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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: **3/21/2022**

SUBJECT: **Propiconazole:** Revised Human Health Draft Risk Assessment of the Conventional Uses to Support Registration Review.

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40 CFR: §180.434

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This memorandum serves as the draft human health risk assessment (DRA) of the dietary, occupational and residential exposure, and aggregate risk from the registered conventional uses of propiconazole, and supersedes the previous DRA (J. Camp et al., D456089, 12/14/2020). The exposure and risk assessment reflecting antimicrobial uses is included in a separate updated DRA for those residential uses only (T. Dole, D464327, 03/21/2022). However, the residential exposures from the antimicrobial uses have been summarized and considered in the aggregate risk assessment in this document. The residential post-application exposures for the textile and carpet fiber antimicrobial uses present risks of concern on their own. Therefore, these individual antimicrobial scenarios were not considered further for evaluating aggregate risk.

This revised DRA incorporates changes as a result of public comments received on the 2020 DRA (J. Camp et al., D462404, 03/21/2022). The following changes have been made:

- HED has reviewed additional propiconazole dermal absorption studies submitted with the public comments. Based on this review, it has been determined that updating the dermal absorption factor (DAF) of 48% used in the previous propiconazole assessment to a revised DAF of 15% is appropriate to evaluate propiconazole dermal exposures.
- The propiconazole occupational handler, occupational post-application, and non-occupational post-application (spray drift) exposure and risk assessments have been revised to include the updated DAF.
- The propiconazole occupational handler exposure and risk assessment has been revised to include the unit input updates from May 2021.
- HED has evaluated the maximum single application rate used to assess the mixer, loader, and applicator backpack scenario for conifer plantations. The occupational and residential exposure assessment has been revised to incorporate a maximum single application rate of 0.0017 lb ai/gal of solution to assess this scenario.
- Residential exposures from the antimicrobial uses of propiconazole were revised as a result of public comments received on the Antimicrobials Division's Human Health and Ecological DRA (T. Dole, D464327, 03/21/2022). The revised residential exposures from the antimicrobial uses are included and have been incorporated into the aggregate risk assessment in this document.
- The aggregate risk assessment has been revised to incorporate updated residential exposures. The residential post-application exposure scenarios demonstrating the lowest MOE value without presenting risks of concern on their own from conventional and antimicrobial uses were selected for use in the aggregate exposure assessment for each subpopulation.

A summary of the findings and an assessment of human risk resulting from the registered conventional uses of propiconazole are provided in this document.

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1.0 Executive Summary

The Health Effects Division (HED) has conducted a human health draft risk assessment (DRA) to evaluate all conventional registrations of the active ingredient (ai) propiconazole, a systemic triazole-type fungicide that provides broad spectrum disease control on a variety of food and non-food crops. This assessment was conducted as part of Registration Review. The Antimicrobials Division (AD) has completed a Human Health and Ecological DRA (S. Hu et al., D459696, 12/01/2020) and revised assessment of residential exposures (T. Dole, D464327, 03/21/2022) to evaluate the antimicrobial registrations of propiconazole. The residential handler and post-application exposures from the revised AD DRA for residential exposures have been summarized and considered in the aggregate risk assessment for this current document.

Use Profile
Permanent tolerances are established (40 CFR §180.434) for the combined residues of propiconazole (1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole)) and its metabolites (determined as 2,4-dichlorobenzoic acid (2,4-DCBA)) in/on a variety of agricultural commodities at levels ranging from 0.05 ppm in/on meat and meat byproducts to 1000 ppm in/on citrus oil. Non-food uses include use on commercial, public, and residential ornamentals, landscapes, and turf. The mode of antifungal action of propiconazole is attributed to the inhibition of CYP51 (lanosterol-14-*a*-demethylase). Inhibition of normal sterol production disrupts cell wall formation and slows or stops the growth of the fungus. Agricultural applications of propiconazole are made using ground, aerial, chemigation, and handheld equipment. Propiconazole is applied to non-food areas by both occupational and residential handlers. Occupational application methods for non-food uses include seed piece dip, tree injection, and handheld equipment (i.e., low-pressure handwand, handgun sprayer, backpack sprayer). Residential applications are made with handheld equipment. Residential uses for antimicrobial household products (e.g., paint and textiles) were evaluated by the Antimicrobials Division in a separate revised DRA (T. Dole, D464327, 03/21/2022).

Exposure Profile
Humans may be exposed to propiconazole in food and drinking water, since propiconazole may be applied directly to growing crops and application may result in propiconazole reaching surface and ground sources of drinking water. In an occupational setting, applicators may be exposed while handling the pesticide prior to application as well as during application. There is also potential for post-application exposure for workers re-entering treated fields. In a residential setting, residential adult handlers may be exposed while handling propiconazole. Furthermore, adults and children may be exposed following the application of products containing propiconazole both indoors and outdoors. Non-occupational exposure resulting from agricultural spray drift onto residential areas may also occur.

Hazard Characterization
The toxicity database for propiconazole is considered complete and adequate for hazard characterization. The primary target organ for propiconazole toxicity in animals is the liver. Liver effects in rats progressed over time and occurred at lower doses with increased duration of dosing in a combined chronic/carcinogenicity study, as lesions indicative of early liver damage, but no such effects were seen in rats after subchronic exposure that caused only decreased body

weight at the highest dose. In contrast, mice in subchronic studies exhibited enlarged livers, increased liver enzymes, and histopathological lesions at similar or slightly lower doses than mice in chronic studies. While no reproductive effects were seen up to the highest dose in a two-generation reproductive study in rats, both maternal and offspring animals displayed an increased incidence of clear cell change and hepatic cellular swelling at the same dose. No neurotoxic effects were seen in a subchronic neurotoxicity (SCN) study up to the highest dose, while limited signs were seen at the highest doses tested in an acute neurotoxicity (ACN) study and a developmental toxicity study in rats. Quantitative susceptibility was seen in the developmental toxicity study as an increased incidence of rudimentary ribs in rat fetuses at a lower dose than that inducing maternal effects. No quantitative fetal or offspring susceptibility was seen in a developmental toxicity study in rabbits or in the two-generation reproduction study in rats. No dermal toxicity was seen in rabbits up to the highest dose tested. All mutagenicity and/or genotoxicity studies were found to be negative. Tumors were seen in the livers of male mice, but not in females or in rats of either sex. Acute oral toxicity is slight (Toxicity Category III), and acute dermal or inhalation toxicity is low (Toxicity Category IV). Propiconazole is slightly irritating to the skin (Toxicity Category IV), is irritating to the eyes (Toxicity Category II), and is considered a skin sensitizer in two out of three studies.

Dose Response

The point of departure (POD) (100 mg/kg/day) for acute dietary exposure in all populations is based on reduced motor activity at time of peak effect, increased time to tail flick in females, and multiple clinical signs observed in the ACN study in rats. The POD (18.1 mg/kg/day) for chronic dietary exposure in the general population is based on several types of liver lesions (e.g., ballooned cells and vacuolation of hepatocytes in males, foci of enlarged hepatocytes in females), in addition to an increased incidence of luminal dilation in the uterus of females and reduced body weights in both sexes, which were seen in the combined chronic/carcinogenicity study in rats.

The POD (42 mg/kg/day) for short-term incidental oral exposure to children and oral exposure in adults, and to short-term to intermediate-term dermal and inhalation exposures, is based on reduced offspring survival, pup body weight, and an increased incidence of hepatic cellular swelling observed in the two-generation reproduction study in rats. A dermal absorption factor (DAF) of 15% was used to extrapolate dermal toxicity from use of an oral study.

For all PODs, the default uncertainty factors (UFs) of interspecies extrapolation and intraspecies variability (10X for each) were applied, along with a Food Quality Protection Act Safety Factor (FQPA SF) of 1X. Therefore, the level of concern (LOC) for residential and occupational exposures is 100. The population adjusted dose (PAD) is equivalent to the reference dose (RfD) for both acute and chronic exposure after applying the UFs and FQPA SF, and is 1 mg/kg/day and 0.18 mg/kg/day, respectively, for each exposure duration.

Propiconazole is considered a Group C- "possible human carcinogen." Quantification of risk using a non-linear approach (i.e., RfD) will adequately account for all chronic toxicity, including carcinogenicity, that could result from exposure to propiconazole.

Dietary Exposure Assessment
Currently, compliance with the tolerance levels is to be determined by measuring propiconazole and all metabolites convertible to 2,4-DCBA, calculated as the stoichiometric equivalent of propiconazole. However, the Metabolism Assessment Review Committee (MARC) previously recommended that the tolerance expression be revised to include parent only (B. Cropp-Kohlligian, TXR 0050349, D279299, 04/04/2002). Therefore, for Registration Review, HED has converted tolerances to parent propiconazole only, where possible.

Partially refined acute and chronic dietary exposure (food and drinking water) assessments were conducted for currently registered uses of propiconazole. The assessments incorporated established and recommended tolerance-level residues adjusted for risk assessment residues of concern for some commodities, average or maximum (acute only) field trial residues for the remaining commodities according to blending classification, 100% crop treated (CT), and HED's 2018 default processing factors (except for tomato paste, tomato puree, orange juice, tangerine juice, lemon juice, lime juice, grapefruit juice, dried prune plum, pineapple juice, and Rapeseed subgroup 20A oil commodities). Modeled estimated drinking water concentrations (EDWCs) were provided by the Environmental Fate and Effects Division (EFED) and incorporated directly into the assessments.

The resulting acute dietary exposure estimates were less than HED's level of concern (<100% of the acute population-adjusted dose (aPAD)) at the 95th percentile of the exposure distribution for the general U.S. population (5.7% aPAD) and all population subgroups. The most highly exposed population subgroup was children 1-2 years old at 19% of the aPAD.

The resulting chronic dietary exposure estimates were less than HED's level of concern (<100% of the chronic population-adjusted dose (cPAD)) for the general U.S. population (5.0% cPAD) and all population subgroups. The most highly exposed population subgroup was children 1-2 years old at 15% of the cPAD.

Although there are registered antimicrobial uses that could result in indirect food contact, these uses are expected to result in minimal dietary exposure compared to the conventional uses of propiconazole. Therefore, AD did not conduct a dietary exposure assessment for the antimicrobial uses of propiconazole. Additionally, drinking water residues are anticipated from the antimicrobial uses of propiconazole; however, they are lower than the residues resulting from the conventional uses and were not assessed separately. See the AD DRA for additional details (S. Hu et al., D459696, 12/01/2020).

The dietary exposure analyses for the common conazole fungicide metabolites, 1,2,4-triazole (T), triazolyl alanine (TA), triazolyl acetic acid (TAA), were recently updated (T. Morton, D461600/D461602, 05/06/2021). The resulting acute and chronic exposure estimates were less than HED's level of concern (<100% of the PAD) for the general U.S. population and all population subgroups.

Residential Exposure and Risk Assessment

Conventional Uses

Residential handler non-cancer exposure and combined (dermal + inhalation) risk estimates were calculated for the registered uses of propiconazole. No risk estimates were of concern at the LOC of 100. Combined margins of exposure (MOEs) range from 1,700-750,000.

There are residential post-application exposures expected for the registered uses of propiconazole. Chemical-specific Turf Transferable Residue (TTR) data were submitted and are consistent with the 2012 Residential SOPs. Using the chemical-specific TTR data and a 7-day average for liquid formulation applications to turf, no risks of concern were identified at the LOC of 100 (MOEs ranging from 880-690,000).

For granular formulations, default TTR data were used since no formulation-specific TTR data are available to assess the granular formulation. No risks of concern were identified at the LOC of 100 (MOEs range from 490-950,000) for adults and/or children 1 to <2 years.

For applications to gardens/trees, chemical-specific dislodgeable foliar residue (DFR) data were previously submitted and have been used to inform the residential post-application exposure assessment for adults and children (6 to <11 years old) contacting treated gardens for liquid and solid formulations of propiconazole. No risks of concern were identified at the LOC of 100 (MOEs range from 370-740).

Antimicrobial Uses

There is potential residential handler and post-application exposure from the existing antimicrobial uses of propiconazole. These exposures were assessed in a separate revised DRA for residential exposures prepared by the Antimicrobials Division (T. Dole, D464327, 03/21/2022). Residential handler inhalation and dermal exposures were assessed for applying paints that are preserved with propiconazole or when using wood preservative products that contain propiconazole. The inhalation MOEs range from 1,800 to 210 million and are not of concern because they are greater than the target LOC of 100. The dermal MOEs range from 650 to 9,300 and are not of concern because they are greater than the target LOC of 100.

There is the potential for residential post-application dermal (adults) exposure and dermal and incidental oral (children) exposures to textiles preserved with propiconazole, carpet that contains propiconazole-treated fibers, poly vinyl chloride (PVC) flooring materials preserved with propiconazole, propiconazole that leaches out of swimming pool liners, and treated decks and playsets constructed with wood that have been pressure treated with propiconazole. The dermal MOEs for textiles (32 to 58) and carpet (3.6) are of concern because they are less than the target LOC of 100. The dermal MOEs for PVC flooring (100), swimming pool liners (5,400 to 7,500) and pressure treated wood (2,600 for southern yellow pine and 1,000 for spruce) are not of concern. The incidental oral MOE of 9.5 for children exposed to carpet fibers preserved with propiconazole is of concern because it is less than the target LOC of 100. The incidental oral MOEs for textiles (220), PVC flooring (530), swimming pool liners (7,900 to 20,000), and

pressure treated wood (1,500 for southern yellow pine and 610) are not of concern.

Aggregate Risk Assessment
Acute and chronic aggregate exposures to propiconazole are anticipated to occur from food and drinking water from conventional product uses only. AD did not conduct a dietary exposure assessment for the antimicrobial uses of propiconazole, since dietary exposure from antimicrobial uses is expected to be minimal compared to that from the conventional agricultural uses of propiconazole and conventional agricultural uses of propiconazole do not result in dietary exposure risks of concern. Drinking water residues are anticipated from the antimicrobial uses of propiconazole; however, they are lower than the residues resulting from the conventional uses and were not assessed separately. See the AD DRA for additional details (S. Hu et al., D459696, 12/01/2020). Since no acute or chronic dietary risks of concern were identified for conventional products, there are no risks of concern for acute and chronic aggregate exposures.

In aggregating short-term risk, the Agency combines background average dietary exposure with short-term residential exposures. The combined exposure may then be used to calculate an MOE for aggregate risk. For adults and children, residential exposures were aggregated with dietary exposures for the appropriate subpopulation and scenario for conventional or antimicrobial uses. Residential handler and/or post-application exposures of concern were identified from antimicrobial products. Therefore, residential post-application exposure scenarios demonstrating the lowest MOE value without presenting risks of concern on their own were selected for use in the aggregate exposure assessment for each subpopulation.

Several exposure scenarios that presented risks of concern on their own were identified with use of antimicrobial products, which are further described in the separate AD revised DRA for residential exposures (T. Dole, D464327, 03/21/2022). These individual scenarios were not considered further for evaluating aggregate risk. Additionally, although the dermal MOE of 100 for dermal exposure to PVC flooring is not of concern on its own, AD recommended that it not be included in the aggregate assessment because it would contribute to an aggregate risk of concern when combined with the other exposures that are included in the aggregate risk assessment. Of the remaining scenarios, the selected residential post-application scenario for short-term adult aggregate exposure is dermal exposure to treated gardens from conventional uses. Combined with the applicable subpopulation dietary exposure, the short-term aggregate MOE is 350. For short-term child (1 to <2 years old) aggregate exposure, the selected residential post-application scenario is dermal and incidental oral exposure to pressure treated wood from antimicrobial uses. Combined with the applicable subpopulation dietary exposure, the short-term aggregate MOE is 310. For the short-term child (6 to <11 years old) aggregate exposure, the selected residential post-application scenario is dermal exposure to treated gardens from conventional uses. Combined with the applicable subpopulation dietary exposure, the short-term aggregate MOE is 470. These aggregate risks from conventional and antimicrobial uses of propiconazole that were considered for inclusion in the aggregate do not fall below the level of concern of 100 and, therefore, are not of concern.

Aggregate Assessment of Free Triazole & its Conjugates
Application of triazole-containing pesticides, such as propiconazole, also results in exposure to the common metabolites, 1,2,4-triazole (T), triazolyl alanine (TA), triazolyl acetic acid (TAA).

Since these are common metabolites from several triazole pesticides and have their own toxicological endpoints, the risk assessment for triazoles will be assessed separately. The dietary exposure and risk analyses for the triazole metabolites were recently updated, and the aggregate estimates remain below HED's level of concern (T. Morton, 5/6/2021, D461601/D461603).

Non-Occupational Spray Drift Assessment
A spray drift assessment was conducted to estimate indirect, non-occupational exposure and risk from nearby agricultural applications. All dermal risk estimates for adults were greater than the LOC (LOC = 100) at the field's edge on the day of application and are not of concern (MOEs range from 2,100-3,800). All combined (dermal and incidental oral) risk estimates for children (1 to <2 years) were greater than the LOC (LOC = 100) at the field's edge on the day of application and are not of concern (MOEs range from 950-1,700).

Occupational Exposure and Risk Assessment
Occupational handler non-cancer exposure and combined risk estimates were calculated for the registered conventional uses of propiconazole. MOEs are presented with baseline attire; scenarios resulting in risks of concern with baseline attire are presented with label-required PPE (chemical-resistant gloves). MOEs range from 54 to 590,000 (LOC=100). There are no risks of concern with label-required PPE.

Occupational handler post-harvest non-cancer exposure and combined (dermal and inhalation) risk estimates were calculated for the registered uses of propiconazole. No risks of concern were identified at the LOC of 100 (MOEs range from 690-22,000).

Using propiconazole-specific DFR data, all occupational post-application non-cancer dermal MOEs are not of concern (MOEs ranging from 240 to 200,000).

There are no occupational post-application combined dermal and inhalation risk estimates of concern (MOEs ≥ 100) for sorters and packers, or indirect inhalation exposures to workers not directly involved in the treatment process from the registered post-harvest uses of propiconazole at baseline attire (i.e., t-shirt, no gloves, and no respirator) (MOEs range from 26,000-840,000).

Propiconazole is classified as Toxicity Category III for acute oral exposures and Toxicity Category IV for dermal and inhalation routes. In the acute toxicity battery, propiconazole was found to be irritating to the eyes (Category II) and slightly irritating to the skin (Category IV) and is a dermal sensitizer. Under 40 CFR §156.208 (c) (2), active ingredients classified as Acute II for acute dermal, eye irritation, and/or primary skin irritation are assigned a 24-hour restricted entry interval (REI). For this reason, HED would recommend a REI of 24 hours, which would be considered protective of post-application exposures for all scenarios using the chemical-specific DFR data from the CA, GA, and SC study sites.

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions

to Address Environmental Justice in Minority Populations and Low-Income Populations.[1]"

Human Studies
This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide to determine their exposure. Appendix C provides additional information on the review of human research used to complete the risk assessment. There is no regulatory barrier to continued reliance on these studies, and all applicable requirements of EPA's Rule for the Protection of Human Subjects of Research (40 CFR Part 26) have been satisfied; see Appendix C.

2.0 Risk Assessment Conclusions

HED is recommending several commodity definition revisions and several tolerance level revisions to be consistent with Organization for Economic Cooperation and Development (OECD) rounding class practice or to further harmonize with established Codex and Canadian maximum residue limits (MRLs). HED has evaluated the hazard and exposure data to estimate the risk to human health that will result from the currently registered conventional uses of propiconazole. No dietary, aggregate, or non-occupational spray drift risks of concern were identified. MOEs are presented with baseline attire; scenarios resulting in risks of concern with baseline attire are presented with label-required PPE (chemical-resistant gloves). MOEs range from 54 to 590,000 (LOC=100). There are no risks of concern with label-required PPE. No occupational post-application or residential risks of concern were identified.

For the antimicrobial uses (assessed in a separate AD DRA and summarized in the Executive Summary of the current document), several residential post-application dermal risk estimates were of concern for propiconazole-treated textiles and carpet; and incidental oral risk estimates were of concern for preserved carpet fibers (T. Dole, D464327, 03/21/2022).

2.1 Data Deficiencies

There are no data deficiencies for propiconazole.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate high-performance liquid chromatography with ultraviolet detection (HPLC/UV) method AG-671A, is available for the determination of residues of propiconazole *per se* in/on plant commodities. This method has undergone a successful tolerance method validation by the Analytical Chemistry Branch of BEAD. The method was forwarded to FDA for inclusion in PAM Volume II. This method has a limit of quantification (LOQ) of 0.02 ppm. The method includes optional detection via HPLC/MS, giving a means of residue confirmation.

[1] https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

For enforcement purposes, the Multiresidue Methods Section 302 (Luke Method; Protocol D) is available for the determination of propiconazole *per se* in/on plant and livestock commodities. The FDA PESTDATA database (PAM Volume I, Appendix I) indicates that propiconazole is completely recovered (>80%) using Multiresidue Methods Section 302. The recovery of propiconazole metabolites CGA-91305, CGA-118244, and 1,2,4-triazole is variable using Section 302. Propiconazole and metabolites CGA-91305, CGA-118244, and 1,2,4-triazole are not recovered using Multiresidue Methods Sections 303 and 304.

Adequate analytical reference standards for propiconazole are currently available in the EPA National Pesticide Standards Repository (NPSR) (email communication between C. Vigo and J. Camp, 10/22/2020).

HED notes that USDA's Pesticide Data Program has used a modified QuEChERS (quick, easy, cheap, effective, rugged, safe) multiresidue method to successfully analyze residues of propiconazole in numerous plant commodities, indicating that the QuEChERS method may be suitable for tolerance enforcement.

2.2.2 Recommended and Established Tolerances

As noted previously, permanent tolerances are currently established for the combined residues of propiconazole and all metabolites convertible to 2,4-DCBA in/on plant and livestock commodities (40 CFR §180.434). The MARC previously recommended that the tolerance expression be revised to include parent only and all tolerances converted to parent only; for risk assessment, the residues of concern should include propiconazole and all metabolites containing the 2,4-DCBA moiety (B. Cropp-Kohlligian, TXR 0050349, D279299, 04/04/2002). HED subsequently concluded that the tolerance expression would be changed during Registration Review (T. Morton et al., D429076, 12/10/2015). HED has determined that the current tolerance expression should be amended to include only parent propiconazole because 1) there are a number of pesticides that have 2,4-DCBA as a common metabolite, and an enforcement agency may not be able to determine if residues are due to misuse of propiconazole or the proper use of other pesticides containing 2,4-DCBA; 2) propiconazole can be detected by FDA multiresidue methods; 3) measuring only parent propiconazole for enforcement is adequate to detect misuse; and 4) inclusion of only parent allows for harmonization with the residue definition for Canada and Codex MRLs.

In accordance with HED's Interim Guidance on Tolerance Expressions (S. Knizner, 05/27/2009), the tolerance expressions for propiconazole under 40 CFR §180.434 require revision to state the following:

(c)(1) *Tolerances with regional registrations.* A tolerance with regional registration, as defined in §180.1(l), is established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of propiconazole (1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole) and its metabolites determined as 2,4-dichlorobenzoic

acid, calculated as the stoichiometric equivalent of propiconazole, in or on the commodities.

(c)(2) *Tolerances with regional registrations*. Tolerances with regional registration, as defined in §180.1(l), are established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only propiconazole, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole, in or on the commodities.

Currently, general tolerances for residues in/on various plant and livestock commodities are listed under 40 CFR §180.434(a)(1) and 40 CFR §180.434(a)(2), due to different tolerance expressions. HED recommends that tolerances currently listed under 40 CFR §180.434(a)(1) with parent only residue data be moved under 40 CFR §180.434(a)(2), since HED recommends tolerance level revisions reflecting parent only for these commodities. There are various established tolerances with no available field trial data measuring residues of parent propiconazole only, only total propiconazole (parent plus all metabolites convertible to 2,4-DCBA). Therefore, HED recommends that these tolerances continue to be listed under 40 CFR §180.434(a)(1), since HED is not recommending tolerance level revisions for these commodities at this time due to the lack of data measuring residues of parent only. Similarly, HED recommends that the tolerances with regional registrations listed under 40 CFR §180.434(c) be separated into 40 CFR §180.434(c)(1) and 40 CFR §180.434(c)(2) to account for different tolerance expressions.

Revisions are recommended at this time to include updated commodity definitions, corrected tolerances per OECD Rounding Class Practice, and revised tolerances to harmonize with various Codex MRLs. Additionally, HED is recommending several tolerance level revisions based on existing residue data to reflect the recommended amended tolerance expression.

Only the recommended commodity definition and tolerance level revisions are presented below in Table 2.2.2.1. For a complete list of the U.S. Canadian, and Codex tolerances/MRLs, refer to Appendix D.

Table 2.2.2.1. Summary of Tolerance Revisions for Propiconazole (40 CFR §180.434)[1].

Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
40 CFR §180.434(a)(1) *General*[2]			
Almond, hulls	7.0	7	Corrected value to be consistent with OECD Rounding Class Practice.
Bean, dry seed	0.40	0.4	Corrected value to be consistent with OECD Rounding Class Practice.
Bean, snap, succulent	--	0.7	Commodity definition correction. Corrected value to be consistent with OECD Rounding Class Practice.
Bean, snap	0.70	Remove	
Bean, succulent shelled	0.10	0.1	Corrected value to be consistent with OECD Rounding Class Practice.
Beet, garden, leaves	--	5.5	Commodity definition correction.[4]
Beet, garden, tops	5.5	Remove	

Table 2.2.2.1. Summary of Tolerance Revisions for Propiconazole (40 CFR §180.434)[1].			
Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
Beet, sugar, dried pulp	1.0	1	Corrected value to be consistent with OECD Rounding Class Practice.
Beet, sugar, leaves	--	10	Commodity definition correction.
Beet, sugar, tops	10	Remove	
Berry, low growing, subgroup 13-07G, except cranberry	--	1.3	Commodity definition correction.[4]
Low growing berry subgroup 13-07G, except cranberry	1.3	Remove	
Bushberry subgroup 13-07B	--	1	Commodity definition correction (editorial). Corrected value to be consistent with OECD Rounding Class Practice.
Bushberry, subgroup 13-07B	1.0	Remove	
Caneberry subgroup 13-07A	--	1	Commodity definition correction (editorial). Corrected value to be consistent with OECD Rounding Class Practice.
Caneberry, subgroup 13-07A	1.0	Remove	
Cattle, kidney	2.0	2	Corrected value to be consistent with OECD Rounding Class Practice.
Cattle, liver	2.0	2	Corrected value to be consistent with OECD Rounding Class Practice.
Cilantro, fresh leaves	--	13	Commodity definition correction.[4]
Cilantro, leaves	13	Remove	
Corn, field, forage	12	15	Recommended tolerance level increase to correct value to be consistent with OECD Rounding Class Practice.
Corn, sweet, forage	6.0	6	Corrected value to be consistent with OECD Rounding Class Practice.
Dillweed	--	30	Commodity definition correction.
Dillweed, fresh leaves	30	Remove	
Goat, kidney	2.0	2	Corrected value to be consistent with OECD Rounding Class Practice.
Goat, liver	2.0	2	Corrected value to be consistent with OECD Rounding Class Practice.
Grain, aspirated fractions	110	150	Recommended tolerance level increase to correct value to be consistent with OECD Rounding Class Practice.
Grass, forage, fodder and hay, group 17, forage	--	0.5	Commodity definition correction.
Grass, forage	0.5	Remove	
Grass, forage, fodder and hay, group 17, hay	--	0.5	Commodity definition correction.
Grass, hay	0.5	Remove	
Grass, forage, fodder and hay, group 17, straw	--	40	Commodity definition correction.
Grass, straw	40	Remove	
Horse, kidney	2.0	2	Corrected value to be consistent with OECD Rounding Class Practice.
Horse, liver	2.0	2	Corrected value to be consistent with OECD Rounding Class Practice.

Table 2.2.2.1. Summary of Tolerance Revisions for Propiconazole (40 CFR §180.434)[1].			
Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
Nut, tree, group 14-12	0.10	0.1	Corrected value to be consistent with OECD Rounding Class Practice.
Onion, bulb, subgroup 3-07A	--	0.2	Commodity definition correction (editorial).
Onion, bulb subgroup 3-07A	0.2	Remove	
Onion, green, subgroup 3-07B	9.0	9	Corrected value to be consistent with OECD Rounding Class Practice.
Peppermint, fresh leaves	--	10	Commodity definition correction. Corrected value to be consistent with OECD Rounding Class Practice.
Peppermint, tops	10.0	Remove	
Pineapple, process residue	7.0	7	Corrected value to be consistent with OECD Rounding Class Practice.
Radish, tops	0.20	Remove	There is an established tolerance for residues in/on *Brassica*, leafy greens, subgroup 4-16B, except watercress. Radish leaves are included in this crop subgroup. Therefore, a separate tolerance for residues in/on Radish, tops is unnecessary.
Rice, grain	7.0	7	Corrected value to be consistent with OECD Rounding Class Practice.
Sheep, kidney	2.0	2	Corrected value to be consistent with OECD Rounding Class Practice.
Sheep, liver	2.0	2	Corrected value to be consistent with OECD Rounding Class Practice.
Sorghum, grain, forage	12	15	Recommended tolerance level increase to correct value to be consistent with OECD Rounding Class Practice.
Soybean, forage	11	15	Recommended tolerance level increase to correct value to be consistent with OECD Rounding Class Practice.
Spearmint, fresh leaves	--	10	Corrected value to be consistent with OECD Rounding Class Practice.
Spearmint, tops	10.0	Remove	
Ti palm, roots	0.30	0.3	Corrected value to be consistent with OECD Rounding Class Practice.
Vegetable, foliage of legume, except soybean, subgroup 7A	--	30	Commodity definition correction. Separate tolerances for residues in/on soybean forage and soybean hay are currently established.
Vegetable, foliage of legume, group 7	30	Remove	
Watercress	6.0	6	Corrected value to be consistent with OECD Rounding Class Practice.
40 CFR §180.434(a)(2) *General*[2]			
Avocado	0.2	0.015	Tolerance level changed to reflect parent only (propiconazole) based on avocado residue data (MRID 5045601). Tolerance level calculated using the OECD MRL calculation procedures.

