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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **June 26th, 2018**

SUBJECT: **Imazalil/Imazalil Sulfate:** Summary of Hazard and Science Policy Council (HASPOC) Meeting on May 17, 2018: Recommendation on the Need for a Comparative Thyroid Assay.

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40 CFR: NA

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Registration Division (7505P)

THROUGH: Evisabel Craig, Ph.D., Co-Chair
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HASPOC
Health Effects Division (7509P)

TO: Krystle Yozzo, Ph.D.
Christina Swartz, Branch Chief
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MEETING ATTENDEES:

HASPOC Members: Elizabeth Mendez, Jonathan Chen, Kelly Lowe*, Michael Metzger, Ray Kent, Chris Schlosser, Anwar Dunbar, Evisabel Craig*
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Presenter: Krystle Yozzo

Other Attendees: Margarita Collantes, Jorge Muniz-Ortiz, Sarah Gallagher, Melinda Wilson, Connor Williams

I. PURPOSE OF MEETING

A draft human health risk assessment is currently being prepared in support of Registration Review for imazalil and imazalil sulfate. The toxicological database for imazalil is complete, however, the database indicates that the thyroid is a target organ. Therefore, it is necessary to determine whether additional data are needed to address uncertainty related to the impact of the disruption of thyroid function during potentially sensitive lifestages (pregnancy, prenatal, and postnatal periods). The Hazard and Science Policy Council (HASPOC) met May 17, 2018 to determine the need for additional data.

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

a. Use and Exposure Profile

Imazalil exists as a base or as its sulfate salt, imazalil sulfate. Imazalil is a systemic imidazole fungicide registered in 1983 to prevent, treat and control diseases caused by a variety of pathogenic organisms (fungi), which include (but are not limited to) Aspergillus in cleaned egg hatchery facilities and equipment prior to introduction of eggs, and blue mold in citrus fruits. Imazalil is formulated as a liquid ready-to-use, pressurized liquid, emulsifiable concentrate, water soluble granule, and impregnated material (used in smoke generators). Imazalil EC end-use products for disinfection of hatchery facilities and equipment are applied as dilute sprays using backpack and mechanical-pressurized handgun sprayers or handheld foggers, while the smoke generator product is applied by igniting the wick of the cannister. It is also applied as a postharvest treatment using foamers, spray brushes, dips, wash tanks, wax and drenches.

On March 4, 2004, imazalil sulfate was registered for use against fungal pests on citrus fruits. It is formulated as a soluble powder, water soluble granule, and a flowable concentrate, and is applied as a postharvest treatment using dip and wash tanks, drenchers, and wax line spray applications.

There is potential for occupational handler dermal and inhalation exposure resulting from post-harvest treatment use of imazalil and its sulfate salt, as well as use of imazalil as a disinfectant of poultry and turkey egg hatchery equipment prior to introduction of eggs. Based on the registered use patterns, short-/intermediate-term dermal and inhalation exposures during the post-harvest

application process (i.e., mixing/loading, applying) for automated conveyer dip/drench/spray treatments, sprays to loaded truck-bed with powered handguns, and disinfection of egg hatchery facilities and equipment are anticipated. Long-term exposure is also anticipated for hatchery handlers as well. There is also potential short-/intermediate-term post-application exposure for people handling treated citrus (i.e., sorting, culling, and packing). Additionally, for workers in the warehouse or packaging facility not directly involved in the automated treatment process, there is potential for indirect inhalation exposure. Long-term occupational exposures are not anticipated for conventional pesticide use.

Applicators and other handlers involved in post-harvest activities must wear baseline clothing (long-sleeved shirt, long pants, socks, and shoes) and personal protective equipment (PPE) ranging from use of chemical resistant gloves to the addition of protective eyewear. One end-use product also requires the use of coveralls and an organic vapor respirator. All handlers involved in disinfection of poultry and turkey egg hatchery equipment must wear baseline clothing (long-sleeved shirt, long pants, socks, and shoes) and in one case, PPE consisting of a chemical resistant apron. Handlers entering the treated areas before the ventilation period is over must wear baseline clothing, gloves, protective eyewear and either dust/mist or organic vapor respirator depending on the end-use product.

