UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **November 12, 2020**

SUBJECT: SABA-10: Summary of Hazard and Science Policy Council (HASPOC) Meeting on October 29, 2020: Recommendations on the Need for a Subchronic Dog Study, an Immunotoxicity Study, and a Subchronic Inhalation Study.

PC Code: TBD
Decision No.: 562510, 562269, 565624
Petition No.: N/A
Risk Assessment Type: N/A
TXR No.: 0058114
MRID No.: 51250801, 51113001, 51124801

DP Barcode: D458559, D457796, D459764
Registration No.: 1021PA90, 1021PA89, 1021PA96
Regulatory Action: N/A
Case No.: N/A
CAS No.: N/A
40 CFR: N/A

FROM: Matthew Zampariello, Executive Secretary
HASPOC
Health Effects Division (7509P)

THROUGH: Whang Phang, Ph.D., Co-Chair
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TO: Emily Rogers, Ph.D., DABT, Toxicologist
Christina Swartz, Branch Chief
Risk Assessment Branch 2 (RAB2)
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MEETING ATTENDEES:

HASPOC Members: Elizabeth Mendez, Angela Gonzales, Michael Metzger, Anwar Dunbar, Kelly Lowe, Evisabel Craig, Greg Ackerman, John Liccione, Krystle Yozzo, Monique Perron, Sarah Dobreniecki, Jeff Dawson, Jacqueline Meadows, Brian VanDeusen, Moana Appleyard, Ruthanne Louden, Jeremy Leonard, Whang Phang,* Cassi Walls,* Matthew Zampariello,** Victoria Kurker**
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Presenter: Emily Rogers, Toxicologist

Other Attendees: Eddie DeLeon, Maryam Muhammad, Gerad Thornton, Kevin Chan, Darius Stanton

I. PURPOSE OF MEETING

SABA-10, a new active ingredient, is in the pre-submission phase of registration. The registrant, McLaughlin Gormley King (MGK) Company, has requested a waiver of the subchronic dog study (MRID 51124801), the immunotoxicity study (MRID 51113001), and the subchronic inhalation study (MRID 51250801). The Hazard and Science Policy Council (HASPOC) met on October 29, 2020 to determine if the required studies are necessary to support the registration for SABA-10 based on the currently available information.

II. SUMMARY OF USE PROFILE, EXPOSURE, AND HAZARD CONSIDERATIONS

a. Use and Exposure Profile

SABA-10 is a new formulation of the previously registered sabadilla alkaloids (PC Code 002201). Sabadilla alkaloids are a food-use insecticide used to control thrips on citrus, avocados and mangos by prolonging the action potential of voltage-gated sodium channels of nerve axons. The Agency concluded that studies with SABA-10 could not be used to satisfy the data requirements for the sabadilla alkaloids for registration review; therefore, SABA-10 is being submitted as a new active ingredient, and an agreement will be made on phase-out of registrations for sabadilla alkaloids. While the sabadilla alkaloids had food uses, SABA-10 is to be proposed as a non-food use insecticide for outdoor use around residences. However, the registrant has stated that food uses may be added in the future.

A pre-submission meeting was held with the registrant, MGK, on July 29, 2020 where MGK described the anticipated use pattern for SABA-10. The registrant is proposing four new end-use products containing the new active ingredient SABA-10. Several of these formulations are co-formulated with the pyrethrins. All proposed end-use products are for use in residential outdoor areas as a crack/crevice and spot treatment use on the outside of homes, on lawns, gardens, and patios/decks. Application methods include handheld sprayer equipment (e.g., backpack sprayer, mist sprayer). Several end-use products will be formulated as Ready-to-Use either as an aerosol can or trigger spray-like bottles. Based on the information provided at the pre-submission meeting, the anticipated application rate range is 0.0012 lb ai/1000 sq ft to 0.0175 lb ai/1000 sq ft. HED is expecting inhalation and dermal exposures for handlers, and dermal and incidental oral exposures (children only) for post-application activities.

