Appendix G:
Multiple Active Ingredient Product Analysis

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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 atrazine 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. 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.

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).

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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 atrazine, 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 atrazine (a conservative assumption that attributes all of the observed toxicity of the formulated product to atrazine) in 4 out of the 13 cases these adjusted 95% confidence intervals overlap with the confidence values of the LD50 value of atrazine. In most of the other instances the adjusted LD50s and/or the confidence intervals are within a factor of 2.

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 13 cases, the estimated LD50s fell either within or near (within 2-fold the LD50) the confidence intervals for the formulated products. Given the overall variability of the available acute toxicity data, the few values that fell near, but outside the confidence intervals are not considered toxicologically significant. 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 atrazine's potential effect on the CRLF when it is co-formulated with other active ingredients can be based on the toxicity of atrazine.

Review of Open Literature Studies on Multiple Active Ingredient Products

Based on a review of the open literature for toxicity data on multiple active ingredient registered products containing atrazine, only one study was found. Hayes et al. (2006) assessed the effect of Bicep II Magnum (reported as 33.3% atrazine, 0.7% atrazine-related products, 26.1% TGAI of S-metolachlor, and 40.2% inert ingredients) to

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

mortality, growth and development, gonadal development, thymus histology, and disease rates (i.e., immune function) in larval leopard frogs (*R. pipiens*). Based on the Agency's review of the Hayes et al. (2006) study, there are a number of uncertainties which confound the ability to interpret the study results. The results of this study, including a discussion of associated uncertainties, are summarized in Section A.2.4d and Table A.16 of Appendix A.

References

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Pesticide Products Formulated with Atrazine and Other Pesticide Active Ingredients

ATRAZINE PRODUCTS [i] [ii]

PRODUCT/TRADE NAME	EPA Reg.No.	% Atrazine	PRODUCT		ADJUSTED FOR ACTIVE INGREDIENT	
			LD 50 (mg/kg)	CI (mg/kg)	LD50 (mg/kg)	CI (mg/kg)
Acetochlor 3.1 + atz 2.5	42750-108	26.9	1338	-		
Acetochlor 4.3 + atz 1.7	42750-106	18.3	2599	1240-5000	475	227-915

PRODUCT/TRADE NAME	EPA Reg.No.	% Atrazine	PRODUCT		ADJUSTED FOR ACTIVE INGREDIENT	
			LD 50 (mg/kg)	CI (mg/kg)	LD50 (mg/kg)	CI (mg/kg)
Banvel + atrazine	51036-307	22.23	ND	ND	ND	ND
Arysta	66330-286	22.23	ND	ND	ND	ND
Basis gold herbicide	352-585	82.44	2245	1656-3044	1851	1365-2509
Bicep ii magnum herbicide	100-817	33	3271	2755-3882	1079	909-1281
Bicep ii magnum manufacturing use	100-1214	33.7	3271	ND	ND	ND
Bicep lite ii magnum herbicide	100-827	28.1	4824	3660-6358	1356	1028-1787
Bicep lite ii magnum manufacturing use	100-1213	28.13	3271	2955-3882	920	831-1092
Bicep magnum	100-886	32	4294	3284-5615	1374	1051-1797
Brawn herbicide	100-1165	33	ND	ND	ND	ND
Bromox + atrazine	71368-68	21.62	ND	ND	ND	ND
Bromoxynil + atrazine herbicide	66222-108	21.62	1140	380-3950	247	82-853
Brox-at herbicide	42750-50	21.62	3981	3319-4775	861	717-1032
Brozine	34704-892	21.62	ND	ND	ND	ND
Buctril + atrazine herbicide	264-477	21.62	ND	ND	ND	ND
Bullet herbicide	524-418	14.5	7500	5521-9779	1088	757-1418
Cadence ATZ	34704-950	34.4	ND	ND	ND	ND
Cadence ATZ Lite	34704-952	16.3	ND	ND	ND	ND
Charger max atz	1381-199	33	ND	ND	ND	ND
Charger max atz lite	1381-208	28.1	ND	ND	ND	ND
Dicamba-zine	53883-143	21.92	ND	ND	ND	ND
Dicambazine	42750-41	22.23	5050	NA Limit Dose	NA Limit Dose	ND
Double team herbicide	66222-113	19.1	>2000	NA Limit Dose	NA Limit Dose	ND
Dpx-mx670 mt	352-600	28.4	ND	ND	ND	ND
Drexel Acetochlor Plus Atrazine	19713-513	16.6	ND	ND	ND	ND
Drexel simazat 4l herbicide	19713-171	21.03	3600	2600-5000	757	547-1052
Drexel simazat 90df	19713-553	44.18	>2000	NA Limit Dose	NA Limit Dose	ND
Drexel trizmet ii	19713-547	33.1	>2000	NA Limit Dose	NA Limit Dose	ND