A quantitative spray drift assessment is not required for any imazalil or its sulfate salt products, since the potential for exposure resulting from spray drift is anticipated to be negligible based on the use profile. Additionally, imazalil is registered for occupational uses only, so residential exposure is not expected and will not be assessed.

b. Toxicity Profile

Imazalil and its sulfate salt are considered to be toxicologically equivalent. The target organs for imazalil are the liver and thyroid. Liver effects were observed after both subchronic and chronic oral exposure in mice, and chronic exposure in rats. In mice, subchronic exposure led to alterations in liver microsomal protein and microsomal cytochrome P450 content along with increased incidence of gross (dark livers) and histopathological (large and/or small vacuoles in the hepatocytes) findings. Chronic exposure also resulted in liver histopathology (increased incidence of focal cellular changes, large vacuoles, and swollen sinusoidal cells in the liver) at a similar dose. In the absence of corresponding changes in clinical chemistry, the findings are considered adaptive. Moreover, liver neoplasm was noted in males in the rat and mouse carcinogenicity study. In rabbits, swollen livers were observed after dermal exposure to 250 mg/kg/day (preliminary study only). No liver effects were observed in the definitive dermal study; however, the study tested doses up to 160 mg/kg/day. Thyroid effects were observed in male rats after chronic exposure and consisted of increased absolute and relative weight as well as microscopic changes in the affected thyroids. Other effects commonly observed in the toxicity database included decreased body weights in the subchronic and developmental rat studies and the dog chronic toxicity study, mortality at the higher doses tested in the mouse (≥80 mg/kg/day) and rabbit (≥20 mg/kg/day) developmental toxicity studies as well as pup mortality (birth to post-natal day 4) in the rat two-generation reproductive toxicity study (≥80 mg/kg/day).

Neurotoxicity was observed in the rat ACN at the highest dose tested; however, this may be an agonal effect since the clinical observations that included yellow material in the abdomen, hypoactivity, tremors, hunched posture, prostration and /or increased respiration were observed prior to or on the day of death. Decreased motor activity and alternations in the functional observational battery (soiled fur, crusty deposits around nose, low arousal, gait changes, and no touch, olfactory or approach response) were also observed in female animals at the time of peak effect on the day of dosing. There were no neurotoxic effects observed in males, and signs of toxicity were limited to decreased body weight gain and food consumption at the highest dose tested (600 mg/kg/d). There was no other evidence of neurotoxicity in the imazalil database. The HASPOC determined that the subchronic neurotoxicity (SCN) and developmental neurotoxicity (DNT) studies (TXR#0056756, J. Leshin, 9/19/2013), as well as the immunotoxicity study are not required at this time (TXR#0056730, U. Habiba, 8/13/2013).

In the prenatal developmental toxicity studies in mice and rabbits, the most common effects noted were increased resorptions, post-implantation loss, and reduced litter size. Other developmental and offspring effects observed in the database included decreased fetal weight (rat developmental toxicity study), pup mortality (rat two-generation reproduction study), and an increased incidence of fetuses and litters with extra 14th pair of ribs (mice only). Imazalil did not cause reproductive toxicity in the rat. Qualitative and quantitative sensitivity/susceptibility was not observed in the database.

III. STUDY WAIVER REQUESTS

a. Comparative Thyroid Assay

A number of pesticides have been shown to perturb thyroid hormone homeostasis *via* reduction of circulating thyroid hormones[1]. This perturbation may be the initial, critical effect leading to adverse effects on the developing nervous system[2,3]. When a chemical causes thyroid effects, there is inherent uncertainty about potential impacts to the developing brain in response to changing thyroid levels. There is also a lack of empirical data on whether pregnant women or the fetus are more or less susceptible, compared to adults, to the impact of chemicals that alter thyroid hormone homeostasis. This gap makes predictions on developmental susceptibility based on data from adult organisms challenging. EPA has developed guidance for conducting a comparative thyroid assay[4] that uses a mechanistic approach to generate thyroid-specific data which can address the uncertainties associated with lifestage susceptibility and allow for the establishment of PODs that would be protective of potential effects of thyroid function

[1] Hurley et al. 1998. Mode of carcinogenic action of pesticides inducing thyroid follicular cell tumors in rodents. Environ. Health Perspect. 106(8): 437-445.
[2] Chan S and Kilby MD. 2000 Thyroid hormone and central nervous system development. J Endocrinol 165:1-8
[3] Fisher DA. 2000. The importance of early management in optimizing IQ in infants with congenital hypothyroidism. J Pediat 136:274-274.
[4] US EPA 2005. Guidance for Thyroid Assays in Pregnant Animals, Fetuses and Postnatal Animals, and Adult Animals. Washington, DC.
[5] Morreale de Escobar, G, Obregón, MJ, Escobar del Rey, F. 2004. Maternal thyroid hormones early in pregnancy and fetal brain development. Best Practices & Research Clinical Endocrinology & Metabolism, Volume 18, Issue 2: 225-248.

disruption in pregnant females on the fetus and newborn. The need for a comparative thyroid assay is based on the following considerations:

