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MEMORANDUM

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HSM-06003

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(original signed by S. Powell)

DATE: August 15, 2006

SUBJECT: COMMENTS ON THE ESTIMATION OF DERMAL ABSORPTION USING THE EXPONENTIAL SATURATION MODEL

This memorandum is in response to your request for comments on the exponential saturation model proposed by Thongsinthusak *et al.* (1999) for use in estimating the dermal absorption of pesticides.

The problem addressed by Thongsinthusak *et al.* (1999) is the convention used in animal studies of dermal absorption of treating all pesticide recovered from the skin of the sacrificed animal (bound skin residue or BSR) as material that would eventually be absorbed into the body. If a dermal absorption study could be continued for an indefinite length of time, it might be determined better whether all BSR were actually absorbed, or whether some remained bound in the skin. In fact, the recommended practice (Zendzian, 1994) is that if a significant amount of residue remains in the skin 24 hours after dosing, then the study should be redone with animals followed for a prolonged period. Thongsinthusak *et al.* (1999) point out that many dermal absorption studies submitted to the Department of Pesticide Regulation (DPR) do not follow this recommendation and do show high levels of BSR 24 hours after dosing. They argue that it is very unlikely that all BSR would be absorbed and that, by treating BSR as absorbed, these studies overestimate dermal absorption. Thongsinthusak *et al.* (1999) propose the exponential saturation model (ESM) as a way to estimate the total percentage of an applied dermal dose that would be excreted in urine, using data from a study that ends well before the total amount has been excreted. In other words, the ESM is used to extrapolate the excretion curve beyond the range of the data.

The mathematical form of the ESM is

$$y = a\left[1 - e^{-b(x-c)}\right]$$

where y is the cumulative percentage of dose recovered in excreta at time x,
a is the asymptotic maximum of y, i.e., the total percentage of dose recovered in excreta,
b is the first-order rate constant for excretion, and
c is a time lag to first excretion.

The values of the parameters *a*, *b* and *c* are estimated using the *x*,*y* data points. The key parameter is *a*, the asymptotic maximum, as this is the estimated total excretion of the dermal dose.

The ESM is a smoothly increasing function whose rate of increase declines until the function reaches an asymptotic plateau (see Fig. 2).

Model is not justified theoretically

Thongsinthusak *et al.* (1999) do not provide biological or other theoretical justification for the choice of this particular model, other than remarking that it is "often used in pharmacokinetics". It appears that the model was chosen primarily because it has easily interpretable parameters. Given that the ESM has not been validated empirically for this purpose, as discussed below, it is essential that it be justified in terms of the underlying absorption, distribution and elimination kinetics.

A critical assumption underlying this use of the ESM is that the time course of excretion follows a single smooth function until excretion is complete. Without a biological justification, it cannot be ruled out that excretion is multiphasic, as could be the case if material were sequestered in body compartments, including the skin, from which it is eliminated at different rates.

Model is not validated empirically

Thongsinthusak *et al.* (1999) do not provide empirical validation of the ESM. Empirical validation would require having data from dermal absorption studies that were carried out long enough that excretion was clearly complete. Total excretion predicted by the ESM using only the early data points could then be compared to the actual measured total excretion. This would show how accurately the model predicted total excretion.

What Thongsinthusak *et al.* (1999) have done is to provide two illustrations of fitting the ESM to data where excretion may or may not have been complete. The first illustration uses human data, so no BSR is involved. Percentage dermal absorption of 12 pesticides estimated using the ESM is compared to the percentages calculated conventionally. The data (Feldmann and Maibach, 1974) are on human volunteers, each given either an intravenous or a dermal dose of one of the pesticides (n=6 in each group). Urine was collected from the volunteers for 5 days (120 hrs) following dosing. Feldmann and Maibach (1974) calculated percentage dermal absorption as 100 x (total excreted after dermal dose)/(total excreted after iv dose). Thongsinthusak *et al.* (1999) used the ESM to extrapolate the total amount excreted. They then recalculated percentage dermal

absorption as 100 x (total excreted after dermal dose)/(total excreted as predicted by ESM). For 9 of the 12 pesticides, percentage dermal absorption calculated by the two methods was virtually the same; for 3 pesticides, percentage dermal absorption calculated using the ESM was considerably higher. The authors conclude that this means excretion was incomplete in these three cases, and that the ESM provides the correct total excretion. While this is one possible explanation of the results, the finding does not eliminate any other competing explanation. Figure 1 illustrates one such competing explanation.

