OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

WASHINGTON, D.C. 20460

January 25th, 2024

MEMORANDUM

SUBJECT: Mancozeb: Response to Public Comments on the Draft Human Health Risk Assessment in Support of Registration Review.

PC Code: 014504
Decision No.: 561555
Petition No.: NA
DP Barcode: D463514
Registration No.: NA
Regulatory Action: Registration Review/ Response to Comments
Risk Assessment Type: Single Chemical Aggregate
Case No.: 643
TXR No.: NA
CAS No.: 8018-01-7
MRID No.: NA
40 CFR: §180-176

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THROUGH: Kelly Lowe, Acting Branch Supervisor
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TO: Ben Tweed, Review Manager
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Introduction

The Pesticide Re-evaluation Division (PRD) has requested that the Health Effects Division (HED) respond to comments received on the December 2020 mancozeb draft human health risk assessment (DRA)

prepared to support Registration Review (EPA Docket: EPA-HQ-OPP-2015-0291).[1] HED has responded below only to the HED-relevant comments from the Mancozeb Task Force (MTF) [EPA-HQ-OPP-2015-0291-0079], the United States Department of Agriculture (USDA) [EPA-HW-2015-0291-70], the National Agricultural Aviation Association (NAAA) [EPA-HQ-OPP-2015-0291-0064], and UPL NA Inc. (UPL) [EPA-HQ-OPP-2015-0291-0080]. The subject comments are either summarized or directly copied below followed by HED's responses.[2] Any submitted comments regarding typographical errors, minor editorial changes, and references, are not directly addressed in the responses below; however, those corrections and edits will be considered for inclusion in future updated documents for mancozeb Registration Review.

Mancozeb Task Force (MTF) Comments [EPA-HQ-OPP-2015-0291-0079]

Hazard/Toxicology

MTF Comment: "*The correct study to assess ^{14}C-ETU dermal absorption in rats is by DiDonato and Longacre 1987. The study consisted of a range-finding study and a definitive study. The most relevant group for calculation of dermal absorption is Group C. In this group, ETU was applied at 0.65 µg/cm^2 for an exposure period of 10 hours and study duration of 7 days. This is an excellent study since not only was the dermal absorption calculated by the recovery method, it was also determined by the percent of dose eliminated in the excreta (urine, feces, and cage wash) of dermally dosed rats divided by the percent of dose eliminated in the excreta of iv dosed rats. Both aspects of the study design and results, the excretion method and the recovery method, support one another*."

"*Historically EPA has used 26% as the dermal absorption value of ETU. This is based on the average of the excretion and the recovery methods used to calculate absorbed dose by the study authors, excluding skin bound residues in the 10-hour skin wash, 7-day sacrifice, low dose group (10 hr/7 day, 0.65 µg/cm2), Appendix H of the study report. For Group C, the percent of the dermal dose absorbed based on the excretion method is 23% and for the recovery method it is 29%, (23% + 29%)/2 = 26%)*."

HED Response: The Agency agrees that the DiDonato and Longacre 1987 study is appropriate to establish a dermal absorption factor (DAF) for ETU. This study was used to derive the 51% DAF presented in the most recent human health risk assessment; however, the MRID was reported incorrectly. When an updated assessment is conducted, the MRID will be properly cited as MRID 40312601. The Agency acknowledges that this is the best available data for ETU; however, there were inconsistencies identified within the study, which included, but were not limited to, the varying amount of radioactivity detected in the urine, ring wash, and application site for the Group C animals, the higher concentration of radioactivity detected in cumulative excreta over time for animal 10281-12 as compared to others, and the higher concentration of radioactivity detected in the tissues of animal 10772-39 as compared to other animals. Regardless, the Agency does not believe the use of this study will underestimate the dermal absorption of ETU.

[1] D. Drew *et al*., 12/14/2020, D457305, Mancozeb and Ethylene Thiourea (ETU): Draft Human Health Risk Assessment (DRA) for Registration Review.

[2] Full comment documents can be found in the Docket (ID: EPA-HQ-OPP-2015-0291)

Under current practice, the Agency does not estimate dermal absorption using data from iv dosed rats. The Agency does agree that the best group for estimating dermal absorption is Group C (0.65 µg/cm^2 dose, 10-hour skin wash, and 7-day sacrifice). The absorbed dose includes the radiolabeled compound recovered from the urine, urine funnel wash, feces, cage wash, carcass, and application site from animals 10264-11, 10281-12, and 10255-14. The sum of the radioactivity provides a dermal absorption factor of 46%. Animal 10253-13 was excluded due to the low overall radioactivity recovered (43.7%) and the discrepancy of this recovery compared to the other three animals tested.