Table 2.2.2.1. Summary of Tolerance Revisions for Propiconazole (40 CFR §180.434)[1].			
Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
Barley, bran	6.0	Remove	Tolerance level changed to reflect parent only (propiconazole) based on barley and wheat residue data (MRIDs 48681702 & 48681704). A tolerance for barley bran is unnecessary based on the available barley magnitude of the residue data and wheat processing data. There are no available barley processing data. The HAFT for residues of parent propiconazole (1.12 ppm) for barley grain in combination with the average processing factor for wheat bran (1.6x) results in a recommended tolerance of 2 ppm using OECD rounding classes, which is the same recommended tolerance level for barley grain. Therefore, residues in/on barley bran are covered by the recommended tolerance for residues in/on barley grain.
Barley, grain	3.0	2	Tolerance level changed to reflect parent only (propiconazole) based on barley residue data (MRID 48681702). Tolerance level calculated using the OECD MRL calculation procedures.
Barley, hay	30	7	Tolerance level changed to reflect parent only (propiconazole) based on barley residue data (MRID 48681702). Tolerance level calculated using the OECD MRL calculation procedures.
Barley, straw	20	10	Tolerance level changed to reflect parent only (propiconazole) based on barley residue data (MRID 48681702). Tolerance level calculated using the OECD MRL calculation procedures.
Cherry subgroup 12-12A	--	3	Commodity definition correction. Harmonization with Codex. HED is recommending for the establishment of separate tolerances for residues in/on crop subgroups 12-12A, 12-12B, and 12-12C. The recommended tolerances resulting from representative crop residue data for crop subgroup 12-12 (cherry, peach, plum) are not within 5X. Therefore, tolerances for residues in/on the crop subgroups are appropriate.
Fruit, stone, group 12-12, except plum	4.0	Remove	

Table 2.2.2.1. Summary of Tolerance Revisions for Propiconazole (40 CFR §180.434)[1].			
Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
			The OECD MRL Calculator recommends a tolerance level of 2 ppm for cherry subgroup 12-12A; however, HED is recommending a tolerance level increase to harmonize with Codex.
Corn, field, grain	0.2	0.05	Harmonization with Codex.
Corn, pop, grain	0.2	0.05	Harmonization with Codex.
Corn, sweet, kernel plus cob with husks removed	0.1	0.05	Harmonization with Codex.
Fruit, citrus, group 10-10	8.0	8	Corrected value to be consistent with OECD Rounding Class Practice. The established tolerance level already reflects residues of parent propiconazole only.
Fruit, citrus, group 10-10, oil	--	1000	Commodity definition correction. The established tolerance level already reflects residues of parent propiconazole only.
Citrus, oil	1000	Remove	
Oat, forage	4.0	3	Tolerance levels changed to reflect parent only (propiconazole) based on oat residue data (MRID 48681703). Tolerance levels calculated using the OECD MRL calculation procedures.
Oat, grain	3.0	0.7	
Oat, hay	15	7	
Oat, straw	10	2	
Peach subgroup 12-12B	--	5	Commodity definition correction. Harmonization with Codex. HED is recommending for the establishment of separate tolerances for residues in/on crop subgroups 12-12A, 12-12B, and 12-12C. The recommended tolerances resulting from representative crop residue data for crop subgroup 12-12 (cherry, peach, plum) are not within 5X. Therefore, tolerances for residues in/on the crop subgroups are appropriate. The OECD MRL Calculator recommends a tolerance level of 4 ppm for peach subgroup 12-12B; however, HED is recommending a tolerance level increase to harmonize with Codex. The OECD MRL Calculator recommends a tolerance level of 0.6 ppm for plum subgroup 12-12C; however, HED is recommending harmonizing with Codex.
Plum subgroup 12-12C	--	0.4	
Fruit, stone, group 12-12, except plum	4.0	Remove	
Plum	0.60	Remove	

Table 2.2.2.1. Summary of Tolerance Revisions for Propiconazole (40 CFR §180.434)[1].			
Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
Rapeseed subgroup 20A	0.30	0.02	Tolerance level changed to reflect parent only (propiconazole) based on canola residue data (MRID 48604486). The OECD MRL Calculator recommends a tolerance level of 0.015 ppm; however, HED is recommending harmonizing with Codex.
Quinoa, grain	3.0	0.09	Tolerance level changed to reflect parent only (propiconazole) based on wheat residue data (MRID 48681704). The Chemistry Science Advisory Council (ChemSAC) previously approved the commodity definitions for individual commodities of the proposed new cereal grain crop group (see minutes from the 4/8/2020 meeting). The ChemSAC approved inclusion of quinoa in the proposed wheat crop subgroup; therefore, tolerances for residues in/on barley grain should be extrapolated from wheat grain. Tolerance level calculated using the OECD MRL calculation procedures.
Rye, bran	0.6	0.15	Tolerance level changed to reflect parent only (propiconazole) based on wheat residue data (MRID 48681704). The HAFT for residues of parent propiconazole (0.0779 ppm) for wheat grain in combination with the average processing factor for wheat bran (1.6x) results in a recommended tolerance of 0.15 ppm using OECD rounding classes.
Rye, forage	9.0	4	Tolerance level changed to reflect parent only (propiconazole) based on rye residue data (MRID 48681701). Tolerance level calculated using the OECD MRL calculation procedures.
Rye, grain	0.3	0.09	Tolerance level changed to reflect parent only (propiconazole) based on wheat grain residue data (MRID 48681704). Tolerance level calculated using the OECD MRL calculation procedures.

Table 2.2.2.1. Summary of Tolerance Revisions for Propiconazole (40 CFR §180.434)[1].			
Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
Rye, straw	10	1.5	Tolerance level changed to reflect parent only (propiconazole) based on rye residue data (MRID 48681701). Tolerance level calculated using the OECD MRL calculation procedures.
Soybean, seed	2.0	0.07	Harmonization with Codex.
Sugarcane, cane	0.4	0.3	Tolerance level changed to reflect parent only (propiconazole) based on sugarcane residue data (MRID 48497001). Tolerance level calculated using the OECD MRL calculation procedures.
Tea, dried[2, 3]	--	4	Commodity definition correction. The existing residue data are on processed (dried) tea (MRID 49432901). The established tolerance level already reflects residues of parent propiconazole only. Corrected value to be consistent with OECD Rounding Class Practice.
Tea[2, 3]	4.0	Remove	
Tomato	3.0	3	Corrected value to be consistent with OECD Rounding Class Practice. The established tolerance level already reflects residues of parent propiconazole only.
Wheat, bran	0.6	0.15	Tolerance level changed to reflect parent only (propiconazole) based on wheat residue data (MRID 48681704). The HAFT for residues of parent propiconazole (0.0779 ppm) for wheat grain in combination with the average processing factor for wheat bran (1.6x) results in a recommended tolerance of 0.15 ppm using OECD rounding classes.
Wheat, forage	15	6	Tolerance level changed to reflect parent only (propiconazole) based on wheat forage residue data (MRID 48681704). Tolerance level calculated using the OECD MRL calculation procedures.
Wheat, grain	0.3	0.09	Tolerance level changed to reflect parent only (propiconazole) based on wheat grain residue data (MRID 48681704). Tolerance level calculated using the OECD MRL calculation procedures.

Table 2.2.2.1. Summary of Tolerance Revisions for Propiconazole (40 CFR §180.434)[1].			
Commodity/ **Correct Commodity Definition**	Established Tolerance (ppm)	Recommended Tolerance (ppm)	Comments
Wheat, hay	30	15	Tolerance level changed to reflect parent only (propiconazole) based on wheat hay residue data (MRID 48681704). Tolerance level calculated using the OECD MRL calculation procedures.
Wheat, straw	20	7	Tolerance level changed to reflect parent only (propiconazole) based on wheat hay residue data (MRID 48681704). Tolerance level calculated using the OECD MRL calculation procedures.
40 CFR §180.434(c)(2) *Tolerances with Regional Registrations*[2]			
Cranberry	1.0	0.3	Harmonization with Codex.

[1] For complete list of established/recommended tolerances see the IRLS in Appendix D.
[2] HED is recommending amending the tolerance expression to include only propiconazole. Therefore, various recommended tolerances reflecting parent only should be moved to 40 CFR §180.434(a)(2) and 40 CFR §180.434(c)(2).
[3] There are no United States registrations for use of propiconazole on tea as of December 24, 2015.
[4] Although the recommended tolerance level is not consistent with OECD Rounding Class Practice, HED is recommending retaining the established tolerance level to be consistent with Canadian MRLs to avoid trade irritant potential.

HED has reviewed tolerances for residues in/on Avocado; Barley, bran; Barley, grain; Barley, hay; Barley, straw; Fruit, stone, group 12-12, except plum; Oat, forage; Oat, grain; Oat, hay; Oat, straw; Plum; Rapeseed subgroup 20A; Quinoa, grain; Rye, bran; Rye, forage, Rye, grain; Rye, straw; Sugarcane, cane; Wheat, bran; Wheat, forage; Wheat, grain; Wheat, hay; and Wheat, straw, where field trial data measuring residues of parent propiconazole are available, and has determined that the current tolerance levels are too high, as tolerances are established for residues of propiconazole and all metabolites convertible to 2,4-DCBA. The OECD MRL calculation procedure was used to determine the recommended tolerance levels for these commodities. The OECD MRL calculator recommends a tolerance level of 0.015 ppm for residues in/on Rapeseed subgroup 20A; however, HED is recommending increasing the tolerance level to 0.02 ppm to harmonize with Codex.

HED is recommending the establishment of separate tolerances for residues in/on crop subgroups 12-12A, 12-12B, and 12-12C. The recommended tolerances resulting from representative crop residue data for crop subgroup 12-12 (cherry, peach, plum) are not within 5X. Therefore, tolerances for residues in/on the crop subgroups are more appropriate. The OECD MRL Calculator recommends a tolerance level of 2 ppm for Cherry subgroup 12-12A, 4 ppm for Peach subgroup 12-12B, and 0.6 ppm for Plum subgroup 12-12C. However, for purposes of harmonization, HED is recommending the following tolerance levels: Cherry subgroup 12-12A (3 ppm), Peach subgroup 12-12B (5 ppm), and Plum subgroup 12-12C (0.4 ppm).

HED has reviewed the tolerances for residues in/on Banana; Barley, straw; Beet, sugar, roots; Corn, field, grain; Corn, pop, grain; Corn, sweet, kernel plus cob with husks removed; Cranberry; Fruit, citrus, group 10-10, oil; Fruit, citrus, group 10-10; Nut, tree, group 14-12; Oat,

straw; Pineapple; Rapeseed subgroup 20A; Rye, straw; Soybean, hay; Soybean, seed; Sugarcane, cane; and Wheat, straw, where equivalent Codex MRLs are established. There are no available U.S. data measuring residues of parent propiconazole only in/on field corn, popcorn, sweet corn, cranberry, or soybean seed. However, the JMPR used residue data reflecting U.S. GAP and residues of parent propiconazole only for these commodities. Therefore, HED is recommending tolerance level revisions for the following commodities for harmonization purposes: Corn, field, grain; Corn, pop, grain; Corn, sweet, kernel plus cob with husks removed; Cranberry; and Soybean, seed.

For the remaining established tolerances, there are no available field trial data measuring residues of parent propiconazole only, only total propiconazole (parent plus all metabolites convertible to 2,4-DCBA). Therefore, HED is not recommending further tolerance level revisions at this time, as the currently established tolerances will be protective of any residues of parent propiconazole only.

For Registration Review, HED is recommending several tolerance changes to livestock feed items; however, these recommendations are all decreases due to the recommended tolerance expression change. Therefore, the previously calculated dietary burdens are not expected to increase with the recommended tolerance changes and no changes to livestock tolerances are necessary at this time.

2.2.3 International Harmonization

Established and HED-recommended U.S. tolerances (listed in 40 CFR §180.434), and Canadian and Codex MRLs are summarized in Appendix D. The Canadian and Codex MRLs are expressed in terms of propiconazole. The U.S. residue definition is not currently harmonized with Canada or Codex. However, HED is recommending amending the tolerance expression to parent only, which will be harmonized with the Canadian and Codex tolerance expressions.

Under Registration Review, HED is recommending several tolerance level revisions in order to reflect residues of only parent propiconazole and/or harmonize with Codex MRLs. For some cases, such as sugar beet roots, HED is not recommending harmonizing the U.S. tolerance level (0.3 ppm) with the Codex MRL (0.02 ppm) due to differences in use patterns.

HED is recommending several tolerance level revisions for the following commodities based on existing residue data, which are now harmonized with Codex MRLs (Table 2.2.2.1): Barley, grain; Cherry subgroup 12-12A; Oat, grain; Peach subgroup 12-12B; Plum subgroup 12-12C; Rapeseed subgroup 20A; Rye, grain; and Wheat, grain.

Additionally, HED is recommending several tolerance level revisions for the following commodities for the purposes of harmonization with Codex MRLs (Table 2.2.2.1): Corn, field, grain; Corn, pop, grain; Corn, sweet, kernel plus cob with husks removed; Cranberry; and Soybean, seed.

Tolerances unable to be revised due to lack of data measuring residues of parent propiconazole only are not harmonized with Canada or Codex due to different residue definitions.

See the International Residue Limit Status Sheet (IRLS) in Appendix D for details.

2.3 Label Recommendations

2.3.1 Recommendations from Residue Reviews

None.

2.3.2 Recommendations from Residential Assessment

None for conventional uses of propiconazole. Refer to the separate revised AD DRA for residential exposures (T. Dole, D464327, 03/21/2022) for recommendations pertinent to antimicrobial uses.

2.3.3 Recommendations from Occupational Assessment

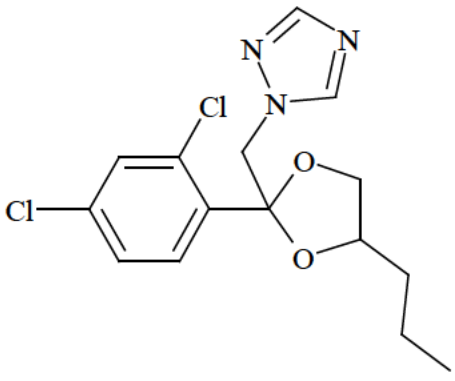
Propiconazole is classified as Toxicity Category III for acute oral exposures and Toxicity Category IV for dermal and inhalation routes. In the acute toxicity battery, propiconazole was found to be irritating to the eyes (Category II) and slightly irritating to the skin (Category IV) and is a dermal sensitizer. Under 40 CFR §156.208 (c) (2), ai's classified as Acute II for acute dermal, eye irritation, and/or primary skin irritation are assigned a 24-hour REI. Therefore, HED is recommending a REI of 24 hours.

3.0 Introduction

3.1 Chemical Identity

Structure and nomenclature are reported in Table 3.1.1.

Table 3.1.1. Nomenclature of Propiconazole.

Compound	
Common name	Propiconazole
Company experimental name	CGA-64250
IUPAC name	1-[2-(2,4_dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1*H*-1,2,4_triazole
CAS name	1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole
CAS #	60207-90-1

3.2 Physical/Chemical Characteristics

Propiconazole is a viscous liquid with a boiling point of 120°C and density of 1.29 g/cm^3. The compound has a vapor pressure of 4.2 x 10^{-7} mm Hg at 25°C, indicating low volatility with little likelihood for exposure in the vapor phase. The octanol/water partition coefficient (log K_{OW}) of 3.72 suggests that it is a hydrophobic compound. Propiconazole is slightly soluble in water (100 ppm at 20°C) and is completely miscible with most organic solvents.

The physiochemical properties for this active ingredient are provided in further detail in Appendix B.

3.3 Pesticide Use Pattern

Propiconazole is registered for conventional and antimicrobial pesticide use. As a conventional chemical, propiconazole is currently registered for use as a broad-spectrum fungicide in both agricultural and non-agricultural settings on turfgrass, ornamentals, fruit and nut trees, and a number of food crops (e.g., corn, sunflower, wheat, barley, rye, citrus fruits, rice, avocado, and sugarcane). Non-food uses include application on golf courses, sod farms, and non-bearing citrus, fruit, and nut trees. As an antimicrobial chemical, it is used as a wood preservative and as an antimicrobial agent in paints, adhesives, coatings, and textiles/paper.

Propiconazole is applied to non-food areas by both occupational and residential handlers. Occupational application methods for non-food uses include seed piece dip, tree injection, post-harvest applications, and handheld equipment (i.e., low-pressure handwand, handgun sprayer, backpack sprayer). Occupational agricultural applications involve aerial, chemigation, or ground (groundboom, airblast, and handheld) equipment. Propiconazole product labels require that applicators and handlers must wear long-sleeved shirt and pants, chemical-resistant gloves, shoes and socks, and protective eyewear. Residential applications are made with handheld equipment.

Registered formulations exist as dry flowable, liquid soluble concentrate, as well as a wettable powder and granule. Registered uses are summarized in the Line by Line, and Maximum Use Scenario Pesticide Label Usage Summary (PLUS) Reports generated as part of the updated PLUS Package (6/04/2020) for propiconazole (122101) by OPP's Biological and Economic Analysis Division (BEAD).

3.4 Anticipated Exposure Pathways

Humans may be exposed to propiconazole in food and drinking water, since propiconazole may be applied directly to growing crops. There are residential, conventional, and antimicrobial uses of propiconazole; and non-occupational exposure to propiconazole via spray drift from the application of conventional products is possible. There is the potential for dermal and inhalation exposures from the residential application of registered conventional propiconazole products by adults. In addition, there is the potential for residential post-application exposures for both adults (dermal only) and children (dermal and incidental oral) from contact with previously treated turf for conventional uses. Occupational exposures are expected from the application (dermal and

inhalation) of conventional propiconazole products and from reentry into previously treated areas (dermal).

The antimicrobial residential exposures were assessed in a separate Human Health and Ecological DRA (S. Hu et al., D459696, 12/01/2020) and revised AD DRA (T. Dole, D464327, 03/21/2022). There is the potential for dermal and inhalation exposures from the residential application of registered antimicrobial products by adults. There is also the potential for residential post-application exposures for both adults (dermal only) and children (dermal and incidental oral) from exposures to household items and clothing manufactured from textiles preserved with propiconazole. Sources of residential exposure from the use of registered antimicrobial products include textiles preserved with propiconazole, carpet that contains propiconazole-treated fibers, PVC flooring materials preserved with propiconazole, propiconazole that leaches out of swimming pool liners, and treated decks and playsets constructed with wood that have been pressure treated with propiconazole.

This risk assessment considers the relevant exposure pathways based on all currently registered conventional uses of propiconazole. Additionally, the aggregate risk assessment considers the relevant exposure pathways based on the currently registered conventional and antimicrobial uses of propiconazole. Residential exposures were aggregated with dietary exposures for the appropriate subpopulation for each scenario for conventional and antimicrobial uses.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (https://www.archives.gov/files/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age and ethnic group. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Spray drift can also potentially result in post-application exposure and it was considered in this analysis. Further considerations are also currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to other types of possible bystander exposures and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The existing toxicology database for propiconazole is complete and contains several guideline and non-guideline studies. No subchronic inhalation toxicity study is available, but the Hazard and Science Policy Council (HASPOC) used a weight of evidence approach to recommend its waiver (K. Rury, TXR 0056387, 08/01/2012). An immunotoxicity study was also recommended for a waiver by the HASPOC (A. Khasawinah, TXR 0056761, D401289, 08/16/2003), with this same recommendation later reaffirmed when evaluating conazoles as a group (A. Dunbar, TXR 0056730, 08/13/2013). The propiconazole toxicity database is considered adequate to assess risk to human health. The following studies were used to characterize propiconazole toxicity in mammals and were considered when designating the points of departure (PODs) for each exposure scenario in the current risk assessment:

- 90-day oral toxicity studies – rat, mouse, male mouse, dog
- 21-day dermal toxicity study – rabbit
- Prenatal developmental toxicity studies – rat, rabbit
- Multigeneration reproduction and fertility effects study – rat
- 1-year chronic toxicity study – dog
- 2-year chronic/carcinogenicity study – rat
- 2-year carcinogenicity study – mouse
- 18-month carcinogenicity study – male mouse
- Acute and subchronic neurotoxicity studies – rat
- Mutagenicity battery
- Metabolism and pharmacokinetics – rat, mouse
- Dermal *in vitro* penetration studies – human skin
- Dermal *in vivo* penetration study – rat
- Tumor promotion study (non-guideline) – rat
- Mechanistic enzyme induction study (non-guideline) – mouse
- Mechanistic hepatocellular proliferation study (non-guideline) – mouse
- Acute studies of oral, dermal, and inhalation toxicity; eye and skin irritation; and skin sensitization

As part of Registration Review for propiconazole, a broad survey of the literature was conducted to identify studies that report toxicity following exposure to propiconazole via exposure routes relevant to human health pesticide risk assessment not accounted for in the Agency's propiconazole toxicity database. The search strategy employed terms restricted to the name of the chemical plus any common synonyms, and common mammalian models to capture as broad a list of publications as possible for the chemical of interest. The search strategy returned 134 studies from the literature. During title/abstract screening of these studies, twelve were identified as containing potentially relevant information (either qualitative or quantitative) for the propiconazole risk assessment. Following a full text review of the identified relevant studies, none were found to contain information that would impact the risk assessment selection of endpoints or PODs. Appendix A.4 has detailed information regarding the literature review.

4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

Absorption, distribution, metabolism, and elimination of propiconazole were characterized in rats administered a single dose of 0.5 mg/kg radiolabeled compound via the oral or intravenous (IV) route, a single oral dose of 0.5 mg/kg radiolabeled compound following daily oral doses of 0.5 mg/kg unlabeled compound, or a single oral dose of 50 mg/kg radiolabeled compound. Both the oral and IV routes resulted in similar patterns of elimination, indicating biliary excretion. No significant differences in the excretion pattern were seen between low and high oral dose groups or with repeated dosing. The test compound was rapidly eliminated, with 81, 94, and 96% of the dose appearing in the urine and feces 1, 2, and 3 days, respectively, after dosing, with most being eliminated within the first 48 hours. Only trace amounts were seen in the tissues, and none in expired air. The primary route of elimination was urine rather than feces in females (43-49% vs. 37-40%) and feces rather than urine in males (48-50% vs. 39-41%) after oral dosing. The distribution of dose in tissues was similar in low and high dose groups. Similar to rats, mice administered 5, 100, or 2500 ppm unlabeled compound daily, followed by a single oral dose of labeled compound at each respective dose, excreted 83-103% the dose within 4 days, with most being excreted in the first 24-48 hours (~64%). More radioactivity, especially at higher doses, was excreted in the urine than in the feces for both female and male mice, in contrast to rats that exhibited the sex-specific differences in elimination routes noted above. Tissue and carcass radioactivity residues were <1% of the administered dose (AD).

No parent material was detected in the feces of IV-dosed rats or in the urine of rats dosed orally. The parent compound was extensively metabolized through hydroxylation, oxidation, and conjugation, with only a small percentage remaining unabsorbed and appearing in the feces of orally-dosed rats. The overall pattern of metabolites detected in the feces was slightly different than that in the urine, with percentages of detected metabolites varying slightly according to sex and dose group. See Appendix A.5 below for details on the metabolic pathways(s) of propiconazole.

4.2.1 Dermal Absorption

The dermal absorption factor (DAF) of 48% used in the previous risk assessment for conventional uses of propiconazole (J. Camp et al., D456089, 12/14/2020) was based on *in vivo* absorption through skin of male rats following exposure for 2, 4, or 10 hours and an immediate washing. The DAF has been revised in this current risk assessment and is based on three recently conducted *in vitro* dermal penetration studies measuring absorption through human skin over a period of 24 hours, with an interim wash at 6 hours. Radioactivity retained in tape strips and the exposed human skin was included in the total absorption estimates to account for absorption through skin after the initial washing, as previous *in vivo* studies (MRIDs 42415701 and 45345901) do not provide sufficient evidence that this potentially absorbable fraction should be excluded from consideration. The resulting absorbed doses from the three studies, using low-concentration spray dilutions of various currently registered formulations, were 14.8%, 20.0%, and 13.5%. The revised DAF selected for use in the current risk assessment is 15%, which is approximately the average of the absorption estimates from the three *in vitro* studies.

To assess the residential handler exposures for the antimicrobial uses of propiconazole as a preservative in latex paints and as a wood preservative in alkyd-based stains, the DAFs for latex paints and alkyd stains were derived from a separate *in vivo* dermal penetration study (MRID 47736503). This study involved male rats that were exposed to a single dermal application of propiconazole in latex paint or alkyd stain for 10 hours, followed by an immediate washing and sacrifice at 10, 24, or 72 hours. With latex paint, recovery was similar regardless of dose or time of sacrifice, and dermal penetration is estimated to be 1%. With stain, there was a general decrease in absorption over time, with similar absorption across doses and an estimated dermal penetration of 26.6%. It is recommended that the formulation-specific DAF be used to assess risks for the respective antimicrobial products (i.e., a DAF of 1% for paints and a DAF of 26.6% for stains).

4.3 Toxicological Effects

The primary target organ for propiconazole is the liver, with mice and rats being the most sensitive of tested species. Following repeated subchronic oral exposures in mice, liver effects included increased liver weights and enlarged livers, which were accompanied by an increase in liver enzymes, decrease in cholesterol, and an increased incidence/severity of hypertrophy and necrosis of liver cells. Similar doses led to analogous liver effects in both sexes in a two-year carcinogenicity study, but these effects progressed in severity over time in male mice, manifesting as benign and malignant tumors. While rats experienced only decreased body weights after subchronic exposure at the highest dose tested, liver effects also progressed in this species, as seen by development of liver lesions in a two-year chronic/carcinogenicity study at lower doses than those in the rat subchronic study. Additionally, an increased incidence of clear cell change (i.e., vacuolation) and/or hepatic cellular swelling (i.e., hypertrophy) was seen in both parental rats and offspring in a two-generation reproduction study. The majority of liver effects in that reproductive study occurred in the F_1 parental animals rather than first generation parents, further supporting evidence that longer exposure periods are necessary to elicit hepatic effects in rats.

In the developmental rat study, there were signs of increased quantitative susceptibility, as an increased incidence of rudimentary ribs was observed at a lower dose in fetuses and litters than that leading to maternal toxicity (ataxia, lethargy, and salivation). The highest dose tested in a developmental rabbit study led to the same maternal and developmental endpoint of an increased incidence of abortions. The liver effects noted above in the two-generation reproduction study (i.e., hepatic cellular swelling and clear-cell change) occurred at a lower dose in parental animals than in pups, and there were no reproductive effects observed.

Observations in dogs after subchronic and chronic exposures suggested only localized sensitivity to the stomach after dietary administration, which is considered not adverse and incidental in the absence of clinical and gross pathological findings. No systemic toxicity was seen in a 21-day repeat-dose dermal study in rabbits, though mild dermal irritation was noted at the highest two doses tested, as an increased incidence of mild to moderate dermatitis in the treated skin area. Signs of neurotoxicity were observed only at the highest dose tested (300 mg/kg) in both an acute neurotoxicity (ACN) study and developmental toxicity study in rats. In contrast, no effects were seen in a subchronic neurotoxicity (SCN) study in rats up to the highest dose tested

(females: 111 mg/kg/day; males: 222 mg/kg/day). All mutagenicity studies were found to be negative.

An acute study suggests that propiconazole is only slightly irritating to the skin (Toxicity Category IV) of rabbits and should not induce mortality or other severe clinical signs after a single dermal dose (Toxicity Category IV; $LD_{50} \geq 5050$ mg/kg). However, it is a confirmed skin sensitizer in two out of three studies in guinea pigs. Propiconazole is slightly acutely toxic via the oral route (Toxicity Category III) and is not acutely toxic via inhalation exposure (Toxicity Category IV). However, it is irritating to the eyes (Toxicity Category II).

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[2]

Together, the available data support the reduction of the Food Quality Protection Act Safety Factor (FQPA SF) to 1X. The toxicity database is complete and considered adequate to evaluate the potential for increased susceptibility of infants and children resulting from exposure to propiconazole. There is evidence of offspring susceptibility in the developmental rat study; however, a clear NOAEL was established for these effects. The SCN study in rats did not demonstrate neurotoxic effects. The ACN study demonstrated effects only at the highest dose. The oral, dermal, and inhalation PODs account for and are protective of the quantitative susceptibility seen in the developmental toxicity study with rats.

4.4.1 Completeness of the Toxicology Database

The propiconazole toxicity database is adequate to evaluate the potential for increased susceptibility in infants and young children for all anticipated propiconazole exposure scenarios, with the exception of a subchronic inhalation study and an immunotoxicity study. The HASPOC recommended to waive the requirement for both studies (K. Rury, TXR 0056387, 08/01/2012; A. Khasawinah, TXR 0056761, D401289, 08/16/2003). The following acceptable studies are available for FQPA consideration: (1) developmental toxicity studies in rats and rabbits; (2) two-generation reproduction study in rats; and (3) acute and subchronic neurotoxicity studies.

4.4.2 Evidence of Neurotoxicity

Evidence of neurotoxicity was seen in the ACN study in the rat only at the highest dose (300 mg/kg), as reduced motor activity in males and females on Day 1 (time of peak effect = 5-6 hours), increased time to tail flick on Day 1 in females, and multiple clinical signs of toxicity (e.g., tiptoe gait, piloerection, paleness, cold to touch, subdued behavior). The only other clinical signs of neurotoxicity in the database were seen in the developmental rat study, as maternal animals exhibiting lethargy, ataxia, salivation, and labored breathing at the highest dose (300 mg/kg/day); those effects are considered to be agonal in nature, as some incidences of coma and death were also seen. No effects were seen in the SCN study in rats up to the highest tested dose (females: 111 mg/kg/day; males: 222 mg/kg/day). There is a low degree of concern for the potential neurotoxic effects of propiconazole since (1) clear NOAELs were identified for the

[2] HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy (https://www.epa.gov/children/epas-policy-evaluating-risk-children).

neurotoxic effects; (2) the neurotoxic effects were not the most sensitive endpoint in the toxicity database (compared to the effects seen in liver, the target organ), and the most sensitive neurotoxic effect was 3-fold to ~20-fold higher than the selected points of departure; and (3) the endpoints chosen for risk assessment are protective of any potential neurotoxicity.

4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

As noted above, there was evidence of increased quantitative sensitivity in the developmental toxicity study in rats. However, the degree of concern is low because the selected endpoints and doses are protective of the observed developmental effects and observed susceptibility. An increased incidence of cleft palate was also seen in fetuses/litters at the highest dose tested in the developmental toxicity study with rats. In the developmental study in rabbits and in the two-generation reproduction and fertility effects study in rats, developmental and/or offspring effects were seen at comparable or higher doses than those leading to parental toxicity.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. The dietary risk assessment is conservative and will not underestimate dietary and/or non-dietary occupational exposure to propiconazole. The dietary assessments utilized tolerance-level residues adjusted for risk assessment residues of concern, maximum or average residue values from field trial data, empirical or HED's 2018 default processing factors, and 100% crop treated. The dietary drinking water assessment used values generated by model and associated modeling parameters which are designed to provide protective, high-end estimates of water concentrations. For these reasons, it can be concluded that the dietary analyses do not underestimate risk from acute or chronic exposure to propiconazole. Similarly, the non-dietary exposures are not underestimated because they are also based on conservative assumptions, including maximum application rates and standard values for unit exposures and acreage treated/amount handled.

