with time course information.
- Dose-response: measures of AChE activity at the time of peak effect for a range of doses (multiple tissues, one or both sexes, sometimes pnd11 animals and adults).

Data Characteristics:

- For most chemicals, we have more than one study, usually a mix of design types; some human data.
- Aggregated (means, standard deviations, sample sizes) for brain AChE, individual data for RBC AChE.
- Units of AChE activity vary among studies.
- Background (control) AChE activity varies among studies (even for the same species—strain).
- In time-course designs, there are few if any measurements before the time of peak effect.

MODEL(S)

We treat the inhibition at time t after the initial dose as a fraction of the peak inhibition, given that dose. In practice we test the implicit independence of dose and half-life in this model by estimating different recovery half-lives at different doses, when the data allow.

$$\text{Fractional Inhibition} = g(d;R,P,D_x,\gamma)\times h(t;T_A)$$

Ignoring the model parameters for the moment, activity is:

$$A\times\left[1-g(d)\times h(t)\right]$$

A represents the background, or control, level of AChE activity, d represents dose, and t represents time after dose administration.

TIME-COURSE MODELS

Two similar time-course models were developed and used in these data. In the first, the onset and recovery of inhibition are treated as first-order processes, resulting in a bi-exponential model for the time course of inhibition. The natural parameters for this model are T_R, the recovery half-life, and T_A, the half-life for the onset of inhibition. The resulting submodel is scaled so the maximum is 1:

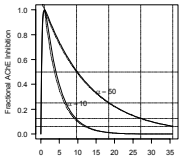
$$h(t) = C_s\left(e^{\frac{\ln(2)}{T_R}t} - e^{\frac{\ln(2)}{T_A}t}\right)$$

$$C_s = \frac{1}{e^{\frac{\ln(2)}{T_R}T^*} - e^{\frac{\ln(2)}{T_A}T^*}} \qquad T^* = \frac{T_R T_A\left(\ln(T_R) - \ln(T_A)\right)}{\ln(2)\left(T_R - T_A\right)}$$

Most data sets have time points at around the time of peak effect so an alternative model was developed: inhibition decays exponentially after the initial time point:

$$h(t;T_R) = e^{-\ln(2)\frac{t-\delta}{T_R}}$$

δ represents the time of the first sample.



Comparison of time course models: simpler model is dotted curve. Time of peak effect = δ = 1, and two different values of $\alpha = T_R/T_A$.

DOSE-RESPONSE MODEL

The dose-response model gives the fraction of inhibition at the time of peak effect. This is an exponential model, reparameterized in terms of the BMD (D_R in the formula), and extended to allow for a maximum level of inhibition ($1 - P$). Including the power γ allows the dose-response to be flatter at the low-dose end (and steeper in the middle).

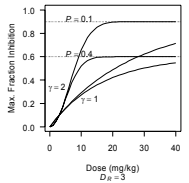
$$g(d;R,P,D_x,\gamma) = (1-P)\left(1-e^{\ln\left(\frac{1-R}{1-P}\right)\left(\frac{d}{D_R}\right)^{\gamma}}\right)$$

R: benchmark response $P = \frac{1-R}{1+e^{-\alpha}}$: 1 - max. inhibition

$D_x = e^{\alpha}$: benchmark dose $\gamma = e^{\gamma^*}$: shape parameter

d: dose

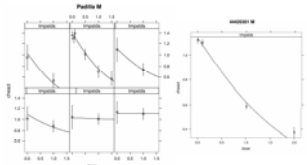
Examples of how the parameters affect the shape of this dose-response model:



ESTIMATION ISSUES

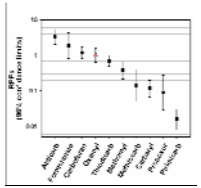
- Rather than select individual data sets (currently the practice in dose-response assessment), we want to fit all data sets for a chemical simultaneously.
- We need to allow for variation among studies, sexes, and time-on-study (in sub-chronic studies).
- The time course parameter T_R may (probably does) depend on dose.
- Some parameters or sets of parameters may not be uniquely estimable with current data.
- The error variance probably depends upon activity level, and may differ among studies.
- Methodology needs to be open and repeatable.

