Winston H. Hickox
Secretary for Environmental Protection

Department of Pesticide Regulation

James W. Wells, Director
830 K Street • Sacramento, California 95814-3510 • www.cdpr.ca.gov

Gray Davis
Governor

M E M O R A N D U M

TO: John Ross, Senior Toxicologist **HSM-99007**
Worker Health and Safety Branch

FROM: Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch
(916) 445-4267

DATE: March 4, 1999

SUBJECT: AMITRAZ: AGREVO USA POSITION STATEMENT ON CALEPA OCCUPATIONAL RISK ASSESSMENT FOR AMITRAZ

At your request, I have reviewed the above report dated February 26, 1999 regarding AgrEvo USA position statement on Cal/EPA's occupational risk assessment for amitraz. I focused my comments on dose levels and dose preparation used in the dermal toxicity study, potential effects of surfactant on dermal absorption, *in vivo* and *in vitro* dermal absorption studies.

I previously reviewed a dermal toxicity study titled, "Amitraz: human volunteer double-blind dermal tolerance study (AgrEvo report reference C000350)." My comments were presented in my review memo dated November 5, 1998 (attached). In brief, the dose levels of technical amitraz used in the dermal toxicity study were 8, 16, and 24 mg/kg BW. These doses (1:1, w/w, in water) were administered to 4 separate sites of 20 cm^2 of the forearm of eight human volunteers. The highest dose was calculated to be 22,800 $\mu g/cm^2$ ((24 mg/kg BW x 76 kg x 1,000 ÷ (4 sites x 20 cm^2/site)). At this dose level, the extrapolated dermal absorption from a study using rats would be negligible (Figure 1). We typically recommend a low dose at 2 to 10 $\mu g/cm^2$ for a dermal absorption study. Dermal absorption of amitraz in rats as shown in Figure 1 is dose dependent. In other words, the dermal absorption is higher for the low dose than the high dose. This dose density (>20,000 $\mu g/cm^2$) is orders of magnitude greater than any normal occupational exposure.

I stated in my previous review memo that a dermal NOEL obtained from a study using technical amitraz may not be applicable to handlers of amitraz or reentry workers unless the registrant has data to substantiate that surfactant(s) in the

formulation do not influence dermal absorption. We do not know if a surfactant and other inert ingredient(s) in Mitac® W, which may be present with dislodgeable foliar residues 14 days after application, can influence dermal absorption. To my knowledge, surfactants in commercial pesticide formulations are typically present at 2-4%. The report did not provide data to verify the claim that it is unlikely that sufficient amounts of the surfactant would be available to influence dermal absorption 14 days after application, especially when dry. It seems to me that the registrant could have tested this hypothesis by including a test in the *in vitro* study of nonformulated amitraz much like the human volunteer study dose.

The present report showed results of *in vitro* penetration studies of Mitac® W using rat and human skin. The dose levels were 10, 1, and 0.1 mg/cm^2. The results indicated that the rate of absorption in humans was approximately 10-fold less than in rats for 10- and 24-hour exposures. It is possible that the *in vivo* dermal absorption of amitraz in humans may be estimated by using the ratio of *in vivo* rat absorption, and *in vitro* rat and human absorption (Thongsinthusak *et al*., 1993), pending further reviews of the final report on *in vitro* studies.

The lack of surfactant(s) and other inert ingredient(s) in the dose and the high dermal dose density used in the dermal toxicity study made the dermal NOEL undesirable for the risk assessment.

Recommendations:

1. The dermal toxicity study should not be used to establish a dermal NOEL because of high dermal doses and the lack of ingredients in commercial formulation in the dermal dose.
2. *In vivo* human dermal absorption may be estimated from the ratio of *in vivo* rat absorption, and *in vitro* rat and human absorption, pending reviews of the final report on *in vitro* studies.

Reference:

Thongsinthusak, T., Ross, J. H., and Meinders, D. 1993. Guidance for the preparation of pesticide exposure assessment documents. HS-1612. WH&S, DPR.

