APPENDIX G.

PRODUCT FORMULATIONS CONTAINING MULTIPLE ACTIVE INGREDIENTS

The Agency does not routinely include, in its risk assessments, an evaluation of mixtures of active ingredients, either those mixtures of multiple active ingredients in product formulations or those in the applicator's tank. In the case of the product formulations of active ingredients (that is, a registered product containing more than one active ingredient), each active ingredient is subject to an individual risk assessment for regulatory decision regarding the active ingredient on a particular use site. If effects data are available for a formulated product containing more than one active ingredient, they may be used qualitatively or quantitatively[1] [2].

Acute oral toxicity data (i.e., LD50 values) from mammalian studies for formulated products that contain EPTC and one or more additional active ingredients are summarized below.

Currently, the Agency's guidance for assessing the potential risk of chemical mixtures is limited to human health applications (USEPA, 2000). However, the guidance includes principles for evaluating mixtures to assess potential interactive effects that are generally applicable. Consistent with EPA's Overview Document (USEPA 2004), the Agency's mixture guidance (USEPA 2000) discusses limitations in quantifying the risk of specified mixtures when there is differential degradation, transport and fate of chemical components following environmental release or application. The LD50 values are potentially useful only to the extent that a wild mammal would consume plants or animals immediately after these dietary items were directly sprayed by the product. Increasing time post application, the differential rates of degradation, transport, etc. for the active ingredients in the formulation only permit a qualitative discussion of potential acute risk (USEPA 2004).

As discussed in USEPA (2000) a quantitative component-based evaluation of mixture toxicity requires data of appropriate quality for each component of a mixture. In this mixture evaluation, LD50s with associated 95% confidence intervals are needed for the formulated product. The same quality of data is also required for each component of the mixture.

[1] Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs, Environmental Protection Agency (January 2004) (Overview Document).

[2] Memorandum to Office of Prevention, Pesticides and Toxic Substance, US EPA conveying an evaluation by the U.S. Fish and Wildlife Service and National Marine Fisheries Service of an approach to assessing the ecological risks of pesticide products (January 2004).

While a quantitative evaluation of the data is not possible with currently accepted scientific methods, as a screening tool, a qualitative analysis can be used to indicate if formulated products exhibit interactive effects (e.g., synergism or antagonism).

In the case of EPTC, a qualitative examination of the trends in LD50 values, with the associated confidence intervals, across the range of percent active ingredient, show no discernable trends in potency that would suggest synergistic (i.e., more than additive) or antagonistic (i.e., less than additive) interactions.

In addition, when the product LD50s, and associated confidence intervals, are adjusted for the percent EPTC (a conservative assumption that attributes all of the observed toxicity of the formulated product to EPTC) the adjusted 95% confidence intervals overlap with the confidence values of the LD50 value of EPTC

To confirm a lack of interactive effects, an alternative approach was used. The LD50s for the formulated products were estimated by considering the proportion and potency of each active ingredient in the mixture using the formula presented below [3], where *r* equals the relative proportion of each active ingredient (ai) in the formulated product (f)

$$\text{Estimated } LD50_{(f)} = [r_{ai1}/LD50_{(ai1)} + r_{ai2}/LD50_{(ai2)}]^{-1}$$

The estimated LD50 formula assumes no synergistic or antagonistic interactions. Estimated LD50 values above or below the LD50 confidence intervals for the formulated product could suggest an interactive effect. In all 3 cases, the estimated LD50s fell within the confidence intervals for the formulated products. These results provide additional confidence that synergistic interactions are unlikely for the formulated products examined.

Based on these evaluations of the best available data and the Agency's existing guidance it is reasonable to conclude that these formulations are reflecting an independent additive toxicity response and not an interactive effect. Given that the active and inert ingredients would not be expected to have similar mechanisms of action, metabolites or toxicokinetic behavior it is also reasonable to conclude that an assumption of dose-addition would be inappropriate. Consequently, an assessment of EPTC's potential effect on the CRLF when it is co-formulated with other active ingredients can be based on the toxicity of EPTC.

[3] Methods described in Tabashnik, BE, Evaluation of Synergism among *Bacillus thuringiensis* Toxins, Appl Environ Microbiol. 1992 Oct;58(10):3343-6.

Pesticide Products Formulated with EPTC and Other Pesticide Active Ingredients

EPTC PRODUCTS[4,5]

PRODUCT/TRADE NAME	EPA Reg.No.	% EPTC	PRODUCT		ADJUSTED FOR ACTIVE INGREDIENT	
			LD 50 (mg/kg)	CI (mg/kg)	LD50 (mg/kg)	CI (mg/kg)
DOUBLEPLAY SELECTIVE HERBICIDE	000100-01083	67.8	1464	1133-2325	993	768-1576
GOWAN EPTAM/ACETOCHLOR 67.8%/16.9% EC HERBICIDE	010163-00285	67.8	1464	1133-2325	993	768-1576
DREXEL POWER PLAY HERBICIDE	019713-00568	67.8	1464	1133-2325	993	768-1576

[4] From registrant submitted data to support registration. Compiled by Office of Pesticide Programs Health Effects Division
[5] EPTC: LD50= 1599 mg/kg; CI= 1294 to 1976 mg/kg.