Bayer CropScience

STUDY TITLE

White Paper: Flubendiamide Benefits, Aquatic Risk Assessment Summary and Proposed Path Forward

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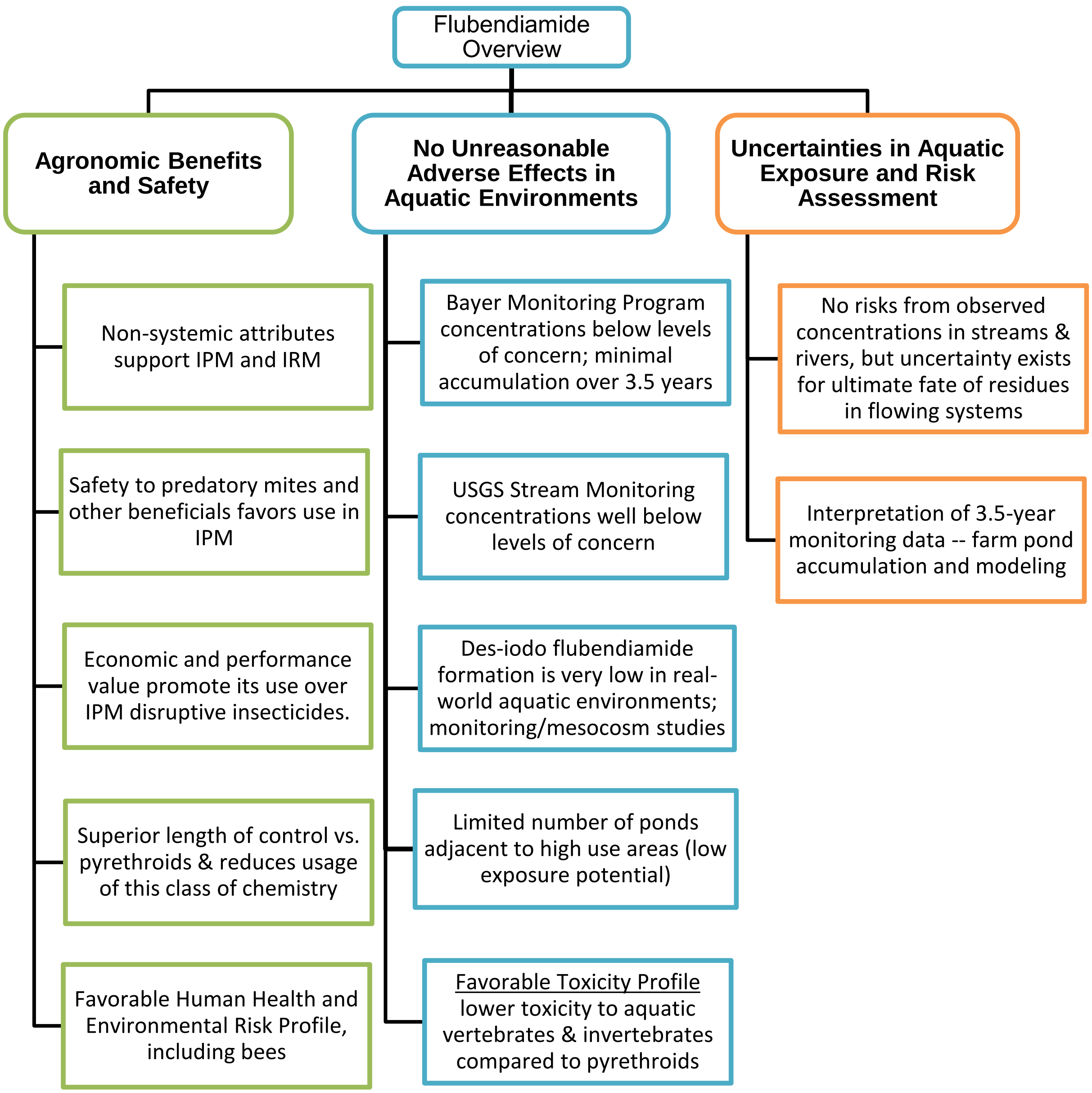
WHITE PAPER: FLUBENDIAMIDE BENEFITS, AQUATIC RISK ASSESSMENT SUMMARY AND PROPOSED PATH FORWARD

1. SUMMARY

Bayer CropScience is providing this 'white paper' to summarize the various documents and discussions from the past few months, and to propose steps in moving the registration process forward. The following chart provides a concise overview of the benefits, aquatic exposure and risk, and the remaining exposure uncertainties pertaining to the use of flubendiamide.



