Cumulative Hazard Assessment: Issues for the FIFRA Scientific Advisory Panel

Appendix 3. Computational details for the empirical dose-time-response and simple PK risk assessment models

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Appendix 3. Computational Details for the Empirical Dose-Time-Response and Simple PK Risk Assessment Models

This appendix provides more technical details about the empirical dose-time-response and the simple pharmacokinetic (PK) risk assessment models than are provided in the main text. Since the two models are very similar, both are covered in this section, with the differences between the two clearly marked. In addition, some specifics about calibrating the simple PK risk assessment model are covered.

Dose-Time Model

It is likely that separate dose-time models will be required for each route of exposure: oral (diet and drinking water), dermal and inhalation. At the time of this writing, only a model for oral exposures has been developed in any detail.

The model for the predicted amount of acetylcholinesterase (AChE) inhibition a given time after a single oral dose, $f(t, d, \boldsymbol{\beta}, \tau)$ is the product of a model for the relationship between *N*-methyl carbamate dose and maximum inhibition, $g(dose, \boldsymbol{\zeta})$, and a model to account for the time course of inhibition after an exposure, $h(t,\boldsymbol{\eta})$; $\boldsymbol{\beta}' = [\boldsymbol{\zeta}', \boldsymbol{\eta}']$. Although essentially the same model is used for both the empirical model and the risk assessment model, they are parameterized slightly differently.

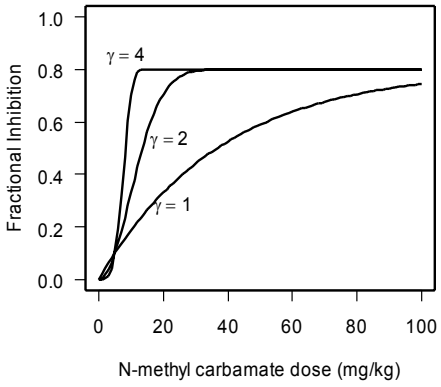

Figure 1. Maximum inhibition as a function of dose. In this example, 5 mg/kg gives 10% inhibition, and the maximum achievable inhibition is 80%.

***Dose-response model*.** Start with a commonly-used exponential model (see, e.g., Slob, 2002) as a descriptor of minimum AChE activity after an acute dose, d:

$$r(d) = A \times \left[P + (1-P) \times e^{-(md)^{\gamma}} \right].$$

This corresponds to a fractional inhibition of $g(d) = (1-P)\left(1 - e^{-(md)^{\gamma}}\right)$. In this model, A represents the background level of AChE activity, $A \times P$ is the smallest level of AChE activity achievable (that is, $[1 - P]$ is the maximum level of inhibition achievable), m is an inverse scale factor for dose, and γ a parameter that governs the shape: when it is greater than 1, the dose-response curve starts out shallow and increases in slope as dose increases. This model is very similar to but simpler than that used in EPA's

Revised OP Cumulative Risk Assessment (USEPA, 2002). The difference lies in the use of the parameter γ to model the low-dose shoulder. In the OP model a more complex submodel was used to mimic the pharmacokinetics of saturable clearance. Although perhaps more biologically realistic, the additional parameters required for this model and some of its mathematical properties made estimating parameters for it quite difficult. Thus, for this model, a simpler approach is being attempted.

It is convenient to reparameterize this model so that the dose that yields a 100×R% level of AChE inhibition, D_R, (that is, the benchmark dose for 100×R% inhibition) is a parameter in the model. This is accomplished by replacing the inverse scale parameter, m by

$m = \frac{\left[-\log\left(\frac{1-P-R}{1-P}\right)\right]^{1/\gamma}}{D_R}$, giving the final model for inhibition as

$(1-P)\left(1-e^{\log\left(\frac{1-R-P}{1-P}\right)\left(\frac{x}{D_R}\right)^{\gamma}}\right)$. Figure 1 shows what this model looks like for R=.1, D_R=5, P=.2, and γ=1,2, and 4.

Parameter estimation in the empirical dose-time response model is simplified if the parameters used are all in the range (-∞, ∞). This can be accomplished by transformation. When estimating parameters the following transformed parameters are used:

- $tP \equiv log(P/(1-P)) \rightarrow 0 < P < 1$
- $lD_R \equiv log(D_R) \rightarrow D_R > 0$
- $lg \equiv log(\gamma) \rightarrow \gamma > 0$

Time course model. Rat gavage studies and very limited human data suggest that the time course of AChE inhibition after an acute exposure is described approximately by the difference of two exponential functions:

$h(t) = h(t, T_R, T_A) = C_0\left(e^{-\frac{\ln(2)t}{T_R}} - e^{-\frac{\ln(2)t}{T_A}}\right)$, where C_o is a constant that controls the maximum amount of inhibition, which occurs at time $T^* = \frac{T_R T_A\left(\ln(T_R) - \ln(T_A)\right)}{\ln(2)(T_R - T_A)}$, and T_A and T_R are half-lives that govern the rate of the absorption and recovery phases of the time course, respectively. We want $h(T^*) \equiv 1$, so $C_0 = \frac{1}{e^{-\frac{T_A(\ln(T_R)-\ln(T_A))}{T_R-T_A}} - e^{-\frac{T_R(\ln(T_R)-\ln(T_A))}{T_R-T_A}}}$.

