APPENDIX A. Multi-Active Ingredients Product Analysis for Cyfluthrin and *Beta*-Cyfluthrin.

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 (USEPA, 2004; USFWS/NMFS/NOAA, 2004).

Analysis of the available open literature and acute oral mammalian LD_{50} data for multiple active ingredient products relative to the single active ingredient (for both cyfluthrin and *beta*-cyfluthrin) is provided below. This data set is limited and a qualitative analysis does not support any broad conclusions about the interactive nature of the cyfluthrins in combination with other pesticides.

Cyfluthrin has registered products that contain multiple active ingredients; there are 17 multi-active ingredient products containing cyfluthrin, which were evaluated in this review. Cyfluthrin can be formulated with imidacloprid, chlorpyrifos, prallethrin, and phostebupirim. There are three cyfluthrin multi-a.i. products that are co-formulated with piperonyl butoxide (PBO), a known synergist. Acute oral toxicity data (*i.e.*, LD_{50} values) from mammalian studies for formulated products that contain cyfluthrin are summarized in **Table A.1** below.

Beta-cyfluthrin has registered products that contain multiple active ingredients; there are nine multi- active ingredient products containing *beta*-cyfluthrin, which were evaluated in this review. *Beta*-cyfluthrin can be formulated with imidacloprid, clothianidin, and phenylphenol (sodium salt). There is one *beta*-cyfluthrin multi-a.i. product that is co-formulated with PBO. Acute oral toxicity data (*i.e.*, LD_{50} values) from mammalian studies for formulated products that contain *beta*-cyfluthrin are summarized in **Table A.2** below.

Currently, the Agency's guidance for assessing the potential risk of chemical mixtures is limited to human health applications; 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 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 LD_{50} 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).

A quantitative component-based evaluation of mixture toxicity requires data of appropriate quality for each component of a mixture. In this mixture evaluation LD_{50}s, 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 some of the formulated products do not have LD_{50} values of the required quality and since LD_{50} values are not available for all the components of these formulations, a quantitative analysis of potential interactive effects 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). The logic behind the analysis of the multiple active ingredient product analysis, from mammalian toxicity data is that if there are multiple studies with the technical formulation for which confidence intervals (CI) are provided for the LD_{50}, then the CI with the smallest lower CI for the LD_{50} (*i.e.*, most toxic LD_{50},) after correcting for %AI, is compared to the LD_{50} upper CI for each formulation, after correcting for %AI. If these confidence intervals do not overlap, then the formulated mixture is considered to be more toxic. When the product LD_{50}s, and associated confidence intervals, are adjusted for the percent cyfluthrin or *beta*-cyfluthrin (a conservative assumption that attributes all of the observed toxicity of the formulated product to the respective chemical – cyfluthrin or *beta*-cyfluthrin); based on this approach, the Health Effects Division (HED) can reach one of three conclusions for the formulations:

- Formulation is no more toxic than single active ingredient
- Formulation is more toxic than single active ingredient
- There is insufficient data to establish difference toxicity

In the case of cyfluthrin, a qualitative examination of the trends in LD_{50} values, with the associated confidence intervals, across the range of percent active ingredient, reveals no definitive conclusions. For all cyfluthrin products analyzed, the data was insufficient to establish a difference in toxicity. For *beta*-cyfluthrin, the data was insufficient to establish a difference in toxicity for all but one product. For one product (TEMPRID SC INSECTICIDE, EPA Reg. No.: 432-1483), there were enough data to determine that the formulation was not more toxic than the a.i. to females. In all other cases, there were insufficient data to make a conclusion.

Table A-1. Summary Table for Multi-A.I. Products – Cyfluthrin.

Product	Current Registration No.	Percent Active Ingredient	Active Ingredient	MRID(s) for Acute Oral Study	Male Oral LD50 (mg/kg)	Female Oral LD50 (mg/kg)	Combined Oral LD50 (mg/kg)	Is Formulation more toxic to males	Is Formulation more toxic to females	Is formulation more toxic to combined sexes
TECHNICAL PRODUCTS										
1	4G2976 4H5416 3125-EUP-188	95.00%	Cyfluthrin	131518	16.2	No data	N/A	N/A	N/A	N/A
					254	No data	N/A	N/A	N/A	N/A
					396	No data	N/A	N/A	N/A	N/A
					500 - 1000	No data	N/A	N/A	N/A	N/A
					590	No data	N/A	N/A	N/A	N/A
					<100	No data	N/A	N/A	N/A	N/A
					609	No data	N/A	N/A	N/A	N/A
2	00264-00745	83.60%	Cyfluthrin	131499	590	1189	N/A	N/A	N/A	N/A
					869	1271	N/A	N/A	N/A	N/A
					291	609	N/A	N/A	N/A	N/A
MULTI-A.I. PRODUCTS										
1	264-770	12	Cyfluthrin	44627905	200	200	200	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
		17	Imidacloprid							
2	279-9553	0.05	Pyrethrins (NO INERT USE)	156368	>5000	>5000	>5000	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
		0.1	Cyfluthrin							
		1	Piperonyl butoxide							
3	279-9556	1	Piperonyl butoxide	156368	>5000	>5000	>5000	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
		0.05	Pyrethrins (NO INERT USE)							
		0.1	Cyfluthrin							
4	432-1378	0.72	Imidacloprid	No data						
		0.72	Cyfluthrin							
5	432-1392	2.94	Imidacloprid	No data						