The application site was included in the total absorbed dose because after the 10-hour skin wash, radioactivity was continually detected in both urine and feces. The Agency does acknowledge a steady increase in the cumulative total radioactivity detected in excreta from the 10-hour wash to day 3, at which time the absorption begins to plateau; however, there is still a slight increase in the radioactivity detected in cumulative excreta from days 3-7. Examining the Group G animals, which were also exposed to a 0.65 µg/cm^2 dose for 10 hours, provides evidence that the radioactivity is not highly sequestered in any particular organ or tissue; therefore, it's possible that the increase in radioactivity detected in excreta over time isn't attributable to radioactivity that was sequestered in tissues. If the amount of compound present in the application site after 3 days did not enter systemic circulation, and there was no sequestration of radioactivity to any particular organ or tissue, the expectation would be for the amount of radioactivity recovered in whole blood and excreta to decline between days 3 and 7 post-exposure. Instead, the radioactivity detected in whole blood samples for the Group C animals remained consistent across the seven-day sampling period. It's possible that a steady-state balance may have occurred from a continual "slow drip" from the application site into systemic circulation. Therefore, including the application site as part of the absorbable dose is most appropriate for this study. As the total recovery, excluding animal 10253-13, was ~93%, a correction for low recovery is not required. Therefore, based on the currently available data, the appropriate DAF for the ETU risk assessment is 46%.

The Agency does recognize that using the available *in vivo* study is conservative given that tape-stripping of the animals was not performed. However, because it's the only available data, the Agency concludes a DAF of 46% is protective and does not underestimate the dermal absorption of ETU. In order to better refine the ETU DAF, the Agency recommends the submission of a human *in vitro* dermal penetration study. EPA has completed a retrospective analysis of dermal triple pack data, which demonstrated that the *in vitro* studies alone provide similar or more protective estimates of dermal absorption, with only limited exceptions[3]. As a result, a human *in vitro* dermal penetration study alone, conducted in accordance with Organization for Economic Co-operation and Development (OECD) 428 guidelines, may be used to derive a DAF. Newly generated dermal absorption data submitted to the Agency will be reviewed and the DAF re-evaluated in the context of the new data. In addition, any relevant updates to the DAF will be incorporated into a revised human health risk assessment.

MTF Comment: "*Skin bound residues were excluded from the calculation of the percentage of dermal absorption since these data meet the OECD criteria for non-inclusion of the application site skin in the absorption of ETU (OECD guidance note 156, 2011; Section 7.1.3, pages 35-37). Cumulative ^{14}C-activity excretion in urine and feces reached a plateau by the 3rd day of study and was completed in 7 days*

[3] Allen et al. (2021) "Retrospective analysis of dermal absorption triple pack data", *ALTEX - Alternatives to animal experimentation*. doi: 10.14573/altex.2101121.

(Figure 5 from DiDonato and Longacre 1987). This meets the OECD 2011 criteria of completion of absorption following a 10-hour dermal application of 2.6 µg 14C-ETU. In addition, there was no increase in blood concentration after day 1 of study (Figure 9 from DiDonato 1987)."

HED Response: The Agency notes that the OECD criteria for non-inclusion of the application site skin is not agreed upon by all regulatory authorities and has not been validated as stated in the OECD guidance document, "*This approach has not been validated with use of real-world data at the time of publication of this guidance document and is based on the expert opinion of the EGDA.*" At this time, the EPA does not utilize the OECD criteria approach on this issue, and instead prefers to compare the decrease in radioactivity at the application site to an increase in radioactivity detected in excreta.