In the empirical model, it is convenient that T^* appear explicitly as a parameter in the model, because toxicology studies are usually designed based on an assumed value for T^*, and focus most time points at times relevant for estimating a rate of recovery, captured by the parameter T_R. Both empirical and risk assessment models in corporate T^* as a parameter. The natural choice for the second parameter for the time-course portion of the model is T_R, because of its straightforward interpretation as the half-life for

the recovery phase. This is, in fact, how the risk assessment model is calibrated. This is done by solving for T_A in terms of T^* and T_R and substitute in the above formulas:

$$T_A = e^{\frac{W\left(-T^*\ln(2)e^{-\frac{T^*\ln(2)+T_R\ln(T_R)}{T_R}}\right)T_R + T^*\ln(2) + T_R\ln(T_R)}{T_R}}$$

, where *W(x)* is Lambert's W function, defined as the function *W(x)* such that $W(x)\times e^{W(x)} = x$ (Corless, et al. 1996). R code for computing *W(x)* is included in Appendix 1.4.

However, in the empirical dose-time-response model, the situation is more complex, and requires a different parameterization. The function $h(t,T_R,T_A)$, with C_0 defined as above, is symmetric in T_R and T_A: $h(t,a,b) = h(t,b,a)$. A solution is to force (by transformation) $\alpha \equiv T_R/T_A$ to be greater than 1.0, and parameterize the time course submodel for the empirical dose-response model in terms of T^* and α. Substituting T_R/α for T_A in the expression for T^* and solving for T_R gives:

$T_R = \frac{T^*\ln(2)(\alpha-1)}{\ln(a)}$. Combining this with $T_A = T_R/\alpha$, by definition of α give the mapping between the parameters (T^*,α), used for parameter estimation, the parameters (T^*, T_R) used in the risk assessment model, and the parameters (T_A, T_R) used internally in the time-course part of the models. As in the dose-response part of the model, constraints on the parameters are enforced by transformation:

- $lT^* \equiv log(T^*) \rightarrow T^* > 0$
- $l\alpha \equiv log(log(\alpha)) \rightarrow \alpha > 1$

Calibration of the Risk Assessment Model

The model for oral exposure described here has several parameters: for the dose-response model, estimates of D_R, γ, and P; for the time course model, estimates of T^* and T_R. Estimates of all these parameters for rats will be available from rat gavage studies for all the *N*-methyl carbamates in this risk assessment, but there are only very limited human data available to develop corresponding parameter estimates for humans. The alternative proposed here is to base human parameters on the estimates from rats, using body-weights (BW) scaling to convert parameters with units of dose or time. Specifically, the following rodent to human extrapolations are proposed:

- P,γ: Use the estimates from rats directly. In the current parameterization of the model, P has little effect on inhibition at low doses, and preliminary estimates suggest that the value of γ is generally around 1.0.
- D_R: This is a benchmark dose, measured in units of mg/kg. O'Flaherty (1989) has argued that for effects that depend upon the area under the curve for tissue dose, that dose should scale as $BW^{3/4}$ scaling across species, while for effects that depend upon peak level, straight BW scaling is more appropriate (since volume of distribution scales approximately as body weight). AChE inhibition should depend on both peak tissue *N*-methyl carbamate concentration and area under the curve, so dose-scaling should fall somewhere between $BW^{3/4}$ and BW^1 power. For safety, choose $BW^{3/4}$ power, which means dividing the D_R determined from rat data by about 4.

- T^*, and T_R: T_R is the reciprocal of a first order rate constant, and T^* scales like one. O'Flaherty (1989) argues that first order rate constants should scale as $BW^{-1/4}$, so half-lives of first order processes should scale as $BW^{1/4}$. Thus values of T^* and T_R for humans should be about four-fold larger than those estimated for rat data.

There is cholinesterase inhibition from human subjects for four *N*-methyl carbamates that may be used to evaluate these scaling decisions.

Total Acetylcholinesterase (AChE) Inhibition in the Simple PK Risk Assessment Model

The following is a more detailed description of how total AChE inhibition is calculated. Suppose a series of exposure "episodes" at times τ_i ($\tau_1 < \tau_2 < ... < \tau_k$). At each τ_i, there are exposures to up to n_i chemicals. Let $A(t)$ represent the amount of uninhibited enzyme at time t; $A(0) = A_0$. Let $I_{ij}(t)$ represent the amount of inhibited enzyme from the j^{th} exposure at τ_i. Finally, define $f(t,d_{ij},\beta_{ij},\tau_i)$ to be the fraction of previously uninhibited enzyme that becomes inhibited after exposure to dose d_{ij} at τ_i, with vector of parameters $\boldsymbol{\beta}_{ij}$, and $F(t) = 1 - \frac{A(t)}{A_0}$, the fraction of inhibited enzyme. Clearly, at $0 \le t \le \tau_1$, $F(t) = 0$, and $A(t) = A_0$. Within any interval $\tau_h < t < \tau_{h+1}$, $A(t) = A_0 - \sum_{l=1}^{h} \sum_{j=1}^{n_l} I_{lj}(t)$, where $I_{lj}(t) = A(\tau_l) f(t, d_{lj}, \boldsymbol{\beta}_{lj}, \tau_l)$.

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