Figure 1 shows a hypothetical biphasic linear model for excretion following a dermal dose. In this hypothetical model, excretion is rapid for the first 52 hours after dosing, then proceeds at a much slower rate until it stops at about 560 hours with 63 percent of the dose excreted. Figure 2 shows the fit of the ESM to the cumulative excretion values from Fig. 1 at 4, 8, 12, 24, 48, 72, 96 and 120 hours after dosing, the same time points measured in the Feldmann and Maibach (1974) human study and used by Thongsinthusak *et al.* (1999) to fit the ESM. Figure 2 shows that the ESM fits the data very well (r^2 = 0.99) and yields a plausible-appearing asymptote of 43.76 percent excretion, 19 percent less than the true total excreted. This illustration is not intended to have any biological validity. Its purpose is to show that the use of the ESM as proposed can only be valid if excretion follows a single function from beginning to end, which has not been demonstrated to be the case.

The second illustration given by Thongsinthusak *et al.* (1999) shows the application of the ESM to animal data on dermal absorption of five pesticides from studies submitted to DPR (Thongsinthusak and Ross, 1998). Thongsinthusak *et al.* (1999) compare percentage dermal absorption estimated using the ESM to the percentages calculated conventionally. The conventional method adds BSR to the total amount excreted, while the ESM method does not add in the BSR, but uses the model to extrapolate total amount excreted. As expected, the ESM method gives lower values of percentage dermal absorption. This does not in any way demonstrate the validity of the ESM, however, as there is no way to know whether the model extrapolations are correct.

Conclusion and recommendations

1. Without theoretical justification or empirical validation, the ESM cannot be recommended for estimating total excretion.

2. Theoretical justification is needed for the assumption that the entire time course of excretion is described by a single function for all chemicals.

3. Empirical validation is needed to show that the ESM can correctly and precisely predict the total excretion of a dose. Validation would require data from dermal absorption studies of a number of pesticides, ideally covering a range of toxicokinetic profiles. The studies would need to be conducted for a sufficient length of time that absorption and excretion were arguably complete.

Two of the chemicals in Thongsinthusak and Ross (1998), tribufos and amitraz, may have been completely excreted during the reported studies and thus might be used to examine the behavior of the ESM. As evidence of near complete excretion for tribufos, the percentage of dose remaining in BSR at the end of the study (168 hours post-dosing) was only 2.8, down from a maximum measured value of 38.0 percent at 4 hours. For amitraz, the percentage of dose remaining in BSR at the end end of the study (120 hours post-dosing) was 0.48, down from a maximum measured value of 12.1 percent at 4 hours. Tables 1 and 2 give the results of fitting the ESM to successively shorter data series from these two studies. For both chemicals, the estimate of maximum percent excreted is relatively robust to dropping data points, remaining approximately the same down to 5 data points with the last at 48 hours post-dosing. It may be noted that the fit of the model is not a good indicator that the model is behaving well, as R^2 is high even at 24 hours, when the predicted maximums are clearly aberrant.

This is only an illustration and is not necessarily the best way to validate the model. It would be desirable to consult with a statistician on the optimal design of a validation study.

Table 1. Maximum excretion of tribufos predicted by the exponential saturation model with successively shorter study lengths [a]

Number of data points used	Last data point used (hrs)	R^2	Predicted maximum excretion (%)
10 (all data)	168	0.99	38.3
9	144	0.99	37.5
8	120	0.99	36.8
7	96	0.99	36.1
6	72	0.99	35.7
5	48	0.99	38.0
4	24	0.99	98.9

[a] Data from Thongsinthusak and Ross (1998)

Table 2. Maximum excretion of amitraz predicted by the exponential saturation model with successively shorter study lengths [a]

Number of data points used	Last data point used (hrs)	R^2	Predicted maximum excretion (%)
8 (all data)	120	0.99	11.7
7	96	0.99	11.8
6	72	0.99	12.1
5	48	0.98	12.3
4	24	0.96	99.0

[a] Data from Thongsinthusak and Ross (1998)