MTF Comment: *"The toxicological point-of-departure in the ETU Extended One Generation Reproduction and Toxicity Study ("EOGRTS") should be changed"…"U.S. EPA defines an adaptive response as a process whereby a cell or organism responds to a xenobiotic without impairment of function"…."In the EOGRTS, low dose exposure at 0.2 mg/kg/day did not significantly alter the thyroid disruption adverse outcome pathway based on the observations of no significant changes in organ weight, inconsistent hormone changes only at PND 4 and limited thyroid and pituitary histopathology observations"…"At 0.2 mg/kg/day ETU, the very slight thyroid and slight pituitary hypertrophy in P1 males denoted an adaptive response to stimulation of the hypothalamic-pituitary-thyroid axis in order to reestablish thyroid hormone homeostasis."*

HED Response: The Agency continues to support a parental and offspring lowest observed adverse effect level (LOAEL) of 0.2 mg/kg/day based on an increased incidence of diffuse follicular cell hypertrophy of the thyroid and hypertrophy of the pars distalis of the pituitary in males [parental generation] and an increase in the incidence and severity of hypertrophy of individual cells of the pars distalis of the pituitary in males, increased TSH in both sexes and decreases in T_4 in postnatal day (PND) 4 pups, and diffuse follicular cell hypertrophy of the thyroid in males [offspring generation]. This conclusion is based on a weight of evidence analysis that considered not only the studies submitted by the registrant but also peer reviewed literature studies including the Maranghi *et al.* publication[4]. In that study, sixty dams were treated daily by gavage administration during pregnancy (gestation days (GDs) 7-20) and lactation ((PNDs 1-22) with 0, 0.1, 0.3, or 1.0 mg/kg/day ETU. The F1 offspring were treated with the same dosing regimen from weaning (PND 23) to sexual maturation (PND 60 for males; PND 70 for females). Histological and histomorphometrical analyses of the thyroid were conducted in dams on PND 23. This data concluded there was an increase in vacuolization of epithelial cells, a reduction in follicular lumen size, a reduction and/or absence of colloid within the same thyroid follicles, a decrease in colloid area, an increase in follicular epithelium height, and a decrease in follicular size at doses ≥0.1 mg/kg/day. Similar histopathological responses were also observed in F1 males and females (PND 23 and/or PND 60 (males); PND 75 (females)). The histology and histomorphometrical analyses conducted in the Maranghi *et al.* article are considered more robust compared to the thyroid histology conducted in the ETU extended one-generation reproductive toxicity study (EOGRTS).

ETU was also screened in the ToxCast program for bioactivity in over 1000 assay endpoints covering myriad *in vitro* biological targets (Kavlock *et al.*, 2012), including high-throughput screening assays for thyroperoxidase (TPO) inhibition and nonspecific protein inhibition (Paul Friedman *et al.*, 2016; Paul *et al.*, 2014). The Amplex UltraRed (AUR)-TPO assay, which is used to detect chemicals that inhibit TPO,

[4] Maranghi, F. *et al*. (2013). Reproductive toxicity and thyroid effects in Sprague Dawley rats exposed to low doses of ethylenethiourea. Food and Chemical Toxicology. 59: 261-271.

was positive for ETU, with a 50% activity concentration (AC50) of 7.76 µM. The nonspecific protein inhibition assay (CCTE_Simmons_Quantilum_inhib_2_dn) run in parallel to the AUR-TPO assay (Paul Friedman, *et al.*, 2016) was also positive in a similar concentration range (2.14 µM) (Table 1, Appendix). ETU did demonstrate greater efficacy and stronger potency than most chemicals screened in the AUR-TPO assay that were positive. Compared to 6-propyl-2-thiouracil (6-PTU) (DTXSID5021209), ETU was slightly less efficacious and less potent by approximately an order of magnitude (Figure 1, Appendix).

Observation of bioactivity in the AUR-TPO assay, and other assay endpoints, in the same low micromolar range as other publications (Doerge, et al., 1990; Tater, et al., 2021) suggests that *in vitro*, one can expect bioactivity and TPO inhibition in this 1-10 micromolar range. Taking all of the ToxCast AC50 values for ETU (ToxCast database invitrodb, version 3.4, to be released Sept 2021), and using reverse dosimetry and generalized toxicokinetic models (Pearce *et al.*, 2017a; Pearce *et al.*, 2017b; Wambaugh *et al.*, 2018) to estimate administered equivalent doses (AEDs), suggests that TPO inhibition in the AUR-TPO assay (with an AC50 of 7.76 µM) may correspond to a mg/kg/day oral dose estimated as approximately 0.2 mg/kg/day in an average human adult (Figure 2, Appendix)[5]. Interestingly, this AED corresponds to the LOAEL established in the ETU EOGRTS, providing further supporting evidence to maintain the LOAEL at 0.2 mg/kg/day.