4.5 Toxicity Endpoint and Point of Departure Selections

Toxicity studies used to set endpoints and select PODs for each exposure scenario are presented in Appendix A.2. The PODs selected in the previous risk assessment for new use of propiconazole on avocado (T. Morton et al., D446376, 07/15/2019) have since been updated to incorporate new data and current HED practices for endpoint selection. The Agency reassessed the toxicity database for propiconazole in accordance with current practices and determined that many of the effects previously noted are no longer considered to be adverse. As a result, several no observed adverse effect levels (NOAELs) and lowest observed affect levels (LOAELs) presented in the toxicology profile table (Appendix A) have been updated to comply with current practices, despite not impacting PODs for risk assessment.

4.5.1 Dose-Response Assessment

Dietary (acute and chronic), incidental oral (short-term), adult oral (short-term), dermal (short- and intermediate-term), and inhalation (short- and intermediate-term) exposures are anticipated for currently registered uses of propiconazole in agricultural and residential settings. Long-term

dermal and inhalation exposures are also anticipated for occupational handlers of antimicrobial products, such as machinists and those working with wood preservatives. Several endpoints have changed since the last risk assessment. There is no longer a female-specific acute dietary endpoint, as the skeletal effects on which this value was based (rudimentary ribs, incomplete ossification) are not considered single-dose effects. Additionally, children and adult PODs are now based on the same endpoint from the two-generation reproductive study in rats. Finally, long-term PODs have been added to account for propiconazole exposures from antimicrobial uses. While not provided here for assessing risks from conventional uses, those long-term PODs are available in the AD DRA (S. Hu et al., D459696, 12/01/2020). The PODs, uncertainty factors (UFs), and calculated reference dose (RfD)/population adjusted dose (PAD) or level of concern (LOC) for each exposure scenario are detailed below.

Acute Dietary (all populations including females 13-49 years of age)
The POD for acute dietary exposure in all populations was based on the NOAEL (100 mg/kg/day) established for the ACN study (MRID 46604601). The LOAEL of 300 mg/kg/day in that study was based on reduced motor activity in males and females on Day 1 (time of peak effect = 5-6 hours), increased time to tail flick on Day 1 in females, and multiple clinical signs of toxicity (tip toe gait, piloerection, and decreased activity in both males and females; subdued behavior, coldness, paleness, and staining around the nose and with urine in females). The ACN study is appropriate for deriving the acute dietary POD because the endpoint was the most sensitive that could be attributed to a single dose and is protective of the adverse cleft palate formation observed at 300 mg/kg/day in the rat developmental toxicity study. The POD is also protective of the NOAEL for cleft palate in that study (90 mg/kg/day), and the small difference between the two values can be attributed to dose spacing. The UFs for interspecies extrapolation (10X) and intraspecies variability (10X) were applied to the NOAEL to calculate the acute reference dose (aRfD = 1.0 mg/kg/day). The acute population adjusted dose (aPAD = 1.0 mg/kg/day) is equivalent to the POD divided by all applicable UFs and taking into account the FQPA SF of 1X.

Chronic Dietary (general population including infants and children)
The POD for chronic dietary exposure in all populations was based on the NOAEL (18.1 mg/kg/day) established for the two-year chronic/carcinogenicity study in rats (MRID 00129918). The LOAEL of 96.4 mg/kg/day was based on several types of liver lesions (e.g., ballooned cells and vacuolation of hepatocytes in males, foci of enlarged hepatocytes in females), in addition to an increased incidence of luminal dilation in the uterus of females and reduced body weights in both sexes. The duration of this study and the route of exposure are appropriate for evaluating risks of chronic dietary exposure. The selected POD is protective of all endpoints in the propiconazole toxicity database, including the cellular swelling and clear cell change seen in the livers of adults and offspring in the two-generation reproduction study. While the parental NOAEL of 8 mg/kg/day in that reproduction study is slightly lower than the selected POD, this is considered an artifact of dose spacing. Furthermore, the majority of liver effects occurred in adults from the F_1 parental generation, supporting the evidence of increasing liver toxicity that progresses over time. The UFs for interspecies extrapolation (10X) and intraspecies variation (10X) were applied to the NOAEL to calculate the chronic reference dose (cRfD = 0.18 mg/kg/day). The chronic population adjusted dose (cPAD = 0.18 mg/kg/day) is equivalent to the POD divided by all applicable UFs and taking into account the FQPA SF of 1X.

Incidental Oral and adult oral (short-term), Dermal (short-term and intermediate-term), and Inhalation (short-term and intermediate-term)
The PODs for short-term incidental oral exposure to children and oral exposure in adults, and for short-term to intermediate-term dermal and inhalation exposures were based on the NOAEL (42 mg/kg/day) established for offspring in the two-generation reproduction study in rats (MRID 00151514). The LOAEL of 192 mg/kg/day for offspring was based on reduced offspring survival and pup body weight, and an increased incidence of hepatic cellular swelling. Similar liver toxicity was seen in adults, along with an increased incidence of hepatic clear cell change. The occurrence of the majority of these liver effects in the F_1 parental generation is consistent with 90-day studies indicating that longer durations of exposure are necessary in eliciting hepatic effects in rats, and the dose route is appropriate to assess risk from oral exposures.

For dermal exposures, a route-specific 21-day study in rabbits is available, but no systemic toxicity was observed up to the highest tested dose of 1000 mg/kg/day, which included investigation of liver effects. However, since increased susceptibility was observed in the database, an oral POD was selected for dermal risk assessment because the dermal toxicity study did not evaluate developmental or reproductive endpoints. A dermal absorption factor (DAF) is required to extrapolate from oral to dermal exposure. The estimated dermal-equivalent POD is 280 mg/kg/day based on the updated DAF of 15% from the *in vitro* dermal penetration studies and the selected POD (42/0.15 = 280). No inhalation study is available in the toxicity database, but it was recommended to be waived by HASPOC based on a weight-of-evidence approach (K. Rury, TXR 0056387, 08/01/2012).

The selected POD is similar to the developmental NOAEL of 30 mg/kg/day in the developmental toxicity study with rats where quantitative susceptibility was seen, with differences attributed to dose-spacing. Thus, the selected POD is considered protective of all populations, including children and females 13-49 years of age. The LOC of 100 is applied to short-term and intermediate-term residential and occupational exposures. This includes UFs of 10X for interspecies extrapolation and 10X for intraspecies variation and the FQPA SF (1X).

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal, and inhalation exposures. Short-term and intermediate-term oral, dermal, and inhalation exposures for adults can be combined because the PODs are based on the same endpoint in the two-generation reproductivity study in rats showing decreased pup survival, decreased pup body weights, and an increased incidence in hepatic cellular swelling. Similarly, incidental oral, dermal, and inhalation exposures to children can be combined because the PODs are based on the same endpoint in the two-generation reproduction study.

4.5.3 Cancer Classification and Risk Assessment Recommendation

There were three *in vivo* studies available to evaluate the carcinogenic potential of propiconazole from chronic exposure. Propiconazole was not carcinogenic to rats or to female mice. Both benign and malignant tumors were seen in the livers of male mice at the highest dose tested in

the two-year carcinogenicity study (2500 ppm; 344.3 mg/kg/day). Tumors seen in a supplemental 18-month study at 850 ppm (108 mg/kg/day) were within the range of historical controls. Propiconazole was not mutagenic in any *in vitro* or *in vivo* assay. The HED Carcinogenicity Peer Review Committee (CPRC) classified propiconazole as Group C- "possible human carcinogen" and recommended that for the purpose of risk characterization the reference dose approach (RfD) be used for quantification of human risk (E. Doyle, TXR 0009771, 09/11/1992).

4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Propiconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations, including Infants and Children and Females 13-49 years of age)	NOAEL = 100 mg/kg	UF_A = 10X UF_H = 10X FQPA SF = 1X	Acute RfD = 1 mg/kg aPAD = 1 mg/kg	Acute neurotoxicity study – rat (MRID 46604601) LOAEL = 300 mg/kg/day based on reduced motor activity at time of peak effect, increased time to tail flick in females, and several clinical signs (tiptoe gait, piloerection, paleness, cold to touch, subdued behavior)
Chronic Dietary (General Population including Infants and Children)	NOAEL = 18.1 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.18 mg/kg/day cPAD = 0.18 mg/kg/day	Chronic/carcinogenicity study – rat (MRID 00129918) LOAEL = 96.4 mg/kg/day based on liver lesions (vacuolation of hepatocytes in males, ballooned cells in the liver of males, and foci of enlarged hepatocytes in females), increased incidence of luminal dilation of the uterus in females, and reduced body weights in both males and females

Table 4.5.4.1. Summary of Toxicological Doses and Endpoints for Propiconazole for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Incidental Oral/Adult Oral Short-Term (1-30 days)	Offspring NOAEL = 42 mg/kg/day	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	Two-generation reproduction and fertility effects study – rat (MRID 00151514) Offspring LOAEL = 192 mg/kg/day based on decreased pup survival and body weights, along with an increased incidence of hepatic cellular swelling
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	Offspring NOAEL = 42 mg/kg/day DAF = 15%	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	Two-generation reproduction and fertility effects study – rat (MRID 00151514) Offspring LOAEL = 192 mg/kg/day based on decreased pup survival and body weights, along with an increased incidence of hepatic cellular swelling
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	Offspring NOAEL = 42 mg/kg/day[1]	UF_A = 10X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 100	Two-generation reproduction and fertility effects study – rat (MRID 00151514) Offspring LOAEL = 192 mg/kg/day based on decreased pup survival and body weights, along with an increased incidence of hepatic cellular swelling
Cancer (oral, dermal, inhalation)	Classification: Group C, possible human carcinogen; RfD approach for risk characterization, (E. Doyle, TXR 0009771, 09/11/1992)			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population-adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. DAF = dermal absorption factor. [1]Inhalation absorption was assumed to be equivalent to oral absorption.

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Propiconazole for Use in Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	Offspring NOAEL = 42 mg/kg/day DAF = 15%	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	Two-generation reproduction and fertility effects study – rat (MRID 00151514) Offspring LOAEL = 192 mg/kg/day based on decreased pup survival and body weights, along with an increased incidence of hepatic cellular swelling
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	Offspring NOAEL = 42 mg/kg/day[1]	UF_A = 10X UF_H = 10X	Occupational LOC for MOE = 100	Two-generation reproduction and fertility effects study – rat (MRID 00151514) Offspring LOAEL = 192 mg/kg/day based on decreased pup survival and body weights, along with an increased incidence of hepatic cellular swelling
Cancer (oral, dermal, inhalation)	Classification: Group C, possible human carcinogen; RfD approach for risk characterization, (E. Doyle, 9/11/1992, TXR 0009771)			

Point of departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no-observed adverse-effect level. LOAEL = lowest-observed adverse-effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern. DAF = dermal absorption factor. [1]Inhalation absorption was assumed to be equivalent to oral absorption.

4.6 Endocrine Disruptor Screening Program

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, sub-chronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its most recent registration decision for propiconazole, the EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA §408(p), propiconazole is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA § 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. The Agency has reviewed all of the assay data received for the List 1[3] chemicals and the conclusions of those reviews are available in the chemical-specific public dockets. Propiconazole is on List 1 and the review conclusions are available in the propiconazole public docket (see EPA-HQ-OPP-2009-0634). A second list of chemicals identified for EDSP screening was published on June 14, 2013,[4] and includes some pesticides scheduled for Registration Review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors. For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, visit the EPA website.[5]

EPA's EDSP is actively pursuing the application of new approach methods (NAMs) to create a more efficient and robust screening program. In October 2020, EPA underwent a reorganization and the EDSP was moved to the Office of Pesticide Programs. This reorganization provides better alignment of the EDSP with the procedures and methods used by the program offices. On July 28, 2021, the Office of Inspector General (OIG) released its new report on the EDSP and made ten recommendations. EPA is also developing a strategic planning document for EDSP which will be available for public comment in 2022. EPA expects additional documents for public release in 2021-2023 that address aspects of EDSP chemical determinations. EPA looks forward to working with stakeholders and the scientific community to accelerate the implementation of this important program into pesticide risk assessments and decision making.

In this DRA, EPA is making no human health or environmental safety findings associated with the EDSP screening of propiconazole. Before completing this registration review, the Agency will make an EDSP FFDCA §408(p) determination.

5.0 Dietary Exposure and Risk Assessment

[3] See https://www regulations.gov/document/EPA-HQ-OPPT-2004-0109-0080 for the Final First List of Chemicals for Tier 1 Screening in the EDSP.

[4] See https://www regulations.gov/document/EPA-HQ-OPPT-2009-0477-0074 for the Final Second List of Chemicals for Tier 1 Screening in the EDSP.

[5] https://www.epa.gov/endocrine-disruption

5.1 Residues of Concern Summary and Rationale

The residues of concern for dietary risk assessment and the tolerance expression are summarized in Table 5.1.1.

The Metabolism Assessment Review Committee (MARC) previously recommended that the tolerance expression be revised to include parent only and all tolerances converted to parent only; for risk assessment, the residues of concern should include propiconazole and all metabolites containing the 2,4-DCBA moiety, expressed in parent equivalents (B. Cropp-Kohlligian, TXR 0050349, D279299, 04/04/2002). Detailed rationale for these conclusions were presented in a previous document (Y. Donovan, D329394, 06/15/2006). HED subsequently concluded that the tolerance expression would be changed during Registration Review (T. Morton et al., D429076, 12/10/2015).

Table 5.1.1. Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression.

Matrix	For Risk Assessment[1]	For Tolerance Expression
Plants	Parent plus all metabolites convertible to 2,4-DCBA	Parent only
Rotational crop	Parent plus all metabolites convertible to 2,4-DCBA	Parent only
Livestock	Parent plus all metabolites convertible to 2,4-DCBA	Parent only
Water	Parent only	N/A

[1] For all triazole-containing pesticides, the triazole-containing metabolites 1,2,4-T, TA, and TAA should also be included as residues of concern for risk assessment purposes only for plant and livestock commodities. Since these metabolites are common to the entire class of triazole-derivative fungicides and because of differential toxicity between the metabolites and the various parent compounds, risks associated with exposure to 1,2,4-T and to TA/TAA are addressed in separate risk assessment documents.

5.2 Food Residue Profile

Adequate residue data are available to support the Registration Review of propiconazole. As noted in Section 3, propiconazole is a systemic broad-spectrum fungicide registered on a variety of agricultural crops and may be applied as a foliar treatment, tree injection treatment, and/or post-harvest treatment for control of disease. Available plant metabolism data (primary and rotated crops) show that plants absorb, metabolize, and translocate propiconazole throughout the plant. Processing studies indicate that residues of propiconazole concentrate in sugar beet molasses, sugar beet dried pulp, citrus oil, pineapple process residue, rice bran, rye bran, and wheat bran. Environmental fate data suggest that propiconazole is persistent and moderately mobile to relatively immobile in most soil environments, depending on the soil's organic matter content. Rotational crop data demonstrate that residues are taken up from the soil and distributed throughout the plant when grown in rotation with directly treated crops. Based on animal metabolism data, residues may end up in milk, ruminant tissues, and swine kidney and liver as a result of feeding livestock treated feed items. Propiconazole residues are not anticipated in eggs or poultry commodities. The established tolerances are supported by adequate field trial data.

5.3 Water Residue Profile

EFED determined that the estimated drinking water concentrations (EDWCs) calculated in the previous drinking water assessment are still valid and should be relied upon for the Registration Review dietary risk assessment (I. Abdel-Saheb, D456202, 10/14/2020).

Therefore, the EDWCs previously provided by EFED in the following memorandum: "Drinking Water Assessment for Proposed New Uses of Propiconazole on Dill, Radish, Leafy Brassica Subgroup 5B, Watercress, Ti palm and Crop Group conversions for Stone Fruit Group 12-12 and Tree Nut Group 14-12" (I. Abdel-Saheb, D423648, 05/27/2015) were incorporated directly into the dietary assessment. Water residues were incorporated in the DEEM-FCID into the food categories "water, direct, all sources" and "water, indirect, all sources."

Higher maximum EDWCs were observed for groundwater than for surface water. Therefore, per EFED recommendation, the acute and chronic dietary assessments incorporated EDWC values of 0.0379 and 0.0351 ppm, respectively.

The EDWCs provided by EFED are summarized in Table 5.3.1.

Table 5.3.1. Estimated Drinking Water Concentrations (EDWCs) for Propiconazole Uses.[1]

Use and Model	Acute EDWCs (µg/L)	Chronic EDWCs (µg/L)
Surface Water [Surface Water Concentration Calculator (SWCC); PA turf scenario]	35.2	18.6 (non-cancer) 14.4 (cancer)
Groundwater [Pesticide Root Zone Model-Groundwater (PRZM-GW); WI sand scenario]	**37.9**	**35.1**

Highest EDWCs identified in **bold.**

[1] For full details, refer to: I. Abdel-Saheb, D423648, 05/27/2015

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Partially refined acute and chronic dietary (food and water) exposure and risk assessments for propiconazole were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This model uses 2003-2008 food consumption data from U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA).

The assessments incorporated established and recommended tolerance-level residues adjusted for risk assessment residues of concern for some commodities, average or maximum (acute only) field trial residues for the remaining commodities according to blending classification, 100% crop treated (CT), and HED's 2018 default processing factors (except for tomato paste, tomato puree, orange juice, tangerine juice, lemon juice, lime juice, grapefruit juice, dried prune plum, pineapple juice, and Rapeseed subgroup 20A oil commodities). Default processing factors are available for tomato paste, tomato puree, orange juice, tangerine juice, lemon juice, lime juice, grapefruit juice, dried prune plum, and pineapple juice. However, processing data are required

for these processed commodities as they are also listed in Table 1 of OCSPP 860.1000. Since the established tolerance levels for the raw agricultural commodities (Tomato; Fruit, citrus, group 10-10, Plum; Pineapple) cover the residues in these processed commodities, separate tolerances are not established or needed for the processed commodities. Therefore, HED's 2018 default processing factors for tomato paste, tomato puree, orange juice, tangerine juice, lemon juice, lime juice, grapefruit juice, dried prune plum, pineapple juice, were not incorporated, and the processing factors were set to 1.0X. The available canola seed residue data demonstrate that residues of propiconazole and metabolites are reduced in canola oil; therefore, the processing factor for oil commodities in Rapeseed subgroup 20A was reduced to 0.2X (MRID 48604486; T. Morton, D408507/D408509/D408510, 02/27/2014).

Currently, compliance with the tolerance levels is to be determined by measuring propiconazole and all metabolites convertible to 2,4-DCBA, calculated as the stoichiometric equivalent of propiconazole. However, since the MARC previously recommended that the tolerance expression be revised to include parent only, HED has converted tolerances to parent propiconazole only, where possible, for Registration Review.

To take into account the residues of concern for risk assessment, field trial data reflecting residues of parent plus all metabolites convertible to 2,4-DCBA were used in the assessments for commodities where the tolerance levels have been recommended to be revised to reflect residues of parent propiconazole only. For remaining commodities with existing tolerances not converted to reflect parent only due to lack of residue data measuring parent propiconazole, tolerance-level residues were incorporated into the acute and chronic dietary assessments, as the established tolerance level accounts for metabolites convertible to 2,4-DCBA. For some of the commodities that were not converted to parent only, field trial residues were incorporated into the chronic assessment.

The established tolerances for residues in/on Tomato; Fruit, citrus, group 10-10; and Tea already reflect residues of parent propiconazole only. For tea, a calculated metabolite conversion factor of 8.3X from tea residue data was incorporated into the dietary assessments to account for all metabolites convertible to 2,4-DCBA. A calculated metabolite conversion factor of 1.2X was applied to citrus fruit field trial residue data and incorporated into the dietary assessments for commodities in Fruit, citrus, group 10-10 to account for all metabolites convertible to 2,4-DCBA. Please refer to the dietary exposure analyses for further details (J. Camp, D459303, 12/14/2020).

Per EFED recommendations, modeled ground water EDWCs of 0.0379 ppm and 0.0351 ppm were used in the acute and chronic analyses, respectively.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute and chronic assessments assumed 100% crop treated for all commodities.

5.4.3 Acute Dietary Risk Assessment

A partially refined acute dietary (food and drinking water) risk assessment was performed for propiconazole. The resulting acute exposure estimates were less than HED's level of concern (<100% of the aPAD) at the 95th percentile of the exposure distribution for the general U.S. population (5.7% aPAD) and all population subgroups. The most highly exposed population subgroup was children 1-2 years old at 19% of the aPAD.

5.4.4 Chronic Dietary Risk Assessment

A partially refined chronic dietary (food and drinking water) risk assessment was performed for propiconazole. The resulting chronic exposure estimates were less than HED's level of concern (<100% of the cPAD) for the general U.S. population (5.0% cPAD) and all population subgroups. The most highly exposed population subgroup was children 1-2 years old at 15% of the cPAD.

5.4.5 Cancer Dietary Risk Assessment

The HED Carcinogenicity Peer Review Committee (CPRC) classified propiconazole as Group C - possible human carcinogen and recommended that for the purpose of risk characterization the Reference Dose (RfD) approach should be used and would be protective. Therefore, a separate quantification of cancer risk was not completed.

5.4.6 Summary Table

Table 5.4.6.1. Summary of Dietary (Food and Drinking Water) Exposure and Risk for Propiconazole.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
General U.S. Population	0.057335	5.7	0.008993	5.0	N/A	N/A
All Infants (<1 year old)	0.079980	8.0	0.016730	9.3		
Children 1-2 years old*	**0.185969**	**19**	**0.027730**	**15**		
Children 3-5 years old	0.151276	15	0.022239	12		
Children 6-12 years old	0.080390	8.0	0.011678	6.5		
Youth 13-19 years old	0.055660	5.6	0.007202	4.0		
Adults 20-49 years old	0.044984	4.5	0.007519	4.2		
Adults 50-99 years old	0.038703	3.9	0.006882	3.8		
Females 13-49 years old	0.444800	4.5	0.006910	3.8		

* The subpopulation with the highest risk estimate is in **bold** text.

5.4.7 Dietary Assessment of Free Triazole and its Conjugates

The dietary exposure analyses for the common conazole fungicide metabolites, 1,2,4-triazole (T), triazolyl alanine (TA), triazolyl acetic acid (TAA), were recently updated (T. Morton,

D461600/D461602, 05/06/2021). The results from the triazole dietary analyses are below HED's level of concern; see Table 5.4.7.1.

Table 5.4.7.1. Summary of Dietary (Food and Drinking Water) Exposure and Risk for the Common Triazole Metabolites Adding the New Uses for Difenoconazole and Mefentrifluconazole.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary		Cancer	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*	Dietary Exposure (mg/kg/day)	Risk
1,2,4-Triazole						
General U.S. Population	0.008150	27	0.001768	35	Not Applicable	Not Applicable
All Infants (< 1 year old)	0.013134	44	0.003508	70		
Children 1-2 years old	**0.020014**	**67**	**0.004306**	**86**		
Children 3-5 years old	0.017646	59	0.003362	67		
Children 6-12 years old	0.010173	34	0.001983	40		
Youth 13-19 years old	0.006726	22	0.001342	27		
Adults 20-49 years old	0.006735	22	0.001591	32		
Adults 50-99 years old	0.006006	20	0.001552	31		
Females 13-49 years old	0.006752	23	0.001573	32		
Triazolylalanine + Triazolylacetic Acid						
General U.S. Population	Not Applicable	Not Applicable	0.013189	15	Not Applicable	Not Applicable
All Infants (< 1 year old)			0.019787	22		
Children 1-2 years old			**0.040964**	**46**		
Children 3-5 years old			0.032416	36		
Children 6-12 years old			0.017755	20		
Youth 13-19 years old			0.010791	12		
Adults 20-49 years old			0.010861	12		
Adults 50-99 years old			0.010274	11		
Females 13-49 years old	**0.070478**	**70**	0.010518	12		

* The values for the highest exposed population for each type of risk assessment are bolded.

6.0 Residential Exposure/Risk Characterization

Existing registered conventional uses on turf and ornamentals result in residential handler and post-application exposures. Residential exposures have been reassessed to reflect updates to the POD selections, appropriate body weight assumptions, as well as to incorporate available TTR and DFR data. Residential exposure to propiconazole is also possible via registered antimicrobial uses in products such as latex paints, wood preservatives, pressure treated wood, preserved textiles, preserved carpets, PVC flooring, and swimming pool liners. These residential exposures were assessed in a separate memo that was prepared by the Antimicrobials Division (T. Dole, D464327, 03/21/2022). The revision of these residential exposures will impact the human health aggregate risk assessment for propiconazole.

6.1 Residential Handler Exposure/Risk Estimates

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed

somewhat differently by HED, as homeowners are assumed to complete all elements of an application without use of any protective equipment.

There are registered propiconazole product labels with residential use sites (e.g., lawns, gardens, trees) that do not require specific clothing (e.g., long sleeve shirt/long pants) and/or PPE, and these labels have been considered in the residential handler assessment for propiconazole.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, residential handler exposure is expected from the registered uses of propiconazole. The quantitative exposure/risk assessment conducted for residential handlers is based on the exposure scenarios listed in Table 6.1.1.

Residential Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption/factor is detailed below.

Application Rate: The maximum single application rates for crop/target groups are available in the PLUS Maximum Use Scenario Report and identified in Table 6.1.1.

Unit Exposures and Area Treated or Amount Handled:
Unit exposure values and estimates for area treated or amount handled were taken from HED's 2012 Residential SOPs[6].

Exposure Duration: Residential handler exposure is expected to be short-term in duration. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners.

Residential Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate exposure and dose for residential handlers can be found in the 2012 Residential SOPs[6].

Combining Exposures/Risk Estimates

Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes were similar. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = Point of Departure (mg/kg/day) ÷ [Combined Dermal + Inhalation dose (mg/kg/day)]

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates

Residential handler non-cancer exposure and combined (dermal + inhalation) risk estimates were calculated for the registered uses of propiconazole. No risk estimates were of concern at the LOC (LOC = 100); combined MOEs range from 1,700-750,000.

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

Table 6.1.1. Residential Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Formulation	Application Equipment	Maximum Application Rate[1]	Area Treated or Amount Handled Daily[2]	Dermal		Inhalation		Total
					Dose (mg/kg/day)[3]	MOE (LOC = 100)[4]	Dose (mg/kg/day)[5]	MOE (LOC = 100)[6]	MOE (LOC = 100)[7]
Gardens/Trees	Liquid	Manually-pressurized handwand	0.000041 lb ai/ft^2	1,200 ft^2	0.0058	7,200	0.000011	3,800,000	7,200
		Hose-end Sprayer			0.0054	7,800	0.000001	49,000,000	7,800
		Backpack			0.012	3,500	0.0001	490,000	3,500
	Dry Flowable	Manually-pressurized handwand			0.0064	6,600	0.0007	62,000	6,000
		Hose-end Sprayer			0.0054	7,800	0.000001	49,000,000	7,800
		Backpack			0.0064	6,000	0.0007	62,000	6,000
	Granule	Push-type rotary spreader	0.00003 lb ai/ft^2		0.000055	770,000	0.0000012	36,000,000	750,000
Lawns/Turf	Liquid	Hose-end Sprayer	1.79 lb ai/A	0.5 A	0.022	1,900	0.0002	170,000	1,800
		Backpack	0.0203 lb ai/gal	5 gal	0.025	1,700		240,000	1,700
	Dry Flowable	Manually-pressurized handwand			0.013	3,200	0.0014	30,000	2,900
		Hose-end Sprayer	1.79 lb ai/A	0.5 A	0.022	1,900	0.0002	170,000	1,800
	Granule	Push-type rotary spreader	1.31 lb ai/A		0.00099	42,000	0.00002	2,000,000	41,000

1 Based on registered labels and BEAD PLUS Package.
2 Based on HED's 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 Dermal Dose = Dermal Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) × Dermal Absorption Factor (15%) ÷ Body Weight (80 kg).
4 Dermal MOE = Dermal NOAEL (42 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A/day or gallons/day) ÷ Body Weight (80 kg).
6 Inhalation MOE = Inhalation NOAEL (42 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
7 Total MOE = NOAEL (42 mg/kg/day) ÷ (Dermal Dose + Inhalation Dose).

6.2 Residential Post-Application Exposure and Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been treated with propiconazole. The quantitative exposure/risk assessment for residential post-application exposures is identified in Table 6.2.1 below.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[7]. While not the only lifestage potentially exposed for these post-application scenarios, the lifestage that is included in the quantitative assessment is health protective for the exposures and risk estimates for any other potentially exposed lifestage.

Residential Post-application Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption/factor is detailed in the 2012 Residential SOPs[7].

Application Rate: The maximum single application rates for crop/target groups are available in the PLUS Maximum Use Scenario Report and identified in Table 6.2.1.

Exposure Duration: For propiconazole, based on the registered uses and label directions (i.e., the minimum re-treatment interval [RTI] of 7 days), short-term exposures are expected.

Residential Post-application Non-Cancer Exposure and Risk Equations
The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs[7].

Combining Exposure and Risk Estimates
Since dermal and incidental oral exposure routes share a common toxicological endpoint, risk estimates have been combined for those routes. The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) should be considered inter-related as it is likely that they occur interspersed amongst each other across time. Combining these scenarios with the dermal exposure scenario would be overly-conservative because of the conservative nature of each individual assessment. Therefore, the post-application exposure scenarios that were combined for children 1 to < 2 years old are the dermal and hand-to-mouth scenarios. This combination should be considered a protective estimate of children's exposure.

Turf Transferable Residues (TTR): A chemical-specific TTR study ("Determination of Transferable Turf Residue on Turf Treated with Banner MAXX (Propiconazole)", EPA MRID No. 45288601) was submitted for propiconazole. The TTR study was reviewed and found to be acceptable for risk assessment (B. Van Deusen, D445667, 03/06/2018). The predicted Day 0 residue was adjusted in the post-application assessment for any differences between the study application rate and the registered application rate for propiconazole. The study summary can be found in the ORE document previously conducted to support the Registration Review of propiconazole (C. Severini, D457373, 12/14/2020).