b. Toxicity Profile

To date, MGK has submitted the following studies for SABA-10: acute toxicity battery, acute neurotoxicity study, combined subchronic oral/neurotoxicity study in rats, developmental studies (rat and rabbit), and reproduction toxicity study. A preliminary toxicology profile table has been provided in Appendix A. These studies have not been formally reviewed, and the conclusions are subject to change. In addition to the 90-day inhalation toxicity study, the 90-day oral toxicity

study in dogs, and the immunotoxicity study in rats, the remaining studies needed for the non-food use submission are the carcinogenicity study in the mouse, the combined/chronic carcinogenicity study in the rat, and the metabolism and pharmacokinetics studies. The registrant has agreed to conduct these remaining studies.

Preliminary analysis of the acute toxicity battery indicates that SABA-10 will be categorized as Toxicity Category III for acute oral and inhalation toxicity and Toxicity Category IV for acute dermal toxicity. It will be categorized as Toxicity Category IV for both eye irritation and dermal irritation and is not a dermal sensitizer. The 28-day dermal toxicity study showed dermal effects at 500 mg/kg/day but no systemic effects up to the limit dose of 1000 mg/kg/day.

The primary effects of SABA-10 are related to neurotoxicity. Clinical signs of neurotoxicity were observed in the acute oral and acute inhalation studies, as well as the neurotoxicity battery (acute and subchronic). In the acute inhalation study, the majority of surviving animals showed hypoactivity, ataxia, tremors, and abnormal gait that resolved after 3-5 days. Hypoactivity and abnormal gait were also initially observed in the acute oral toxicity study. In the acute neurotoxicity study, the primary effects were abnormal gait, slight ataxia, slight hypoactivity, slight hyperactivity and hypersalivation. These effects were observed between 1 and 6 hours following daily dosing, and this pattern continued for the duration of the study. In the combined 90-day oral toxicity/subchronic neurotoxicity study, neurotoxic signs were not observed, however relative brain weights were increased in both sexes.

Clinical signs of neurotoxicity were also observed in maternal animals in the developmental studies, where there was no evidence of increased susceptibility. In the developmental rat study, decreased body weight, ataxia, abnormal gait, hypoactivity, irregular respiration and hypersalivation were observed at doses equal to or greater than that at which decreased fetal weights were observed. In the developmental rabbit study, malformations were observed in the presence of neurotoxic signs in the does, which included abnormal gait, hypoactivity, and excessive salivation. Increased quantitative susceptibility was observed in the reproduction toxicity study. Decreased relative spleen weights and histopathological changes in the spleen (decreased cellularity of the white pulp and pigmented macrophages) were observed in adult females at a higher dose than decreased relative spleen weights and body weights in the offspring. There were no effects on reproduction.

III. STUDY WAIVER REQUESTS

a. Subchronic Dog Study

The registrant provided a waiver for the 90-day dog study (MRID 51124801). The two major arguments were:

- Based on retrospective analyses performed by the registrant, the use of dogs as a second species adds little to the prediction of adverse human effects.

- An examination of the results of the 90-day dog studies and 90-day studies in rats with pyrethroids indicates the rat is more sensitive.

- In the waiver request document, the registrant stated that, "the sabadilla alkaloids share the same mode of action with naturally occurring pyrethrins and synthetic pyrethroids: interaction with voltage-gated sodium channels. The interaction results in prolonged opening of the channels leading to persistent activation and nerve hyperexcitability."

At this time, the subchronic dog study is required according to 40 CFR Part 158.500 data requirements. Data demonstrating the mechanism of action of the sabadilla alkaloids or SABA-10 have not been presented to the Agency; therefore, the Agency cannot conclude that sabadilla alkaloids or SABA-10 share a common mode of action (MOA) with the pyrethrins and/or pyrethroids. The sabadilla alkaloids were not included in the Agency's common mechanism grouping for the pyrethrins and synthetic pyrethroids (K. Whitby, D394956, 10/04/2011). Some of the neurotoxic signs observed with SABA-10 are consistent with pyrethroids; however, tremors and choreoathetosis, the hallmarks of toxicity of type I and type II pyrethroids, respectively, were not the predominant neurotoxic signs observed in the SABA-10 database. Tremors were only observed in the acute inhalation study and the acute neurotoxicity study (ACN), and choreoathetosis was not noted in any study. Furthermore, although sabadilla alkaloids have been shown to possess insecticidal activity due to their action on sodium channels (e.g., Bloomquist, 1996), the receptor has not been isolated and experiments indicate it is distinct from that of pyrethroids (Ujvary, 2010). In order to consider that SABA-10 has the same MOA as pyrethrins and/or pyrethroids, additional information would need to be presented to the Agency to support this claim.

