IMAZAPYR

APPENDIX K

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 imazapyr 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.

[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 imazapyr, 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. Of the 16 formulated products, only one product (EPA Reg. No. 241-384) has a definitive LD50 value and associated confidence interval. When this product LD50 and its associated confidence interval, are adjusted for the percent dicamba (58.9%) the adjusted LD 50 value of 2,281 mg/kg which is not statistically or biologically distinct from the LD50 of dicamba (2,740 mg/kg; CI range of 2010 to 3740) or the LD50 of the sodium salt of diacamba (>5050 mg/kg). 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 imazapyr's potential effect on the CRLF when it is co-formulated with other active ingredients can based on the toxicity of imazapyr..

Regarding the potential toxicity of formulated products to aquatic life, there are open literature data on the snail *Biomphalaria tenegophila*, (ECOTOX 80947), which provides a 72-hour LC50 of 46.0 mg/L for technical imazapyr. In the same study a formulation containing imazapyr acid, as the active ingredient, and nonylphenol, was also tested. The LC50 of this formulation (Arsenal 250), which is not registered in the United States, was 20 mg/L. The authors of this study concluded that nonylphenol (LC50 of 12.6 mg/L) was likely responsible for the toxicity of the formulation.

Based on a qualitative evaluation of this data and the Agency's existing guidance, it is reasonable to conclude that this formulation is reflecting an independent additive toxicity response and not an interactive effect. Given that imazapyr and the inert ingredients (including nonylphenol) would not be expected to have similar mechanisms of action, metabolites, or toixcokinetic behavior, it is also reasonable to conclude that an assumption of does-addition would be inappropriate.

Consequently, an assessment of imazapyr's potential effect on the invertebrate forage base of the CRLF with this formulation (if it were registered in the United States) would be based on toxicity of imazapyr itself.

Pesticide Products Formulated with Imazapyr and Other Pesticide Active Ingredients

IMAZAPYR PRODUCTS [i] [ii]

PRODUCT/TRADE NAME	EPA Reg.No.	% Imazapyr	PRODUCT LD50 (mg/kg)	PRODUCT CI (mg/kg	ADJUSTED FOR ACTIVE INGREDIENT LD50 (mg/kg)	ADJUSTED FOR ACTIVE INGREDIENT CI (mg/kg)
Ac 513,995 dg herbicide[iii]	241-384	4	3873	697-7171	155	28-287
EH 1135 PGR	2217-802	0.15	>5000	NA Limit Dose	NA Limit Dose	NA Limit Dose
Lightning herbicide	241-377	17.5	No Data (ND)	ND	ND	ND
Liquid lightning herbicide	241-400	5.05	>5000	NA Limit Dose	NA Limit Dose	NA Limit Dose
Rainbow weed killer 4031	13283-19	0.5	ND	ND	ND	ND
Sahara dg herbicide	241-372	7.78	>5000	NA Limit Dose	NA Limit Dose	NA Limit Dose
Onestep herbicide	241-414	8.36	>5000	NA Limit Dose	NA Limit Dose	NA Limit Dose
Ssi maxim topsite 2.5g herbicide	34913-22	0.5	ND	ND	ND	ND
Imazuron E-Pro	79676-54	7.78	>5000	NA Limit Dose	NA Limit Dose	NA Limit Dose

PRODUCT/TRADE NAME	EPA Reg.No.	% Imazapyr	PRODUCT		ADJUSTED FOR ACTIVE INGREDIENT	
			LD50 (mg/kg)	CI (mg/kg	LD50 (mg/kg)	CI (mg/kg)
Triox Vegetation Killer	239-2622	0.08	ND	ND	ND	ND
Ortho Groundclear	239-2657	0.08	>5000	NA Limit Dose	NA Limit Dose	NA Limit Dose
Ground Clear RTU	239-2686	0.016	>5000	NA Limit Dose	NA Limit Dose	NA Limit Dose
GF-1248	62719-526	2.39	ND	ND	ND	ND
Mohave 70 EG Bareground	74477-9	7.78	>2000	NA Limit Dose	NA Limit Dose	NA Limit Dose
Topsite 2.5g herbicide	241-344	0.5	ND	ND	ND	ND

[i] From registrant submitted data to support registration. Compiled by Office of Pesticide Programs Health Effects Division.
[ii] Imazapyr LD50= >5000 mg/kg; CI= N/A
[iii] Formulated with 58.9% dicamba sodium salt. The dicamba adjusted LD 50 for the formulated product = 2281 mg/kg. The Dicamba sodium salt LD 50 >5050 mg/kg, CI= N/A since LD50 is the Limit Dose. The dicamba LD 50 = 2740 mg/kg, CI= 2010 to 3740.