1,3-DICHLOROPROPENE

APPENDIX A

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 1,3-dichloropropene 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.

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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).

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 1,3-dichloropropene, of the ten formulated products (all containing chloropicrin as the second active ingredient), only one product (Reg. No. 062719-00012) has a definitive LD50 value and associated confidence interval. When this product LD50 and its associated interval, are adjusted for the percent 1,3-dichloropropene (81.2%) the adjusted LD50 value of 246 mg/kg (CI range 119-419) is not statistically or biologically distinct from the LD50 of 1,3-dichloropropene (224 mg/kg).

To confirm a lack of interactive effects, the LD50 for the formulated product was estimated by considering the proportion and potency of each active ingredient in the mixture using the formula presented below, where *r* equals the relative proportion of each active ingredient (ai) in the formulated product (f) [3]

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

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. Applying the above formula for Reg. No. 062719-00012 containing 81.2% 1,3-dichloropropene and 16.5% chloropicrin (LD50= 37.5 mg/kg), the estimated LD50 is 125 mg/kg. The estimated LD50 fell near (within 2-fold the LD50) the confidence intervals for the formulated product. Given the overall variability of the available acute toxicity data, a value that falls near, but outside the confidence intervals is not considered toxicologically significant. These results provide additional confidence that synergistic interactions are unlikely for the formulated product examined.

Based on this qualitative evaluation 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 1,3-dichloropropene's potential effect on the California red-legged frog (CRLF) when it is co-formulated with other active ingredients can be based on the toxicity of 1,3-dichloropropene.

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[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 1,3-dichloropropene and Other Pesticide Active Ingredients

1,3-DICHLOROPROPENE PRODUCTS[4,5]

PRODUCT/TRADE NAME	EPA Reg.No.	% 1,3 Dichloropronene	PRODUCT		ADJUSTED FOR ACTIVE INGREDIENT	
			LD 50 (mg/kg)	CI (mg/kg)	LD50 (mg/kg)	CI (mg/kg)
PIC CLOR 60	008536-00008	39	data waived[6]	N/A	N/A	N/A
PIC-CLOR 15	008536-00021	82.9	data waived	N/A	N/A	N/A
PIC-CLOR 30	008536-00022	68.2	data waived	N/A	N/A	N/A
TRI-FORM 40/60	011220-00015	37.6	data waived	N/A	N/A	N/A
TELONE C-15	011220-00020	82.9	data waived	N/A	N/A	N/A
TRI-FORM 30	011220-00021	68.2	data waived	N/A	N/A	N/A
TRI-FORM 35	011220-00022	63.4	data waived	N/A	N/A	N/A
TELONE C-17	062719-00012	81.2	304	147-516	246	119-419
TELONE C-35	062719-00302	63.4	data waived	N/A	N/A	N/A
INLINE	062719-00348	60.8	>100	No Data	No CI Data	No CI Data

[4] From registrant submitted data to support registration. Compiled by Office of Pesticide Programs Registration Division.
[5] 1,3-Dichloropronene: LD50= 224 mg/kg
[6] Data waived= the acute oral toxicity guideline was waived and classified as Toxicity Category I for the acute oral study requirement.