Based on a WOE approach, considering all the available SABA-10 hazard and exposure data, the HASPOC recommends that a 90-day oral toxicity study in the dog is not waived at this time. This approach included the following considerations: (1) a subchronic dog study is required per 40 CFR Part 158.500 data requirements; (2) while rats are more sensitive than dogs in studies with pyrethroids, this argument cannot be applied to SABA-10 because there is a lack of data/information indicating SABA-10 shares a MOA with pyrethroids; (3) neurotoxic effects in studies with SABA-10 are inconsistent with pyrethroids; and (4) no data have been provided to substantiate the registrant's hypothesis that SABA-10 and pyrethroids have a common MOA.

b. Immunotoxicity

The registrant's arguments to waive the immunotoxicity study are provided in MRID 51113001. These arguments were considered for the following:

1. **Indicators for potential immunotoxicity:** Changes in spleen weights and histopathology were observed in all generations in the 2-generation reproduction study. Changes in absolute spleen weights were observed in adult males and females of the F0 and F1 generations at the high dose (↓15-18%), in F1 weanling males and females at the mid (↓13-16%) and high (↓16%) doses, and in F2 males and females at the mid (↓12-18%) and high (↓15-21%) doses. Decreased relative spleen weights were also observed in F0 and F1 adult females, and in F1 and F2 weanlings of both sexes. The decrease in relative spleen weights in adult females was 13% at the high dose in the F0 generation and 14% at the high dose in the F1 generation. In high dose F0 adult females, changes in

spleen weights were accompanied by decreased cellularity of the white pulp in 4/28 animals and pigmented macrophages in 3/28 animals; however, no histopathological changes in the spleen were observed in the F1 generation. Relative spleen weights were decreased by 9% in both the mid- and high-dose groups of the F1 males and by 6-8% in F1 females. In the F2 offspring, relative spleen weights were decreased in the mid- and high-dose groups by 7-8% in males and by 11-14% in females. In addition to decreased relative spleen weights, decreased litter weights and decreased body weights were observed in offspring at the mid and high doses. Because effects in parental animals only occurred at the high dose, there is quantitative susceptibility in the 2-generation reproduction study.

Parameter	Findings
Hematology Indicators (WBC changes)	None
Clinical Chemistry Indicators (A/G Ratio)	None
Organ Weight Indicators (Spleen, Thymus)	Decreased absolute and relative spleen weights in adults (≥68 mg/kg/day) and offspring (≥45 mg/kg/day) of both generations in the 2-generation reproduction study
Histopathology Indicators (Spleen, Thymus, Lymph nodes)	Decreased cellularity of the white pulp and pigmented macrophages in the spleen noted in F0 adult females in the 2-generation reproduction study (≥68 mg/kg/day)
Toxicity Profile (Target Organ)	Nervous system and spleen

2. **Evidence for immunotoxicity from SAR chemicals:** Immunotoxicity studies were not conducted with the sabadilla alkaloids. In the two guideline studies that were submitted for the sabadilla alkaloids (90-day rat and developmental rat), there were no effects indicative of immunotoxicity. In the waiver request document, the registrant stated that due to structural similarity and lack of evidence of immunotoxicity of pyrethroids, sabadilla alkaloids would not be expected to be immunotoxic. As previously stated, the Agency does not consider sabadilla alkaloids to be similar to pyrethroids. Additional information would be needed to support this argument.