MTF Comment: *"The FQPA Safety Factor should be reduced to at most 3X"…"The 10X default FQPA SF over-estimates the risk associated with ETU chronic dietary exposure"…"As a result, the uncertainty factors for ETU chronic dietary, incidental, dermal, and inhalation should be 90X (3X to account for inter-species extrapolation, 10X to account for intra-species variation, and 3X FQPA SF)."*

HED Response: The Agency disagrees with the conclusion that the 10X FQPA SF should be reduced to 3X. There still remains uncertainty as to the offspring NOAEL in the ETU EOGRTS, which is further enhanced by the offspring histopathological data presented in the Maranghi *et al.* publication at dose levels ≥0.1 mg/kg/day and ETU's known antithyroid properties.

Occupational and Residential Assessment

MTF Comment: Several of the MTF comments were regarding the residential post-application scenarios. The Task Force noted that the registrants market their products in the golf course and commercial sod farm markets where the need for disease control is greatest. Thus, exposures by children in those other scenarios are unlikely. Additionally, the Task Force notes mancozeb products for use on ornamentals are marketed strictly to professional, commercial, and/or production nurseries and greenhouses, not to homeowners or for direct applications to residential sites and members are willing to make additional label changes if needed to clarify the use of mancozeb products.

HED Response: HED appreciates the additional information regarding potential residential use sites assessed. HED agrees that updated label language would address and remove the need for a residential post-application exposure assessment for all use sites with the exception of golf courses. As golf course

[5]This AED estimation makes a number of assumptions, including the use of the nominal assay concentration, no extrahepatic metabolism and hepatic metabolism is first order, renal clearance is proportional to glomerular filtration rate, no biliary excretion or enterohepatic recirculation occurs, and 100% bioavailability (all of an oral dose is received by the liver through the portal vein). The calculations were performed using the publicly available R library "httk," for high-throughput toxicokinetics (v2.0.4), assuming the median human individual in terms of interindividual toxicokinetic variability, restrictive clearance, and a three-compartment steady state model.

is a registered use, post-application exposure for the following age ranges would still be included in the assessment: adults, youth (11 to <16 years old), and children (6 to <11 years old) per the 2012 Residential SOPs.[6]

MTF Comment: Several comments from the Task Force were related to the Agency use of a DAF of 51% for calculation of all residential and occupational dermal cancer and non-cancer ETU exposures. The Task Force believes that the DAF should be changed to 26%.

HED Response: See HED response regarding DAF under *Hazard/Toxicology* section above.

MTF Comment: For purposes of calculating golfing exposure the Mancozeb Task Force has replaced 52 days of exposure per year with 19 days of exposure per year as cited by the "Reregistration Eligibility Decision for Mancozeb, September 2005". This value was based on data supplied by the National Golf Federation.

HED Response: HED appreciates the additional information for days of golf course exposure per year and would welcome further information to refine the cancer risk associated with golf course exposure. The current assumption from HED assumes exposure one game per week with 52 exposures per 365 days.[7] HED believes this to be a more appropriate assumption than 19-20 days as it is more representative to protect a wide range of golf players including recreational (less frequent) and professional (more frequent) players. The 2020 data from the National Golf Federation gives no indication as to what type of player was included in the data (recreational, professional, age groups, etc.), if there are additional years of data available, what temporal areas were included in the data, etc. which could potentially be utilized to refine this assessment.

MTF Comment: On page 61 of the DHHRA, the Agency states: "Maximum applications rates were used in this assessment, although for the cancer assessment typical rates may be more representative." The Mancozeb Task Force concurs with this statement and will work with the Agency to gather appropriate information related to typical application use rates for mancozeb.

HED Response: OPP's Biological and Economic Analysis Division (BEAD) is currently working to obtain typical use rates for several mancozeb use scenarios. Where available and appropriate, HED will update the cancer assessments using typical use rate refinements.

UPL NA Inc. Comments [EPA-HQ-OPP-2015-0291-0080]

Occupational and Residential Assessment

UPL Comment: For concerns related to applications with backpacks and mechanically pressurized hand-guns, the Agricultural Handler Exposure Task Force (AHETF) recently completed a new survey on pesticide use with hand-held equipment in U.S. greenhouse and nursery facilities (Bruce, 2019) that has been submitted to EPA. The report indicates that the default assumption of 1000 gallons per day of material handled for handgun pesticide application is approximately 2.5 times larger than even 95th

[6] http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

[7] ExpoSAC Meeting Minutes, February 9, 2017.

percentile of typical values. We encourage EPA to take this information into account for Mancozeb and ETU.