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

Residential Post-Application Exposure and Risk Summary/Characterization

Per the 2012 Residential Standard Operating Procedures for Residential Pesticide Exposure Assessment (commonly referred to as the 2012 Residential SOPs), HED uses the Day 0 TTR value, whether measured using chemical-specific data, or estimated by use of default transfer values, to assess short-term adult and child 1 to < 2 years old exposures to contact with treated turf. This conservative methodology assumes that an adult or child is exposed to Day 0 residues, at high levels of contact, for 1.5 hours every day for the full short-term exposure duration. While the use of chemical-specific TTR data in residential post-application non-cancer risk assessments represent a refinement of the 2012 Residential SOPs methods, HED believes the methodologies and inputs used for residential post-application exposure and risk assessment are intentionally conservative and protective of human health.

As stated above, HED assumes that adults and children are engaged in high contact activities during each daily exposure to treated turf. The rates of these daily exposures are quantified by use of the transfer coefficient (TC) input. Consistent with the 2012 Residential SOPs, The TC values used for adults and children are derived from data gathered while adult human volunteers performed an approximate 2-hour composite routine consisting of 12 sequential activities which children and adults routinely engage on residential turf[8]. Activities conducted during the 2-hour composite ranged from passive (e.g., walking, crawling), active (e.g., playing frisbee, soccer, games) and hard direct activities (football and tumbling). HED assumes that these high-level activities occur for 1.5 hours daily which is based on the 50% percentile of the time spent outdoors daily for adults and children from the Exposure Factors Handbook 2011 Edition (U.S. EPA, 2011; Table 16-20). The high contact activity, and extended duration of time conducting these activities daily over the course of the full short-term exposure duration yield a health protective estimate of residue loading onto the skin from contact with treated turf.

Once the dermal exposure is estimated for children, the 2012 Residential SOPs describe the methods to estimate the exposures that could occur from hand-to-mouth activity, or a child placing his/her hand in their mouths following contact with treated turf. For residential post-application hand-to-mouth assessment, EPA assumes that a child places their hands in their mouth 14 times per hour (as based on a meta-analysis of hand-to-mouth frequencies outdoors) over 1.5 hours, and that the residues on the hands resulting from contact with treated turf are fully replenished every fourth mouthing event[8]. As described above for dermal exposures, these hand-to-mouth exposures would also be expected to be repeated daily for 30 days and assume contact with Day 0 TTR residues for the full short-term exposure duration. These conservative inputs combine to result in a health protective estimate of hand-to-mouth exposure from contact with treated turf.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates

HED considered the modeled daily residue dissipation and averaged the TTR residue of the California site (0.151 µg/cm^2) over 7 days (the minimum RTI for all registered products). The resulting risks using the 7-day average TTR data uses conservative SOP inputs (i.e., high levels of contact, 1.5 hour daily exposure, 30 subsequent days of exposure, 14 hand-to-mouth events per hour with hand residues fully reloaded every fourth mouthing event), but assumes, in effect,

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

a child 1 to < 2 years old was exposed daily over the course of the exposure duration (i.e., 1 to 30 days for short-term exposure) to residue equivalent to the 7-day average modeled TTR (avg.=0.04 µg/cm^2).

When considering residue averaging, various factors should be considered in order to match the exposure patterns with the toxicological data. If the toxicological time-to-effect can be determined, and if that time period is longer than one day (e.g., repeated dosing is required to elicit an effect), an average exposure accounting for dissipation may be used as a refinement to better match the dosing time/duration required to elicit the effect in the toxicity study. A time-to-effect was unable to be determined for propiconazole. However, no significant acute effects were observed in the toxicity database, other than some clinical signs at a high dose. The endpoint used for the dermal and incidental oral exposure routes is considered to be a result of repeat dosing. The evidence that repeated doses are needed to elicit effects on the target organ of the liver is supported by progression of liver effects over time in both oral rat and mice studies, along with liver effects seen in the two-generation reproduction and fertility effects study in the rat occurring primarily in F_1 parental animals rather than in first-generation parents. Additionally, no adverse effects were seen in the 21-day dermal study in rabbits, for which liver was investigated. As a result, it is assumed that target organ effects would not be expected to occur before 7 days of dosing. Thus, an average exposure accounting for dissipation that can occur over the 7-day period may be used as a refinement to better match the dosing time/duration required to elicit the effect in the toxicity study.

Based on RTIs (minimum of 7 days) of the residential turf products, the toxicology effects based on repeated dosing, as well as the conservatism of the SOP inputs, the modeled 7-day average TTR data is considered a reasonable refinement of post-application exposures from turf contact and is not expected to underestimate risk. Table 6.2.2 presents the residential post-application exposure and risks to treated turf using the modeled 7-day average TTR data with the updated DAF. No risks of concern were identified at the LOC of 100 (MOEs range from 880-690,000).

Table 6.2.2. Residential Post-Application Non-Cancer Exposure and Risk Estimates for Liquid Formulations of Propiconazole on Lawns/Turf.

Lifestage	Use Site	Post-application Exposure Scenario		Application Rate[2]	Dose (mg/kg/day)[3]	MOEs (LOC = 100)[4]	Combined MOEs (LOC=100)[5]
		Activity[1]	Route of Exposure				
CA Site 7-Day Average TTR Residue = 0.04 µg/cm^2							
Adult	Treated Turf	High contact lawn activities after liquid application	Dermal	1.79	0.0203	2,100	NA
Child (11 to <16 years old)	Treated Turf	Mowing Activities	Dermal		0.00048	88,000	NA
		Golfing Activities			0.00186	23,000	NA
Child (6 to <11 years old)	Treated Turf	Golfing Activities	Dermal		0.0022	19,000	NA
Child (1 to <2 years old)	Treated Turf	High contact lawn activities after liquid application	Dermal		0.0402	1,000	880
		Contact after liquid application	Hand to Mouth		0.0055	7,600	

Table 6.2.2. Residential Post-Application Non-Cancer Exposure and Risk Estimates for Liquid Formulations of Propiconazole on Lawns/Turf.

Lifestage	Use Site	Post-application Exposure Scenario		Application Rate[2]	Dose (mg/kg/day)[3]	MOEs (LOC = 100)[4]	Combined MOEs (LOC=100)[5]
		Activity[1]	Route of Exposure				
			Object to Mouth		0.0002	250,000	NA
			Soil Ingestion		0.00006	690,000	NA

1 Residential paint uses were not considered in this assessment but have been evaluated as an antimicrobial use.
2 Based on registered labels and BEAD PLUS Package.
3 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
4 MOE = POD (42 mg/kg/day) ÷ Dose (mg/kg/day).
5 Combined MOE = 1 ÷ [(1/dermal MOE) + (1/inhalation MOE) + (1/incidental oral MOE)], where applicable.

Table 6.2.3 presents the residential post-application exposure and risks to propiconazole for the granule formulation using the default approach for calculating the TTR, as the submitted chemical-specific TTR data measures exposure to turf treated with liquid formulations of propiconazole and would be overly conservative following a granular application, with the updated DAF. No risks of concern were identified at the LOC of 100 (MOEs range from 490-950,000).

Table 6.2.3. Residential Post-Application Non-Cancer Exposure and Risk Estimates for Granular Formulation of Propiconazole on Lawns/Turf.

Lifestage	Use Site	Post-application Exposure Scenario		Application Rate[2]	Dose (mg/kg/day)[3]	MOEs[4]	Combined MOEs (LOC=100)[5]
		Activity[1]	Route of Exposure				
Default Day 0 TTR Residue = 0.029 µg/cm^2							
Adult	Treated Turf	High contact lawn activities after solid application	Dermal	1.31	0.0165	2,500	NA
Child (11 to <16 years old)	Treated Turf	Mowing Activities	Dermal		0.00035	120,000	NA
		Golfing Activities			0.0014	31,000	NA
Child (6 to <11 years old)	Treated Turf	Golfing Activities	Dermal		0.0016	26,000	NA
Child (1 to <2 years old)	Treated Turf	High contact lawn activities after solid application	Dermal		0.0324	1,300	1,220
		Contact after solid application	Hand to Mouth		0.002	21,000	
			Object to Mouth		0.00012	340,000	NA
			Soil Ingestion		0.00004	950,000	NA
			Episodic Ingestion		0.20	490	NA

1 Residential paint uses were not considered in this assessment but have been evaluated as an antimicrobial use.
2 Based on EPA Reg. No. 100-1378.
3 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
4 MOE = POD (42 mg/kg/day) ÷ Dose (mg/kg/day).
5 Combined MOE = 1 ÷ [(1/dermal MOE) + (1/inhalation MOE) + (1/incidental oral MOE)], where applicable.

Chemical-specific DFR data were previously submitted, as described in Section 11, and have been used to inform the residential exposure assessment for adults and children (6 to <11 years old) contacting treated gardens for liquid and solid formulations of propiconazole presented in Table 6.2.4, below. No risks of concern were identified on Day 0 after application at the LOC of 100 (MOEs range from 370-740).

Table 6.2.4. Residential Post-Application Non-Cancer Exposure and Risk Estimates for Propiconazole on Gardens/Trees.

Lifestage	Post-application Exposure Scenario		Application Rate[1]	Dose (mg/kg/day)[2]	MOEs (LOC = 100)[3]
	Use Site/Activity	Route of Exposure			
Day 0 DFR Residue: 3.256 µg/cm^2					
Adult	Contact with treated gardens after liquid application	Dermal	1.79	0.113	370
Child (6 to <11 years old)				0.077	540
Day 0 DFR Residue: 2.383 µg/cm^2					
Adult	Contact with treated gardens after solid application	Dermal	1.31	0.083	510
Child (6 to <11 years old)				0.057	740

1 Based on registered labels and BEAD PLUS Package.
2 Dose (mg/kg/day) algorithms provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
3 MOE = POD (42 mg/kg/day) ÷ Dose (mg/kg/day).
4 Based on maximum single application rate for liquid formulations to gardens/trees.
5 Based on maximum single application rate for solid (G) formulations to gardens/trees.

6.3 Residential Risk Estimates for Use in Aggregate Assessment

For the antimicrobial uses of propiconazole, several residential post-application dermal risk estimates were of concern on their own (i.e., below the LOC of 100) for propiconazole-treated textiles and carpet; and incidental oral risk estimates were of concern on their own for preserved carpet fibers. Additionally, although the dermal MOE of 100 for dermal exposure to PVC flooring is not of concern on its own, AD recommended that it not be included in the aggregate assessment because it would contribute to an aggregate risk of concern when combined with the other exposures that are included in the aggregate risk assessment. Additional details regarding these scenarios of concern for antimicrobial products are provided in the AD revised DRA for residential exposures (T. Dole, D464327, 03/21/2022). The scenarios already found to be of concern were not considered further for the aggregate assessment but are described in detail in the AD revised DRA for residential exposures (T. Dole, D464327, 03/21/2022).

Table 6.3.1 reflects the updated residential risk estimates demonstrating the lowest MOE value without presenting risks of concern on their own from conventional and antimicrobial products, recommended for use in the aggregate assessment for propiconazole.

- The recommended residential exposure for use in the adult aggregate assessment reflects dermal exposure from contact with treated gardens after liquid applications.
- The recommended residential exposure for use in the children 11 to <16 years old aggregate assessment reflects dermal and incidental oral exposure from post-application contact with propiconazole-treated swimming pool liners.
- The recommended residential exposure for use in the children 6 to <11 years old aggregate assessment reflects dermal exposure from contact with treated gardens after

liquid applications.

- The recommended residential exposure for use in the children 1 to <2 years old aggregate assessment reflects dermal and incidental oral exposure from post-application contact with pressure treated wood.

Table 6.3.1. Recommendations for Residential Exposures for the Propiconazole Aggregate Assessment.

Lifestage	Post-Application Exposure Scenario	Dose (mg/kg/day)[1]				MOE[2]			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total[3]
Adult[4]	Contact with treated gardens after liquid application	0.113	N/A	N/A	0.113	370	N/A	N/A	370
Children (11 to <16 years old)[5]	Contact with treated pool liners	0.0065	N/A	0.0030	0.0095	6500	N/A	14,000	4,400
Children (6 to <11 years old)[4]	Contact with treated gardens after liquid application	0.077	N/A	N/A	0.077	540	N/A	N/A	540
Children (1 to <2 years)[5]	Contact with treated wood	0.040	N/A	0.069	0.109	1,000	N/A	610	380

[1] Dose (mg/kg/day) algorithms for adults and children (6 to <11 years old) provided in 2012 Residential SOPs (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).

[2] MOE = POD (42 mg/kg/day) ÷ Dose (mg/kg/day).

[3] Total = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental Oral MOE), where applicable.

[4] Based on Day 0 DFR Residue: Table 6.2.4.

[5] These doses and MOEs are from a separate memo prepared by the Antimicrobials Division: T. Dole, D464327, 03/21/2022 (see Section 5.0).

7.0 Aggregate Exposure/Risk Characterization

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. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard (e.g., a NOAEL or PAD), or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. Food and residential exposures from propiconazole have been aggregated since those exposure pathways are relevant for risk assessment. Both antimicrobial and conventional uses are presented in this aggregate assessment. The residential post-application exposure scenarios demonstrating the lowest MOE values without presenting risks of concern on their own from conventional and antimicrobial uses were selected for use in the aggregate exposure assessment for each subpopulation.

The previous aggregate human health risk assessment for free triazoles and its conjugates was recently updated and the aggregate estimates are below HED's level of concern (T. Morton, D461600/D461602, 05/06/2021).

7.1 Acute Aggregate Risk

The only propiconazole exposures relevant to the acute duration are food and water; therefore, the acute dietary risk estimates serve as the acute aggregate risk assessment. The acute risk estimates for all populations resulting from aggregate exposure to propiconazole in food and drinking water are below HED's level of concern. The food and drinking water exposure estimate for the most highly exposed subgroup is 19% of the aPAD for children 1-2 years old. Refer to Section 5.4.3 for a detailed discussion of the acute dietary assessment conducted for conventional propiconazole uses.

Although there are registered antimicrobial uses that could result in indirect food contact, these uses are expected to result in minimal dietary exposure compared to the conventional uses of propiconazole. Therefore, AD did not conduct a dietary exposure assessment for the antimicrobial uses of propiconazole. Additionally, drinking water residues are anticipated from the antimicrobial uses; however, they are lower than the residues resulting from the conventional uses and were not assessed separately. See the AD DRA for additional details (S. Hu et al., D459696, 12/01/2020).

7.2 Short-Term Aggregate Risk

Short-term aggregate assessments include exposures that will occur from one to thirty days. There is potential for short-term handler and post-application exposure associated with the residential use of conventional products on turf and gardens. Residential exposure associated with the use of antimicrobial products on latex paints, wood preservatives, pressure treated wood, preserved textiles, preserved carpets, PVC flooring, and swimming pool liners is also possible. There is also potential for short-term residential handler exposure to antimicrobial products from applying propiconazole-treated wood preservatives and latex paints, and post-application exposure to pressure treated wood, preserved textiles, preserved carpets, PVC flooring, and swimming pool liners. For food and water, the exposure is taken from the chronic dietary assessment. For adults and children, residential post-application exposure scenarios demonstrating the lowest MOE value without presenting risks of concern on their own from conventional and antimicrobial uses were aggregated with dietary exposures for the appropriate subpopulation for each scenario. Refer to Section 6.3 for the residential exposures recommended for use in aggregate assessment.

Table 7.2.1 aggregates the short-term risk for adults, children 1 to <2 years old, and children 6 to <11 years old from dermal and incidental oral residential exposure and from consumption of food and water. The short-term aggregate risk MOE of 350 for adults does not fall below HED's LOC (LOC=100), and therefore is not of concern. The short-term aggregate risk MOE of 310 for children 1 to <2 years old does not fall below HED's LOC (LOC=100), and therefore is not of concern. The short-term aggregate risk MOE of 470 for children 6 to <11 years old does not fall below HED's LOC (LOC=100), and therefore is not of concern.

Table 7.2.1. Short-Term Aggregate Risk Calculations.							
Population	Short- or Intermediate-Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure mg/kg/day	Residential Exposure mg/kg/day[3]	Total Exposure mg/kg/day[4]	Aggregate MOE (food, water, and residential)[5]
Adults	42	100	0.42	0.007519	0.113	0.120519	350
Children (1 to 2 years old)	42	100	0.42	0.027730	0.109	0.13673	310
Children (6 to <11 years old)	42	100	0.42	0.011678	0.077	0.088678	470

[1] NOAEL=42 mg/kg/day; Target LOC=100, 2-generation reproduction and fertility effects study – rat (10x for interspecies extrapolation, 10x for intraspecies variation, and 1x FQPA SF).
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
[3] Residential Exposure = [Dermal exposure + Incidental oral exposure (where applicable)]. Source of residential exposure values used in aggregate assessment: Table 6.3.1.
[4] Total Exposure = Avg Food & Water Exposure + Residential Exposure. Source of average chronic food & water exposure for adults, children 1-2 years old, and children 6-12 years old: Table 5.4.6.
[5] Aggregate MOE = [NOAEL/(Avg Food & Water Exposure + Residential Exposure)].

7.3 Intermediate-Term Aggregate Risk

Intermediate-term aggregate assessments include exposures that will occur from thirty days to six months. The only residential use scenarios that will result in potential intermediate-term exposures to propiconazole are from antimicrobial uses. For propiconazole, based on the registered antimicrobial uses, both short- and intermediate-term exposures are expected. Additionally, for both short- and intermediate-term durations, the PODs selected are the same. Therefore, risk estimates provided by the Antimicrobial Division are considered protective of both durations and a separate intermediate-term aggregate assessment was not performed.

7.4 Chronic Aggregate Risk

Chronic or long-term aggregate assessments include exposures that will exceed six months. The only propiconazole exposures relevant to the chronic duration are food and water; therefore, the chronic dietary risk estimates serve as the chronic aggregate risk assessment. The chronic risk estimates for all populations, resulting from aggregate exposure to propiconazole in food and drinking water are below EPA's level of concern. The food and drinking water exposure estimate for the most highly exposed subgroup is 15% of the cPAD for children 1-2 years old. See Section 5.4.4 for a detailed discussion of the chronic dietary assessment conducted for conventional propiconazole uses.

AD did not conduct a dietary exposure assessment for the antimicrobial uses of propiconazole. Additionally, drinking water residues are anticipated from the antimicrobial uses; however, they are lower than the residues resulting from the conventional uses and were not assessed separately. See the AD DRA for additional details (S. Hu et al., D459696, 12/01/2020).

7.5 Cancer Aggregate Risk

As the risks estimated based on the chronic reference dose are protective of cancer effects, no separate cancer risk assessment is necessary. The chronic dietary aggregate risk assessment is below the Agency's level of concern.

8.0 Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods (e.g., groundboom and airblast) employed for propiconazole. The Agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the Agency's Spray Drift website for more information) [9]. The Agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift.* This document outlines the quantification of indirect non-occupational exposure to drift.

Off-target movement of pesticides can occur via many types of pathways, and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those they may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products. The maximum registered application rate to turf (1.79 lb ai/A) would result in risk estimates from residential post-application exposure to be protective of non-occupational spray drift risk estimates. However, TTR data was averaged for the residential post-application exposure assessment. Due to this refinement of the turf post-application scenario, these risk estimates are not considered representative of the spray drift assessment methodology; therefore, a spray drift assessment was still conducted.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[10] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted.

[9] Available: http://www.epa.gov/reducing-pesticide-drift

[10] This approach is consistent with the requirements of the EPA's Worker Protection Standard.

Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment. Chemical-specific TTR data and the TTR value for the worst-case study site (California-specific predicted day 0 residue: 0.151 µg/cm^2) were used for this assessment.

In order to evaluate the drift potential and associated risks, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of propiconazole. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs)*.

A screening approach was developed based on the use of the AgDrift model in situations where specific label guidance that defines application parameters is not available.[11] AgDrift is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). Section 8.1 provides the screening level drift related risk estimates.
In many cases, risks are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to account for this issue and to provide additional risk management options additional spray drift deposition fractions were also considered. These drift estimates represent plausible options for pesticide labels.

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Propiconazole is used on a variety of agricultural crops and can be applied via groundboom, airblast, and aerial equipment. The recommended drift scenario screening level options are listed below:

- **Groundboom applications** are based on the AgDrift option for high boom height and using very fine to fine spray type using the 90th percentile results.
- **Orchard airblast applications** are based on the AgDrift option for Sparse (Young/Dormant) tree canopies.

[11] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#AgDrift

- **Aerial applications** are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).[12]

Exposures were considered for 50 feet wide lawns where the nearest side of the property was directly adjoining the treated field (at field edge) and at varied distances up to 300 feet downwind of a treated field. Results are presented in Tables 8.1.1 and 8.1.2 and indicate all dermal risk estimates for adults were greater than the LOC (LOC = 100) at the field's edge and are not of concern (MOEs range from 2,100-3,800) with use of chemical-specific TTR data. All combined (dermal and incidental oral) risk estimates for children (1 to <2 years) were greater than the LOC (LOC = 100) at the field's edge and are not of concern (MOEs range from 950-1,700).

Table 8.1.1. Children (1>2 years old) Risk Estimates Related to Indirect Exposure to Spray Drift for Propiconazole for Combined Oral (HTM) and Dermal Routes of Exposure.

Application Equipment	Spray Type/ Nozzle Configuration	Application Rate (lb ai/A)	TTR[1] (ug/cm2)	At Edge Combined MOE[2] (LOC = 100)
Aerial	***Fine to Medium***	1.78	0.151	950
Groundboom	***High Boom Very fine to Fine***			1,300
Airblast	***Sparse***			1,700

1. Based on Day 0 TTR data from California site: Table 6.2.2.
2. MOEs at various distances from field edge = combined dermal plus incidental oral MOEs. Dermal POD = 42 mg/kg/day and Incidental oral POD = 42 mg/kg/day. The dermal and incidental oral doses are calculated using the algorithms provided in the Turf Residential SOPs (http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide), and the TTR used in the calculations is the estimated TTR * drift fraction of spray drift that deposits on lawns at various distances from the field edge.

Table 8.1.2. Adult Risk Estimates Related to Indirect Exposure to Spray Drift for Propiconazole for the Dermal Route of Exposure.

Application Equipment	Spray Type/ Nozzle Configuration	Application Rate (lb ai/A)	TTR[1] (ug/cm2)	At Edge Combined MOE[2] (LOC = 100)
Aerial	***Fine to Medium***	1.78	0.151	2,100
Groundboom	***High Boom Very fine to Fine***			2,900
Airblast	***Sparse***			3,800

1. Based on Day 0 TTR data from California site: Table 6.2.2.
2. MOEs at various distances from field edge = Dermal POD (42 mg/kg/day) ÷ Dose (mg/kg/day), where the dermal dose is calculated using the algorithms provided in the Turf Residential SOPs (http://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide), and the TTR used in the calculations is the estimated TTR * drift fraction of spray drift that deposits on lawns at various distances from the field edge

[12] AgDrift allows for consideration of even finer spray patterns characterized as very fine to fine. However, this spray pattern was not selected as the common screening basis since it is used less commonly for most agriculture

9.0 Non-Occupational Bystander Post-Application Inhalation Exposure and Risk Estimates

Volatilization of pesticides may be a source of post-application inhalation exposure to individuals nearby pesticide applications. The Agency sought expert advice and input on issues related to volatilization of pesticides from FIFRA Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[13]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (*Human Health Bystander Screening Level Analysis: Volatilization of Conventional Pesticides*[14]).

During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for propiconazole.

10.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to propiconazole and any other substances[15]. Although the conazole fungicides (triazoles) produce 1,2,4 triazole and its acid-conjugated metabolites (triazolylalanine and triazolylacetic acid), 1,2,4 triazole and its acid-conjugated metabolites do not contribute to the toxicity of the parent conazole fungicides (triazoles). The Agency has assessed the aggregate risks from the 1,2,4 triazole and its acid-conjugated metabolites (triazolylalanine and triazolylacetic acid) separately. Propiconazole does not appear to produce any other toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that propiconazole has a common mechanism of toxicity with other substances. In 2016, EPA's Office of Pesticide Programs released a guidance document titled, *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* [https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework]. This document provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach beginning with the evaluation of available toxicological information and if necessary, followed by a risk-based screening approach. This framework supplements the existing guidance documents for establishing common mechanism groups (CMGs)[16] and conducting cumulative risk assessments (CRA)[17]. During Registration Review, the Agency will utilize this framework to determine if the available toxicological data for propiconazole suggests a candidate CMG may be established with other pesticides. If a CMG is established, a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure.

[13] http://archive.epa.gov/scipoly/sap/meetings/web/pdf/120309meetingminutes.pdf
[14] https://www.regulations.gov/document/EPA-HQ-OPP-2014-0219-0002
[15] EPA's assessments of conazoles prior to the development of the 2016 Framework document noted the lack of conclusive data to make a common mechanism of toxicity finding for the conazoles.
[16] Guidance for Identifying Pesticide Chemicals and Other Substances that have a Common Mechanism of Toxicity (USEPA, 1999)
[17] Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (USEPA, 2002)

11.0 Occupational Exposure/Risk Characterization

11.1 Short-/Intermediate-Term Occupational Handler Exposure and Risk Estimates

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered uses of propiconazole. The quantitative exposure/risk assessment conducted for occupational handlers is based on the exposure scenarios listed in Table 11.1.1.

Occupational Handler Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption/factor is detailed below on an individual basis.

Application Rate: The maximum single application rates for crop/target groups are available in the Line by Line, and Maximum Use Scenario Pesticide Label Usage Summary (PLUS) Reports generated as part of the updated PLUS Package (06/04/2020) for propiconazole (122101) by OPP's Biological and Economic Analysis Division (BEAD).

Unit Exposures: It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data) and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[18]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[19].

Area Treated or Amount Handled: Inputs for area treated and amount handled were based on information in ExpoSAC Policy 9.2 and for post-harvest treatments, the values for the amount treated or handled is based on the HED ExpoSAC Post-Harvest Commodity Pesticide Treatments Policy/Guidance.

[18] Available: https://www.epa.gov/sites/production/files/2020-03/documents/opp-hed-pesticide-handler-surrogate-unit-exposure-table-march-2020.pdf
[19] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Post-Harvest Commodity and Bulb-Dip Amount Handled: The inputs for post-harvest commodity and bulb-dip amount handled are based on the HED ExpoSAC Policy/Guidance for Assessment of Occupational Exposure for Post-Harvest Commodity Pesticide Treatments, the amount handled in a day (*Maxey, S.W., and Murphy, P.G. 1994. Evaluation of Post-Application Exposures to Sodium O-phenylphenate Tetrahydrate/O-phenylphenol to Workers during Post-Harvest Activities at Pear and Citrus Fruit Packaging Facilities. Unpublished study by Dow Chemical. October 19, 1994. EPA MRID 43432901*).

Post-harvest treatment is primarily made via automatic dipping/drenching or spraying as the commodity passes down a conveyor belt. HED has concluded that the likelihood that non-automated post-harvest facilities are in operation is minimal, since large commercial facilities tend to dominate the market. While it is acknowledged that there may be exposure during the actual manual (non-automated) dip applications, HED does not currently have data to assess this type of scenario.

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region). For propiconazole, based on the registered uses and label directions (i.e., multiple applications per season and minimum RTI of 7 days, short- and intermediate-term exposures are expected.

Personal Protective Equipment: Estimates of dermal and inhalation exposure were calculated for various levels of PPE. Results are presented for "baseline," defined as a single layer of clothing consisting of a long-sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves, respirator, etc). Propiconazole product labels require that applicators and handlers must wear long-sleeved shirt and pants, chemical-resistant gloves, shoes and socks, and protective eyewear.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in the ORE document previously conducted to support the Registration Review of propiconazole (C. Severini, D457373, 12/14/2020).

Combining Exposures/Risk Estimates:

Dermal and inhalation risk estimates were combined in this assessment, since the toxicological effects for these exposure routes were similar. Dermal and inhalation risk estimates were combined using the following formula:

Total MOE = Point of Departure (mg/kg/day) ÷ [Combined dermal + inhalation dose (mg/kg/day)]

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

Occupational handler non-cancer exposure and combined risk estimates were calculated for the registered uses of propiconazole and can be found in Table 11.1.1. MOEs are presented with baseline attire; scenarios resulting in risks of concern in baseline attire are presented with label-required PPE. MOEs range from 54 to 590,000 (LOC=100). There are no risks of concern with label-required PPE.

The Agency matches quantitative occupational exposure assessment with appropriate characterization of exposure potential. While HED presents quantitative risk estimates for human flaggers where appropriate, agricultural aviation has changed dramatically over the past two decades. According the 2012 National Agricultural Aviation Association (NAAA) survey of their membership, the use of GPS for swath guidance in agricultural aviation has grown steadily from the mid 1990's. Over the same time period, the use of human flaggers for aerial pesticide applications has decreased steadily from ~15% in the late 1990's to only 1% in the most recent (2012) NAAA survey. The Agency will continue to monitor all available information sources to best assess and characterize the exposure potential for human flaggers in agricultural aerial applications.

HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure during aerial applications (covering both airplanes and helicopters) of liquid formulations to pilots in enclosed cockpits (data from AHETF) and of granule formulations in enclosed cockpits (data from PHED). Therefore, risks to pilots are assessed using the engineering control (enclosed cockpits) and baseline attire (long-sleeve shirt, long pants, shoes, and socks); use of the data in this fashion is consistent with the Agency's Worker Protection Standard (WPS) stipulations for engineering controls, which says label-required PPE for applicators can be reduced when using an enclosed cockpit (40 CFR 170.240(d)(6)(iii)) as well as a provision regarding use of gloves for aerial applications (40 CFR 170.240(d)(6)(i)), which says pilots are not required to wear protective gloves for the duration of the application. With this level of protection, there are no risk estimates of concern for applicators.