3. **Risk assessment considerations:** SABA-10 is in the pre-submission phase, and endpoints have not yet been selected for this chemical. SABA-10 appears to be neurotoxic, particularly through the gavage route. Spleen effects observed in the reproduction toxicity study were not seen in any other study in the database or in studies with the sabadilla alkaloids. The developmental rabbit study provides the most sensitive point of departure (POD) in the database with a no observed adverse effect level (NOAEL) of 15 mg/kg/day and lowest observed adverse effect level (LOAEL) of 25 mg/kg/day based on mortality, abnormal gait, hypoactivity, excessive salivation, and decreased uterine weights in the does, as well as fetal malformations. Spleen effects in the 2-generation reproduction toxicity study occurred at a higher dose (LOAEL = 45 mg/kg/day) than neurotoxicity observed in the developmental rabbit study. It is unlikely

that an immunotoxicity study would provide a lower point of departure for risk assessment.

Based on a WOE approach, considering all the available SABA-10 hazard and exposure data, the HASPOC recommends that an immunotoxicity study be waived at this time. This approach included the following considerations: (1) effects on the spleen were only observed in the 2-generation reproduction study with SABA-10; (2) spleen effects were not observed in any other studies with SABA-10 or studies available for sabadilla alkaloids; (3) neurotoxicity is the predominant effect in the SABA-10 database, with the rabbit being the most sensitive species (4) neurotoxicity occurred at lower doses than spleen effects observed in the 2 generation reproduction study; and (5) it is unlikely that an immunotoxicity study would identify a lower POD for risk assessment. This recommendation is based on the information currently available on the toxicity and proposed use pattern of SABA-10. If any new information is obtained and/or there are changes to the use pattern that would impact this decision, HASPOC may reconsider the need for this study.

c. Subchronic Inhalation Study

The registrant makes several arguments against the need for a subchronic inhalation study (MRID 51250801). The first is the generalization that inhalation exposure to an aerosol, as in the case of SABA-10, produces systemic toxicity similar to that of oral exposures. The registrant states that while inhalation exposures are expected to be more toxic due to direct systemic absorption and lack of first pass metabolism, SABA-10 is an aerosol composed of particles large enough to be deposited in the upper airway. Particles of this size would be trapped in mucous and swallowed, thus resulting in exposure that is more similar to oral exposure. This may occur, however, there is still potential for portal of entry effects that the inhalation lethality study does not evaluate that remain a concern for the Agency.

The registrant also states that the relative toxicity of SABA-10 via the oral and inhalation routes is similar. The registrant estimated the delivered dose (oral dose) using the LC50 from the acute inhalation study for females. The inhalation LC50 for females could not be empirically derived because females were not tested at the low concentration due to mortality at the two higher concentrations. The inhalation LC50 for females was estimated by choosing the value halfway between the two higher air concentrations that could be tested in females (estimated LC50 = 1.275 mg/L). Using the estimated value for females in the calculation, the delivered dose at the LC50 was 235 mg/kg, which the registrant points out is similar to the oral LD50 of 310 mg/kg. However, if one assumes that the LC50 for females would have been similar to that of males by substituting the empirically derived LC50 for males (0.57 mg/L) into the same equation, the delivered dose at the inhalation LC50 would be 105 mg/kg, which is two-fold lower than the oral LD50 of 310 mg/kg. This suggests that SABA-10 may be more toxic via the inhalation route and supports the need for a subchronic inhalation study.

In addition to the above comparison, the registrant's argument that SABA-10 has similar toxicity via the oral and inhalation routes is partly predicated on the registrant's assertion that the sabadilla alkaloids have MOAs that are similar to pyrethroids. The registrant makes reference to a study of 15 pyrethroids conducted by the Agency in 2015 where oral equivalent doses

calculated from inhalation studies were compared to oral PODs used for risk assessment. The registrant states that sabadilla alkaloids behave like the 6 pyrethroids that did not have inhalation PODs that were more sensitive than oral PODs; however, comparison of the equivalent doses from the oral and inhalation lethality studies above suggests that SABA-10 may be more toxic via the inhalation route. Furthermore, the registrant's assertion that sabadilla alkaloids are similar to pyrethroids in structure and MOA is unsupported, as previously discussed.