HED Response: HED did assess greenhouse and nursery facilities with the recent AHETF survey on pesticide use with handheld equipment which includes the amount handled of 300 gallons per day for nurseries and 175 gallons per day for greenhouses (Bruce, 2019; MRID 50821601). The data utilized for orchard/vineyard, landscaping (trees/shrubs/bushes), and typical acreage field crops is more representative for these use sites than the greenhouse and nursery study, which accounts for 1000 gallons per day (AHETF; MRID 49478602). The data are considered the most reliable data for assessing exposure and risk to individuals applying liquid spray pesticides via handgun sprayer in utility rights-of-ways (ROW) or areas of similar terrain and foliage/vegetation (shrubs/bushes/vines/etc.).

Residue Chemistry and Dietary Assessment

UPL Comment: *"Without receiving EPA's source and calculations for metiram import data, it is not possible for UPL to determine if the computed risk for metiram imports (estimated 15% of bananas and 35% of grape wine) was calculated accordingly throughout this risk assessment."*

HED Response: Import share of consumption estimates for bananas and grape wine (bottled) treated with metiram were provided by BEAD and incorporated into the HED dietary assessment for refinement. See Attachment 12 (BEAD Analysis of Import Share of U.S. Consumption of Bananas and Wine (Grapes) for Mancozeb and Metiram) of the 12/14/2020 mancozeb dietary risk assessment to view BEAD's memorandum which details the sources and rationale for the banana and grape wine import consumption estimates.[8]

UPL Comment: *"When EPA National Pesticide Standards Repository (NPSR) requests replenishment of analytical standards for mancozeb, UPL will provide."*

HED Response: HED works with the EPA National Pesticide Standards Repository (NPSR) to ensure analytical standards are available for monitoring established pesticide tolerances. The HED draft assessment therefore serves as an official request for the replenishment of analytical standards for mancozeb.

UPL Comment: *"SLN labels will be drafted and submitted by UPL to applicable states to include a maximum total rate of mancozeb that can be applied to tobacco. For both Manzate Pro-Stick and Penncozeb 75DF, the maximum use rate is 2.0 lb per acre (1.5 lb mancozeb per acre) with maximum annual use rate of 12.0 lbs per acre (9.0 lbs mancozeb per acre per year)."*

HED Response: HED appreciates UPL's cooperation in drafting labels specifying the pattern of use followed for treating tobacco with mancozeb to allow for the evaluation of the available tobacco field

[8] P. Savoia, 12/14/2020, D459634 & D459635, Mancozeb. Acute, Chronic, and Cancer Dietary Exposure and Risk Assessments of Food and Drinking Water for the Ethylene Bisdithiocarbamate (EBDC) Fungicide Mancozeb, as well as Aggregate Dietary Assessment of the Common Metabolite/Degradate Ethylene Thiourea (ETU) Resulting from the Combined Uses of the EBDC Fungicides Mancozeb and Metiram to Support Registration Review.

trial data. HED reminds UPL to also include the specified interval followed for retreatment as well as the pre-harvest interval on the product labeling.

UPL Comment: *"UPL is providing an academic research publication on mancozeb pyrolysis. Pyrolysis of Mancozeb takes place between 20 ◦C and 950 ◦C and lead essentially to CS2 and H2S emissions with formation at 950 ◦C of MnS and ZnS. The purpose of this study is to help risk assessment during storage fire incidents, but may also be applicable with risk assessment for pesticide registration."*

HED Response: Guideline 860.1000 specifies the residue chemistry studies required to assess the exposure of humans to residues on tobacco. One such study is a pyrolysis study which is to be conducted in a similar manner to a plant metabolism study by identifying and characterizing the pyrolysis products resulting from the total toxic residue. Unfortunately, the provided academic research publication does not satisfy this data requirement for pyrolysis study as it does not characterize the fate of residues in burning cigarettes using a radiolabeled mancozeb test substance.

UPL Comment: *"UPL will draft current SLN labels to include the specified maximum total seasonal rate allowed for treating tobacco with mancozeb and submit to the applicable states. However, UPL respectfully disagrees that the residue data submitted for safflower seed (Budgeon, 2018) is inadequate. The study (MRID) was conducted at 0.0010 lb ai/cwt. Hundredweight converted to pound active ingredient is 0.112 lb mancozeb."*

HED Response: HED appreciates UPL's cooperation in drafting labels specifying the pattern of use followed for treating tobacco with mancozeb to allow for the evaluation of the available tobacco field trial data. Regarding the residue data submitted for safflower, HED has re-evaluated calculation of the rate based on seed conversion and will re-evaluate the safflower data that has been provided accordingly.