Flubendiamide brings an important benefit to growers of many crops and BCS is working to maintain a safe and viable product for the US growers. After years of testing that included EPA-approved field study designs in support of the 2008 registration decision, Bayer CropScience (BCS) concludes that use of flubendiamide presents no imminent harm to the environment, including no unreasonable adverse effects to aquatic species. EFED does not reach the same conclusion of environmental safety, noting a concern for accumulation in aquatic systems after years of continuous use in reasonably high risk environments – i.e. vulnerable farm ponds receiving direct runoff from treated fields.

Some uncertainties lead to the difference in opinion between BCS and EFED on the potential for aquatic risks to invertebrates, but these uncertainties can be addressed with appropriate continuation of on-going monitoring and/or additional monitoring and studies. It is critically important to BCS and growers that an agreeable path forward is determined for continued registration and agricultural use of flubendiamide.

2. AGRONOMIC BENEFITS

Flubendiamide is a foliar applied selective insecticide, formulated as a water-based suspension concentrate (SC) containing 4 pounds active ingredient per gallon, known in the marketplace as Belt® SC Insecticide. Chemically, flubendiamide is a phthalic acid diamide and is listed in Group 28 as a Ryanodine Receptor Modulator. Flubendiamide offers unique attributes that make it compatible with and easily integrated into IPM and IRM programs in over 200 crops, providing broad-spectrum control of over 95 lepidopteran insect pests, including driver species like beet armyworm, navel orangeworm, soybean looper, corn earworm and tobacco budworm. The specific benefits that flubendiamide offers to growers are detailed below (Nelson, 2015).

2.1 Non-systemicity of flubendiamide is a benefit for Integrated Pest Management (IPM) and Insecticide Resistance Management (IRM) in many crops.

The non-systemicity of flubendiamide gives growers the option to apply a treatment window approach to insecticide resistance management. Treatment windows are described in IRAC documents as a method for controlling the exposure of an insect population to a specific mode of action by alternating chemistries in a pattern to minimize extended periods of exposure to one mode of action.

2.2 Safety to predatory mites and other beneficial arthropods favors flubendiamide use in IPM systems.

Unlike pyrethroids, flubendiamide does not harm predatory mites in various crops and, as a result, does not flare mites. Flubendiamide has been tested under semi-field and field conditions for its selectivity against key beneficial arthropods and has been found to be harmless to slightly harmful on the relevant beneficial insects, based on the International Organization for Biological and Integrated Control classification. Safety to predatory mites and other beneficial arthropods favors flubendiamide use in IPM systems.

2.3 Flubendiamide offers a mode of action (MOA) with no known cross resistance to alternative modes of action for management of IR lepidopteran insect pests in over 200 crops.

Flubendiamide is greatly needed to help manage insect resistance because it brings broad spectrum Lepidoptera control; a Group 28 Ryanodine Receptor Modulator MOA; and proven performance for the control of driver IR insects in alfalfa, almond, peanuts, soybeans, tobacco and over 200 other crops. Insect resistance is spreading rapidly; many insecticides are no longer providing consistent control. Insecticides like flubendiamide, offering a unique MOA, are desperately needed by growers.

2.4 Flubendiamide offers superior length of control compared to pyrethroid insecticides. Removal of flubendiamide from the marketplace would increase the use of pyrethroids.

Flubendiamide works by ingestion, and when used according to label directions, poses minimal risk to beneficial arthropods while providing long residual control of target insects. Flubendiamide is an “IPM friendly”, high performance product that promotes reduced overall insecticide use by negating any short-term need for repeated insecticide applications. Pyrethroids have contact activity, comparatively short residual activity, and are highly disruptive to beneficial populations. As a result, pyrethroids provide a relatively short length of control of target pests.

The removal of BELT from the market increases the risk of growers returning to IPM-disruptive chemistries - such as organophosphates and pyrethroids - which pose environmental risk and human safety issues.

2.5 Flubendiamide has low acute toxicity, a short REI/PHI and a favorable human health and environmental risk profile which ensures minimal impact on applicators, field workers and the environment, including bees.

With a “Caution” signal word, 12 hour REI, favorable PHI’s, and high IPM and IRM compatibility, flubendiamide offers safety and flexibility equal to chlorantraniliprole and methoxyfenozide, and superior to the other commercial standards. Methomyl has a “Danger” signal word, while bifenthrin, cyfluthrin and lambda-cyhalothrin have “Warning” signal words and are classified as Restricted Use pesticides due to risks they pose to fish and aquatic organisms.