The registrant proposes to assess portal of entry effects by conducting *in vitro* assays using cultured human airway epithelium. At this time, the *in vitro* assays are being considered in particular cases where data and/or information is available to support their use to evaluate inhalation toxicity. The use of a three-dimensional *in vitro* test system was originally proposed to refine inhalation risk assessment for a chemical known to be a contact irritant (chlorothalonil); however, there is no indication that SABA-10 is a corrosive or irritating chemical. The registrant also mentions in their waiver request that *in vitro* assays are currently being run for MGK-264, pyrethrins, and piperonyl butoxide (PBO). The use of *in vitro* studies for these chemicals is still under consideration and requires review of the data once available. For these chemicals, *in vivo* studies are available demonstrating portal of entry irritant effects in laboratory animals following inhalation exposure. As a result, information on portal of entry inhalation toxicity was already available for these chemicals. This is not the case for SABA-10. Therefore, based on the available information, an approach utilizing *in vitro* assays to evaluate inhalation toxicity is not feasible at this time for SABA-10.

When considering the scientific information available to waive (or not waive) an inhalation study, in the past, OPP has used a set of criteria involving 1) the potential for irritation and corrosivity, 2) the potential for volatilization, 3) aerosol particle size, 4) the acute inhalation toxicity category and 5) an extrapolated MOE (e.g., MOEs 10 times higher than the target). In 2009, OPP developed an issue paper on risk assessment approaches for semi-volatile pesticides[1]. As part of that issue paper, an analysis was conducted on a comparison of oral and inhalation experimental toxicology studies. In general, this analysis showed that the degree to which oral PODs were protective of potential inhalation toxicity varied. In many cases the oral POD was protective, but in some, the inhalation PODs were significantly more sensitive. Currently, OPP uses a weight of the evidence (WOE) approach discussed below which builds upon experience using the previously used criteria listed above and informed by the 2009 SAP[1]. As approaches for route to route extrapolation evolve and improve in the future, OPP may, if appropriate, bring additional considerations into the WOE analysis. Thus, the considerations listed below are not exhaustive, but rather provide an outline of what may be considered in the WOE analysis.

Inhalation exposure can be to vapors, droplets, and/or particles/dusts. The form of this exposure is determined by a number of factors including physical-chemical properties, use pattern, and exposure scenario. This interim WOE approach considers:

[1] Scientific Issues Associated with Field Volatilization of Conventional Pesticides (https://www regulations.gov/document?D=EPA-HQ-OPP-2009-0687-0006)

1. **Physical-chemical properties:**

   SABA-10 is a new formulation of the previously registered sabadilla alkaloids. SABA-10 contains approximately 10% of the alkaloids veratridine and cevadine, approximately 0.22% sabadine, and approximately 0.42% cevine. Physical-chemical property information is not available for SABA-10 or the sabadilla alkaloids. The RED for sabadilla alkaloids indicates that chemical properties were estimated based on quantitative structure activity relationships. Vapor pressure and Henry's law constant are key considerations with respect to the volatilization after sprays have settled. An EFED report referenced in the RED stated that for the sabadilla alkaloids, the vapor pressure and Henry's Law constants are negligible. Although the numerical QSAR estimated vapor pressure values were not reported, the information presented indicates that the potential volatilization from water or from moist soil is very limited, and similarly that the potential for inhalation exposure is minimal. However, low vapor pressure and/or Henry's law constant does not preclude exposure to droplets or particles/dusts. Definitive information regarding the physical-chemical properties of SABA-10 is not available, and the Agency is concerned about inhalation exposure of handlers.

2. **Use pattern & exposure scenarios:** Any application scenario that leads to inhalation exposure to droplets needs to be considered in the WOE analysis for an inhalation toxicology study waiver request. Post-application exposures to particles/dusts should also be considered for workers performing activities in previously treated fields and to individuals in residential homes that have been previously treated. Based on the proposed use pattern described during the pre-submission meeting on July 29, 2020, residential and occupational handlers will be exposed to SABA-10 via inhalation.