PRODUCT/TRADE NAME	EPA Reg.No.	% Atrazine	PRODUCT		ADJUSTED FOR ACTIVE INGREDIENT	
			LD 50 (mg/kg)	CI (mg/kg)	LD50 (mg/kg)	CI (mg/kg)
Dupont cinch atz herbicide	352-624	33	ND	ND	ND	ND
Dupont cinch atz lite herbicide	352-623	28.1	ND	ND	ND	ND
Dupont steadfast atz herbicide	352-619	85.3	ND	ND	ND	ND
Dupont Breakfree ATZ Lite	352-723	16.3	ND	ND	ND	ND
Dupont DPX-QDN33	352-724	24.4	ND	ND	ND	ND
Establish Life	SD060001	29.5	ND	ND	ND	ND
Expert herbicide	100-1161	22.9	>2000	NA Limit Dose	ND	ND
Fultime selective herbicide	62719-371	16.6	>5000	NA Limit Dose	ND	ND
G-max lite	7969-200	29.5	500-2000	NA Limit Dose	NA Limit Dose	ND
G-max lite	SD030001	29.5	ND	ND	ND	ND
Guardsman max herbicide	7969-192	35.3	500-2000	NA Limit Dose	NA Limit Dose	ND
Harness xtra 5.6l herbicide	524-485	26.9	1338	ND	ND	ND
Harness xtra herbicide	524-480	18.3	1249	ND	ND	ND
Keystone la	62719-479	16.3	>2000	NA Limit Dose	NA Limit Dose	ND
Keystone* herbicide	62719-368	24.4	2242	1272-3952	547	310-964
Laddok 5l herbicide	51036-415	24.4	ND	ND	ND	ND
Lariat herbicide	524-329	16	4800	3840-6050	768	614-968
Liberty atz herbicide	264-668	31.75	2119	NA Limit Dose	NA Limit Dose	ND
Lumax selective herbicide	100-1152	11	2865	NA Limit Dose	NA Limit Dose	ND
Makhteshim-Agan (Triangle)	66222-131	28.6	ND	ND	ND	ND
Makhteshim-Agan (Parallel Plus)	66222-132	30	>2000	NA Limit Dose	NA Limit Dose	ND
Marksman herbicide	7969-136	22.23	ND	ND	ND	ND
Metolachlor at	19713-593	27.4	>2000	NA Limit Dose	NA Limit Dose	ND
Mon 58442 herbicide	524-497	16.2	3105	NA Limit Dose	NA Limit Dose	ND
Mon 58494 herbicide	524-511	14.5	ND	ND	ND	ND

PRODUCT/TRADE NAME	EPA Reg.No.	% Atrazine	PRODUCT		ADJUSTED FOR ACTIVE INGREDIENT	
			LD 50 (mg/kg)	CI (mg/kg)	LD50 (mg/kg)	CI (mg/kg)
Mon 78088 herbicide	524-509	20.9	3980	NA Limit Dose	NA Limit Dose	ND
Newconcept herbicide	100-1201	19	4144	1485-20000	787	282-3800
Parallel plus	11603-41	30	ND	ND	ND	ND
Prompt 5l herbicide	51036-363	25	ND	ND	ND	ND
Rifle plus herbicide	34704-860	22.23	ND	ND	ND	ND
Shotgun flowable herbicide	34704-728	24.24	>5000	NA Limit Dose	NA Limit Dose	ND
Stalwart extra	60063-23	33	>2000	NA Limit Dose	NA Limit Dose	ND
Stratos dicamba+atrazine agricultural	33658-16	21.92	ND	ND	ND	ND
Southern Max	538-301	1.067	>5000	NA Limit Dose	NA Limit Dose	ND
Tremor at	33270-13	24.4	ND	ND	ND	ND
Tremor at lite	33270-14	16.3	ND	ND	ND	ND
Triangle herbicide	11603-39	28.6	>2000	NA Limit Dose	NA Limit Dose	ND
Volley atz lite tenkoz herbicide	55467-6	16.3	ND	ND	ND	ND
Volley atz tenkoz herbicide	55467-7	24.4	ND	ND	ND	ND

[i] From registrant submitted data to support registration. Compiled by Office of Pesticide Programs Health Effects Division.

[ii] Atrazine: LD50= 1869 mg/kg; CI= 1485 to 2487 mg/kg.