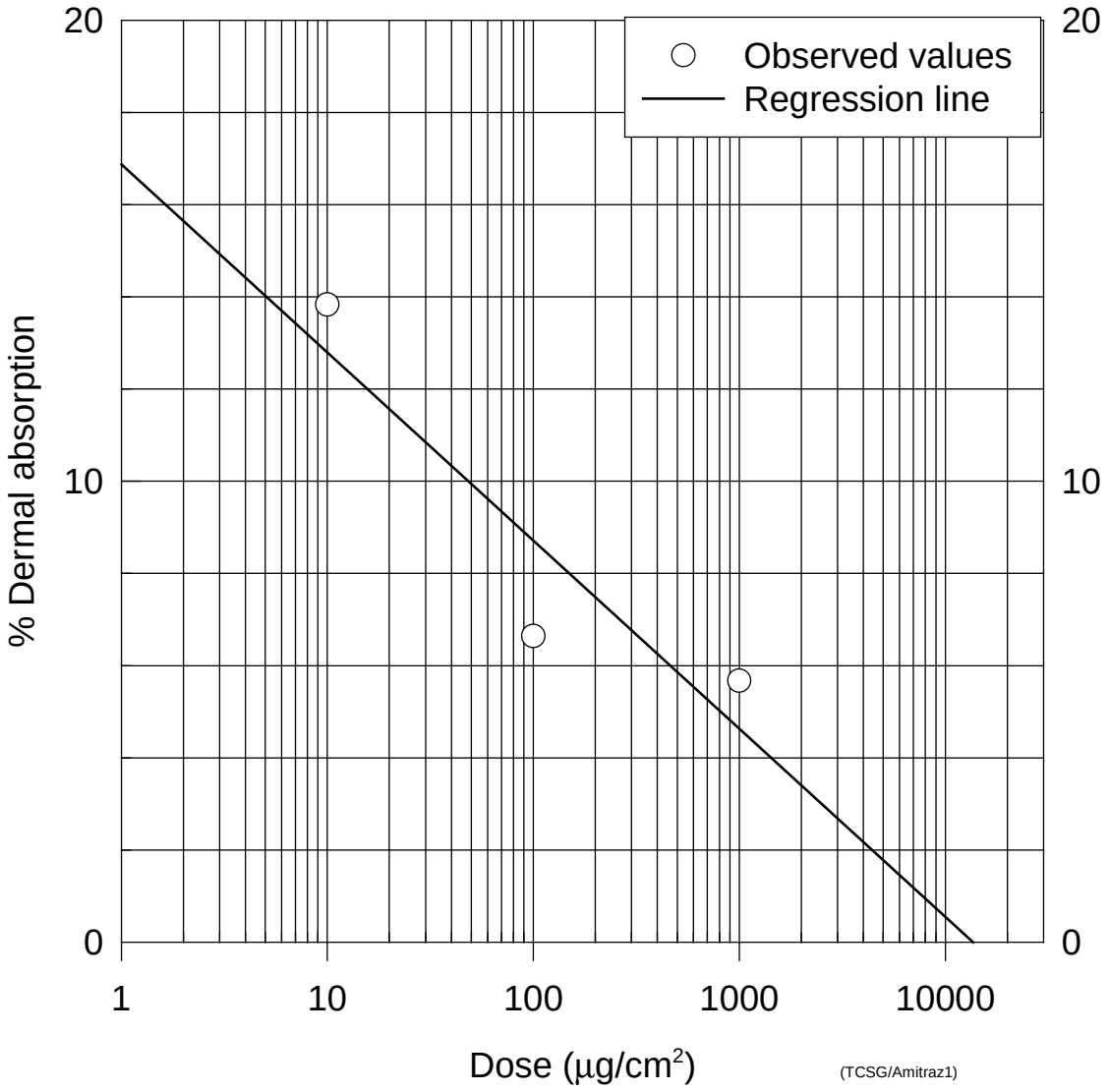
cc: John Sanders
Dave Haskell

(Dermal/HSM-99007)

Figure 1. Dermal Absorption of Amitraz in Adult Male Rats

(10-hour exposure)

$Y = -4.08\text{Log}(X) + 16.87$; $r^2 = 0.8377$



This graph was constructed from: Thongsinthusak, T. 1994. Amitraz: Dermal absorption in the rat. A memorandum dated October 28, 1994 to Gary Varnado. WH&S, DPR.