EXAMPLE OF DOSE-TIME RESPONSE MODEL: OXAMYL

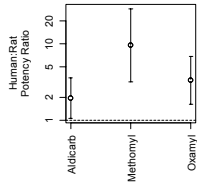


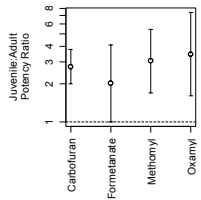
Notice, two different studies (Padilla and 44420301). The Padilla study includes observations at multiple times post dosing (tmpstds, indicated graphically in the panel above each dose-response graph). Points are means, error bars are 95% confidence intervals for the means, and solid curves are the fitted model.

SOME RESULTS



Relative potency factors (relative to Oxamyl) for inhibition of brain AChE in rats. Symbols are the central estimates, and error bars are approximate 95% confidence intervals. Note the log scale – potencies range over two orders of magnitude.





Estimates of adult human to rodent and rodent post-natal day 11 to adult potency ratios. Note the log vertical axis. Error bars represent approximate 95% confidence intervals for the estimated potency ratios.

RPFs and GENERAL DOSE-ADDITIVITY

The RPF approach is strictly appropriate for evaluating cumulative risk when dose-response curves for the component compounds differ only by a scale factor on dose. However, even when this condition is not met, it may be reasonable to assume non-interaction. Berenbaum argues for a more general expression for the dose-response of a non-interacting mixture

Suppose d is the total dose of a mixture whose *ith* component is a fraction (by mass) q_i of the total mixture, and $D_i(r)$ is the dose of the *ith* component that yields response r, that is, the inverse of the dose-response function. Then the following is true for a mixture (or cumulative exposure) that shows no interaction:

$$1 = \sum_i \frac{q_i d}{D_i(r)} = d\sum_i \frac{q_i}{D_i(r)}$$

This formula can be solved directly for d in terms of r to get, for example, the predicted BMD for the mixture:

$$D_{mix}(R) = \frac{1}{\sum_i \frac{q_i}{D_i(R)}}$$

The predicted toxicity of the same mixture, assuming that the RPF approach is correct, is based on converting the dose of each component of the mixture into a toxicologically equivalent dose of the index chemical (index *I*), then using the dose-response of the index chemical on this equivalent dose:

$$R = f_I\left(\sum_i \frac{D_I(R)}{D_i(R)} q_i D_{mix}(R)\right)$$

This can be explicitly solved for $D_{tpf}(R)$:

$$D_{mix}(R) = \frac{1}{\sum_i \frac{q_i}{D_i(R)}}$$

which is the same as equation (1). That is, the dose-response curve based on RPF assumptions coincides with the dose-response curve based on more general dose-additivity assumptions at the BMD, when all BMDs are based on the same response level.

This means, in particular, that risk characterization methods for cumulative exposures that are based only on the BMD, such as the margin of exposure approach used in the EPA's pesticide Cumulative Risk Assessments, are unaffected by whether the dose-response curves are consistent with the RPF dose-response shape assumptions as long as dose-additivity can be assumed. Using either model for mixture dose-response, the margins of exposure we calculate based on the benchmark dose will be identical.

Results/Conclusions

• The data for all NMCs evaluated were consistent with the exponential dose-time response model;
• Recovery half-lives increase with increasing dose, when multiple dose-levels were available.
• Juveniles tend to be more sensitive than adults (on a mg/kg basis, acute dose), in the four compounds with data. In addition, in three of the four compounds the juvenile recovery half-life was longer.
• Human adults tend to be more sensitive than rats (again, on a mg/kg bases, acute dose), for the three compounds with data.
• Dose-response relationships for the NMCs are not entirely consistent with RPF-based dose-response reconstruction. However, assuming more general dose-additivity would generate the same risk analysis based on MOEs.

Impact and Outcomes

This analysis was used in the Agency's preliminary cumulative risk assessment released in August, 2005, and will be used in the revised risk assessment due in August, 2006.

Future Directions

The single-chemical modeling as described here is essentially complete. The next step will involve adapting the model shown here for genuine mixture data.

References

US EPA, Preliminary *N*-methyl Carbamate Cumulative Risk Assessment. http://www.epa.gov/pesticides/cumulative/common_mech_groups.htm#carbamate

Long Term Goal III