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.														
Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Mixer/Loader														
Dry Flowable, Aerial, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	227	SL/No G	8.96	No-R	1.78	lb ai/acre	60	acres	0.0454	930	0.012	3500	730
Dry Flowable, Aerial, Broadcast	Orchard/Vineyard	227	SL/No G	8.96	No-R	0.225	lb ai/acre	350	acres	0.0336	1300	0.00883	4800	1000
Dry Flowable, Aerial, Broadcast	Sod	227	SL/No G	8.96	No-R	0.442	lb ai/acre	350	acres	0.0658	640	0.0174	2400	510
Dry Flowable, Aerial, Broadcast	Field crop, typical	227	SL/No G	8.96	No-R	0.225	lb ai/acre	350	acres	0.0336	1300	0.00883	4800	1000
Wettable Powder, Backpack, Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	77.7	SL/No G	2.75	No-R	0.178	lb ai/gallon solution	1000	gallons solution	0.0259	1600	0.00613	6900	1300
Wettable Powder, Mechanically-pressurized Handgun, Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	77.7	SL/No G	2.75	No-R	0.178	lb ai/gallon solution	1000	gallons solution	0.0259	1600	0.00613	6900	1300
Liquid, Backpack, Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	220	SL/No G	0.219	No-R	0.178	lb ai/gallon solution	1000	gallons solution	0.0735	570	0.000488	86000	570
Liquid, Mechanically-pressurized Handgun, Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	220	SL/No G	0.219	No-R	0.178	lb ai/gallon solution	1000	gallons solution	0.0735	570	0.000488	86000	570
Dry Flowable, Backpack, Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	227	SL/No G	8.96	No-R	0.178	lb ai/gallon solution	1000	gallons solution	0.0758	550	0.0199	2100	440
Dry Flowable, Mechanically-pressurized Handgun, Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	227	SL/No G	8.96	No-R	0.178	lb ai/gallon solution	1000	gallons solution	0.0758	550	0.0199	2100	440
Dry Flowable, Aerial, Broadcast	Field crop, high-acreage	227	SL/No G	8.96	No-R	0.225	lb ai/acre	1200	acres	0.115	370	0.0303	1400	290

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Dry Flowable, Aerial, Broadcast	Forestry	227	SL/No G	8.96	No-R	0.297	lb ai/acre	1200	acres	0.152	280	0.0399	1100	220
Dry Flowable, Aerial, Broadcast	Conifer plantation	227	SL/No G	8.96	No-R	0.297	lb ai/acre	1200	acres	0.152	280	0.0399	1100	220
Dry Flowable, Airblast, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	227	SL/No G	8.96	No-R	1.78	lb ai/acre	20	acres	0.0152	2800	0.00399	11000	2200
Dry Flowable, Airblast, Broadcast	Orchard/Vineyard	227	SL/No G	8.96	No-R	0.225	lb ai/acre	40	acres	0.00383	11000	0.00101	42000	8700
Dry Flowable, Chemigation, Broadcast	Orchard/Vineyard	227	SL/No G	8.96	No-R	0.225	lb ai/acre	350	acres	0.0336	1300	0.00883	4800	1000
Dry Flowable, Chemigation, Broadcast	Sod	227	SL/No G	8.96	No-R	0.297	lb ai/acre	350	acres	0.0443	950	0.0116	3600	750
Dry Flowable, Chemigation, Broadcast	Field crop, typical	227	SL/No G	8.96	No-R	0.225	lb ai/acre	350	acres	0.0336	1300	0.00883	4800	1000
Dry Flowable, Chemigation, Broadcast	Field crop, high-acreage	227	SL/No G	8.96	No-R	0.225	lb ai/acre	350	acres	0.0336	1300	0.00883	4800	1000
Dry Flowable, Chemigation, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	227	SL/No G	8.96	No-R	1.78	lb ai/acre	60	acres	0.0454	930	0.012	3500	730
Dry Flowable, Chemigation, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	227	SL/No G	8.96	No-R	0.297	lb ai/acre	60	acres	0.00759	5500	0.002	21000	4400
Dry Flowable, Groundboom, Broadcast	Golf course (tees and greens only)	227	SL/No G	8.96	No-R	1.78	lb ai/acre	5	acres	0.00379	11000	0.000996	42000	8700
Dry Flowable, Groundboom, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	227	SL/No G	8.96	No-R	1.78	lb ai/acre	5	acres	0.00379	11000	0.000996	42000	8700
Dry Flowable, Groundboom, Broadcast	Golf course (fairways, tees, greens)	227	SL/No G	8.96	No-R	1.78	lb ai/acre	40	acres	0.0304	1400	0.00798	5300	1100

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Dry Flowable, Groundboom, Broadcast	Field-grown ornamental crops	227	SL/No G	8.96	No-R	0.225	lb ai/acre	40	acres	0.00383	11000	0.00101	42000	8700
Dry Flowable, Groundboom, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	227	SL/No G	8.96	No-R	0.297	lb ai/acre	60	acres	0.00759	5500	0.002	21000	4400
Dry Flowable, Groundboom, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	227	SL/No G	8.96	No-R	1.78	lb ai/acre	60	acres	0.0454	930	0.012	3500	730
Dry Flowable, Groundboom, Broadcast	Sod	227	SL/No G	8.96	No-R	0.297	lb ai/acre	80	acres	0.0101	4200	0.00266	16000	3300
Dry Flowable, Groundboom, Broadcast	Orchard/Vineyard	227	SL/No G	8.96	No-R	0.225	lb ai/acre	40	acres	0.00383	11000	0.00101	42000	8700
Dry Flowable, Groundboom, Broadcast	Field crop, typical	227	SL/No G	8.96	No-R	0.225	lb ai/acre	80	acres	0.00767	5500	0.00201	21000	4400
Dry Flowable, Groundboom, Broadcast	Field crop, high-acreage	227	SL/No G	8.96	No-R	0.225	lb ai/acre	200	acres	0.0191	2200	0.00504	8300	1700
Liquid, Aerial, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	220	SL/No G	0.219	No-R	0.297	lb ai/acre	60	acres	0.00735	5700	0.0000488	860000	5700
Liquid, Aerial, Broadcast	Orchard/Vineyard	220	SL/No G	0.219	No-R	0.225	lb ai/acre	350	acres	0.0324	1300	0.000215	200000	1300
Liquid, Aerial, Broadcast	Sod	220	SL/No G	0.219	No-R	0.297	lb ai/acre	350	acres	0.0429	980	0.000285	150000	970
Liquid, Aerial, Broadcast	Field crop, typical	220	SL/No G	0.219	No-R	0.225	lb ai/acre	350	acres	0.0324	1300	0.000215	200000	1300
Liquid, Aerial, Broadcast	Field crop, high-acreage	220	SL/No G	0.219	No-R	0.225	lb ai/acre	1200	acres	0.111	380	0.000739	57000	380
Liquid, Aerial, Broadcast	Forestry	220	SL/No G	0.219	No-R	0.297	lb ai/acre	1200	acres	0.147	290	0.000976	43000	290
Liquid, Aerial, Broadcast	Conifer plantation	220	SL/No G	0.219	No-R	0.297	lb ai/acre	1200	acres	0.147	290	0.000976	43000	290

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Liquid, Airblast, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	220	SL/No G	0.219	No-R	0.297	lb ai/acre	20	acres	0.00246	17000	0.0000163	2600000	17000
Liquid, Airblast, Broadcast	Orchard/Vineyard	220	SL/No G	0.219	No-R	0.225	lb ai/acre	40	acres	0.00371	11000	0.0000246	1700000	11000
Liquid, Chemigation, Broadcast	Orchard/Vineyard	220	SL/No G	0.219	No-R	0.225	lb ai/acre	350	acres	0.0324	1300	0.000215	200000	1300
Liquid, Chemigation, Broadcast	Sod	220	SL/No G	0.219	No-R	0.297	lb ai/acre	350	acres	0.0429	980	0.000285	150000	970
Liquid, Chemigation, Broadcast	Field crop, typical	220	SL/No G	0.219	No-R	0.225	lb ai/acre	350	acres	0.0324	1300	0.000215	200000	1300
Liquid, Chemigation, Broadcast	Field crop, high-acreage	220	SL/No G	0.219	No-R	0.225	lb ai/acre	350	acres	0.0324	1300	0.000215	200000	1300
Liquid, Chemigation, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	220	SL/No G	0.219	No-R	1.78	lb ai/acre	60	acres	0.0441	950	0.000293	140000	940
Liquid, Chemigation, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	220	SL/No G	0.219	No-R	0.297	lb ai/acre	60	acres	0.00735	5700	0.0000488	860000	5700
Liquid, Groundboom, Broadcast	Golf course (tees and greens only)	220	SL/No G	0.219	No-R	1.78	lb ai/acre	5	acres	0.00368	11000	0.0000244	1700000	11000
Liquid, Groundboom, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	220	SL/No G	0.219	No-R	1.78	lb ai/acre	5	acres	0.00368	11000	0.0000244	1700000	11000
Liquid, Groundboom, Broadcast	Golf course (fairways, tees, greens)	220	SL/No G	0.219	No-R	1.78	lb ai/acre	40	acres	0.0294	1400	0.000195	220000	1400
Liquid, Groundboom, Broadcast	Field-grown ornamental crops	220	SL/No G	0.219	No-R	0.225	lb ai/acre	40	acres	0.00371	11000	0.0000246	1700000	11000
Liquid, Groundboom, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	220	SL/No G	0.219	No-R	0.297	lb ai/acre	60	acres	0.00735	5700	0.0000488	860000	5700

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Liquid, Groundboom, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	220	SL/No G	0.219	No-R	1.78	lb ai/acre	60	acres	0.0441	950	0.000293	140000	940
Liquid, Groundboom, Broadcast	Sod	220	SL/No G	0.219	No-R	0.297	lb ai/acre	80	acres	0.00981	4300	0.000065	650000	4300
Liquid, Groundboom, Broadcast	Orchard/Vineyard	220	SL/No G	0.219	No-R	0.225	lb ai/acre	40	acres	0.00371	11000	0.0000246	1700000	11000
Liquid, Groundboom, Broadcast	Field crop, typical	220	SL/No G	0.219	No-R	0.225	lb ai/acre	80	acres	0.00743	5700	0.0000493	850000	5700
Liquid, Groundboom, Broadcast	Field crop, high-acreage	220	SL/No G	0.219	No-R	0.225	lb ai/acre	200	acres	0.0186	2300	0.000123	340000	2300
Wettable Powder, Aerial, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	77.7	SL/No G	2.75	No-R	0.297	lb ai/acre	60	acres	0.00259	16000	0.000613	69000	13000
Wettable Powder, Aerial, Broadcast	Orchard/Vineyard	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	350	acres	0.0115	3700	0.00271	15000	3000
Wettable Powder, Aerial, Broadcast	Sod	77.7	SL/No G	2.75	No-R	0.297	lb ai/acre	350	acres	0.0152	2800	0.00358	12000	2300
Wettable Powder, Aerial, Broadcast	Field crop, typical	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	350	acres	0.0115	3700	0.00271	15000	3000
Wettable Powder, Aerial, Broadcast	Forestry	77.7	SL/No G	2.75	No-R	0.297	lb ai/acre	1200	acres	0.0519	810	0.0123	3400	650
Wettable Powder, Aerial, Broadcast	Conifer plantation	77.7	SL/No G	2.75	No-R	0.297	lb ai/acre	1200	acres	0.0519	810	0.0123	3400	650
Wettable Powder, Aerial, Broadcast	Field crop, high-acreage	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	1200	acres	0.0394	1100	0.00929	4500	880

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Wettable Powder, Airblast, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	77.7	SL/No G	2.75	No-R	0.297	lb ai/acre	20	acres	0.000866	48000	0.000204	210000	39000
Wettable Powder, Airblast, Broadcast	Orchard/Vineyard	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	40	acres	0.00131	32000	0.00031	140000	26000
Wettable Powder, Chemigation, Broadcast	Orchard/Vineyard	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	350	acres	0.0115	3700	0.00271	15000	3000
Wettable Powder, Chemigation, Broadcast	Sod	77.7	SL/No G	2.75	No-R	0.297	lb ai/acre	350	acres	0.0152	2800	0.00358	12000	2300
Wettable Powder, Chemigation, Broadcast	Field crop, typical	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	350	acres	0.0115	3700	0.00271	15000	3000
Wettable Powder, Chemigation, Broadcast	Field crop, high-acreage	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	350	acres	0.0115	3700	0.00271	15000	3000
Wettable Powder, Chemigation, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	77.7	SL/No G	2.75	No-R	1.78	lb ai/acre	60	acres	0.0156	2700	0.00368	11000	2200
Wettable Powder, Chemigation, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	77.7	SL/No G	2.75	No-R	0.297	lb ai/acre	60	acres	0.00259	16000	0.000613	69000	13000
Wettable Powder, Groundboom, Broadcast	Golf course (tees and greens only)	77.7	SL/No G	2.75	No-R	1.78	lb ai/acre	5	acres	0.0013	32000	0.000306	140000	26000
Wettable Powder, Groundboom, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	77.7	SL/No G	2.75	No-R	1.78	lb ai/acre	5	acres	0.0013	32000	0.000306	140000	26000
Wettable Powder, Groundboom, Broadcast	Golf course (fairways, tees, greens)	77.7	SL/No G	2.75	No-R	1.78	lb ai/acre	40	acres	0.0104	4000	0.00245	17000	3200

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Wettable Powder, Groundboom, Broadcast	Field-grown ornamental crops	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	40	acres	0.00131	32000	0.00031	140000	26000
Wettable Powder, Groundboom, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	77.7	SL/No G	2.75	No-R	0.297	lb ai/acre	60	acres	0.00259	16000	0.000613	69000	13000
Wettable Powder, Groundboom, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	77.7	SL/No G	2.75	No-R	1.78	lb ai/acre	60	acres	0.0156	2700	0.00368	11000	2200
Wettable Powder, Groundboom, Broadcast	Sod	77.7	SL/No G	2.75	No-R	0.297	lb ai/acre	80	acres	0.00347	12000	0.000816	51000	9700
Wettable Powder, Groundboom, Broadcast	Orchard/Vineyard	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	40	acres	0.00131	32000	0.00031	140000	26000
Wettable Powder, Groundboom, Broadcast	Field crop, typical	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	80	acres	0.00263	16000	0.000619	68000	13000
Wettable Powder, Groundboom, Broadcast	Field crop, high-acreage	77.7	SL/No G	2.75	No-R	0.225	lb ai/acre	200	acres	0.00656	6400	0.00155	27000	5200
Applicator														
Spray (all starting formulations), Aerial, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	2.08	EC/G	0.0049	EC/No-R	0.297	lb ai/acre	60	acres	0.0000696	600000	0.00000109	39000000	590000
Spray (all starting formulations), Aerial, Broadcast	Orchard/Vineyard	2.08	EC/G	0.0049	EC/No-R	0.225	lb ai/acre	350	acres	0.000308	140000	0.00000483	8700000	140000
Spray (all starting formulations), Aerial, Broadcast	Sod	2.08	EC/G	0.0049	EC/No-R	0.297	lb ai/acre	350	acres	0.000405	100000	0.00000636	6600000	99000

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Spray (all starting formulations), Aerial, Broadcast	Field crop, typical	2.08	EC/G	0.0049	EC/No-R	0.225	lb ai/acre	350	acres	0.000308	140000	0.00000483	8700000	140000
Spray (all starting formulations), Aerial, Broadcast	Field crop, high-acreage	2.08	EC/G	0.0049	EC/No-R	0.225	lb ai/acre	1200	acres	0.00105	40000	0.0000165	2500000	39000
Spray (all starting formulations), Aerial, Broadcast	Forestry	2.08	EC/G	0.0049	EC/No-R	0.297	lb ai/acre	1200	acres	0.00139	30000	0.0000219	1900000	30000
Spray (all starting formulations), Aerial, Broadcast	Conifer plantation	2.08	EC/G	0.0049	EC/No-R	0.297	lb ai/acre	1200	acres	0.00139	30000	0.0000219	1900000	30000
Spray (all starting formulations), Airblast, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	1770	SL/No G	4.71	No-R	0.297	lb ai/acre	20	acres	0.0197	2100	0.00035	120000	2100
Spray (all starting formulations), Airblast, Broadcast	Orchard/Vineyard	1770	SL/No G	4.71	No-R	0.225	lb ai/acre	40	acres	0.0298	1400	0.00053	79000	1400
Spray (all starting formulations), Groundboom, Broadcast	Golf course (tees and greens only)	78.6	SL/No G	0.34	No-R	1.78	lb ai/acre	5	acres	0.00131	32000	0.0000379	1100000	31000
Spray (all starting formulations), Groundboom, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	78.6	SL/No G	0.34	No-R	1.78	lb ai/acre	5	acres	0.00131	32000	0.0000379	1100000	31000
Spray (all starting formulations), Groundboom, Broadcast	Golf course (fairways, tees, greens)	78.6	SL/No G	0.34	No-R	1.78	lb ai/acre	40	acres	0.0105	4000	0.000303	140000	3900

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.															
Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Spray (all starting formulations), Groundboom, Broadcast	Field-grown ornamental crops	78.6	SL/No G	0.34	No-R	0.225	lb ai/acre	40	acres	0.00133	32000	0.0000383	1100000	31000
Spray (all starting formulations), Groundboom, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	78.6	SL/No G	0.34	No-R	0.297	lb ai/acre	60	acres	0.00263	16000	0.0000758	550000	16000
Spray (all starting formulations), Groundboom, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	78.6	SL/No G	0.34	No-R	1.78	lb ai/acre	60	acres	0.0157	2700	0.000454	93000	2600
Spray (all starting formulations), Groundboom, Broadcast	Sod	78.6	SL/No G	0.34	No-R	0.297	lb ai/acre	80	acres	0.00351	12000	0.000101	420000	12000
Spray (all starting formulations), Groundboom, Broadcast	Orchard/Vineyard	78.6	SL/No G	0.34	No-R	0.225	lb ai/acre	40	acres	0.00133	32000	0.0000383	1100000	31000
Spray (all starting formulations), Groundboom, Broadcast	Field crop, typical	78.6	SL/No G	0.34	No-R	0.225	lb ai/acre	80	acres	0.00264	16000	0.0000765	550000	16000
Spray (all starting formulations), Groundboom, Broadcast	Field crop, high-acreage	78.6	SL/No G	0.34	No-R	0.225	lb ai/acre	200	acres	0.00664	6300	0.000191	220000	6100
Flagger														
Spray (all starting formulations), Aerial, Broadcast	Nursery (ornamentals, vegetables, trees, container stock)	11	SL/No G	0.202	No-R	0.297	lb ai/acre	60	acres	0.000368	110000	0.000045	930000	98000

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.															
Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Spray (all starting formulations), Aerial, Broadcast	Orchard/Vineyard	11	SL/No G	0.202	No-R	0.225	lb ai/acre	350	acres	0.00162	26000	0.000199	210000	23000
Spray (all starting formulations), Aerial, Broadcast	Sod	11	SL/No G	0.202	No-R	0.297	lb ai/acre	350	acres	0.00214	20000	0.000263	160000	18000
Spray (all starting formulations), Aerial, Broadcast	Field crop, typical	11	SL/No G	0.202	No-R	0.225	lb ai/acre	350	acres	0.00162	26000	0.000199	210000	23000
Spray (all starting formulations), Aerial, Broadcast	Field crop, high-acreage	11	SL/No G	0.202	No-R	0.225	lb ai/acre	350	acres	0.00162	26000	0.000199	210000	23000
Mixer/Loader/Applicator														
Dry Flowable, Backpack, Ground/soil-directed	Orchard/Vineyard	8260	SL/No G	2.58	No-R	0.178	lb ai/gallon solution	40	gallons solution	0.11	380	0.00023	180000	380
Dry Flowable, Backpack, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	13200	SL/No G	140	No-R	0.0297	lb ai/gallon solution	7	gallons solution	0.00514	8200	0.000364	120000	7700
Dry Flowable, Backpack, Broadcast	Forestry	58400	SL/No G	69.1	No-R	0.0297	lb ai/gallon solution	40	gallons solution	0.13	320	0.00103	41000	320
Dry Flowable, Backpack, Ground/soil-directed	Conifer plantation	8260	SL/No G	2.58	No-R	0.0017	lb ai/gallon solution	40	gallons solution	0.00105	40000	0.00000219	19000000	40000
Dry Flowable, Backpack, Broadcast	Conifer plantation	58400	SL/No G	69.1	No-R	0.0017	lb ai/gallon solution	40	gallons solution	0.00744	5600	0.0000588	710000	5600
Dry Flowable, Backpack, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	58400	SL/No G	69.1	No-R	0.178	lb ai/gallon solution	40	gallons solution	0.78	54	0.00615	6800	54
		30500	SL/G							0.407	100			100

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Dry Flowable, Mechanically-pressurized Handgun, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	5950	SL/No G	448	No-R	0.0297	lb ai/gallon solution	175	gallons solution	0.0579	730	0.0291	1400	480
Dry Flowable, Mechanically-pressurized Handgun, Broadcast	Golf course (tees and greens only)	1960	SL/No G	42	No-R	1.78	lb ai/acre	5	acres	0.0326	1300	0.00468	9000	1100
Dry Flowable, Mechanically-pressurized Handgun, Broadcast	Golf course (fairways, tees, greens)	1960	SL/No G	42	No-R	1.78	lb ai/acre	5	acres	0.0326	1300	0.00468	9000	1100
Dry Flowable, Mechanically-pressurized Handgun, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	1960	SL/No G	42	No-R	1.78	lb ai/acre	5	acres	0.0326	1300	0.00468	9000	1100
Liquid, Backpack, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	13200	SL/No G	140	No-R	0.0297	lb ai/gallon solution	7	gallons solution	0.00514	8200	0.000364	120000	7700
Liquid, Backpack, Broadcast	Forestry	58400	SL/No G	69.1	No-R	0.0297	lb ai/gallon solution	40	gallons solution	0.13	320	0.00103	41000	320
Liquid, Backpack, Ground/soil-directed	Conifer plantation	8260	SL/No G	2.58	No-R	0.0017	lb ai/gallon solution	40	gallons solution	0.00105	40000	0.00000219	19000000	40000
Liquid, Backpack, Broadcast	Conifer plantation	58400	SL/No G	69.1	No-R	0.0017	lb ai/gallon solution	40	gallons solution	0.00744	5600	0.0000588	710000	5600
Liquid, Backpack, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	58400	SL/No G	69.1	No-R	0.178	lb ai/gallon solution	40	gallons solution	0.78	54	0.00615	6800	54
		30500	SL/G							0.407	100			100
Liquid, Mechanically-pressurized Handgun, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	5950	SL/No G	448	No-R	0.0297	lb ai/gallon solution	175	gallons solution	0.0579	730	0.0291	1400	480

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Liquid, Mechanically-pressurized Handgun, Broadcast	Golf course (tees and greens only)	1140	SL/No G	1.9	No-R	1.78	lb ai/acre	5	acres	0.0189	2200	0.000211	200000	2200
Liquid, Mechanically-pressurized Handgun, Broadcast	Golf course (fairways, tees, greens)	1140	SL/No G	1.9	No-R	1.78	lb ai/acre	5	acres	0.0189	2200	0.000211	200000	2200
Liquid, Mechanically-pressurized Handgun, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	1140	SL/No G	1.9	No-R	1.78	lb ai/acre	5	acres	0.0189	2200	0.000211	200000	2200
Wettable Powder, Backpack, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	13200	SL/No G	140	No-R	0.0297	lb ai/gallon solution	7	gallons solution	0.00514	8200	0.000364	120000	7700
Wettable Powder, Backpack, Broadcast	Forestry	58400	SL/No G	69.1	No-R	0.0297	lb ai/gallon solution	40	gallons solution	0.13	320	0.00103	41000	320
Wettable Powder, Backpack, Ground/soil-directed	Conifer plantation	8260	SL/No G	2.58	No-R	0.0017	lb ai/gallon solution	40	gallons solution	0.00105	40000	0.00000219	19000000	40000
Wettable Powder, Backpack, Broadcast	Conifer plantation	58400	SL/No G	69.1	No-R	0.0017	lb ai/gallon solution	40	gallons solution	0.00744	5600	0.0000588	710000	5600
Wettable Powder, Backpack, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	58400	SL/No G	69.1	No-R	0.178	lb ai/gallon solution	40	gallons solution	0.78	54	0.00615	6800	54
		30500	SL/G							0.407	100			100
Wettable Powder, Mechanically-pressurized Handgun, Broadcast	Greenhouse (ornamentals, roses, cut flowers, container stock, vegetables)	5950	SL/No G	448	No-R	0.0297	lb ai/gallon solution	175	gallons solution	0.0579	730	0.0291	1400	480

Table 11.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Propiconazole.

Exposure Scenario	Crop or Target	Dermal Unit Exposure (µg/lb ai	Level of PPE or Engineering Controls	Inhalation Unit Exposure (µg/lb ai)	Level of PPE or Engineering Controls	Maximum Application Rate	App Rate Unit	Area Treated or Amount Handled Daily	Area Treated/Amount Handled Unit	Dermal		Inhalation		Total
										Dose (mg/kg/day)	MOE	Dose (mg/kg/day	MOE	MOE
Wettable Powder, Mechanically-pressurized Handgun, Broadcast	Golf course (tees and greens only)	1650	SL/No G	250	No-R	1.78	lb ai/acre	5	acres	0.0276	1500	0.0279	1500	750
Wettable Powder, Mechanically-pressurized Handgun, Broadcast	Golf course (fairways, tees, greens)	1650	SL/No G	250	No-R	1.78	lb ai/acre	5	acres	0.0276	1500	0.0279	1500	750
Wettable Powder, Mechanically-pressurized Handgun, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	1650	SL/No G	250	No-R	1.78	lb ai/acre	5	acres	0.0276	1500	0.0279	1500	750
Loader/Applicator														
Dry Flowable, Backpack, Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	58400	SL/No G	69.1	No-R	0.178	lb ai/gallon solution	40	gallons solution	0.78	54	0.00615	6800	54
		30500	SL/G							0.407	100			100
Liquid, Backpack, Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	58400	SL/No G	69.1	No-R	0.178	lb ai/gallon solution	40	gallons solution	0.78	54	0.00615	6800	54
		30500	SL/G							0.407	100			100
Wettable Powder, Backpack, Broadcast	Rights-of-way (e.g., utilities, railroad, roadways)	58400	SL/No G	69.1	No-R	0.178	lb ai/gallon solution	40	gallons solution	0.78	54	0.00615	6800	54
		30500	SL/G							0.407	100			100

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data); Level of PPE: Baseline, PPE, Eng. Controls.
2 Based on registered labels and PLUS Report Package.
3 Exposure Science Advisory Council Policy #9.2.
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) × DAF (15%) ÷ BW (80 kg).
5 Dermal MOE = Dermal NOAEL (42 mg/kg/day) ÷ Dermal Dose (mg/kg/day).
6 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (80 kg).
7 Inhalation MOE = Inhalation NOAEL (42 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).
8 Total MOE = NOAEL (42 mg/kg/day) ÷ (Dermal Dose + Inhalation Dose) **OR** Total MOE = 1 ÷ (1/Dermal MOE + 1/Inhalation MOE).

Occupational handler post-harvest non-cancer exposure and combined (dermal + inhalation) risk estimates were calculated for the registered uses of propiconazole. No risks of concern were identified at the LOC of 100 (MOEs range from 690-22,000); risk estimates are presented in Table 11.1.2, below.

Table 11.1.2. Occupational Handler Short- and Intermediate-Term Exposure and Risk Estimates for Registered Post-Harvest and Bulb-Dip Uses of Propiconazole.

Exposure Scenario	Application Rate (lb ai/gal)[1]	Amount ai Handled (gal solution)[2]	Dermal Unit Exposure		Inhalation Unit Exposure		Dermal Dose (mg/kg/day)	Inhalation Dose (mg/kg/day)	Dermal MOE[5]	Inhalation MOE[6]	Total MOE[7]
			µg/lb ai[3]	Level of Protection	µg/lb ai[4]	Level of Protection					
Mixing/Loading, Closed System, Post-Harvest Treatment in an Automated System	0.0045	25,000	8.6	EC	0.083	EC	0.002	0.0001	23,000	360,000	22,000
Mixing/Loading Dry Flowables for Post-Harvest Treatment in an Automated System			227	SL/NG	8.96	NR	0.05	0.01	880	3300	690
Mixing/Loading Liquids for Post-Harvest Treatment in an Automated System			220	SL/NG	0.219	NR	0.05	0.0003	910	140000	900
Mixing/Loading Wettable Powders for Post-Harvest Treatment in an Automated System			77.7	SL/NG	2.75	NR	0.02	0.004	2,600	11000	2,100

1 Maximum application rate based on representative labels in BEAD Plus Package; Crops include: citrus fruits (10-10), pineapple, stone fruits, pome fruits, tomato.
2 Based on ExpoSAC Post-Harvest Policy (M. Crowley, FEB-2018).
3 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/ gal) × Amount Handled Daily (gal/day) × DAF (15%) ÷ BW (80 kg).
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/ gal) × Amount Handled Daily (gal/day) ÷ BW (80 kg).
5 Dermal MOE = Dermal NOAEL (42 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). (LOC = 100).
6 Inhalation MOE = Inhalation NOAEL (42 mg/kg/day) ÷ Inhalation Dose (mg/kg/day). (LOC = 100).
7 Total MOE = NOAEL (42 mg/kg/day) ÷ (Dermal Dose + Inhalation Dose)

11.2 Short-/Intermediate -Term Occupational Post-Application Exposure and Risk Estimates

11.2.1 Dermal Occupational Post-Application Risk

Occupational Post-application Dermal Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments. Each assumption/factor is detailed below on an individual basis.

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. For propiconazole, based on the registered uses and label directions (i.e., multiple applications per season and minimum RTI of 7 days), short- and intermediate-term exposures are expected.

Transfer Coefficients: It is the policy of HED to use the best available data to assess post-application exposure. Sources of generic post-application data, used as surrogate data in the absence of chemical-specific data, are derived from ARTF exposure monitoring studies, and, as proprietary data, are subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting post-application exposure that are used in this assessment, known as "transfer coefficients", are presented in the ExpoSAC Policy 3[20]" which, along with additional information about the ARTF data, can be found at the Agency website[20]. A summary of the anticipated post-application activities and associated transfer coefficients for the proposed crops/use sites can be found in the Occupational Pesticide Reentry Exposure Calculator (D464253_propi_occupational_pesticide_reentry_calculator.xlsx) spreadsheet associated with this risk assessment.

Application Rate: The maximum single application rates for crop/target groups are available in the PLUS Maximum Use Scenario Report.

Exposure Time: The average occupational workday is assumed to be 8 hours.

Dislodgeable Foliar Residues: In accordance with the updated Part 158 data requirements (2007), one or more DFR studies are required when a pesticide has residential or occupational uses that could result in post-application dermal exposure. Of the DFR studies submitted and previously reviewed, the study on peaches has been incorporated into this exposure assessment (K. O'Rourke, D261299, 04/13/2016; MRID 44959701). The study summary can be found in the ORE document previously conducted to support the Registration Review of propiconazole (C. Severini, D457373, 12/14/2020).

Occupational Post-application Non-Cancer Dermal Exposure and Risk Estimate Equations
The algorithms used to estimate non-cancer exposure and dose for occupational post-application workers can be found in Appendix A of the ORE document previously conducted to support the Registration Review of propiconazole (C. Severini, D457373, 12/14/2020).

[20] Available: https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

Occupational Post-application Non-Cancer Dermal Risk Estimates
Using the chemical specific propiconazole DFR data, no post-application non-cancer dermal MOEs resulted in risks of concern on Day 0 after application. MOEs range from 240 to 200,000 (LOC = 100). Risk estimates can be found in the Occupational Pesticide Reentry Exposure Calculator (D464253_propi_occupational_pesticide_reentry_calculator.xlsx) spreadsheet associated with this risk assessment.