1. **Evidence for thyroid toxicity in the imazalil database:** Following chronic oral exposures to rats, macro and microscopic effects in the thyroid, without effects on thyroid weight, were observed in males at the same doses as the liver effects. The thyroid effects observed in males at the LOAEL of 65.8 mg/kg/d included swollen thyroid (15/50), increased tissue mass (2/50), and cystic focal follicular hyperplasia (13/50). No adverse effects on thyroid weights and hormones were observed following inhalation exposure in rats at the highest dose tested (0.20 mg/L; equivalent to an animal equivalent dose [AED] = 13.2 mg/kg/day; assuming a rat body weight of 0.225 kg). Additionally, no adverse effects on thyroid weights were observed following dermal exposure in rabbits, subchronic oral exposure in rats, or in the other available studies in dogs, mice, or rabbits.

2. **Margins of Exposure (MOE):** For the draft human health risk assessment for imazalil, the point of departure (POD) selected for evaluating inhalation exposure was not based on thyroid effects and no thyroid effects were observed up to the highest dose tested (0.20 mg/L); therefore, there is low concern for thyroid sensitivity following inhalation exposures. Furthermore, using the POD from the inhalation study, post-harvest handler MOEs ranged from 440-19,000,000 and hatchery handler MOEs ranged from 280 to 83,000 with a level of concern (LOC) of 30, so there are no risks of concern for handlers.

   There are no non-cancer occupational post-application risk estimates of concern associated with post-harvest use of imazalil. Post-application inhalation MOEs for sorters and packers resulted in a MOE of 320 with no respirator. Post-application inhalation exposure to other workers not directly involved in the process based on ambient air monitoring resulted in an inhalation MOE of 7,000 with no respirator. However, the non-cancer post-application disinfection of hatchery MOE for the smoke application is 3 when the ventilation rate is 0.5 air changes per hour (ACH) as specified on the label. The MOE for the smoke application is 30 when the ventilation rate is 1.3 ACH and is not of concern. The MOE for the fog application is 230 when the ventilation rate is 0.5 ACH and is not concern.

   The post application risks associated with hatchery use are driven by the low ventilation rates that are specified on the imazalil labels. Hatchery facilities have high ventilation rates to ensure high hatching rates and low chick mortality. For example, the product label for SynergizeTM (66171-7), which contains glutaraldehyde and ADBAC, lists application rates and reentry intervals for Hatchery Room Incubators and Hatchers that have air change rates ranging from 8 to 24 ACH. If these ventilation systems are activated immediately after an imazalil application, the resulting exposures will be much lower than was estimated using the ventilation rates specified on the imazalil labels. Thus, the MOEs are expected to be above the LOC with typical ventilation rates.

   A quantitative risk assessment was not conducted for incidental oral (lack of exposure via this pathway) or dermal (lack of toxicity via this pathway) exposures.

3. **Chronic Population-Adjusted Doses:** In the Registration Review draft human health risk assessment, the chronic population-adjusted dose (cPAD) of 0.11 mg/kg/day was based on the NOAEL of 10.8 mg/kg/day from the rat carcinogenicity and a 100-fold uncertainty factor (10X for interspecies extrapolation, 10X for intraspecies variation, and 1X for Food Quality Protection Act Safety Factor). The LOAEL of 65.8 mg/kg/day was based on reductions in body weight and weight gain and macro and microscopic effects in the liver (M/F) and thyroid (M). The chronic dietary assessment was refined using PDP monitoring data for citrus and banana commodities. In the chronic assessment, all population subgroups used <1% of the cPAD.

4. **Aggregate Risk Estimates:** In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. For imazalil, there are no residential or drinking water exposures expected based on the use pattern. Therefore, aggregate risk is equivalent to chronic dietary (food only) risk.

IV. HASPOC CONCLUSIONS

Based on a WOE approach, the HASPOC concludes that a comparative thyroid assay in rats (comparing pregnant animals, fetuses, postnatal animals, and adult animals) is not required for imazalil. This approach considered all of the available hazard and exposure information for imazalil, including: (1) the hazard database includes thyroid effects in the carcinogenicity study in rats at the study LOAEL, but there is no concern due to the 6x dose-spread between the NOAEL and LOAEL; (2) the point of departure (PODs) selected for evaluating inhalation exposure were not based on thyroid effects, and incidental oral and dermal risk assessments were not required; and (3) chronic dietary risk is low (%cPAD values ≤1% for all subpopulations). If there are updates to the risk assessment that would have a considerable impact on the risk estimates for imazalil, the need for this study will need to be reevaluated.