Flubendiamide is also much **less toxic to bees** than most of the competitor products, specifically pyrethroids (details in Section 3.4), and was not among the pesticides listed in “EPA’s Proposal to Mitigate Exposure to Bees from Acutely Toxic Pesticide Products” (May 28, 2015).

A comparison of flubendiamide and competitors for several agronomic parameters is provided in the following table (Table 1).

Table 1. Comparative Toxicity of Flubendiamide and Competitive Standards for Applicators, Field Workers, and Beneficial Populations

	Flubendiamide	Bifenthrin	Chlorantraniliprole	Cyfluthrin	Lambda-Cyhalothrin	Indoxacarb	Methomyl	Methoxyfenozide	Spinetoram
Label Signal Word	Caution*	Warning Restricted Use	Caution	Warning Restricted Use	Warning Restricted Use	Caution	Danger Restricted Use	Caution	Caution
Re-Entry Interval (REI)	12 hours	12 hours	4 hours	12 hours	24 hours	12 hours	2-4 days	4 hours	4 hours
Beneficial Insect Toxicity	Low	High	Low	High	High	Low	High	Low	Moderate
Bee Toxicity	Low	High	Low	High	High	High	Moderate	Low	High
Secondary Pest Flaring (mites, etc)	Low	High	Low	High	High	Low	Moderate	Low	Moderate
IPM Compatibility	High	Low	High	Low	Low	High	Low	High	Moderate
IRM Compatibility	High	Low (pyrethroid resistance)	High	Low (pyrethroid resistance)	Low (pyrethroid resistance)	Moderate	Low	High	Low (spinosad cross-resistance)
Feeding Cessation	<1-2 hours	>4 hours	<1-2 hours	>4 hours	>4 hours	2-4 hours	2-4 hours	>4 hours	<1-2 hours
Residual Activity on Lepidopteran Pests	Long	Short	Long	Short	Short	Short	Moderate	Moderate	Moderate
Residual Activity on Beneficials	Short	Long	Short	Moderate	Moderate	Moderate	Moderate	None	Moderate
Primary Activity	Ingestion	Contact	Ingestion	Contact	Contact	Ingestion	Contact	Ingestion	Ingestion

Source: Product labels. *Attributes rating scale:
Green: Consistently meets or exceeds customer expectations; limited to no effects on beneficial arthropods, does not flare secondary pests, compatible with IPM programs
Yellow: Sometimes meets customer expectations; significant effects on beneficial arthropods, may flare secondary pests, limited compatibility with IPM programs.
Red: Does not meet customer expectations; severe effects on most beneficial arthropods, routinely flares secondary pests, not compatible with IPM programs.

3. EVIDENCE FOR NO UNREASONABLE ADVERSE EFFECTS IN AQUATIC ENVIRONMENTS

3.1 3.5-Year High Tier Monitoring Program – Concentrations well below levels of concern

Monitoring results from streams and rivers from the BCS study sites in North Carolina and Georgia (Xu, 2014) show maximum concentrations of flubendiamide and des-iodo flubendiamide that are **14 to 400 times below** the levels of concern (NOEC) for aquatic invertebrates, indicating a clear level of safety.

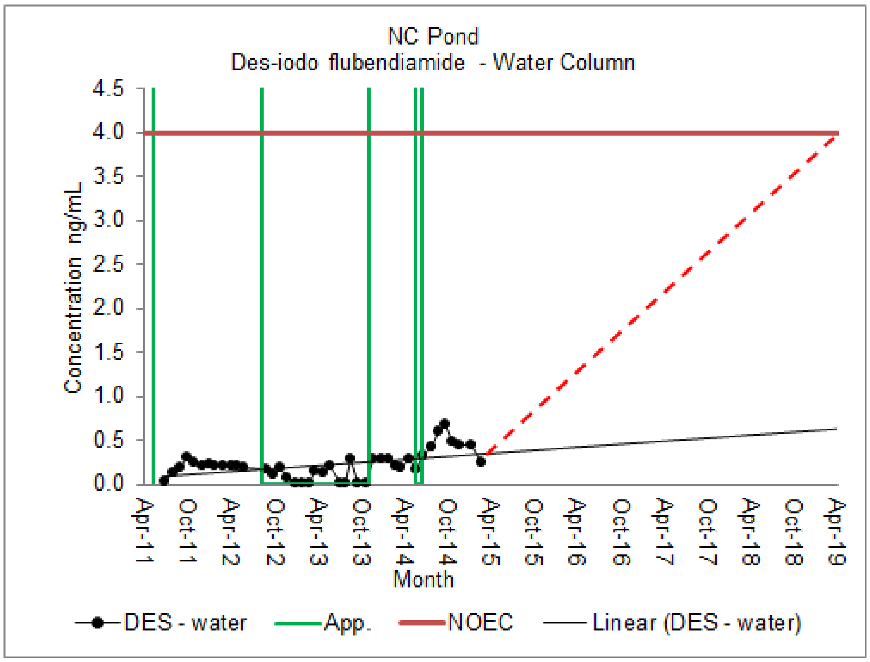
In the ponds from the BCS monitoring sites, the concentrations are **9 to 195 times below** the NOEC. Even when adjusted to the maximum application rates for row crops, the concentrations are **2 to 50 times below** the NOECs.