Restricted Entry Interval
Propiconazole is classified as Toxicity Category III for acute oral exposures and Toxicity Category IV for dermal and inhalation routes. In the acute toxicity battery, propiconazole was found to be irritating to the eyes (Category II) and slightly irritating to the skin (Category IV) and is a dermal sensitizer. Under 40 CFR §156.208 (c) (2), ai's classified as Acute II for acute dermal, eye irritation, and/or primary skin irritation are assigned a 24-hour REI. For this reason, HED would recommend a REI of 24 hours.

11.2.2 Inhalation Occupational Post-Application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from FIFRA Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[21]. The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (*Human Health Bystander Screening Level Analysis: Volatilization of Conventional Pesticides*[22]). During Registration Review, the Agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for propiconazole.

Occupational Post-Application Inhalation Exposure Data and Assumptions:

Post-harvest Uses:
There is the potential for occupational post-application inhalation exposures in post-harvest treatment facilities. During automated treatments, dermal and inhalation exposure is anticipated for workers performing sorting and packing tasks. Since the workers experience exposure following the treatment, this is technically "post-application" exposure; however, unlike other post-application activities (e.g., harvesting, scouting, etc.), this treatment is not governed by the Worker Protection Standard (WPS) and potential re-entry intervals (REIs). Additionally, for workers in the warehouse or packaging facility not directly involved in the automated treatment process, there is potential for indirect inhalation exposure. Exposures for these various scenarios are assessed using HED ExpoSAC Policy/Guidance "Assessment of Occupational Exposure for Post-Harvest Commodity Pesticide Treatments". A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessment. Each assumption and factor is detailed below on an individual basis.

[21] http://archive.epa.gov/scipoly/sap/meetings/web/pdf/120309meetingminutes.pdf
[22] https://www.regulations.gov/document/EPA-HQ-OPP-2014-0219-0002

Exposure Duration: HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many things, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational post-application workers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region).

For propiconazole, based on the registered commodity post-harvest and bulb-dip uses, both short- and intermediate-term exposures are expected for occupational handlers in post-harvest facilities because it could be applied over several months to the registered crops. Additionally, the occupational inhalation POD is applicable to both durations; therefore, the assessment is protective of both short- and intermediate-term exposures. Long-term exposures are not expected because exposures resulting from post-harvest uses are likely a series of short- or intermediate-term exposures, rather than a continuous long-term exposure duration to propiconazole.

Exposure Time: The average occupational workday is assumed to be 8 hours.

Occupational Post-Application Non-Cancer Inhalation Risk Estimates:

There are no occupational post-application combined dermal and inhalation risk estimates of concern (MOEs ≥ 100) for sorters and packers, or indirect inhalation exposures to workers not directly involved in the treatment process from the registered post-harvest uses of propiconazole at baseline attire (i.e., t-shirt, no gloves, and no respirator) (MOEs range from 26,000-840,000). See Table 11.2.2.1 and 11.2.2.2 for details.

Table 11.2.2.1. Occupational Post-Application Non-Cancer Inhalation Exposure and Risk Estimates for Propiconazole.

Crop/Site[1]	Activities	Max App. Rate (% ai in solution)[2]	Dermal Unit Exposure (µg/% ai)[3]	Inhalation Unit Exposure (µg/% ai)[3]	Dermal Dose (mg/kg/day)[4]	Inhalation Dose (mg/kg/day)[5]	Dermal MOE[6] (LOC = 100)	Inhalation MOE[7] (LOC = 100)	Total MOE (LOC=100)[8]
Post-Harvest	Sorter	0.013	21,600	6,720	0.0005	0.0011	80,000	38,000	26,000
	Packer		15,300	6,760	0.0004	0.0011	110,000	38,000	29,000

1. Crops include: citrus fruit group (10-10), caneberry, bushberry, pineapple, stone fruits, sugarcane, and tomato
2. Maximum application rate based on representative label (Reg. No. 100-617). 4 fl oz product / 100 gal water
3. Based on Table 2 in ExpoSAC Policy/Guidance "Assessment of Occupational Exposure for Post-Harvest Commodity Pesticide Treatments" (M. Crowley, FEB-2018); Level of mitigation: T-shirt/NG = t-shirt and no gloves; NR = no respirator
4. Dermal Dose = Dermal Unit Exposure (µg/% ai) × Conversion Factor (0.001 mg/µg) × Application Rate (% ai in solution) × DAF (15%) ÷ BW (80 kg)
5. Inhalation Dose = [Unit Exposure (µg/% ai) * Application Rate (% ai in solution) * Adjustment Factor (0.001 µg/mg)] ÷ Body Weight (80 kg)
6. Dermal MOE = Dermal POD (42 mg/kg/day) ÷ Dermal Dose.
7. Inhalation MOE = Inhalation POD (42 mg/kg/day) ÷ Inhalation Dose.
8. Total MOE = NOAEL (42 mg/kg/day) ÷ (Dermal Dose + Inhalation Dose)

Table 11.2.2.2. Occupational Post-Application Non-Cancer Indirect Inhalation Exposure and Risk Estimates for Propiconazole.				
Crop/Site[1]	Max App. Rate (% ai in solution)	Inhalation Unit Exposure (µg/% ai)[2]	Inhalation Dose (mg/kg/day)[3]	MOE[4] (LOC = 1000)
		Baseline	Baseline	Baseline
Post-Harvest	0.013	307	0.0001	840,000

1. Crops include: citrus fruit group (10-10), caneberry, bushberry, pineapple, stone fruits, sugarcane, and tomato
2. Based on Table 4 in ExpoSAC Policy/Guidance "Assessment of Occupational Exposure for Post-Harvest Commodity Pesticide Treatments" (M. Crowley, FEB-2018); Level of mitigation: NR = no respirator
3. Inhalation Dose = [Unit Exposure (µg/% ai) * Application Rate (% ai in solution) * Adjustment Factor (0.001 µg/mg)] ÷ Body Weight (80 kg)]
4. Inhalation MOE = Inhalation POD (42 mg/kg/day) ÷ Inhalation Dose

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments.

Although a quantitative occupational post-application inhalation exposure assessment was not performed, an inhalation exposure assessment was performed for occupational/commercial handlers. Handler exposure resulting from application of pesticides outdoors is likely to result in higher exposure than post-application exposure. Therefore, it is expected that these handler inhalation exposure estimates would be protective of most occupational post-application inhalation exposure scenarios.

Furthermore, inhalation exposure during dusty mechanical activities such as shaking and mechanical harvesting is another potential source of post-application inhalation exposure. However, the airblast applicator scenario is believed to represent a reasonable worst-case surrogate estimate of post-application inhalation exposure during these dusty mechanical harvesting activities. The non-cancer inhalation risk estimate for commercial airblast application is not of concern (i.e., MOE > 100).

The Worker Protection Standard for Agricultural Pesticides contains requirements for protecting workers from inhalation exposures during and after greenhouse applications through the use of ventilation requirements. [40 CFR 170.110, (3) (Restrictions associated with pesticide applications)].

12.0 Incident and Epidemiological Data Review

Propiconazole incidents were previously reviewed in 2015 (E. Evans and S. Recore, D429078, 11/24/2015). At that time, based on the low frequency and severity of propiconazole incident cases reported to Incident Data System (IDS) and CDC's National Institute of Occupational Safety and Health (NIOSH) Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides further investigation was not warranted.

In the current IDS analysis from January 1, 2015 to June 10, 2020, five propiconazole incidents involving a single active ingredient and 19 propiconazole incidents involving multiple active ingredients were reported to Main IDS; there were 88 propiconazole incidents reported to

Aggregate IDS. A query of SENSOR-Pesticides 2012-2017 identified 28 cases involving propiconazole.

Based on the continued low frequency of propiconazole incidents reported to both IDS and SENSOR-Pesticides, there does not appear to be a concern at this time.

The Agricultural Health Study (AHS) is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's NIOSH, and the US EPA. One publication, investigating the potential association between propiconazole exposure and human health effects was reviewed. Based on our review of this study, there is *insufficient epidemiological evidence* for the health effect allergic and non-allergic wheeze investigated in the AHS study reported here. The Agency will continue to monitor the epidemiology data, and -- if a concern is triggered -- additional analysis will be conducted (S. Recore et al., D459302, 09/15/2020).

13.0 References

A. Dunbar, 8/13/2013, TXR 0056730, Conazole Fungicides: Summary of Hazard and Science Policy Council (HASPOC) Meeting on July 25, 2013: Recommendations on Data Requirement for Immunotoxicity Studies for Conazole Pesticides.

A. Khasawinah, 08/16/2003, TXR 0056761, D401289, Propiconazole: Response to an Immunotoxicity study waiver request.

B. Cropp-Kohlligian, 04/04/2002, D279299, TXR 0050349, Propiconazole (122101): Results of the HED Metabolism Assessment Review Committee (MARC) Meetings Held on 18-December-2001 and 08-January-2002.

B. Van Deusen, 07/15/2019, D446377, Propiconazole. Occupational and Residential Exposure Assessment for Proposed New Use on Avocado and Crop Group expansions and conversions for Root Vegetables Except Sugar Beet Subgroup 1B, Brassica, Leafy Greens, Subgroup 4-16B, Except Watercress, Leaf Petiole Vegetable Subgroup 22B, Celtuce, Florence Fennel and Swiss Chard.

B. Van Deusen, 03/06/2018, D445667, Propiconazole. Review of Determination of Transferable Turf Residues on Turf Treated with Propiconazole Applied in a Liquid Formulation.

C. Severini, 12/14/2020, D457373, Propiconazole. Occupational and Residential Exposure Risk Assessment for Registration Review.

E. Doyle, 09/11/1992, TXR 0009771, Fifth Carcinogenicity Peer Review of Propiconazole.

E. Evans and S. Recore, 11/24/2015, D429078, Propiconazole: Tier I (Scoping) Review of Human Incidents and Epidemiology.

I. Abdel-Saheb, 10/14/2020, D456202, Propiconazole – Streamlined Drinking Water Assessment for Registration Review.

I. Abdel-Saheb, 05/27/2015, D423648, Drinking Water Assessment for Proposed New Uses of Propiconazole on Dill, Radish, Leafy Brassica Subgroup 5B, Watercress, Ti palm and Crop Group conversions for Stone Fruit Group 12-12 and Tree Nut Group 14-12.

J. Camp, 12/14/2020, D459303, Propiconazole: Acute and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the Registration Review Risk Assessment.

J. Camp et al., 03/21/2022, D462404, Propiconazole: Response to Comments on the Human Health Draft Risk Assessment for Registration Review.

J. Camp et al., 12/14/2020, D456089, Propiconazole. Human Health Draft Risk Assessment of the Conventional Uses to Support Registration Review.

K. O'Rourke, 04/13/2016, D261299, Secondary Review of "Dissipation of Dislodgeable Foliar Residues of Two Formulations of Propiconazole (Orbit™ and Orbit™ 45W) Applied to Peaches."

K. Rury, 08/01/2012, TXR 0056387, Propiconazole: Summary of Hazard and Science Policy Council (HASPOC) Meeting of June 21, 2012: Recommendations on the need for a 28-day inhalation study and a subchronic neurotoxicity study.

S. Hu et al., 12/01/2020, D459696, Registration Review Draft Risk Assessment for the Antimicrobial Uses of Propiconazole.

S. Knizner, 05/27/2009, No DP Barcode, Interim Guidance on Tolerance Expressions.

S. Recore et al., 09/15/2020, D459302, Propiconazole: Tier I Update Review of Human Incidents and Epidemiology for Draft Risk Assessment.

T. Dole, 03/21/2022, D464327, Propiconazole Antimicrobial Uses: Revised Registration Review Draft Risk Assessment of Residential Exposures.

T. Morton, 05/06/2021, D461601/D461603, Common Triazole Metabolites: Updated Aggregate Human Health Risk Assessment to Address the Establishment of a Difenoconazole Tolerances with No U.S. Registration for Imported Avocado, Section 3 Registrations on Corn, Peanut, and Caneberrt 13-07A and Mefentrifluconazole Tolerances with no U.S. Registration for Imported Banana and Coffee.

T. Morton, 05/06/2021, D461600/D461602, Common Triazole Metabolites: Updated Dietary (Food + Water) Exposure and Risk Assessment to Address the Establishment of a Difenoconazole Tolerances with No U.S. Registration for Imported Avocado, Section 3 Registrations on Corn, Peanut, and Caneberrt 13-07A and Mefentrifluconazole Tolerances with no U.S. Registration for Imported Banana and Coffee.

T. Morton, 02/27/2014, D408507, D408509/D408510, Propiconazole: New Foliar Use and Tolerance in/on Rapeseed subgroup 20A. Summary of Analytical Chemistry and Residue Data.

T. Morton et al., 07/15/2019, D446376, Propiconazole Human Health Risk Assessment for the New Use of Propiconazole on Avocado, along with Conversion to *Brassica*, leafy greens, subgroup 4-16B, except watercress, Leaf petiole vegetable subgroup 22B, Celtuce, Florence fennel, Swiss chard, and the expansion to Vegetable, root, except sugar beet, subgroup 1B.

T. Morton et al., 12/10/2015, D429076, Propiconazole: Human Health Risk Scoping Document in Support of Registration Review.

Y. Donovan, 07/31/2006, D238458, Propiconazole. Petitions for Tolerances on Field, Vegetable and Fruit Crops. Summary of Analytical Chemistry and Residue Data. Petition Numbers: 2F6371, 6E4788, 7E4860, and 8E4931.

Y. Donovan, 06/15/2006, D329394, Propiconazole (122101): Reregistration Eligibility Decision (RED) Document; Revised Residue Chemistry Considerations.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food uses for **Propiconazole** are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Study		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Acute Eye Irritation	yes	yes
870.2500	Acute Dermal Irritation	yes	yes
870.2600	Skin Sensitization	yes	yes
870.3100	90-Day Oral Toxicity in Rodents	yes	yes
870.3150	90-Day Oral Toxicity in Nonrodents	yes	yes
870.3200	21/28-Day Dermal Toxicity	yes	yes
870.3250	90-Day Dermal Toxicity	no	--
870.3465	90-Day Inhalation Toxicity	yes	waived[1]
870.3700a	Prenatal Developmental Toxicity (rodent)	yes	yes
870.3700b	Prenatal Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction and Fertility Effects	yes	yes
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Carcinogenicity (rat)	yes	yes[2]
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Combined Chronic Toxicity/Carcinogenicity	yes	yes[2]
870.5100	Mutagenicity—Bacterial Reverse Mutation Test	yes	yes
870.5300	Mutagenicity—Mammalian Cell Gene Mutation Test	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity	no	--
870.7485	Metabolism and Pharmacokinetics	yes	yes
870.7600	Dermal Penetration	no	yes
870.7800	Immunotoxicity	yes	waived[3]

[1] Recommended for a waiver by the HASPOC (K. Rury, TXR 0056387, 08/01/2012)

[2] Chronic toxicity (rat) and Oncogenicity (rat) study requirements were satisfied by the combined Chronic/Oncogenicity study in rats

[3] Recommended for a waiver by the HASPOC (A. Khasawinah, TXR 0056761, D401289, 08/16/2003)

A.2 Toxicity Profiles

Table A.2.1. Acute Toxicity Profile – Propiconazole [PC Code 122101]				
Guideline No.	Study Type/TXR/Classification	MRID (year)	Results	Toxicity Category
870.1100	Acute Oral (rat) TXR 5008502 **Acceptable/Guideline**	47240707 (2006)	LD_{50} = 985 mg/kg (F)	III
870.1200	Acute Dermal (rat) TXR 5008502 **Acceptable/Guideline**	47240708 (2006)	LD_{50} > 5050 mg/kg (M & F)	IV
870.1300	Acute Inhalation (rat) TXR 5008502 **Acceptable/Guideline**	47240709 (2007)	LC_{50} > 2.20 mg/L (M & F)	IV
	Acute Inhalation (rat) TXR 0050197 **Acceptable/Guideline**	41594801 (1988)	LC_{50} > 5.84 mg/L (M & F)	IV
870.2400	Primary Eye Irritation (rabbit) TXR 5008502 **Acceptable/Guideline**	47240710 (2006)	Corneal opacity observed in 3/6 rabbits after 24 h, with clearance in one rabbit on day 4, one rabbit on day 7, and final rabbit on day 10; mildly irritating	II
870.2500	Primary Skin Irritation (rabbit) TXR 5008502 **Acceptable/Guideline**	47270711 (2006)	Very slight erythema on 6/6, 5/6, 2/6, 2/6, and 2/6 rabbits 1, 24, 48, 72 hours, and day 7, respectively after patch removal; slightly irritating	IV
870.2600	Dermal Sensitization (guinea pig) TXR 5008502 **Acceptable/Guideline**	47240712 (2006)	Not sensitizing (Buehler Method)	N/A
	Dermal Sensitization (guinea pig) TXR 5000014 **Acceptable/Guideline**	44949501 (1999)	Dermal sensitizer (Maximization Test)	N/A
	Dermal Sensitization (guinea pig) TXR 5010542 **Acceptable/Guideline**	47718423 (2008)	Dermal sensitizer (Magnusson-Kligman)	NA

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile – Propiconazole [PC122101]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3100 90-Day Oral Toxicity (rat)	00058606 (1979) 93194032 (1997) TXR 0000789, 0050446, 0058106 **Acceptable/Guideline** 0, 240, 1200, 6000 ppm in diet M: 0, 15.85, 76.08, 461.73 mg/kg/day F: 0, 16.82, 77.59, 400.90 mg/kg/day	NOAEL = 1200 ppm (76.08/77.59 mg/kg/day) LOAEL = 6000 ppm (461.73/400 mg/kg/day) based on reduced body weights in both sexes

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile – Propiconazole [PC122101]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3100 90-Day Oral Toxicity (mouse)	42050501 (1990) TXR 0009373, 0050446, 0058106 **Acceptable/Guideline** F: 0, 20, 500, 2500 ppm in diet 0, 3.4, 85, 434 mg/kg/day M: 0, 20, 500, 850, 1450, 2500 ppm in diet 0, 2.7, 65, 112, 194, 352 mg/kg/day	Females: NOAEL = 500 ppm (85 mg/kg/day) LOAEL = 2500 ppm (434 mg/kg/day), based on increases in liver enzymes (AST and ALT) and changes in histopathology (incidences and severity of hypertrophy and necrosis) that accompany enlarged livers and increased liver weights Males: NOAEL = 850 ppm (112 mg/kg/day) LOAEL = 1450 ppm (194 mg/kg/day), based on changes in histology (incidences and severity of hypertrophy and necrosis) that accompany enlarged livers and increased liver weights and changes in serum chemistry (decreased cholesterol and increased ALT)
870.3100 90-Day Oral Toxicity (mouse)	42050502 (1991) TXR 0009373, 0050446, 0058106 **Acceptable/Guideline** 0, 20, 500, 850, 1450, 2500 ppm in diet 0, 2.7, 65, 112, 194, 352 mg/kg/day (Males only)	NOAEL = 850 ppm (112 mg/kg/day) LOAEL = 1450 ppm (194 mg/kg/day) based on increases in liver weights, enlargement of liver, changes in histopathology (incidences and severity of hypertrophy, necrosis, and vacuolation), and changes in serum chemistry (decreases in cholesterol and increases in sorbitol dehydrogenase and ALT)
870.3100 90-Day Oral Toxicity (mouse)	45215801 (1997) TXR 0009373, 0050446 **Acceptable/Non-Guideline** 0, 20, 500, 850, 1450, 2500 ppm in diet 0, 2.7, 65, 112, 194, 352 mg/kg/day (Males only)	Based on the information in this supplemental study, in combination with the information provided in both the main male mice subchronic study (MRID 42050502) and another subchronic study at the same doses for male mice (MRID 42050501), the LOAEL and NOAEL are 1450 ppm (194 mg/kg/day) and 850 ppm (112 mg/kg/day), respectively.
870.3150 90-Day Oral Toxicity (dog)	00058607 (1979) 93194033 (1990) TXR 0000789, 0050446, 0058106 **Acceptable/Guideline** 0, 50, 250, 1250 ppm in diet 0, 1.25, 6.25, 31.25 mg/kg/day	NOAEL = 31.25 mg/kg/day LOAEL = not established The presence of lymphoid follicles in the mucous membrane in the pyloric part of the stomach are likely incidental and may be caused by inflammation or bacterial infection, and are not considered adverse treatment-related effects
870.3200 21-Day Dermal Toxicity (rabbit)	00116591 (1982) 93194034 (1990) TXR 0003994, 0050446, 0058106 **Acceptable/Guideline** 0, 3, 30, 1000 mg/kg/day applied on the intact and abraded skin with an impervious cuff 6 hours/day for 5 days/week	NOAEL = 1000 mg/kg/day LOAEL = not established No systemic toxicity was observed up to the limit dose; mild to moderate dermal irritation was observed at 30 mg/kg/day

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile – Propiconazole [PC122101]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3465 28-Day Inhalation Toxicity	Recommended to be waived per HASPOC (K. Rury, TXR 0056387, 08/01/2012)	
870.3700a Prenatal Developmental (rat)	40425001 (1987) TXR 0006731, 0050446, 0058106 **Acceptable/Guideline** 0, 30, 90, 300 mg/kg/day by oral gavage in aqueous suspension (3% corn starch and 0.5% Tween 80) days 6 to 16 of gestation	**Maternal** NOAEL = 90 mg/kg/day **Maternal** LOAEL = 300 mg/kg/day based on significant increases in ataxia, lethargy, and salivation, *Females originally given 360 mg/kg/day as high dose, but severe symptoms (e.g., bradypnea, hypothermia, prostration, and coma) resulted in lowering it on 6th day **Developmental** NOAEL = 30 mg/kg/day **Developmental** LOAEL = 90 mg/kg/day based on an increased incidence of rudimentary ribs in fetuses and litters *At highest dose, incidence of cleft palate in fetuses is outside the historical control range (0.7% vs. 0-0.35%)
870.3700a Prenatal Developmental (rat)	40425002 (1987) TXR 0006731, 0050446 **Acceptable/Non-Guideline** 0, 300 mg/kg/day by oral gavage in aqueous suspension (3% corn starch and 0.5% Tween 80) days 6 to 15 of gestation	This study was designed to confirm the finding of cleft palate in the main developmental study (MRID 40425001). Severe maternal toxicity beginning day 6 included statistically significant increases in ataxia, coma, lethargy, prostration, salivation, and audible/labored breathing and biologically significant increases in ptosis, lacrimation, paleness, and death. Fetal weights significantly lower for both sexes. No statistically significant external abnormalities. Cleft palate in 2/2064 (0.1%) fetuses and in 2/158 (1.3%) litters.
870.3700b Prenatal Developmental (rabbit)	40425004 (1986) TXR 0050446, 0005782, 0006457, 0006731, 0058106 **Acceptable/Guideline** 0, 100, 250, 400 mg/kg/day by oral gavage in aqueous suspension (3% corn starch and 0.5% Tween 80) days 7 to 19 of gestation	**Maternal** NOAEL = 250 mg/kg/day **Maternal** LOAEL = 400 mg/kg/day based on an increased incidence of abortions **Developmental** NOAEL = 250 mg/kg/day **Developmental** LOAEL = 400 mg/kg/day based on an increased incidence of abortions

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile – Propiconazole [PC122101]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.3800 Two-Generation Reproduction and Fertility Effects (rat)	00151514 (1985) 93194041 (1990) TXR 0005352, 0050446 **Acceptable/Guideline** 0, 100, 500, 2500 ppm in diet PM: 0, 8, 42, 192 mg/kg/day PF: 0, 9.4, 43, 223 mg/kg/day F_1M: 0, 10, 52, 263 mg/kg/day F_1F: 0, 10, 52, 263 mg/kg/day	**Parental** NOAEL = 100 ppm (8/9.4 mg/kg/day) **Parental** LOAEL = 500 ppm (42/43 mg/kg/day) based on an increased incidence of hepatic cellular swelling and clear-cell change **Reproductive** NOAEL = 2500 ppm (263 mg/kg/day) **Reproductive** LOAEL > 2500 ppm (263 mg/kg/day) **Offspring** NOAEL = 500 ppm (42-52 mg/kg/day) **Offspring** LOAEL = 2500 ppm (192-263 mg/kg/day) based on decreased offspring survival and pup body weights, along with an increased incidence of hepatic lesions (cellular swelling)
870.4100b 1-Year Chronic Toxicity (dog)	00151515 (1985) TXR 0005352, 0050446, 0058106 **Acceptable/Guideline** 0, 5, 50, 250 ppm in diet M: 0, 0.2, 1.9, 8.4 mg/kg/day F: 0, 0.2, 1.9, 8.9 mg/kg/day	NOAEL = 250 ppm (8.4/8.9 mg/kg/day) LOAEL = not established *Hyperemia seen in stomach of 3/5 males in high-dose group (mild irritation) after dosing period. This irritation is likely related to treatment, but in absence of other clinical or pathological effects, this is not considered adverse. No histopathological effects were seen in animals allowed to recover an additional 28 days.
870.4200b 2-Year Carcinogenicity (mouse)	00129570 (1982) 00151503 (1985) 93194037 (1990) TXR 0004287, 0005352, 0050446, 0058106 **Acceptable/Guideline** 0, 100, 500, 2500 ppm in diet M: 0, 10, 49.4, 344.3 mg/kg/day F: 0, 10.8, 55.6, 340.3 mg/kg/day	NOAEL = 500 ppm (49.4/55.6 mg/kg/day) LOAEL = 2500 ppm (344.3/340.3 mg/kg/day) based on decreased body weights, increased liver weights, and an accompanying increase in liver enzymes (glutamic pyruvate transaminase, glutamic oxaloacetic transaminase, and alkaline phosphatase), non-neoplastic liver effects and histopathology (increased incidence and severity of centrilobular hepatocyte enlargement in males, increased fat deposition and vacuolation of hepatocytes in females, and enlarged livers in both sexes) *Treatment-related tumors observed in males at the highest dose; not seen in females or males in the two lower doses
870.4200b 18-Month Carcinogenicity (mouse)	44381401 (1997) TXR 0013082, 0058106 **Acceptable/Guideline** 0, 100, 500, 850 ppm in diet 0, 11, 59, 108 mg/kg/day (Males only)	NOAEL = 500 ppm (59 mg/kg/day) LOAEL = 850 ppm (108 mg/kg/day) based on a significant increase in absolute and relative liver weights, enlarged livers, and hypertrophy, accompanied by changes in clinical chemistry (decreased serum cholesterol and increased sorbitol dehydrogenase) *Tumors observed at highest dose, but incidence is within historical control range

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile – Propiconazole [PC122101]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.4300 2-Year Combined Chronic Toxicity/Carcinogenicity (rat)	00129918 (1982) 00151502 (1985) 93194035 (1990) TXR 0004295, 0005352, 0050446 **Acceptable/Guideline** 0, 100, 500, 2500 ppm in diet M: 0, 3.6, 18.1, 96.4 mg/kg/day F: 0, 4.6, 23.3, 100.6 mg/kg/day	NOAEL = 500 ppm (18.1/23.3 mg/kg/day) LOAEL = 2500 ppm (96.4/100.6 mg/kg/day) based on liver lesions (vacuolation of hepatocytes in males, ballooned cells in the liver of males, foci of enlarged hepatocytes in females) increased incidence of luminal dilation of the uterus in females and reduced body weights in both males and females
870.5100 Gene Mutation (Ames Assay) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537	00058601 (1979) TXR 000789, 0050446 **Unacceptable** 0, 25, 75, 225, 675, 2025 µg/plate in DMSO	**Negative** for gene mutation, with and without S9 mammalian metabolic activation *Material not tested up to cytotoxic dose
870.5300 *In vitro* Cell Transformation Assay (BALB/3T3)	00133349 (1982) TXR 0004276, 0050446 **Acceptable/Guideline** 0, 1.16, 2.31, 4.63, 9.25, 18.50 µg/mL	**Negative** for measurable cell transformation at any dose *Highest dose tested resulted in 25% reduction in colony forming ability
870.5385 Bone Marrow Chromosomal Aberration (Chinese hamster)	00058603 (1979) TXR 0000789, 0050446 **Acceptable/Guideline** 0, 251, 502, 1004 mg/kg by oral gavage in polyethylene glycol 400 on 2 consecutive days	Negative for mutagenicity. No evidence of increased aberrations.
870.5550 Unscheduled DNA Synthesis (human fibroblasts)	00133347 (1982) 00151508 (1985) TXR 0004276, 0050446 **Acceptable/Guideline** 0, 0.07, 0.37, 1.86, 9.32 µg/mL	**Negative** for induced DNA damage up to 9.32 µg/mL *Highest tested concentration allowed for 25% cell viability
870.5550 Unscheduled DNA Synthesis (rat hepatocytes)	00133348 (1982) 00151509 (1985) 93194044 (1990) TXR 0005352, 0004276, 0050446 **Acceptable/Guideline** 0, 0.67, 3.34, 16.69, 83.47 µg/mL in DMSO	**Negative** for induced DNA damage up to 83.47 µg/mL *Highest tested concentration allowed for 25% cell viability