Product	Current Registration No.	Percent Active Ingredient	Active Ingredient	MRID(s) for Acute Oral Study	Male Oral LD50 (mg/kg)	Female Oral LD50 (mg/kg)	Combined Oral LD50 (mg/kg)	Is Formulation more toxic to males	Is Formulation more toxic to females	Is formulation more toxic to combined sexes
		0.7	Cyfluthrin							
6	432-1393	0.7 2.94	Cyfluthrin Imidacloprid	No data						
7	499-405	8 1.6	Chlorpyrifos Cyfluthrin	42906302	0.92	0.34	0.63	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
8	499-443	0.1 0.03	Cyfluthrin Prallethrin	43811902	>5000	>5000	>5000	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
9	499-462	0.1 0.5 1	Cyfluthrin Pyrethrins (NO INERT USE) Piperonyl butoxide	42097602	>5000	>5000	>5000	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
10	4822-573	0.03 0.04	Cyfluthrin Prallethrin	47901805	No data	>5000	N/A	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
11	4822-574	0.03 0.04	Cyfluthrin Prallethrin	47901805	N/A	N/A	>5000	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
12	4822-581	0.05 0.02	Cyfluthrin Prallethrin	48444607	N/A	N/A	>5000	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
13	4822-582	0.2	Pyrethrins (NO INERT USE)	No data						

Product	Current Registration No.	Percent Active Ingredient	Active Ingredient	MRID(s) for Acute Oral Study	Male Oral LD50 (mg/kg)	Female Oral LD50 (mg/kg)	Combined Oral LD50 (mg/kg)	Is Formulation more toxic to males	Is Formulation more toxic to females	Is formulation more toxic to combined sexes
		0.5	Piperonyl butoxide							
		0.05	Cyfluthrin							
14	5481-9028	4.45	Phostebupirim	No data						
		0.22	Cyfluthrin							
15	5481-9029	0.1	Cyfluthrin	No data						
		2	Phostebupirim							
16	5481-9030	0.1	Cyfluthrin	No data						
		2	Phostebupirim							
17	5481-9032	3.6	Phostebupirim	4409802	145	53	99	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
		0.18	Cyfluthrin							

Table A-2. Summary Table for Multi-A.I. Products – *Beta*-Cyfluthrin.

Product	Current Registration No.	Percent Active Ingredient	Active Ingredient	MRID(s) for Acute Oral Study	Male Oral LD50 (mg/kg)	Female Oral LD50 (mg/kg)	Combined Oral LD50 (mg/kg)	Is Formulation more toxic to males	Is Formulation more toxic to females	Is formulation more toxic to combined sexes
TECHNICAL PRODUCTS										
1	03125-EIO	99.10%	*beta*-Cyfluthrin	41244104	84	77	N/A	N/A	N/A	N/A
					141	108	N/A	N/A	N/A	N/A
				41244103	91	165	N/A	N/A	N/A	N/A
				41244102	380	651	N/A	N/A	N/A	N/A
					655	1369	N/A	N/A	N/A	N/A
				41244101	211	336	N/A	N/A	N/A	N/A
					307	343	N/A	N/A	N/A	N/A
MULTI-A.I. PRODUCTS										
1	264-1056	4.6	*beta*-Cyfluthrin	4700780	>500	>500	>500	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
		34.3	Clothianidin							
2	264-1104	10.5	*beta*-Cyfluthrin	No data						
		21	Imidacloprid							

Product	Current Registration No.	Percent Active Ingredient	Active Ingredient	MRID(s) for Acute Oral Study	Male Oral LD50 (mg/kg)	Female Oral LD50 (mg/kg)	Combined Oral LD50 (mg/kg)	Is Formulation more toxic to males	Is Formulation more toxic to females	Is formulation more toxic to combined sexes
3	432-1483	10.5 21	*beta*-Cyfluthrin Imidacloprid	47393002		1044		Insufficient data to establish different toxicity	Formulation not more toxic than single AI	Insufficient data to establish different toxicity
4	11556-131	20 8	Piperonyl butoxide *beta*-Cyfluthrin	No data						
5	72155-28	0.012 0.0015	Imidacloprid *beta*-Cyfluthrin	N data						
6	72155-29	0.36 0.72	*beta*-Cyfluthrin Imidacloprid	No data						
7	72155-31	0.05 0.15	*beta*-Cyfluthrin Imidacloprid	No data						
8	72155-80	0.3 0.05	o-Phenylphenol, sodium salt *beta*-Cyfluthrin	46992502	N/A	>2000	N/A	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity	Insufficient data to establish different toxicity
9	TX110001	 12.7	Imidacloprid *beta*-Cyfluthrin	No data						

References:

USEPA. 2004. *Overview of the Ecological Risk Assessment Process in the Office of Pesticide Programs*. United States Environmental Protection Agency (USEPA). Environmental Fate and Effects Division. Office of Pesticide Programs. Available athttp://www.epa.gov/espp/consultation/ecorisk-overview.pdf (Accessed 12/05/2002).