A brief summary of the maximum concentrations are provided in Table 2.

Table 2. Summary of flubendiamide and des-iodo flubendiamide monitoring concentrations and comparison to levels of concern (NOEC)

> CBI1 text located in the Confidential Business Information<

The lack of imminent concern for aquatic environments is graphically represented in the following figure that shows des-iodo flubendiamide concentrations in the water column of the NC pond in comparison to the level of concern (NOEC). The red dashed line represents the *unprecedented* increase in concentrations that would need to occur to bring concentrations to the levels and timing predicted by the EPA exposure models (Dyer et al. 2015).



Note: concentrations were increased by factors to represent potential residues for the maximum label rate of 4 x 0.094 lb a.i./acre for row crops

The highest concentrations observed at these sites have tended to occur during the most recent growing season, which is being interpreted by EFED as a long-term accumulation pattern. However, these results can also be explained as annual fluctuations due to application timings and rates (specifically higher rates in NC).

3.2 <u>USGS Stream Monitoring – Concentrations well below levels of concern</u>

> CBI2 text located in the Confidential Business Information<

3.3 <u>Low extent of des-iodo flubendiamide formation</u>

Concern by EFED is focused the lack of a definitive degradation pathway for des-iodo flubendiamide, but it is critical to recognize that formation of des-iodo flubendiamide is limited in the typically aerobic or semi-aerobic aquatic environments, thus explaining the extremely low concentrations being observed in the monitoring programs (≤0.17 μg/L; **50 to 400 times below** levels of concern) and mesocosm study.

3.4 Limited numbers of ponds adjacent to high use areas

BCS provided an overview of the potential overlap of agricultural fields with surface water bodies in areas with high flubendiamide use (Dyer and McConnell, 2015). In California, there are few agricultural fields that drain into farm ponds. Consequently, modeled exposure concentrations are representing only a very small fraction of the agricultural landscape. In the southeast, there are more ponds which may drain agricultural fields, and the expected exposure in these areas would be similar to the BCS monitoring sites in NC and GA.

3.5 Lower toxicity compared to main competitor products

Flubendiamide has a favorable toxicity profile to terrestrial organisms including honey bees. As presented in Table 3, flubendiamide is non-toxic to honey bees on an acute basis while pyrethroids are highly toxic. In addition to a favorable toxicity profile to honey bees, flubendiamide has been found to be harmless to slightly harmful (IOBC classification) to key beneficial arthropods in IPM systems (Nelson, 2015).

Table 3. Honey Bee Contact Toxicity of Flubendiamide and Competitor Insecticides

Chemical	48 hour Contact LD_{50} (μg a.i./bee)	48 hour Oral LD_{50} (μg a.i./bee)
Flubendiamide	>200	>200
Bifenthrin	1.875[A]	NA
Gamma-cyhalothrin	0.0061	NA
Lambda-cyhalothrin	0.038	0.909
Permethrin	0.024	0.13
Cypermethrin	0.023	0.172
Deltamethrin	0.11	0.19
Cyfluthrin	0.037	NA
Fenpropathrin	NA	NA
Esfenvalerate	NA	NA

NA = Registrant submitted study not available
[A] Endpoint presented in μg formulation/bee for a 0.8% bifenthrin EC formulation. Registrant submitted data not available for technical active ingredient.