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile – Propiconazole [PC122101]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.5575 Mitotic Gene Conversion Assay (*Saccharomyces cerevisiae*)	00133343 (1982) TXR 0005352, 0004276, 0050446 **Acceptable/Guideline** 10, 30, 90, 270 µg/mL in DMSO	**Negative** for mutagenicity - no increase in adenine dependent cells, convertants or revertants *Concentrations ≥ 30 µg/mL had an inhibitory effect on yeast cell growth
870.5450 Dominant Lethal Assay (mouse)	00058602 (1979) TXR 0000789, 0050446 **Acceptable/Guideline** 165 or 495 mg/kg as single dose by oral gavage	**Negative** for dominant lethal effects in the progeny of male mice treated with propiconazole
870.6200a Acute Neurotoxicity (rat)	46604601 (2005) TXR 0053685, 0053790, 0058106 **Acceptable/Guideline** 0, 30, 100, 300 mg/kg by a single oral gavage in corn oil and observed for 14 days	NOAEL = 100 mg/kg LOAEL = 300 mg/kg based on reduced motor activity in males and females on Day 1 (time of peak effect), increased time to tail flick on Day 1 in females, and multiple clinical signs of toxicity (tip toe gait, piloerection, and decreased activity in both males and females; subdued behavior, coldness, paleness, and staining around the nose and with urine in females)
870.6200b Subchronic Neurotoxicity (rat)	49300503 (2013) TXR 0056920, 0058106 **Acceptable/Guideline** F: 0, 200, 600, 1500 ppm in diet 0, 15, 45, 111 mg/kg/day M: 0, 200, 500, 3500 ppm in diet 0, 13, 38, 222 mg/kg/day	Female: NOAEL = 1500 ppm (111 mg/kg/day) LOAEL = not established Male: NOAEL = 3500 ppm (222 mg/kg/day) LOAEL = not established *No effects seen in females. Body weight gains decreased in males at highest dose by 18% in first week, but body weights remained at least 95% of controls, and body weight gains returned to control levels after the first week. There were no neuropathological findings in either sex.
870.7485 Metabolism and Pharmacokinetics (rat)	42403901 (1983) TXR 0010014, 0011313, 0050446 **Acceptable/Guideline** 31.4 mg/kg as single oral dose in water/ethanol/propylene glycol 200 (50/30/20 v/v/v); 14C at the triazole-[3,5] position	The test compound was rapidly metabolized, with 81, 94 and 96% of the radioactivity appearing in the urine and feces 1,2, and 3 days, respectively after dosing. Slightly more was eliminated in the urine compared to the feces (5:4 ratio). The n-propyl side chain is first metabolized to α, ß, and γ hydroxy derivatives and then to α,ß and ß,γ diols. The α,ß diol is further metabolized to an α-hydroxy carboxy acid derivative, a major metabolite appearing in the urine. The side chain is then decarboxylated to yield acetic and formic acid derivatives. After the dioxolane ring is cleaved, several metabolic reactions can occur, leading in general to the hydroxylation of the dichlorophenyl and triazole rings. Sulfation seems to be the preferential route of secondary metabolism and accounts for 5.5% of the AD.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile – Propiconazole [PC122101]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.7485 Metabolism and Pharmacokinetics (rat)	41326701 (1989) TXR 0008052, 0050446 **Acceptable/Guideline** Single dose of 0.5 mg/kg via oral or IV or single oral dose of 50 mg/kg or oral doses of unlabeled 0.5 mg/kg/day for 14 days followed by single oral dose of labeled 0.5 mg/kg; 14C at the phenyl-[U] position	Both the oral and IV routes resulted in similar patterns of ^{14}C elimination, suggesting biliary excretion. Renal elimination data suggest that 35-50% of the oral dose was absorbed. More than 90% of the administered radioactivity was eliminated in the urine and feces 168 hours after dosing, with most being eliminated within the first 48 hours. Only trace amounts were seen in the tissues, and none in expired air. The primary route of elimination was urine in females (43-49% vs. 37-40%) and feces in males (48-50% vs. 39-41%) for both oral and IV dosing, except for similar contributions of renal and fecal excretion in males intravenously dosed (~42-43% each). No significant differences in the excretion pattern were seen between the low and high oral dose groups or the repeated dosing group. The distribution of radioactivity in tissues was similar in low and high dose groups. No parent material was detected in the feces of the IV-dosed group. No parent compound was detected in the urine of rats dosed orally. The parent compound was extensively metabolized through hydroxylation, oxidation, and conjugation, with only a small percentage remaining unabsorbed and appearing in the feces. The overall pattern of metabolites detected in the feces was slightly different than in the urine, with percentages of detected metabolites varying slightly according to sex and dose group.
870.7485 Metabolism and Pharmacokinetics (rat)	00074506 (1979) 00074507 (1981) TXR 0005782, 0050446 **Acceptable/Guideline** 31.4 mg/kg as single oral dose with label at triazole-[3,5] position or 32.5 mg/kg as single oral dose with label at phenyl-[U] position	Study focused on urinary and fecal metabolites. Similar metabolic profiles for the two labels suggesting that the bridge between the phenyl ring and the triazole ring remained intact. Metabolic pathway: cleavage of dioxolane ring through the oxidation of the propyl side chain, with subsequent dechlorination and conjugation and through the oxidation of the propyl side chain. Urinary and fecal metabolites, except for the presence of parent in feces.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile – Propiconazole [PC122101]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
870.7485 Metabolism and Pharmacokinetics (mouse and rat)	00164795 (1986) TXR 0005782, 0050446 **Acceptable/Non-guideline** 5, 100, or 2500 ppm fed in diet to mice for 21 days, followed by single oral dose of phenyl-[U-^{14}C] at respective concentration 9.4 mg/kg phenyl-[U-^{14}C] given to two male mice as single oral dose	Rats excreted slightly more radioactivity in the feces than in the urine (54% vs. 48%). Similar to rats, mice excreted 83-103% within 4 days, with most being excreted in the first 24-48 hours. More radioactivity, especially at the higher two doses, was excreted in the urine than in the feces for both female and male mice. Tissue and carcass radioactivity residues were <1% of the administered dose (AD). Labeling the phenyl location suggests that a major metabolic pathway in mice proceeds through elimination of the dioxolane ring to produce a ketone that is then reduced to a corresponding alcohol. Both of these derivatives are found in plants and livestock. In males this represents 30% of the AD whereas in the females it represents 15% of the AD. Mice cleaved the dioxolane ring to a greater extent (70% & and 40% for males and females, respectively) than do male rats (30%).
870.7600 Dermal *in vivo* Penetration (rat)	42415701 (1986) 45345901 (2001) TXR 0005782, 0010242, 0050446, 0058106 **Acceptable/Guideline** 0, 0.01, 0.1, 1 mg/cm^2; ^{14}C at the triazole-[3,5] position; radioactive test compound was added to the 3.6 EC formulated product (45.8% active ingredient and 54.2% inert substances) and applied as an aqueous suspension	Propiconazole was applied dermally as an aqueous suspension to shaved skin of the dorso-lumbar region. One group was exposed for 24 hours, while the other groups were exposed for 10 or 24 hours, followed by an immediate washing and 72-hour post-exposure phase. This study is an addendum to an earlier study where groups of male rats were treated similarly but exposed for 2, 4, or 10 hours prior to sacrifice, with no post-exposure phase. The rate of absorption appeared to be saturated at the highest dose; at the low and mid dose levels, there was generally a time-dependent increase in the amount of material absorbed. The average dermal absorption of propiconazole over a 10- hour period at an exposure level of 0.01 mg/cm^2 is approximately 48%
OECD 428 Dermal *in vitro* penetration (human skin)	51525101 (2015) TXR 0058218 **Acceptable/Guideline** 10 µL/cm^2 applied to human split thickness skin (0.64 cm^2) and left unoccluded for 24 hours, with interim wash at 6 hours, and final wash and processing at 24 hours Concentrated formulation of 250 g/L and in-use spray dilution of 0.42 g/L	Absorption of propiconazole increased to 24 hours post-dose for both the concentrate and spray dilution, with similar profiles for all skin samples. Total absorption was 0.69% of the AD for the concentrate and 14.8% for the spray dilution.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile – Propiconazole [PC122101]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
OECD 428 Dermal *in vitro* penetration (human skin)	51525102 (2016) TXR 0058218 **Acceptable/Guideline** 10 µL/cm^2 applied to human split thickness skin (0.64 cm^2) and left unoccluded for 24 hours, with interim wash at 6 hours, and final wash and processing at 24 hours Concentrated formulation of 122.4 g/L, high-concentration in-use spray dilution of 0.612 g/L, and low-concentration in-use spray dilution of 0.204 g/L	Mass balance for all individual samples exposed to the concentrate, high concentration spray dilution, or low concentration spray dilution was 100 ± 10%, with mean total recoveries of 96.4%, 99.7%, and 96.3%, respectively, of the administered dose (AD). Total absorption was 1.15% of the AD for the concentrate, 14.4% for the high concentration spray dilution, and 20.0% for the low concentration spray dilution.
OECD 428 Dermal *in vitro* penetration (human skin)	51525103 (2015) TXR 0058218 **Acceptable/Guideline** 10 µL/cm^2 applied to human split thickness skin (0.64 cm^2) and left unoccluded for 24 hours, with interim wash at 6 hours, and final wash and processing at 24 hours Concentrated formulation of 161.6 g/L, high-concentration in-use spray dilution of 1.30 g/L, and low-concentration in-use spray dilution of 0.486 g/L	Mass balance for all individual samples exposed to the concentrate, high concentration dilution, or low concentration dilution was 100 ± 10%, with mean total recoveries of 102.0%, 96.7%, and 96.6%, respectively, of the administered dose (AD). Absorption of propiconazole increased to 24 hours post-dose for both the concentrate and spray dilutions, with similar profiles for all skin samples. Total absorption was 0.17% of the AD for the concentrate, 7.72% for the high concentration spray dilution, and 13.5% for the low concentration spray dilution.
870.7800 Immunotoxicity	Recommended to be waived per HASPOC (A. Khasawinah, TXR 0056761, D401289, 08/16/2003)	
Tumor promotion (rat)	00151517 (1984) TXR 0005352, 0050446 **Acceptable/Non-guideline** 140 µmol DENA/kg injected (IP) in newborns as initiator 2000 ppm in diet for 8 weeks 500 ppm phenobarbital as positive control	Propiconazole caused proliferative changes, with or without pretreatment with an initiator (DENA; nitrosodiethylamine), in the rat liver similar to phenobarbital (500 ppm), a known liver tumor promoter.

Table A.2.2 Subchronic, Chronic, and Other Toxicity Profile – Propiconazole [PC122101]		
Guideline No./ Study Type	**MRID No. (year)/ Classification/Doses**	**Results**
Hepatic biochemical/enzyme induction (mouse)	45215803 (1998) TXR 0014523 **Acceptable/Non-guideline** 0, 850, 2500 ppm in diet for 14 days 0, 149, 578 mg/kg/day 850 ppm phenobarbital as positive control	Male CD-1 mice exhibited increases in liver weights and enzyme production in a manner comparable to that observed with phenobarbital, a known tumor promoter. Treatment at 850 ppm (149 mg/kg bw/day) resulted in a lower induction of all enzymes than at the highest dose of 2500 ppm (478 mg/kg bw/day), but dose-dependency was still evident. In general, there was a significant induction in microsomal and cytosolic enzyme activities of subfamilies CYP2B, CYP2A, and CYP3A, along with slight increases in enzymes involved in testosterone oxidation and conjugation (e.g., testosterone 16α-hydroxylase, UDP-glucuronosyltransferase, and glutathione S-transferase). There were no effects on enzymes of the subfamilies CYP1A and CYP4A. Propiconazole is not a 3-MC or mixed type inducer, but causes a pure PB-type induction of cytochrome P450 activity. The effects of propiconazole treatment on mouse liver weights and liver enzymes were comparable to those produced by phenobarbital, a known liver enzyme inducer and liver tumor promoter. The authors concluded that propiconazole can thus be considered a strong phenobarbital-type inducer of xenobiotic metabolizing enzymes in the mouse.
Hepatocellular proliferation (mouse)	45215802 (1999) TXR 0014523 **Acceptable/Non-guideline** 0, 850, 2500 ppm in diet for 60 days 0, 127, 353 mg/kg/day 850 ppm phenobarbital as positive control	Propiconazole induced hepatomegaly that was attributed to a sharp and transient initial induction of hepatocellular proliferation, followed by a sustained treatment-related hypertrophy in a manner similar to 850 ppm phenobarbital. Increased mitotic activity was observed in all treated groups, and both the high-dose (353 mg/kg/day) and phenobarbital group induced minimal to moderate necrosis and hypertrophy, primarily in the centrilobular and midzonal sections of the liver.

A.3 Hazard Identification and Endpoint Selection

A.3.1 Acute Reference Dose (aRfD) - Females age 13-49

No study selected, as effects seen in the toxicity database could not be attributed to a single dose, except for cleft palate observed in the developmental toxicity study in rats at the highest dose tested. This dose is greater than that selected for acute exposure to the general population, and so the endpoint has been removed.

A.3.2 Acute Reference Dose (aRfD) - All Populations

Study Selected: Acute Neurotoxicity – Rat
MRID No.: 46604601
Executive Summary: See Appendix A.6
Dose and Endpoint for Risk Assessment: NOAEL = 100 mg/kg based on reduced motor activity in males and females on Day 1 (time of peak effect), increased time to tail flick on Day 1 in females, and multiple clinical signs of toxicity (tip toe gait, piloerection, and decreased activity in both males and females; subdued behavior, coldness, paleness, and staining around the nose and with urine in females) seen at 300 mg/kg.
Comments about Study/Endpoint/Uncertainty Factors: The duration and route of exposure for the ACN study are appropriate for deriving the acute dietary POD, and the endpoint was the most sensitive that could be attributed to a single dose. The effects noted are considered secondary, rather than due to direct neurotoxicity, and the nervous system is not known to be a target for propiconazole. The LOAEL has been raised from 100 mg/kg (NOAEL of 30 mg/kg) because effects used to set those previous values occurred at a very low incidence. Cleft palate is considered a single-dose effect, and the fetal incidence at the highest dose (0.7%) in the developmental toxicity study with rats was outside of the historical control range (0-0.33%). However, the selected POD is protective of the cleft palate observed in fetuses/litters in the developmental toxicity study, as the difference between this value and the NOAEL for that effect (90 mg/kg/day) can be attributed to dose spacing. The uncertainty factors (UFs) for interspecies extrapolation (10X) and intraspecies variability (10X) were applied to the NOAEL to calculate the acute reference dose (aRfD = 1.0 mg/kg). The acute population adjusted dose (aPAD = 1.0 mg/kg) is equivalent to the POD divided by all applicable UFs and taking into account the FPQA SF of 1X.

A.3.3 Chronic Reference Dose (cRfD) All Populations

Study Selected: Combined Chronic Toxicity/Carcinogenicity – Rat
MRID No.: 00129918
Executive Summary: See Appendix A.6
Dose and Endpoint for Risk Assessment: NOAEL = 18.1 mg/kg/day based on liver lesions (vacuolation of hepatocytes in males, ballooned cells in the liver of males, foci of enlarged hepatocytes in females) increased incidence of luminal dilation of the uterus in females and reduced body weights in both males and females seen at 96.4 mg/kg/day.
Comments about Study/Endpoint/Uncertainty Factors: This study is appropriate for both the duration of exposure and population of concern for a chronic dietary endpoint. An alternative candidate is the parental NOAEL (8 mg/kg/day) from the two-generation reproduction and fertility effects study in rats. The LOAEL from that study is based on an increased incidence of

hepatic cellular swelling and clear cell-change at 42 mg/kg/day that can signify the onset of more extreme liver damage at higher doses and longer exposures. The effects are consistent with propiconazole's toxicity profile, and both values are lower than those causing the similar lesions observed in the 2-year rat study. However, the small difference between the values from the two studies can be considered an artifact of dose spacing. Furthermore, the majority of liver effects occurred in adults from the F_1 generation rather than the parental generation, supporting the evidence of increasing liver toxicity that progresses over time. The selected POD is protective of the cellular swelling and clear cell change seen in the livers of adults and offspring in the two-generation reproductive study. The uncertainty factors (UFs) for interspecies extrapolation (10X) and intraspecies variability (10X) were applied to the NOAEL to calculate the chronic reference dose (cRfD = 0.18 mg/kg/day). The chronic population adjusted dose (cPAD = 1.0 mg/kg/day) is equivalent to the POD divided by all applicable UFs and taking into account the FPQA SF of 1X.

A.3.4 Incidental Oral/Adult Oral Exposure (Short-Term)

Study Selected: Reproduction and Fertility Effects Study – Rat
MRID No.: 00151514
Executive Summary: See Appendix A.6
Dose and Endpoint for Risk Assessment: NOAEL = 42 mg/kg/day based on decreased survival and body weights of pups, and an increased incidence of hepatic cellular swelling seen at 96.4 mg/kg/day. The route and duration of exposure are appropriate for incidental oral exposure to children and oral exposure to adults. The POD is protective of the susceptibility seen in the developmental toxicity study with rats at 90 mg/kg/day. The level of concern (LOC) for the margin of exposure (MOE) is 100. The UFs for interspecies extrapolation (10X) and intraspecies variation (10X) were applied, along with the FQPA SF of 1X.

A.3.5 Dermal Exposure (Short-Term and Intermediate-Term)

Study Selected: Reproduction and Fertility Effects Study – Rat
MRID No.: 00151514
Executive Summary: See Appendix A.6
Dose and Endpoint for Risk Assessment: NOAEL = 42 mg/kg/day based on decreased survival and body weights of pups, and an increased incidence of hepatic cellular swelling seen at 96.4 mg/kg/day. A route-specific study in rabbits is available, but no systemic effects were seen up to the highest tested dose of 1000 mg/kg/day (limit dose). An endpoint was selected from an oral study because the dermal study did not evaluate developmental or reproductive effects. The two-generation reproduction toxicity study was selected for dermal exposure to both children and adults (instead of the developmental toxicity study) because it is appropriate for the duration of exposure and is protective of all populations including children and females 1-49 years of age, as it accounts for the susceptibility seen in the developmental toxicity with rats. Because an oral study was selected for the dermal exposure scenario, a dermal absorption factor (DAF) of 15%, derived from the *in vivo* dermal penetration study in rats, was used for extrapolation. The extrapolated dermal dose is 280 mg/kg/day (42/0.15 = 280). The LOC for the MOE is 100. The UFs for interspecies extrapolation (10X) and intraspecies variation (10X) were applied, along with the FQPA SF of 1X for residential exposures.

A.3.6 Inhalation Exposure (Short-Term and Intermediate-Term)

Study Selected: Reproduction and Fertility Effects Study – Rat
MRID No.: 00151514
Executive Summary: See Appendix A.6
Dose and Endpoint for Risk Assessment: NOAEL = 42 mg/kg/day based on decreased survival and body weights of pups, and an increased incidence of hepatic cellular swelling seen at 96.4 mg/kg/day. No subchronic inhalation study is available, but the requirement for such a study was recommended for a waiver by the Hazard and Science Policy Council (HASPOC) using a weight of evidence approach (K. Rury, TXR 0056387, 08/01/2012). The two-generation reproduction toxicity study was selected for dermal exposure to both children and adults (instead of the developmental toxicity study) because it is appropriate for the duration of exposure and is protective of all populations including children and females 1-49 years of age, as it accounts for the susceptibility seen in the developmental toxicity with rats. The LOC for the MOE is 100. The UFs for interspecies extrapolation (10X) and intraspecies variation (10X) were applied, along with the FQPA SF of 1X for residential exposures.

A.4 Literature Search for Propiconazole

Date and Time of Search: 11/06/2019; 01:45 pm

Search Details:

((Propiconazole)) AND (rat OR mouse OR dog OR rabbit OR monkey OR mammal)

PubMed hits: 134

Number of Swift Articles: 72 for Animal

Number of Swift Articles: 94 for Human

Number of Swift Articles: 0 for No Tag

A.5 Metabolic Pathway(s) of Propiconazole

The n-propyl side chain of propiconazole is first metabolized to α, ß, and γ hydroxy derivatives and then to α,ß and ß,γ diols. The α,ß diol is further metabolized to an α-hydroxy carboxy acid derivative, a major metabolite appearing in the urine. The side chain is then decarboxylated to yield acetic and formic acid derivatives. After the dioxolane ring is cleaved, several metabolic reactions can occur, leading in general to the hydroxylation of the dichlorophenyl and triazole rings. Sulfation seems to be the preferential route of secondary metabolism and accounts for 5.5% of the administered dose. The percentages of fecal metabolites extracted and identified after labeling at either the triazole or phenyl location are similar, suggesting that the bridge between the triazole ring and the phenyl ring remains intact. Labeling the phenyl location also suggests that a major metabolic pathway in mice proceeds through elimination of the dioxolane ring to produce a ketone that is then reduced to a corresponding alcohol. Both of these derivatives are found in plants and livestock.

A.6 Updated Executive Summaries

A.6.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity – Rat
MRID 00058606 and 93194032
In a 90-day oral toxicity study (MRIDs 00058606 and 93194032), CGA 64250 (Batch No. 35/1 P1, 90.0% purity) was administered to 20 ~ 4-week old Tif (RAIF) SPF rats/sex/dose in the diet at dose levels of 0, 240, 1200, or 6000 ppm (0, 15.85, 76.08 and 461.73 mg/kg/day in males and 0, 16.82, 77.59 and 400.90 mg/kg/day in females, respectively) for 13 weeks. Food and water were available ad libitum, except for overnight fasting prior to blood removal and urinalysis. Hematology, urine, and blood chemistry were measured in 20 random rats/sex/group at weeks 4, 8, and 13 between the hours of 8:00 and 9:00 AM.

No clinical symptoms nor any signs of local and/or systemic toxicity were observed. The survival and mean food consumption of animals was unaffected by the treatment. The body weight of all males and females at 6000 ppm was significantly decreased from weeks 2-13 (79-87% of control for males and 80-92% of control for females). Female body weight was also significantly decreased at 1200 ppm from weeks 9-13 (92-93% of control), and during four weeks in the low-dose group (97-98% of control), though these slight decreases are not considered biologically significant or adverse as they are less than a 10% reduction.

For all animals in the 6000 ppm group, absolute organ weights (heart, kidney, and adrenal glands in males; kidneys and heart in females) were decreased, and relative organ weights (to body weight) increased, while organ to brain weight ratio mostly decreased. Liver weights relative to body weight were significantly higher, though absolute liver weights and liver weights relative to brain weight were comparable to controls. The toxicological significance of these changes in organ weights is unclear in the absence of any accompanying histopathology but is considered not to be adverse.

Opthalmic, auditory, and urinalysis findings showed no evidence of treatment-related effects. Erythrocyte count, hematocrit, and hemoglobin concentration were found to be slightly lower in females at 6000 ppm. A marginal increase was seen in alkaline phosphatase activity in the high-dose female rats at week 13 and in g-glutamyl transpeptidase activity in male and female rats of the high-dose groups at weeks 4, 8, and 13. Histopathology examination of the spleen of all female rats from the 6000 ppm group showed a slight increase in hemosiderosis. The observed changes noted above were all minimal and are not considered toxicologically significant.

The **LOAEL** is 6000 ppm (461.73 mg/kg/day for males and 400.90 mg/kg/day for females), based on reduced body weights in both sexes. The **NOAEL** is 1200 ppm (76.08 mg/kg/day for males and 77. 59 mg/kg/day for females).

This 90-day oral toxicity study in the rat is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OCSPP 870.3100; OECD 408) in rats.

COMMENTS: This Executive Summary has revised the previous LOAEL of 1200 ppm (77.59

mg/kg/day) and NOAEL of 240 ppm (16.82 mg/kg/day) in females. The previous values were based on reduced body weight gain. The values in this revised DER are based on similar effects, but the reductions in body weight and body weight gain at 1200 ppm in females are no longer considered to be adverse, since the percent decrease in body weight was less than 10%. As a result, the LOAEL and NOAEL for females have been raised to 6000 ppm and 1200 ppm, respectively. The values for males have remained unchanged. In addition to raising the NOAEL and LOAEL for females, this updated DER includes tables of body and organ weights for both sexes during the study period.

COMPLIANCE: The study predated the GLP guidelines. A phase 3 summary (MRID 93194032) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides a data confidentiality statement.

870.3100 90-Day Oral Toxicity – Mouse

MRID 42050501

In a subchronic oral toxicity study (MRID 42050501) propiconazole was administered as CGA 64250 (92.0% purity, batch number FL-850083) to 7-week old Crl:CD-1 (ICR) BR (Swiss) mice (20/sex/dose) at dietary concentrations of 0, 20, 500, or 2500 ppm (0, 2.7, 65, 352 mg/kg/day in males and 0, 3.4, 85, 434 mg/kg/day in females, respectively) for 17 weeks. Two additional groups of male mice (20/group) were also administered the test material at 850 or 1450 ppm (112 and 194 mg/kg/day, respectively).

Twice daily inspections of the animals revealed no clinical signs and mortality attributable to the administration of the test article. There were no treatment-related effects on the body weight or food consumption in treated mice. Ophthalmological examinations of all animals at the termination of the study revealed no treatment-related eye lesions.

Clinical chemistry analysis was limited to liver only. Hematology was not performed. A significant increase in alanine aminotransferase (ALT) occurred after 17 weeks in males at ≥1450 ppm and in females at 13 and 17 weeks at 2500 ppm. Aspartate aminotransferase (AST) increased significantly in females at the 17-week interval at 2500 ppm, with no significant findings for this enzyme in males. The increase in both ALT and AST in females at the 2500 ppm dose level indicates adverse liver damage. Males showed significant decreases in serum cholesterol at ≥1450 ppm after 13 weeks (↓45%) and at ≥850 ppm after 17 weeks (↓25%). However, given the lack of effects in females and on other clinical parameters in males at 850 ppm, the decrease in serum cholesterol at this dose in not considered adverse. While there was a lack of significant changes or inconsistency in the dose-response for AST in males, this enzyme is not as specific to the liver as ALT.

Statistically significant increases in liver weights (absolute: 114%-191% of control, and relative to body weight: 113%-204% or relative to brain weight: 116%-193%) were found in the male animals at ≥500 ppm and in the female mice at 2500 ppm (179% of control, 183% relative to body weight and 188% relative to brain weight). In the absence of accompanying biological changes in liver enzymes at the 500 ppm and 850 ppm dose levels, the changes in liver weight in males at these two lowest doses were not considered to be adverse.

Gross pathological examination of the livers from the male mice revealed a significant increase in liver enlargement (≥1450 ppm) and focal discoloration (2500 ppm). The female mice showed a significant increase in liver enlargement at 2500 ppm. Male mice showed a dose-related increase in both the incidence and severity of histopathological lesions of the liver, while the females showed significant increases only at 2500 ppm. At the 500 and 850 ppm dose levels, all diagnosed hypertrophy in the males was mild; moderate hypertrophy was present in 9/20 and 18/20 animals in the 1450 and 2500 ppm groups, respectively. In females at the 2500 ppm dose, 14/20 showed minimal to mild hypertrophy, while 3/20 were classified with moderate hypertrophy. Necrosis occurred both as scattered individual cell foci and multicellular areas. Necrosis was present in males at ≥500 ppm but was only significant at ≥1450 ppm. The severity and incidence of the necrosis for males in the 1450 ppm group was minimal for 2/20, mild for 5/20 and moderate for 1/20. At 2500 ppm 7/20 and 5/20 male mice showed minimal and mild necrosis, respectively. Cellular necrosis in males was minimal for 2/20 at 1450 ppm and 7/20 at 2500 ppm and mild for 5/20 at 2500 ppm. For females at 2500 ppm 6/20 showed mild necrosis, with minimal cellular necrosis in 1/20 females. The increase in incidence and/or severity of both hypertrophy and necrosis at 1400 ppm in males and at 2500 ppm in females are considered to be adverse liver effects related to treatment, especially when accompanied by gross pathological changes in liver at these dose levels in the respective sexes.

Vacuolation also occurred as scattered individual foci and multicellular areas. Significant vacuolation was present in males in the 500 ppm group, but this does not appear to be related to treatment in a dose-dependent manner. Significant vacuolation was also present in the 2500 ppm group where 2/20, 7/20 and 1/20 showed minimal, mild and moderate vacuolation, respectively. No compound-related effect was found when sections of male livers were stained using Oil Red 0, since nearly all sections (including the controls) were stained for microvesicular lipid. As with necrosis, vacuolation in both sexes was found to be mostly minimal to mild. Because of the lack of dose-response with vacuolation in males, a lack of significant changes in females, and a lack of findings in stained liver sections, the increased vacuolation in males is considered to be of little toxicological significance. In all, males appeared to be more sensitive to the test article than females.

The **LOAEL** is 1450 ppm in males (194 mg/kg bw/day) based on changes in histology (incidences and severity of hypertrophy and necrosis) that accompany enlarged livers, increased liver weights, and changes in serum chemistry (decreases in cholesterol and increases in ALT). The LOAEL is 2500 ppm in females (434 mg/kg bw/day), based on increases in liver enzymes (AST and ALT) and changes in histopathology (incidences and severity of hypertrophy and necrosis) that accompany enlarged livers and increased liver weights. The **NOAEL** is 850 ppm for males (112 mg/kg bw/day) and 500 ppm for females (85 mg/kg bw/day).

This 90-day oral toxicity study in the mouse is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OCSPP 870.3100; OECD 408) in mice.

COMMENTS: This Executive Summary has revised the previous LOAEL and NOAEL for males of 500 ppm (65 mg/kg/day) and 20 ppm (2.7 mg/kg/day), while it has not changed that for females. The previous value for males was based on an increase in absolute and relative liver weights and histopathological changes. However, the only significant histopathological change

seen at this dose level was an increase in cellular vacuolation, and this did not occur-in a dose-dependent manner. Under revised guidelines, an increase in absolute/relative liver weights and hypertrophy in the absence of changes in clinical chemistry is not considered adverse, and this was the case for both the 500 ppm and 850 ppm dose levels, other than the decrease in serum cholesterol in the latter dose. However, this decrease in cholesterol is also not considered adverse, as there were no changes in other liver enzymes at 850 ppm. The significant increase in the incidence of hypertrophy in males at 850 ppm is not considered adverse, as all lesions were graded as minimal and due to the lack of histopathological changes and changes in serum chemistry other than cholesterol. Although there was no significant increase in AST in males at either time point of measurement, ALT and cholesterol were both seen to change at 1450 ppm. Serum cholesterol was observed to decrease at both time points, while ALT experienced a significant increase at only the last timepoint. The large standard deviation is noted in regard to the control animals at this first time point, while the mean and standard deviation for ALT at the 1450 ppm dose level remain the same at both time points, which appears to influence the statistical significance level. When evaluating these changes in clinical chemistry along with changes in gross and microscopic histopathological lesions, enlarged livers, and increased liver weights that also occur at this dose level, the weight-of-evidence suggests that the LOAEL for males is 1450 ppm. In addition to raising the LOAEL for males to 1450 ppm, this updated DER has included tables of body weights, organ weights, clinical chemistry findings, and liver histopathology.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

MRID 42050502

In a 90-day oral toxicity study (MRID 42050502), propiconazole was administered as CGA 64250 (92.0% purity, batch number FL-850083) to 37-day old Crl:CD-1 (ICR) BR (Swiss) male mice (40/dose) at dietary concentrations of 0, 20, 500, 850, 1450, or 2500 ppm (0, 2.7, 65, 112, 194, 352 mg/kg/day) for 13 weeks. One group of 10 males/dose was sacrificed after 4 weeks, a second group of 10 males/dose after 8 weeks and the third group of 20 males/dose was sacrificed after 13 weeks. Animals were provided food and water ad libitum. This study was conducted to determine the maximum tolerated dose (MTD).

