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 hexazinone 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 mixture 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. Given that many of the formulated products do not have LD50 values of the required quality and since LD50 values are not available for all the components of these formulations a quantitative analysis of potential interactive effects is not possible.

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[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).

In the case of hexazinone, only two products (EPA Reg. Nos. 352-603 and 352-618) have definitive product oral LD50 values. Although there are no confidence intervals associated with these products, the LD50 values for the products (1421 and 2073 mg/kg, respectively) are greater than the LD50 value for hexazinone (1200 mg/kg) and therefore do not indicate that the formulated products exhibit interactive effects. No further analysis is possible when LD50 values with associated confidence intervals are not available.

Because the active ingredients are not expected to have similar mechanisms of action, metabolites, or toxicokinetic behavior, it is reasonable to conclude that an assumption of dose-addition would be inappropriate. Consequently, an assessment based on the toxicity of hexazinone is the only reasonable approach that employs the available data to address the potential acute risks of the formulated products.

Pesticide Products Formulated with Hexazione and Other Pesticide Active Ingredients

HEXAZIONE PRODUCTS [3] [4]

			PRODUCT		ADJUSTED FOR ACTIVE INGREDIENT		
PRODUCT/TRADE NAME	**EPA Reg.No.**	**% Hexazione**	**LD 50 (mg/kg)**	**CI (mg/kg)**	**A.I Adjusted CI (mg/kg)**	**A.I Adjusted LD50 (mg/kg)**	**PM**
Oustar Herbicide	352-603	63.2	1421	No Data	No Data	No Data	
Dupont K-4 Herbicide	352-618	13.2	2073	No Data	No Data	No Data	
Dupont Westar Herbicide	352-626	68.6	No Data[5]	No Data	No Data	No Data	
Dupont Velpar Alfamax MP Herbicide	352-634	35.3	No Data	No Data	No Data	No Data	
Dupont Velpar K-4 Max Herbicide	352-663	17.3	No Data[5]	No Data	No Data	No Data	
Dupont Velpar Alfamax Herbicide	352-665	35.3	No Data[5]	No Data	No Data	No Data	
Dupont Velpar Alfamax Gold	352-666	23.1	No Data[5]	No Data	No Data	No Data	

[3] From registrant submitted data to support registration. Compiled by Office of Pesticide Programs Health Effects Division.
[4] Hexazione: rat oral LD50= 1200 mg/kg
[5] Data waiver granted