Aquatic invertebrates are the most sensitive aquatic taxa to flubendiamide exposure, which is often the case for insecticides. The lowest aquatic toxicity endpoint for flubendiamide and des-iodo flubendiamide is the overlaying water NOEC (4.0 μg des-iodo flubendiamide/L; MRID 46817023) from a spiked water study with *Chironomus riparius* following OECD guideline 219. Compared to aquatic invertebrate water column NOECs for pyrethroids, flubendiamide and des-iodo flubendiamide are orders of magnitude less toxic (Table 4).

Table 4. Summary of Lowest Freshwater and Marine/Estuarine Water Column Chronic NOEC for Flubendiamide and Competitor Insecticides

Chemical	NOEC (µg a.i./L)	Species	Reference
Flubendiamide	33.3	*Daphnia magna*	MRID 46816944
	≥20	*Americamysis bahia*	MRID 46816946
Des-iodo flubendiamide	4.0	*Chironomus riparius*	MRID 46817023
	NA	*Americamysis bahia*	
Bifenthrin	0.0008	*Hyalella azteca*	MRID 46938301
	0.0015	*Americamysis bahia*	MRID 46938301
Gamma-cyhalothrin	0.00218	*Daphnia magna*	MRID 46938301
	NA	*Americamysis bahia*	
Lambda-cyhalothrin	0.00198	*Daphnia magna*	MRID 46938301
	0.00022	*Americamysis bahia*	MRID 46938301
Permethrin	0.03	*Brachycentrus americanus*	MRID 46938301
	0.0078	*Americamysis bahia*	MRID 46938301
Cypermethrin	0.0075	*Daphnia magna*	MRID 46938301
	0.00059	*Americamysis bahia*	MRID 46938301
Deltamethrin	0.0041	*Daphnia magna*	MRID 46938301
	0.00073	*Americamysis bahia*	MRID 46938301
Cyfluthrin	0.001	*Hyalella azteca*	MRID 49641101
	0.00017	*Americamysis bahia*	MRID 46938301
Fenpropathrin	0.22	*Daphnia magna*	MRID 46938301
	0.012	*Americamysis bahia*	MRID 46938301
Esfenvalerate	0.052	*Daphnia magna*	MRID 46938301
	0.00017	*Americamysis bahia*	MRID 49641101

NA: not available

Table 5 presents the Aquatic Life Benchmarks (for freshwater species) for flubendiamide, des-iodo flubendiamide, and pyrethroids. These values are estimates of the concentrations below which adverse effects are not expected. Data on the maximum concentrations of flubendiamide and des-iodo flubendiamide from BCS and USGS monitoring programs for streams, rivers, and ponds (see section 3.1 and 3.2 for details) demonstrate a clear margin of safety against unreasonable adverse effects to aquatic life.

Table 5. Aquatic Life Benchmarks for Flubendiamide and Competitor Insecticides

Chemical	Fish[A] (µg a.i./L)		Aquatic Invertebrates[A] (µg a.i./L)	
	Acute	Chronic	Acute	Chronic
Flubendiamide	>32.55[B]	60.5[B]	>27.4[C]	33.3[C]
Des-iodo flubendiamide	NA	NA	>440.5[C]	4.0[C]
Bifenthrin	0.013[D]	0.012[D]	0.00025[D]	0.0008[D]
Gamma-cyhalothrin	0.0235[D]	NA	0.000265[D]	0.00218[D]
Lambda-cyhalothrin	0.039[D]	0.031[D]	0.00015[D]	0.00198[D]
Permethrin	0.75[D]	0.14[D]	0.0035[D]	0.03[D]
Cypermethrin	0.44[D]	0.077[D]	0.00028[D]	0.0075[D]
Alpha-cypermethrin	2.8[D]	NA	0.150[D]	NA
Deltamethrin	0.075[D]	0.017[D]	0.000085[D]	0.0041[D]
Cyfluthrin	0.1255[D]	0.025[D]	0.000275[D]	0.001[D]
Beta-cyfluthrin	0.044[D]	NA	0.145[D]	NA
Fenpropathrin	1.1[D]	0.091[D]	0.00145[D]	0.22[D]
Esfenvalerate	0.07[E]	0.017[E]	0.000425[D]	0.052[D]

[A] Benchmarks are calculated as the lowest freshwater toxicity value for a given taxa, multiplied by the LOC. The LOC for acute fish and acute invertebrates is 0.5, while the LOC for chronic fish and chronic invertebrates is 1.

