Attachment 1:
Interaction Effects of Mixture Components on Toxicity of Pesticides

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September, 2008

Pesticide formulations themselves are typically a mixture of an active ingredient and other co-formulants including surfactants. In addition, pesticides in are commonly applied in mixtures of multiple herbicides plus additional adjuvants. With respect to the toxicity of these mixtures, a question is whether the mixtures of several different pesticides and adjuvants pose a greatly increased risk compared to the sum of the toxicities of the individual compounds. The fundamental types of interactions between compounds in a mixture are:

- *Additive*: no interaction; overall toxicity is equal to the sum of the toxicities of the individual components
- *Antagonistic*: toxicity of the mixture is less than additive
- *Synergistic*: toxicity of the mixture is greater than additive

It is important to point out that the enhanced performance of a pesticide active ingredient by a surfactant is not due to synergism, but due to increased absorption of the active ingredient as a result of the surfactant's wetting and spreading action (Bakke, 2002). Among the possible true interaction effects, the synergistic effects are clearly of most concern. Prediction of such synergistic effects is complicated by the existence of various different mechanisms through which synergism can occur (Tatum, 2004).

A review of scientific literature on the combination effects from herbicide mixtures indicates that the observed effects of pesticides (and toxicants in general) from the same class (e.g., between several herbicides) are often additive in nature (Faust et al., 1993, 1994, 2003; Bakke, 2002; Esher and Hermens, 2002; Cedergreen et al., 2007). Even mixtures of herbicides with different modes of action generally show concentration additivity in their toxicity effects (Faust et al., 2003; George and Liber, 2007). Substantial synergistic effects (factor greater than two) have only been observed with mixtures of insectides (Thompson, 1996; Deneer, 2000). Significant antagonistic effects have also been observed (Cedergreen et al., 2007).

The concentration addition (CA) model is based on the additivity of toxicity in proportion to the concentration of the individual compounds. The usefulness of this CA model for describing the toxic effects on aquatic organism show was assessed by Deneer (2000). Based on a review of almost three decades of literature data, it was shown that in more than 90% of the mixtures evaluated, the CA model predicted the aquatic toxicity within a factor of two. For mixtures of compounds with different modes of action, the CA model predictions are usually indistinguishable from the experimental results. Substantial deviations from CA occurred only with mixtures of certain insecticides.

Belden et al. (2007) evaluated the accuracy of models for predicting toxicity of pesticide mixtures. The CA model was the most often tested model in over 200 experiments and had observed effective concentration within a factor of 2 of the predicted values. Overall, it was

concluded that the results indicate that the CA model is a slightly conservative, but broadly applicable model with relatively small likelihood of underestimating effects due to interactions.

More advanced models for predicting the toxicity of pesticide mixtures include the probabilistic ecological risk assessment-toxic equivalent (PERA-TE) (George and Liber, 2007) and the independent action model (Faust et al., 2003). These models allow more accurate predictions as long as detailed information on the mixture components and their toxicity is available. The alternative CA model approach resulted in moderate overestimation of mixture toxicity compared to observed results (Faust et al., 2003). It was concluded that in a regulatory context the CA model may be a defendable and precautionary approach to address the toxicity issues from mixtures of herbicides.

With respect to surfactants, it has been pointed out that the use of concentration addition leads to more accurate prediction compared to the average-structure model (Boeije et al., 2006). The CA model is further supported by the fact that most surfactants have a similar mechanism of toxicity action, i.e., the reduction of surface tension at membranes.

The review of mixture toxicity suggests that mixtures of different herbicides and adjuvants generally do not pose a greatly increased risk compared to the sum of the toxicities of the individual compounds. The concentration addition model appears to adequately describe and predict the toxicity of herbicide mixtures. The worst case with herbicide mixtures would be mildly synergistic (up to a factor of two). In an overall risk characterization, potential synergistic effects could be accounted for by, for example, considering a safety factor.

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