UPL Comment: *"UPL respectfully disagrees with EPA that the confined rotational crop study was conducted at an insufficient rate. The target application rate was 3.9 kg/ha (3.5 lb/acre) which is the approximate maximum seasonal use rate. For example, the maximum labeled use rates by crop for Manzate Pro-Stick Fungicide, EPA Registration No. 70506-234, are all below 3.5 lb/acre as noted in the table that follows."*

CROP USE SITE	LB PER ACRE	LB AI PER ACRE
Asparagus	2.0	1.5
Barley, Oat, Rye, Wheat	2.0	1.5
Broccoli	2.1	1.6
Cabbage	2.1	1.6
Corn	2.5	1.1
Cucurbit	3.0	2.3
Lettuce	2.1	1.6
Peanut	2.0	1.5
Pepper	3.2	2.4
Potato	2.0	1.5

*Labeled tree nuts and permanent crops (i.e. banana) are not included as they are not rotated.

HED Response: The rates for the crop use sites listed by UPL are the corresponding maximum single application rates that can be applied at one time for treating these crops. Guideline 860.1850 specifies that confined accumulation in rotational crops studies are to be conducted at the maximum seasonal label rate (1x) using a radiolabeled test substance applied to the appropriate soil type (usually a sandy loam) using three rotated crops (small grain, leafy vegetable, and root crop) planted at the appropriate soil aging interval (1, 4, and 12 months). Upon review, the highest total seasonal rates for labeled crops treated with mancozeb which can be grown in rotation include corn at 18 lb ai/A/season, cucurbit vegetables at 19.2 lb ai/A/season, and dry bulb onions at 24 lb ai/A/season. As dry bulb onions are grown in rotation at the highest seasonal rate, the confined rotational study should be conducted at the corresponding seasonal rate of 24 lb ai/A/season, and not 3.5 lb ai/A.

UPL Comment: *"Whereas UPL appreciates that HED is considering global harmonization for mancozeb tolerance, UPL remains in agreement that any attempt to harmonize should be deferred until reviews are complete. UPL kindly requests that EPA consult with the industry, and other key stakeholders possibly as a 60-day comment period, before making any changes to mancozeb tolerances in the U.S."*

HED Response: HED appreciates that UPL agrees with EPA's decision to defer its consideration of tolerance harmonization until both Canada and Codex complete their respective re-reviews of the ethylenebis dithiocarbamate (EBDC) fungicides.

NAAA Comments [EPA-HQ-OPP-2015-0291-0064]

Occupational and Residential Assessment

NAAA Comment: NAAA is concerned that the Tier 1 level is being used in the AgDRIFT drift models for the risk assessments of mancozeb. The assumptions made in the Tier 1 model do not accurately reflect how modern agricultural aircraft are setup to apply pesticides. NAAA recommends using the Tier 3 model instead with the assumptions described in our letter sent to the EPA in June of 2020.

HED Response: EPA appreciates the additional information on aerial application practices and continues to work with the industry to update and improve modeling methods to better reflect such practices. At this time, HED plans to continue to use Tier I assumptions in its spray drift modeling. This approach has been through a public comment process and relies on both default assumptions as well as chemical-specific label instructions. The resulting outputs provide risk estimates for a variety of nozzle types and spray configurations, taking into account potential drift reduction strategies. While HED intends to continue to use the current modeling approach at this time, we would welcome further discussion and information on the proposed approach, including consideration of implementation strategies for any revised approach such as label language and a consideration of a standard set of best practices for aerial applicators to prevent drift.

USDA [EPA-HQ-OPP-2015-0291-0070]

Occupational and Residential Assessment

USDA Comment: USDA notes that the Agricultural Handler Exposure Task Force (AHETF) provided EPA with data on mixing and loading pesticides in enclosed systems. The AHETF study better represents handler exposure in current closed system environments and is expected to serve as a reliable replacement for the existing Pesticide Handler Exposure Database (PHED) scenario. USDA understands that EPA recently finalized its review of this data and is in the process of updating its exposure surrogate reference table and occupational pesticide handler exposure calculator. In light of these new data, we request that EPA update its risk estimates for relevant occupational handler scenarios of concern.