3. **Margins of Exposure (MOEs):** The size of the MOEs for inhalation scenarios calculated using an oral toxicity study should be considered in the WOE analysis for an inhalation toxicology study waiver request. In the past, OPP has used MOEs of approximately 10 times higher than the level of concern (LOC) as a benchmark for waiver requests. The 2009 analysis suggests this is ample for most pesticides, but not all. As a result, MOEs 10X over the LOC will be considered in combination with other factors discussed here. This is a pre-submission waiver request. A proposed label has not been provided and the only information regarding the use pattern and application rates was described in a pre-submission meeting with the registrant. Preliminary inhalation MOEs were calculated using an oral point of departure based on the developmental rabbit study, which had a NOAEL of 15 mg/kg/day and LOAEL of 25 mg/kg/day based on fetal malformations. Using the application rates provided at the pre-submission meeting, preliminary MOEs were above 10X the LOC of 100 for all inhalation exposure scenarios. For residential handlers, MOEs ranged from 23,000 to 2,700,00 and from 1,300 to 530,000 for occupational handlers. See Appendix B for a summary of these preliminary inhalation risk estimates.

4. **Inhalation Toxicity:** The only inhalation toxicity information for SABA-10 comes from the acute toxicity studies. SABA-10 does not appear to have irritating properties based on the dermal and eye irritation studies. Based on preliminary review, SABA-10 will be

categorized as Toxicity Category III for acute inhalation toxicity. The LC50 in males was 0.57 mg/L calculated by probit analysis. The LC50 could not be calculated for females because none were tested at the low dose due to high mortality at the two higher doses. In males, at the lowest dose tested (0.055 mg/L), 2/5 males were hypoactive but recovered by day 3. At 0.52 mg/L, 2/5 males and 1/5 females died within 3 days. All animals that died were hypoactive and exhibited ataxia, abnormal respiration, reduced fecal volume, tremors, nasal discharge, abnormal gait and were cold to the touch. Gross necropsy revealed discoloration of the lungs and distention of the stomach and intestines. Survivors exhibited neurotoxic signs similar to those observed in the animals that died, but the animals fully recovered by day 5.

5. **Evidence of Inhalation Toxicity from Related Chemicals:** For considering a waiver request for an inhalation toxicity study, the Agency will evaluate the toxicity database of the chemical under review as well as other pesticides which share the same mode of action (MOA) and/or have structural similarity. These pesticides can provide important information regarding potential inhalation toxicity. Specifically, if other similar pesticides show inhalation toxicity studies to be more sensitive than the oral point of departure, an inhalation toxicity study may be required, depending on the exposure profile. Other toxicological considerations may include, but are not limited to, oral absorption, dose spread, temporal effects and evidence of life stage susceptibility. Irritating or corrosive compounds will be considered in the context of exposure estimates and the likelihood that irritation effects may be more sensitive than a systemic effect.

   SABA-10 has not been assigned to any particular class of pesticides. An acute inhalation toxicity study was conducted with the sabadilla alkaloids (Tox Category IV), but a subchronic inhalation toxicity study was not conducted.

   The registrant has stated that the sabadilla alkaloids in SABA-10 are pyrethroid-like in structure and MOA; however, for reasons stated previously, the Agency does not consider the sabadilla alkaloids to be similar to pyrethroids, and further information would need to be submitted to support this claim.

Based on a WOE approach, the HASPOC recommends that the subchronic inhalation toxicity study be waived at this time for SABA-10. This approach considered all of the available hazard and exposure information for SABA-10, including: (1) physical-chemical properties of the sabadilla alkaloids presented in the RED were estimated based on structure activity relationships; (2) SABA-10 does not appear to have irritating properties based on the dermal and eye irritation studies, and preliminary review of acute toxicity data indicates that SABA-10 will be categorized as Toxicity Category III for acute inhalation toxicity. (3) based on the use pattern and application rates described during the pre-submission meeting with the registrant, preliminary MOEs using an oral POD were greater than 10X the LOC of 100 for all scenarios. The need for an inhalation study may be reconsidered if there are changes to the information presented at the pre-submission meeting, including changes to the use pattern, increased application rates, or changes to the toxicity evaluation.