[B] Endpoint obtained from: Flubendiamide and des-iodo flubendiamide data obtained from: EPA. 2010. Ecological Risk Assessment for the New Use of Flubendiamide on Alfalfa, Globe Artichoke, Low Growing Berry Subgroup (Except Cranberry), Peanut, Pistachio, Small Fruit Vine Climbing Subgroup (Except Fuzzy Kiwi Fruit), Sorghum, Sugarcane, Sunflower, Safflower and Turnip Greens, and Rate Increase on Brassica Leafy Vegetables. Washington, DC: U.S. Environmental Protection Agency. 90 p.

[C] Endpoint obtained from: Dyer and Hall, 2014. Flubendiamide aquatic risk - Summary of surface water monitoring and toxicity testing. Bayer CropScience LP, RTP, NC, USA. Report No. US0453. MRID 49415302

[D] Endpoint obtained from: Giddings and Wirtz, 2013. The toxicity of nine pyrethroid insecticides to aquatic organisms. PWG Report No. PWG-ERA-12. MRID 46938301

[E] Endpoint obtained from: Giddings and Wirtz, 2015. Compilation and evaluation of aquatic toxicity data for synthetic pyrethroids: data added since 2012. PWG Report No. PWG-ERA-12A. MRID 49641101

4. UNCERTAINTIES / DIFFERING INTERPRETATIONS IN AQUATIC RISK ASSESSMENT

4.1 Fate of flubendiamide and des-iodo flubendiamide in streams under real world conditions

There are no short or long-term aquatic risks from the very low concentrations of flubendiamide and des-iodo flubendiamide in streams and rivers in areas of flubendiamide use, however, EFED questions the ultimate fate of these low level residues. BCS describes a photolytic degradation pathway in the recently submitted document (Dyer and McConnell, 2015) that is consistent with the observed degradation of flubendiamide in the mesocosm study, without formation of des-iodo flubendiamide.

4.2 Interpretation of 3.5-Year Monitoring Data -- farm pond accumulation

BCS continues to support the conclusion that the higher tier monitoring data show limited, if any accumulation of residues, and that these monitoring data can be effectively reproduced through higher-tier exposure modeling approaches. EFED counters there is clear evidence of accumulation and that the standard modeling methodology is appropriate. There is agreement that the 3.5 year field study duration is insufficient to quantify the longer-term accumulation potential under real world conditions. The study is continuing through the 2015 growing season and is expected to confirm the standard exposure modeling use by EFED is too conservative compared to real-world exposures. It may take several two to three more years to fully confirm the accumulation profile anticipated by EFED is not occurring.

The resolution of the accumulation questions is critical for a scientifically sound assessment of des-iodo flubendiamide exposure, which shows dramatic increases in the estimated (predicted) exposure, while monitoring data is showing extremely low concentrations in natural aquatic environments.

5. PROPOSED PATH FORWARD

BCS is working to maintain its registration of safe flubendiamide uses, in support of this beneficial tool for growers in the United States. Within the regulatory risk assessment framework, BCS provided options for higher tier modeling that provides a conservative but more appropriate representation of real-world monitoring data for farm ponds.

The available monitoring data indicates that aquatic risk levels have not been exceeded in ponds, streams or rivers. If accumulation is occurring in ponds, the process is slow and if risk levels might be exceeded, this would only occur after many years of use at maximum label rates, and still constrained by very specific climatic and agronomic conditions (e.g. edge-of-field farm pond with no flow through).

Our overview also indicated that in many agricultural settings where flubendiamide is used, farm ponds will have sufficient flow-through of water (areas with high precipitation, such as the southeast) to prevent significant accumulation, while in drier climates such as the California Central Valley, very few ponds exist in agricultural fields and therefore the potential for accumulation in farm ponds is negligible.

Addressing the differences in interpretation of these data by BCS and EFED will require continued monitoring of flubendiamide and des-iodo flubendiamide in water bodies for a period of several more years (e.g. the BCS and USGS monitoring programs), to show the modeling estimates are overestimating real-world concentrations. The risk assessment may also benefit from consideration of additional information on degradation of flubendiamide and des-iodo flubendiamide under natural conditions. This work will allow for resolution of the exposure uncertainties, and lead to a well informed decision on the lack of risk to aquatic invertebrates from the use of flubendiamide. BCS remains committed to continue this environmental fate investigation as all parties concluded more time is needed to confirm the environmental safety of flubendiamide in environmentally sensitive water bodies, such as farm ponds.

6. REFERENCES

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