HED Response: HED thanks the USDA for their comment and the appropriate spreadsheets have been updated to reflect these changes. These updated handler exposure assessments will be included in a revised DRA.

Residue Chemistry and Dietary Assessment

USDA Comment: "USDA supports EPA's recommendations to modify several existing tolerances in accordance with current OECD rounding class procedures, as well as updated crop groupings and commodity definitions. We appreciate EPA's ongoing international MRL harmonization efforts and note that EPA is deferring harmonization recommendations at this time, due to the pending reevaluation of EBDC fungicides by Codex (as well as Canada). USDA would be pleased to provide EPA with additional input on future MRL harmonization opportunities, if needed."

HED Response: HED appreciates USDA's support of the tolerance revisions recommended for mancozeb and the decision to defer the consideration of tolerance harmonization until both Canada and Codex complete their respective re-reviews of the ethylenebis dithiocarbamate (EBDC) fungicides.

Appendix

Table 1. AUR-TPO Assay Suite Results				
Chemical Abbreviation	**Assay Endpoint ID**	**Assay Endpoint Name**	**AC50 (µM)**	**Maximum Median Response (%)**
ETU	1848	CCTE_Simmons_Quantilum_inhib_2_dn	2.14	99.2
ETU	1508	CCTE_Simmons_AUR_TPO_dn	7.76	85.3
PTU	1508	CCTE_Simmons_AUR_TPO_dn	0.23	95.7

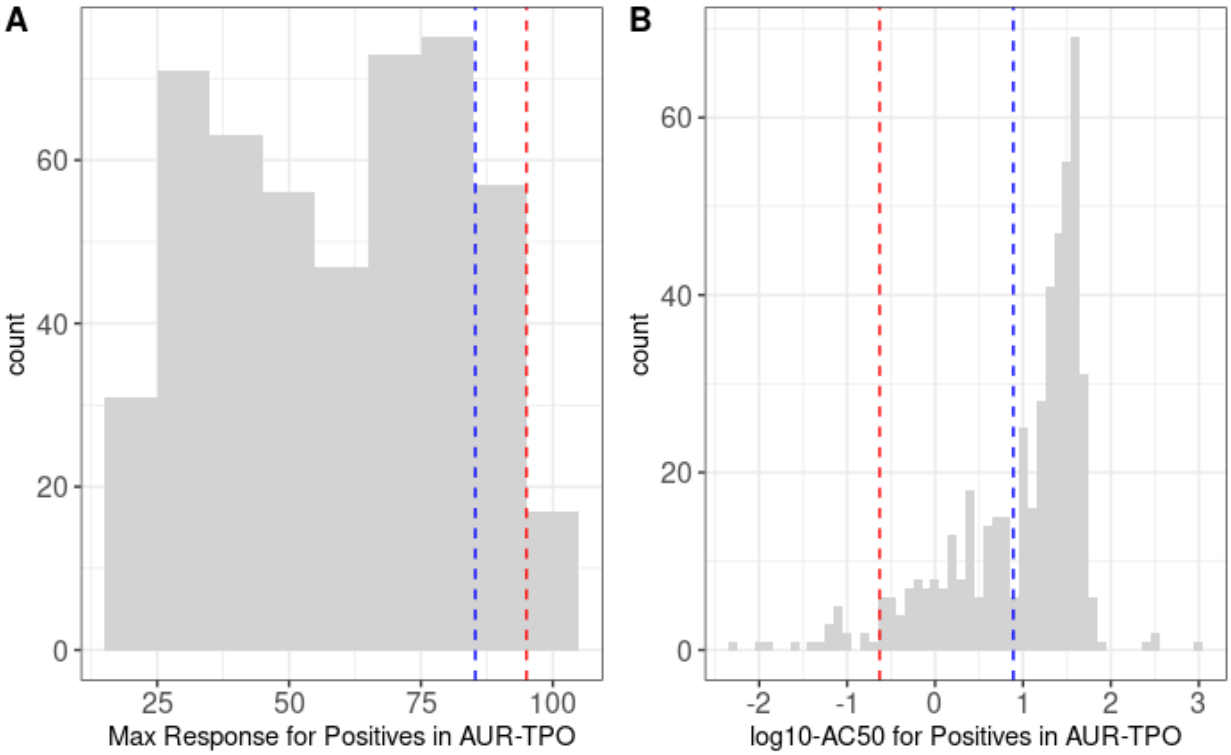

Figure 1. Comparison to Other Positives
The maximum median response (A) and the log10-AC50 values (µM) (B) for all of the positives in the AUR-TPO assay are illustrated. The blue dashed line represents the value for ETU and the red dashed line represents the values for PTU.