IV. HASPOC CONCLUSIONS

Based on a WOE approach, considering all the available hazard and exposure data for SABA-10, the HASPOC recommends the subchronic dog study **not to be waived**; the subchronic inhalation study and immunotoxicity studies are **to be waived,** at this time. These recommendations were based on information provided during the pre-submission phase. If changes to the use pattern or new toxicity information becomes available that would impact these recommendations, HASPOC will reconsider the need for these studies.

References

Bloomquist, J.R. 1996. Ion channels as targets for insecticides. Annual Reviews in Entomology 31:163-190.

K. Whitby. October 4, 2011. Pyrethroid Cumulative Risk Assessment. D394576.

Ujvary, I. 2010. Pest control agents from natural products. In: Krieger, R., editor. Hayes' Handbook of Pesticide Toxicology. 3rd ed., Academic Press. pp. 119-229.

APPENDIX A. Preliminary Analysis of the SABA-10 Toxicology Database

Table A.1 Acute Toxicity Profile – SABA-10

Guideline No.	Study Type	Results	Toxicity Category
870.1100	Acute Oral- Rat	F: LD_{50} = 550 mg/kg	III
870.1200	Acute Dermal- Rat	M: LD50 >5,000 mg/kg F: LD50 >5,000 mg/kg	IV
870.1300	Acute Inhalation- Rat	M: LC_{50} = 0.57 mg/L	III
870.2400	Primary Eye Irritation	Mildly irritating	IV
870.2500	Primary Dermal Irritation	Slightly irritating	IV
870.2600	Dermal Sensitization	Not a dermal sensitizer	NA

Table A.2. Subchronic, Chronic and Other Toxicity Profile-SABA-10

Chemical	Guideline No.	Study Type	Doses	Results
SABA-10	870.3465/ 870.6200b	90-Day oral toxicity/Subchronic neurotoxicity (rat)	0, 15, 50, 150 mg/kg/day	Systemic LOAEL = 150 mg/kg/day based on decreased body weight and increased relative brain weights in males and females NOAEL = 50 mg/kg/day Neurotoxicity LOAEL = Not established NOAEL = 150 mg/kg/day

Table A.2. Subchronic, Chronic and Other Toxicity Profile-SABA-10				
Chemical	**Guideline No.**	**Study Type**	**Doses**	**Results**
SABA-10	870.3200	21/28-day dermal toxicity (rat)	0, 250, 500, 1000 mg/kg/day	Systemic LOAEL = not established NOAEL = ≥ 1000 mg/kg/day Dermal LOAEL =500 mg/kg/day based on skin microscopic and macroscopic findings at the site of test article administration and correlating clinical observations NOAEL = 250 mg/kg/day
SABA-10	870.3700	Prenatal developmental toxicity (rat)	0, 35, 75, 150 mg/kg/day	Maternal: LOAEL = 75 mg/kg/day based on hypersalivation (21%) At 150 mg/kg/day: decreased body weight, ataxia, abnormal gait, hypoactivity, irregular respiration, and hypersalivation NOAEL = 35 mg/kg/day Developmental: LOAEL = 150 mg/kg/day based on decreased fetal weights (14%) NOAEL = 75 mg/kg/day
SABA-10	870.3700	Prenatal developmental toxicity(rabbit)	0, 5, 15, 25 mg/kg/day	Maternal: LOAEL = 25 mg/kg/day based on mortality, abnormal gait, hypoactivity, excessive salivation, decreased uterine weights NOAEL = 15 mg/kg/day Developmental: LOAEL = 25 mg/kg/day based on malformations NOAEL = 15 mg/kg/day