References

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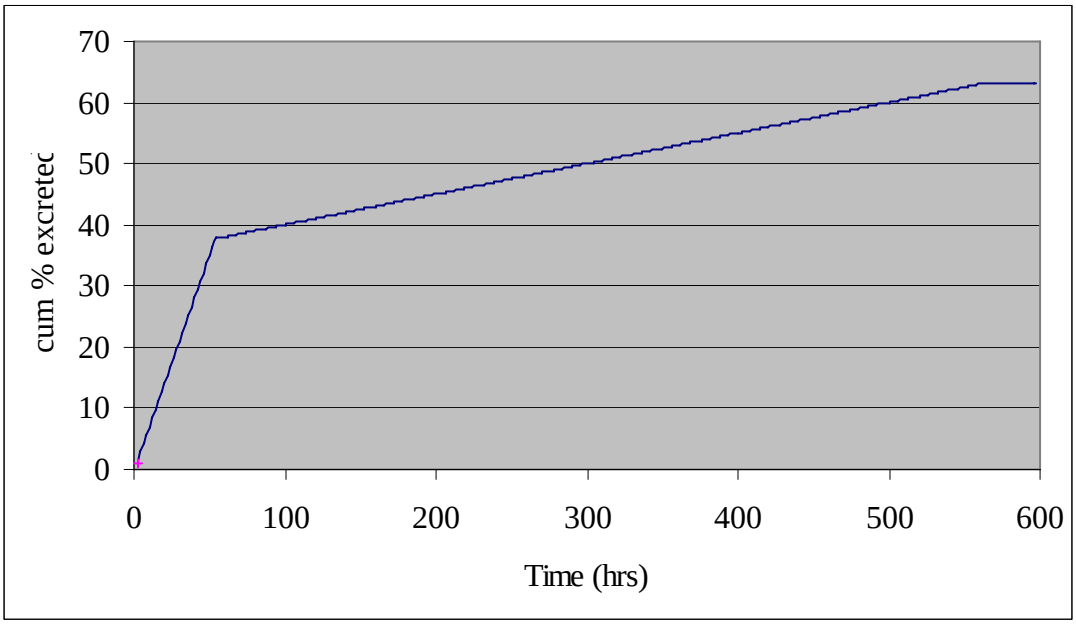

Fig. 1. Hypothetical biphasic excretion of a dermally applied pesticide: cumulative excretion is rapid and linear for 52 hours, then proceeds linearly but more slowly until stopping at about 560 hrs.

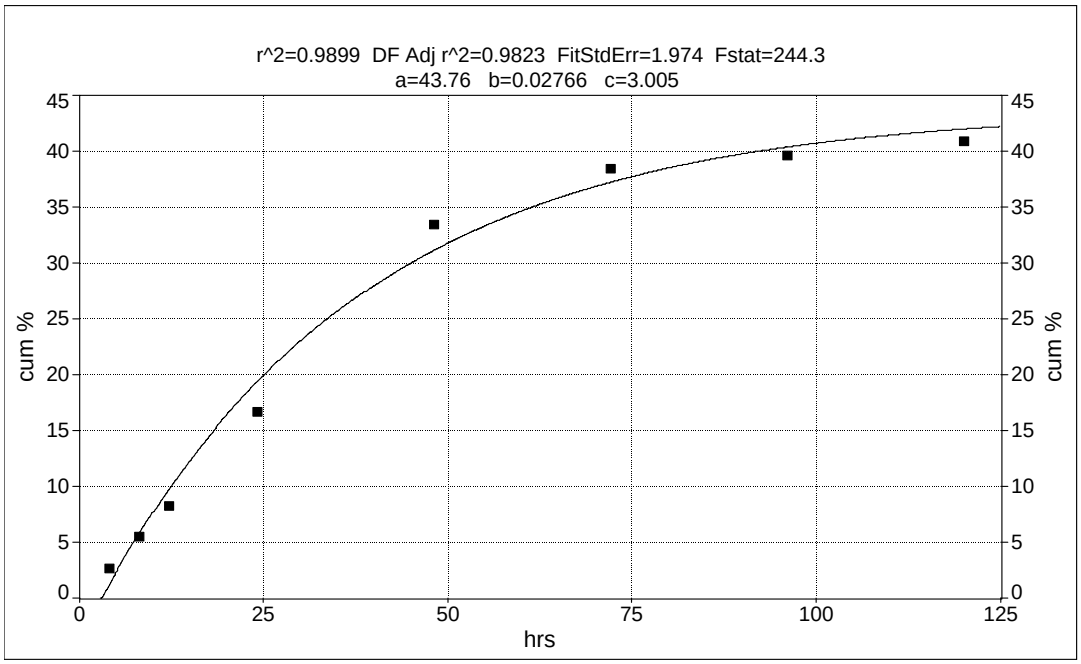

Fig. 2. The exponential saturation model fit to 8 points from the biphasic linear model in Fig. 1.