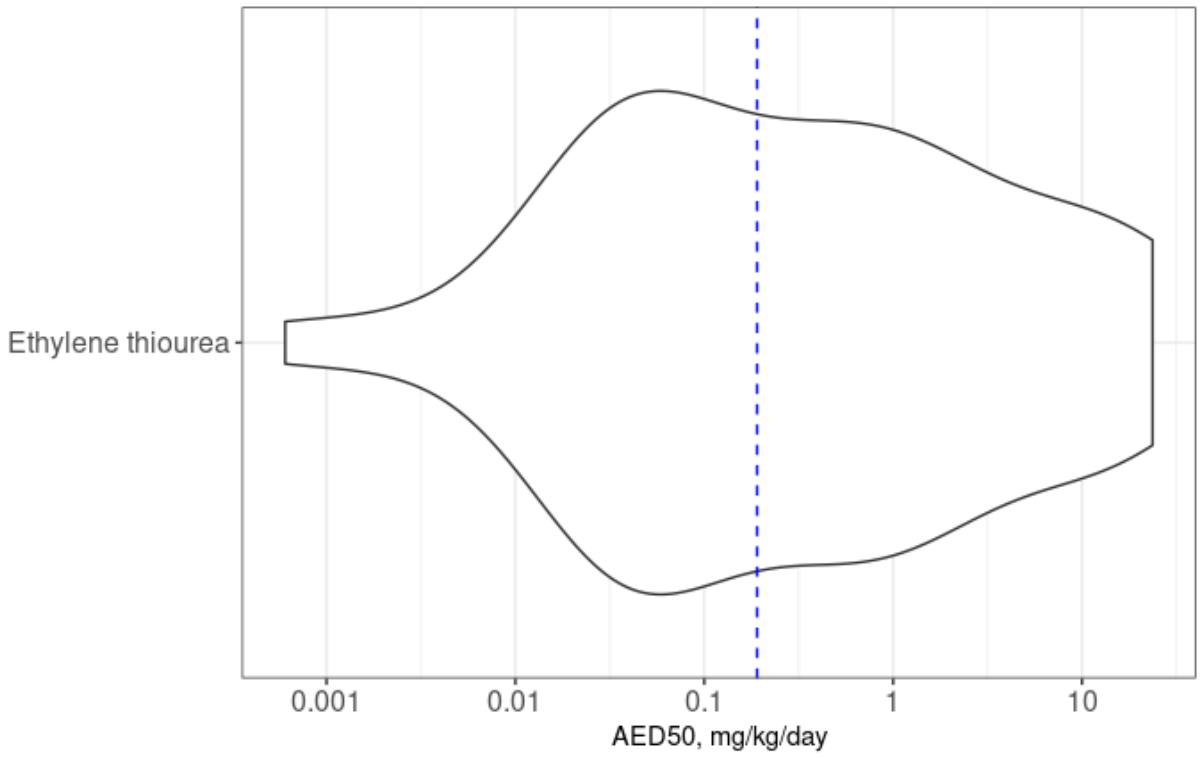

Figure 2. Violin plot of administered equivalent doses (AEDs) for ETU
All of the AC50 values in ToxCast for ETU were used to estimate corresponding AEDs in mg/kg/day dose units, using a three-compartment steady state model. The blue dashed line indicates an AED = 0.2 mg/kg/day, the value obtained for the CCTE_Simmons_AUR_TPO_dn AC50 of 7.76 µM. The calculations were performed using the publicly available R library "httk," for high-throughput toxicokinetics (v2.0.4), assuming the median human individual in terms of interindividual toxicokinetic variability, restrictive clearance, and a three-compartment steady state model.

References

Doerge, D. R., and Takazawa, R. S. (1990). Mechanism of thyroid peroxidase inhibition by ethylenethiourea. *Chem Res Toxicol* **3**(2), 98-101.

Kavlock, R., Chandler, K., Houck, K., Hunter, S., Judson, R., Kleinstreuer, N., Knudsen, T., Martin, M., Padilla, S., Reif, D.*, et al.* (2012). Update on EPA's ToxCast program: providing high throughput decision support tools for chemical risk management. *Chem Res Toxicol* **25**(7), 1287-302.

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