Table A.2. Subchronic, Chronic and Other Toxicity Profile-SABA-10				
Chemical	**Guideline No.**	**Study Type**	**Doses**	**Results**
SABA-10	870.3800	Reproduction and fertility effects (rat)	0, 22, 45, 68 mg/kg/day	Parental: LOAEL = 68 mg/kg/day based on decreased spleen weights and histopathology NOAEL= 45 mg/kg/day Reproduction: LOAEL = not established NOAEL = 68 mg/kg/day Offspring: LOAEL = 45 mg/kg/day based on decreased pup body weights and spleen weights in F1 and F2 generations NOAEL = 22 mg/kg/day
SABA-10	870.6200a	Acute neurotoxicity screening battery-oral (rat)	0, 50, 200, 400 mg/kg	Systemic LOAEL = not established NOAEL = 400 mg/kg Neurotoxicity LOAEL = 200 mg/kg based on abnormal gait, slight ataxia, slight hypoactivity, slight hyperactivity, and hypersalivation in females NOAEL = 50 mg/kg

All tables are based on the most up-to-date information available at the time of the HASPOC meeting and are subject to change. Note: These studies have not been formally reviewed, and the conclusions are subject to change.

APPENDIX B. Preliminary Risk Estimates for SABA-10 Occupational and Non-Occupational Inhalation Exposure

Table B.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for SABA-10.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering control	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Inhalation	
										Dose (mg/kg/day)	MOE
Applicator											
Liquid, Trigger-spray bottle, C&C	Residential Living Spaces (homes, apartments)	3660	SL/No G	61.2	No-R	0.54	lb ai/acre	1	acre	0.000478	31,000
Liquid, Trigger-spray bottle, Spot	Landscaping, turf (lawns, athletic fields, parks, etc.)	3660	SL/No G	61.2	No-R	0.54	lb ai/acre	1	acre	0.000478	31,000
Pressurized Liquid, Aerosol can, C&C	Residential Living Spaces (homes, apartments)	190000	SL/No G	1041	No-R	0.54	lb ai/acre	1	acre	0.00814	1,800
Mixer/Loader/Applicator											
Liquid, Backpack, Spot	Landscaping, turf (lawns, athletic fields, parks, etc.)	8260	SL/No G	2.58	No-R	0.76	lb ai/gallon solution	1	acre	0.0000284	530,000
Liquid, Manually-pressurized Handwand, C&C	Residential Living Spaces (homes, apartments)	29000	SL/No G	1044	No-R	0.76	lb ai/gallon solution	1	acre	0.0115	1,300

Table B.2. Residential Handler Non-Cancer Exposure and Risk Estimates for SABA-10.

Scenario	Formulation	Application Equipment/Method	Application Rate	Units	Area Treated or Amount Handled Daily	Units (per day)	Inhalation Unit Exposure (mg/lb ai)	Inhalation Exposure (mg/day) (Rounded)	Inhalation Absorbed Dose (mg/kg/day) (Rounded)	Inhalation MOE (Rounded)
Gardens / Trees	Liquid concentrate	Manually-pressurized handwand	0.0000175	lb ai/ft^2	1200	ft^2	0.018	0.00038	0.0000055	2,700,000
Gardens / Trees	Liquid concentrate	Backpack	0.0000175	lb ai/ft^2	1200	ft^2	0.14	0.0029	0.000043	350,000
Gardens / Trees	Ready-to-use	Aerosol can	0.0000123	lb ai/ft^2	1200	ft^2	3	0.044	0.00064	23,000
Lawns / Turf	Ready-to-use	Aerosol can	0.0000123	lb ai/ft^2	1200	ft^2	3	0.044	0.00064	23,000
Gardens / Trees	Ready-to-use	Trigger-spray bottle	0.0000123	lb ai/ft^2	1200	ft^2	0.061	0.0009	0.000013	1,100,000
Lawns / Turf	Ready-to-use	Trigger-spray bottle	0.0000123	lb ai/ft^2	1200	ft^2	0.061	0.0009	0.000013	1,100,000

All tables are based on the most up-to-date information available at the time of the HASPOC meeting and are subject to change.