Twice daily inspections of the animals revealed no clinical signs and mortality attributable to the administration of the test article. Significant reductions in weekly body weights relative to the control were observed in animals in the 2500 ppm group during the first 8 weeks of the study and in animals in the 1450 ppm group at week 4. The slight reductions in body weight (93-98% of controls) suggest that these changes in weight are not treatment-related adverse effects for the animals. Food consumption did not vary in a dose-related manner and showed inconsistencies in decreasing or increasing relative to the controls over time, and the statistically significant increases and decreases in food efficiency for nearly all dose levels were not considered to be treatment-related.

Statistically significant increases in absolute and relative liver weights (to body weight), and in liver weights relative to brain weight, were found in the animals at ≥850 ppm at all time points. Only relative liver weight was increased significantly for animals at 500 ppm at all timepoints,

with absolute liver weights and weights relative to brain weight significantly increased at just the final timepoint for this dose level.

There were no treatment-related eye lesions noted. Only serum clinical chemistry was measured. Hematology and urinalysis were not performed. A significant decrease in serum cholesterol was seen at week 13 in the 500 ppm group (↓17%), at weeks 4 and 13 in the 850 ppm group (↓30%), and at all timepoints in the 1450 and 2500 ppm groups (↓37-64%). A significant increase in sorbitol dehydrogenase was seen in the 850 ppm group at weeks 4 and 13 (↑40-70%) and at all timepoints in the 1450 and 2500 ppm groups (↑74-163%). Alanine aminotransferase (ALT), which is a serum enzyme associated with hepatic necrosis, was significantly higher in the 1450 and 2500 ppm groups at all timepoints (2.4-fold and 3.4-fold, respectively). Only liver enzymes were measured. The lack of significant changes in either ALT or aspartate aminotransferase (AST), which is another enzyme indicating liver damage, at 850 ppm suggest the increases in serum cholesterol and sorbitol dehydrogenase are of little toxicological significance at this dose level. While AST was not seen to be significantly changed at any timepoint or dose level, it is less specific to the liver compared to ALT. The statistically significant changes in ALT, cholesterol, and sorbitol dehydrogenase at the two highest dose levels are considered to be adverse.

Necropsy findings of toxicological significance were confined to the liver and included discoloration, enlargement, focal discoloration, friability, and prominent lobular architecture. While some enlargement was observed in the 850 ppm group, this effect occurred at a much higher incidence in the 1450 and 2500 ppm groups, and so the statistically significant increases at the lower dose level are not considered to be adverse. There were no neoplastic findings. Non-neoplastic findings of toxicological significance included hepatocellular hypertrophy, vacuolation, and necrosis. The vacuolation and necrosis occurred both as scattered individual cell foci and multicellular areas. There was a dose-related trend for increased incidence and severity of each histopathological lesion. While the incidence of hypertrophy was seen to significantly increase in the two lowest dose groups, the majority of lesions were only graded as mild, whereas the majority of lesions in the two highest dose groups were graded as moderate. Although significant, the increase in the incidence of necrosis in the 850 ppm dose group was much lower than that in the two highest dose groups, and lesions were graded only as minimal to mild compared to mild to moderate grades in the latter. Therefore, the significant increases in hypertrophy and/or necrosis at the 500 ppm and 850 ppm dose levels are not considered adverse. The dose-related increase in the incidence and severity of hypertrophy, necrosis, and vacuolation is considered adverse at ≥1450 ppm. None of the lesions were classified as either marked or severe. Hypertrophy was generally centrilobular in orientation but was occasionally panacinar (more diffuse). A significant increase in the incidence of mineralization was seen only at 2500 ppm and was suggested by the study authors to be the sequelae to previous foci of necrosis (dystrophic calcification).

The **LOAEL** is 1450 ppm (194 mg/kg/day), based on increases in liver weights, enlargement of liver, changes in histopathology (incidences and severity of hypertrophy, necrosis, and vacuolation), and changes in serum chemistry (decreases in cholesterol and increases in sorbitol dehydrogenase and ALT). The **NOAEL** is 850 ppm (112 mg/kg/day).

This 90-day oral toxicity study in the male mouse is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OCSPP 870.3100; OECD 408) in mice.

COMMENTS: This Executive Summary has revised the previous LOAEL and NOAEL for male mice of 500 ppm (65 mg/kg/day) and 20 ppm (2.7 mg/kg/day), respectively. The previous value for males was based on an increase in absolute and relative liver weights and histopathological lesions (hypertrophy, necrosis, vacuolation). However, the only significant histopathological change seen at this dose level was an increase in hypertrophy. Under revised guidelines, an increase in absolute/relative liver weights and hypertrophy in the absence of changes in clinical chemistry is not considered adverse, and this was the case for the 500 ppm dose level, other than the decrease in serum cholesterol at week 13. However, this decrease in cholesterol is also not considered adverse, as there were no changes in any other liver enzyme at 500 ppm. It could be argued that a LOAEL could be set at 850 ppm, as both sorbitol dehydrogenase and cholesterol are significantly altered at this dose level. However, these changes are observed only at weeks 4 and 13 and so are not consistent over time. In addition to these serum constituents, ALT is significantly increased at both the 1450 and 2500 ppm dose groups in a similar manner and at all time points, suggesting the changes in serum chemistry at these two higher dose levels are more representative of liver damage, especially when accompanied by changes in cholesterol and sorbitol hydrogenase at these dose levels. While focal discoloration and hypertrophy are found at similar incidences in the 850 ppm group as the two higher dose groups, the incidences of enlarged livers and necrosis are much greater in the latter two. It is also at these two higher dose groups where vacuolation becomes more prominent and where severity in liver pathology is increased. Together, this evidence suggests that the LOAEL is 1450 ppm and so has been raised from 500 ppm. These findings also agree those of a prior study (MRID 42040501), in which the majority of significant liver effects were seen only at ≥ 1450 ppm. In addition to raising the LOAEL, this updated DER has included tables of body and liver weights, food consumption, clinical chemistry findings, and liver histopathology.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

870.3150 90-Day Oral Toxicity – Dog

MRID 00058607 and 93194033

In a 90-day oral toxicity study (MRIDs 00058607 and 93194033), CGA 64250 technical (88.0% purity, batch number 35/5) was administered to 19-28 week old pure-bred Beagle dogs (4/sex/dose) at dietary concentrations of 0, 50, 250, or 1250 ppm (0, 1.25, 6.25, 31.25 mg/kg/day based on a dose conversion factor for dogs of 1 ppm = 0.025 mg/kg/day) for 13 weeks. Dogs ranged from 7.9-13.0 kg for males and 6.0-11.6 kg for females. The dogs were housed in kennels equipped with underfloor heating and provided a pelleted food diet and water ad libitum (but not more than 350 g/day/animal in the case of food). Hematology, urine, and blood chemistry were measured in 32 randomized dogs from the four groups before treatment and at weeks 4, 8, and 13 between the hours of 8:00 and 9:00 AM.

Some animals of all groups, including controls, showed slight to moderate diarrhea during the whole study. Survival, body weight gain, clinical chemistry, urinalysis, ophthalmic and auditory examinations, and organ weights revealed no treatment related effects. Females in the high-dose

group temporarily consumed less food than the control dogs, but otherwise food consumption among all groups was similar.

Necropsy showed that in 3/4 of male dogs from the highest dosage group (1250 ppm), a slightly granular surface in the pyloric and propyloric part of the stomach occurred. Apart from this finding, no gross anatomical changes were seen either in treated or in control dogs. Microscopically, in 3 out of 4 male dogs from the highest dose-group and 1 out of 4 female dogs from the 250 ppm group, a slightly increased amount of lymphoid follicles in the mucous membrane of the pyloric part of the stomach was seen. However, this was not seen in the high dose females. The toxicological significance of this finding is unclear, but it is considered incidental in nature and not adverse. Rather, the development of lymphoid follicles in the stomach could be due to bacterial infection or tissue inflammation.

The **NOAEL** is 1250 ppm (31.25 mg/kg bw/day), which is the highest dose tested. The **LOAEL** was not determined.

This 90-day oral toxicity study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OCSPP 870.3150; OECD 409) in non-rodents.

COMMENTS: This Executive Summary revises the previous LOAEL of 250 ppm (6.25 mg/kg/day) and NOAEL of 50 ppm (1.25 mg/kg/day). The study authors considered the NOAEL to be 1250 ppm due to the lack of treatment-related changes in clinical symptoms, mortality, food consumption, body weight, clinical laboratory investigations, and pathology. The LOAEL and NOAEL values in an earlier DER were based on the finding of lymphoid follicles in the mucous membrane of the pyloric part of the stomach. The authors of the study report stated that the finding of the lymphoid follicles was incidental and likely not related to treatment. The presence of these follicles in only one female of the 250 ppm group does not seem to be strong enough evidence to set the LOAEL at this value. It could be argued that the presence of these follicles in 75% of the males in the high-dose group acts as stronger evidence and that the LOAEL could be set to 1250 ppm. However, a literature search reveals that lymphoid follicles in the mucous membrane of the stomach are primarily affiliated with bacterial infection, especially in regard to *Helicobacter pylori*[18,19]. Inflammation may also lead to the formation of such follicles, but this in itself is non-adverse and can be reversed upon ceasing treatment.

Furthermore, no females in the high-dose group present the signs that the one female in the 250 ppm group and the 3 males in the high-dose group do, so there are dose inconsistencies. The slight decrease in food consumption in females in the high-dose group could result in potentially less severe effects. Upon further inspection, two females in this group fed at exactly the same rate as females from the other groups and males from all groups. One female consumed slightly less food the first four weeks, but also consumed less food overall before the study commenced.

[18] Genta, RM and HW Hamner. 1994. The significance of lymphoid follicles in the interpretation of gastric biopsy specimens. Arch Pathol Lab Med 118(7): 740-743.

[19] Chen, XY, WZ Liu, Y Shi, DZ Zhang, SD Xiao, and GNJ Tytgat. 2001. Helicobacter pylori associated gastric diseases and lymphoid tissue hyperplasia in gastric antral mucosa. J Clin Pathol 55:133-137.

One female fed at a significantly lower rate (67-84% of other animals) from weeks 1 to 13. It appears that this one female is driving the trend towards a temporary reduction in food consumption, and so in general females fed at the same rates as males. Therefore, they would be expected to be exposed to the same levels of compound as males, and if lymphoid follicle formation was treatment-related, it could be assumed that they would also exhibit stomach mucosal effects. Because they do not, and due to dosing inconsistencies, this effect is no longer considered treatment-related, and so the NOAEL has been raised to the highest dose tested. In addition to the revised NOAEL and LOAEL, this updated DER has included tables of food consumption for males and females.

COMPLIANCE: The study predated the GLP guidelines. A phase 3 summary (MRID 93194033) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides a data confidentiality statement.

870.3200 21-Day Dermal Toxicity – Rabbit
MRID 00116591 and 93194034
In a 21-day dermal toxicity study (MRIDs 00116591 and 93194034), CGA-64250 technical (90.7%, Batch No. FL-810858) was applied to the shaved skin of ~12-16 week old 1.72-2.535 kg Albino New Zealand White Rabbits (20/sex/dose) at dose levels of 0 (11 males and 9 females), 3 (11 males and 9 females), 30 (10 males and 10 females), or 1000 (13 males and 7 females) mg/kg/day over a 21-day period. The test material was applied on the intact and abraded skin with an impervious cuff for 6 hours/day for five days/week for three weeks. Rabbit feed and water were provided ad libitum.

One female rabbit in the high-dose group experienced diarrhea, decreased activity, and decreased body tone after the first treatment on day 1, these same signs as well as weight loss on day 2, and was found dead on day 3. One male in the low-dose group was found dead on the day of necropsy (day 23) without any prior signs of stress. Histopathological analysis revealed cause of death as infectious hemorrhagic bronchopneumonia. Neither death was considered compound-related. Diarrhea was observed in one control female, 2 males and 2 females in the low-dose group, and 3 males and 1 female in the mid-dose group; this effect was not considered to be related to treatment. There were no treatment-related deaths or signs of systemic toxicity and no treatment-related effects on body weight, food consumption, or opthalmology, hematological and clinical chemistry parameters. There were no compound related gross necropsy, organ weight effects or histopathological findings.

Skin irritation was noted in the 30 and 1000 mg/kg/day groups beginning at day 2 and persisted for the remainder of the study with maximum irritation indexes of 1.0 and 4.1, respectively. Signs of irritation were noted in the 3.0 mg/kg/day group beginning on day 15 in males only with the highest irritation index of 0.3 at day 19.

There were dose-related mild, to moderate, skin lesions in treated animals compared to controls in all dose groups. Mild, to marked, microscopic changes occurred in a variable number of untreated skin sections in both control and treated rabbits, which the study authors attribute to mechanical irritation. The majority of incidences were mild or moderate in severity.

The **LOAEL for systemic effects** was not established. The **NOAEL for systemic effects** is 1000 mg/kg bw/day. The **LOAEL for skin effects** is 30 mg/kg bw/day based on mild to moderate dermal irritation. The **NOAEL for skin effects** is 3 mg/kg bw/day.

COMMENTS: This revised Executive Summary has raised the previous LOAEL for skin effects from 3 mg/kg/day to 30 mg/kg/day. The previous LOAEL was based on mild dermal irritation (hyperkeratosis, acanthosis, mild dilation of blood vessels, and mononuclear cells and/or heterophils in the proximal dermis. Several of these effects were not noted in the tables provided in the main text of the study report, which prompted further investigation of the results for individual animals in the appendices. Those results show that acanthosis and hyperkeratosis occur at the lowest dose only in two animals (one effect for each) and do not occur at the mid-dose. The hyperkeratosis, acanthosis, mild dilation of blood vessels, and heterophil infiltration that contribute to the majority of the previous LOAEL effects were seen to occur only in one animal at the highest dose. As there were some findings of moderate skin irritation at both the 30 mg/kg/day and 1000 mg/kg/day doses, the LOAEL statement from the original DER has been changed to reflect this, with the low incidence of mild irritation at the lowest dose no longer considered adverse. This updated DER now also includes tables of body weights for males and females, as well as histopathologic incidence and severity of skin lesions.

The 21-day dermal study in the rabbit is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a dermal toxicity study (OCSPP 870.3200; OECD 410) in non-rodents.

COMPLIANCE: This study predated the GLP Guidelines. A phase 3 summary (MRID 93194034) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides a data confidentiality statement.

A.6.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat
MRID 40425001
In a developmental toxicity study (MRID 40425001), CGA 64250 technical (92.1% purity, Batch no. FL 850083) was administered to 24 CL:COBS CD (SD) BR VAF/PLUS virgin female rats/dose by oral gavage in aqueous suspensions (3% corn starch containing 0.5% Tween 80) at dose levels of 0, 30, 90 or 300 mg/kg/day from days 6 through 16 of gestation. High dose animals initially received 360 mg/kg/day up to five days, but because of severe symptoms this was reduced to 300 mg/kg/day.

There was no treatment-related effect on mortality. There were no clinical signs in the low-dose group, and the only sign in the mid-dose group was with one female that exhibited rales. Severe compound-related maternal toxicity was observed at the high dose level during the first five days of dosing beginning on day 8 of gestation at 360 mg/kg/day. These effects included statistically significant increases in the incidence of lethargy, ataxia, salivation, and biologically significant increases in prostration, hypothermia, and bradypnea. The incidence of these effects versus control is as follows: lethargy (9/23 vs 0/24 in controls), salivation (4/23 vs 0/24 in controls) and ataxia (3/23 vs 0/24 in controls). After lowering the dose to 300 mg/kg/day on day 6, the severity and frequency of these effects decreased rapidly. A review of clinical signs for individual

animals revealed that the prostration, hypothermia, and bradypnea occurred only prior to lowering of the dose to 300 mg/kg/day. A non-guideline study (MRID 40425002) was conducted soon after this main study, and exposed maternal rats to only the highest dose. In addition to the clinical signs listed above, 17/189 (9%) rats were comatose at the highest dose compared to no controls in that non-guideline study (See Table 9 below).

Mean food consumption was significantly reduced in the 300 mg/kg/day group on days 7-10 and in the 90 mg/kg/day group on days 8-9 and 10-11. These intervals correspond to the first few days of dosing and can be correlated with the severe maternal toxicity observed in the high-dose group and the less pronounced maternal toxicity in the mid-dose group. Maternal body weights in all dosed groups were not affected by the treatments. No significant treatment-related effects on uterine weights, corpora lutea, live and dead fetuses, fetal weights, and resorption were reported.

The **maternal LOAEL** is 300 mg/kg/day, based on significant increases in ataxia, lethargy, and salivation. The **maternal NOAEL** is 90 mg/kg bw/day.

There were no significant differences in body weights or sex ratios of offspring between the control and treatment groups. There were no statistically significant effects of treatment on gross or visceral observations. Out of 1141 apparently viable fetuses, gross observations revealed two with malformations. One female fetus from the mid-dose group exhibited a cleft lip, cleft palate, club foot, and micromelia. One female fetus from the high-dose group exhibited anasarca. Visceral examinations of 593 fetuses revealed three with abnormalities. A separate female fetus in the mid-dose group had a cleft/hare lip, while a separate female fetus in the high-dose group had a cleft palate; the same female fetus in the high-dose group with anasarca was seen by visceral examination to also have a cleft palate, hydromelia, and a protruding tongue. There is no incidence of cleft palate in historical control or low-dose data from 19 teratology studies conducted by these same laboratory investigators. Historical data for the mid- and high-doses from these same 19 teratology studies include an incidence of 0.33% and 0.55-0.70% by fetus for each dose respectively; when evaluating by litter, these incidences are 4.56% and 7.14-9.09% for the mid-dose and high-dose, respectively. The historical control incidence of cleft palate in other laboratories is 0-0.35% by fetus. The incidence of cleft palate in the current study for the mid-dose group was 0.33% and for the high-dose group was 0.7% by fetus (4.55% and 9.09% by litter for the mid- and high-dose groups, respectively). The study authors noted that fetal malformations, such as cleft palate, could be a consequence of maternal toxicity but that malformations related to compound treatment could also be possible. The original EPA reviewers suggested that the cleft palate incidence was underreported because only half of the fetuses were examined viscerally, which was the procedure that led to the majority of findings for this condition. They also concluded that the low incidence of this finding, along with skeletal anomalies, was indicative of delayed development, and so the incidence of cleft palate in rat fetuses/litters at the high dose is considered adverse. Furthermore, cleft palate is considered a single-dose effect, and has recently been genetically linked to neural tube defects. In the non-guideline study, two fetuses from different litters exhibited cleft palate (0.1% fetal incidence and 1.3% litter incidence; See table 10 below).

A statistically significant increase in the incidence of shortened or absent renal papillae and

dilated ureters was seen in the fetuses in the high-dose group, and were thought by the study authors to represent slight delays in the normal development of the urinary system secondary to maternal toxicity rather than fetotoxicity. When evaluating these effects by litter, there were no differences from the control.

Skeletal malformations and variations were examined in 548 fetuses, and there were no treatment-related effects. A rudimentary 13th thoracic rib was seen in 3 control fetuses, 1 low-dose fetus, and one high-dose fetus. The same female from the mid-dose group afflicted with multiple abnormalities was also seen to have agenesis of the lacrimal bone. There was an increase in the incidence of minor skeletal abnormalities that included rudimentary ribs (non-significant) and non-ossified sternebrae (statistically significant) in the mid- and high-dose groups. These skeletal malformations were considered by the study authors to result from maternal effects rather than a specific fetal effect, in the absence of other fetal effects. The original EPA reviewers noted the dose-related trend of rudimentary ribs (0, 0.7%, 3%, 39% in the control and 30, 90, 300 mg/kg/d groups, respectively). The incidence of non-ossified sternebrae in the control was 38%, compared to 57% in the mid-dose group and 72% in the high-dose group. When evaluating these effects by litter, there was no difference from the

control for non-ossified sternebrae. The incidence of rudimentary ribs by litter exhibited a statistically significant dose-related increase (0%, 4.5%, 18% and 73% for the control and 0, 30, 90, 300 mg/kg/d groups, respectively).

The **developmental LOAEL** is 90 mg/kg bw/day, based on an increased litter incidence of rudimentary ribs. The **developmental NOAEL** is 30 mg/kg bw/day.

The developmental toxicity study in the rat is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; OECD 414) in the rat.

COMMENTS: This Executive Summary has been revised to expand upon the conclusions of the previous review and to change the wording in the NOAEL/LOAEL statements for maternal and developmental toxicity, without changing their actual values. The original and updated DERs consider all maternal clinical signs seen at the highest dose, regardless of whether this was 360 or 300 mg/kg/day. The main text of the study report and primary table of clinical incidences also do not distinguish between the two dose values for these effects. However, a closer review of the incidence of these effects for the individual animals in the appendix of the study report reveals that many occur prior to lowering the dose to 300 mg/kg/day on day 6. Therefore, the maternal LOAEL statement has been changed to reflect only those statistically or biologically significant effects seen after lowering the dose.

The original and updated DER documents provided information only for fetal abnormalities, while this current document also includes information for litter abnormalities. While the NOAEL/LOAEL values themselves have not changed, the original statement was based on the endpoints of an increased incidence of rudimentary ribs, cleft palate malformations (0.3%), and non-ossified sternebrae, as well as increased incidence of shortened and absent renal papillae. The increase in non-ossified sternebrae and absent/shortened renal papillae is no longer

considered significant when evaluating on a per-litter vs. per-fetus basis. Additionally, the 0.3% fetal incidence for cleft palate at 90 mg/kg bw/day is within the historical control range of 0-0.35% noted by other laboratories, and so is not considered toxicologically adverse. The 0.7% fetal incidence of cleft palate in the 300 mg/kg bw/day dose group is considered adverse, as it falls outside the historical control range. While the litter incidence of rudimentary ribs is much lower for the mid-dose than the high-dose group (18% vs. 72%), it is still considered significantly different from the control at the $p < 0.05$ level, and so the 90 mg/kg/d dose has been retained as the LOAEL.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided.

870.3700b Prenatal Developmental Toxicity Study – Rabbit
MRID 40425004 and 00164800
In a developmental toxicity study (MRIDs 40425004 and 00164800) CGA 64250 (92.1% purity, Batch# FL 850083) was administered to 19 pregnant New Zealand White rabbits/dose (sexually mature females artificially inseminated and weighing 6-7 lbs.) by oral gavage in aqueous suspensions (3% corn starch containing 0.5% Tween 80) at dose levels of 0, 100, 250, or 400 mg/kg/day from days 7 through 19 of gestation at a volume of 5.0 ml/kg/day. Food and water were provided ad libitum. All animals were observed daily for clinical signs. They were weighed on days 0, 7, 10, 14, 20, 24, and 29 of gestation, and food consumption was measured for gestational days (GD) 5 to 29.

On GD 29, females were sacrificed, and the fetuses removed. The following observations were made: macroscopic abnormalities of the reproductive tract of dams; number of corpora lutea in each ovary; weight of gravid uterus; numbers of live fetuses and number and distributions of resorption sites in each uterine horn; placental weights; fetal weights; external abnormalities and sex of each fetus; examination of soft tissue and skeletal abnormalities of each fetus upon sacrifice.

In the original study report (MRID 00164800), statistical analyses were presented on data obtained from pregnant rabbits surviving until GD 29, but excluded data for nine other pregnant animals that were found dead or required sacrifice prior to termination of the study. Additionally, data was excluded for one high-dose female that was pregnant but had no viable fetuses at terminal sacrifice. Upon request prior to issuance of the final report, the study authors provided this information as a revised statistical analyses in an amendment report (MRID 40425004).

Overall survival was good for all treated and control animals. There were two deaths, one dam from the control group and one from the mid-dose group; the death of one of the animals was due to a dosing accident. One control animal delivered early, and one dam from the mid-dose group aborted early. In the high-dose group, 5/19 animals were sacrificed early due to abortion or early delivery.

During the dosing period (days 7 to 19 of gestation), food consumption for females in the high- and mid-dose groups was consistently and significantly less than that of the control animals (43-60% of the controls and 58-77% of the controls in the high-dose and mid-dose groups, respectively). Once dosing was stopped, food consumption of these animals was generally

increased. Maternal body weight in the mid- and high-dose groups decreased by greater amounts in a time-dependent manner from GD 7 to 19 (95-98% of the control), though only the decrease for animals in the high-dose group weighed on GD 20 (91% of the control) was found to be statistically significant. As with food consumption, stopping the treatments resulted in an increase in both body weight and body weight gain for the remainder of the study period. The changes in body weights are not considered adverse, however, as they were less than 10%.

Animals in the high-dose group experienced a higher incidence of stool alterations (18/19 vs. 11/19 in controls). There was also a statistically significant increase in the number of abortions (5/19 vs. 1/19). The earliest abortion occurred on GD 22, while the remainder occurred on GD 26, and one female delivered early on GD 29. Other parameters were comparable between control and treated animals.

Developmental parameters were relatively similar between control and treated animals. An apparent increase in the mean value of resorption numbers in the high-dose group was heavily influenced by a completely resorbed litter for one female. The mean number of live fetuses, fetal weights, and offspring sex ratios were comparable between control and treated groups. There were also no significant differences in visceral or skeletal malformations between fetuses in the control and treated groups. A significant increase in the incidence of the formation of a 13th rib in fetuses at the highest dose was shown to be associated with the maternal toxicity of other studies. However, this same effect in litters is not considered significant at this dose. There was no increase in the incidence of cleft lip or cleft palate in treated animals.

The **maternal LOAEL** is 400 mg/kg/day, based on an increased incidence of abortions in pregnant rabbits. The **maternal NOAEL** is 250 mg/kg/day. The **developmental LOAEL** is 400 mg/kg bw/day, based on an increased incidence of abortions in maternal animals. The **developmental NOAEL** is 250 mg/kg bw/day.

This developmental toxicity study in the rabbit is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; OECD 414) in rabbits.

COMMENTS: This Executive Summary has revised the previous maternal LOAEL and NOAEL of 250 mg/kg/day and 100 mg/kg/day, respectively. These original values were based on reduced dam body weight gain and decreased food consumption during the dosing period. While these effects did appear related to treatment, they are no longer considered adverse because of their subsequent increase once dosing had ceased and because the decrease in body weights was less than 10%. The study report considered the developmental toxicity LOAEL to be 400 mg/kg bw/day based on an increased incidence of a 13th rib in fetuses, but the original DER felt this to be within the maternal toxicity level of other studies and so set the NOAEL at 400 mg/kg bw/day. While the increased incidence of a 13th rib in the fetuses of the high-dose group is significant, this is not the case when evaluating the same effect by litter. However, the increased incidence of abortions can be considered both a maternal and developmental effect, which has led to assigning the LOAEL for developmental toxicity to its original value of 400 mg/kg bw/day. In addition to revising the maternal LOAEL and NOAEL, this updated DER includes tables of clinical signs, food consumption, body weights, and weight gains for maternal

animals. It also includes tables of skeletal malformations by fetus and litter.

A.6.3 Chronic Toxicity

870.4100b Chronic Toxicity – Dog

MRID 00151515

In a chronic toxicity study (MRID 00151515), propiconazole was fed as CGA-64250 technical (90.2% purity, batch # FL-831527) to 4-6 month old beagle dogs (7/sex/dose for the control and high-dose group and 5/sex/group for the low- and mid-dose groups) at dietary dose levels of 0, 5, 50 or 250 ppm (time weighted average dietary concentrations based on mean food consumption are: 1.2±0.2, 13.0±2.0, 59.0±8.0 mg/kg/week or 0.2, 1.9, 8.4 mg/kg/day for males and 1.3±0.2, 13.0±2.0, 62.0±10.0 mg/kg/week or 0.2, 1.9 , 8.9 mg/kg/day for females, respectively) for a period of 52 weeks. These doses were based on a 3-month study in dogs fed 50, 250 or 1,250 ppm where a LOAEL of 250 ppm was set based on changes in the pyloric region of the stomach. Two dogs per sex in the control and high-dose group were held for an additional 28 days so that they might recover by being fed a basal diet containing no test material. All other animals were sacrificed after 52 weeks. Animals were provided food and water ad libitum. Hematology, clinical chemistry measurements, and urinalysis were conducted before treatment and at months 3, 6, and 12 (and 13 in the case of the recovery animals).

All animals survived through the 53-week dosing period. A breakout of mange in the colony led to alopecia, skin sores, and thinning of hair in both sexes in all groups and was not attributed to the test compound. No treatment related effects were noted in mean body weights, body weight gains, mean food consumption, hematologic and clinical chemistry, ophthalmology findings, electrocardiograms, organ weights, and gross pathological findings. Urine specific gravity in males was significantly increased at 50 and 250 ppm after three months, but after 6 and 12 months, values at these dose levels were comparable to controls, and so the initial increase is not considered toxicologically significant.

Histopathologic examinations revealed hyperemia of the mucosa of the stomach in 3/5 of the 250 ppm males, and no comparable findings were seen in the control males or females of any group. Functional hypertrophy of the mammary gland was reported in 1/5 control females, 1/5 receiving 5 ppm, 2/5 receiving 50 ppm, and 3/5 receiving 250 ppm of the test material. All other findings, including the necropsy and histopathological examination of the dogs in the recovery period were unremarkable other than functional hypertrophy of the mammary gland in 1/2 females receiving 250 ppm. This suggests that while the irritation of the mucosa in the high-dose group is likely compound-related, these effects are not adverse.

Deficiencies in the study included a non-homogeneous distribution of the test material in the mid-and high-dose groups during weeks 14-21. Analytical results showed the mean propiconazole concentrations for the 50 ppm diet ranged from 38 to 47 ppm and for the 250 ppm diet ranged from 161 to 518 ppm during this period. According to study authors this was due to mixing problems and crystallization of the test material during refrigeration storage. The test material was reported to be stable at room temperature; however, it was stored at room temperature only during the later-half of the study and heated to 50-98^{o} C prior to feed preparation. Nevertheless, the diet analysis data indicated the test material was stable throughout the study.

The **NOAEL** is 250 ppm (8.4 mg/kg/day for males and 8.9 mg/kg/day for females), which is the highest dose tested. The **LOAEL** is > 250 ppm.

This chronic study in the dog is **Acceptable/Guideline** and satisfies the guideline requirement for a chronic oral study [OCSPP 870.4100, OECD 452] in dogs.

COMMENTS: This Executive Summary has revised the previous LOAEL of 250 ppm (8.4 mg/kg/day) and NOAEL of 50 ppm (1.9 mg/kg/day). These previous values were based on hyperemia in the stomach of 3/5 males, indicating mild irritation of the mucosa. The study author concluded that the no-observable-effect-level (NOEL) for the study was 250 ppm, and this was changed to the LOAEL in the original DER. While, this irritation is likely related to treatment of the compound, an absence of clinical and gross pathological effects, combined with no histopathological changes seen after the recovery period, suggest this irritation is not adverse to the animals. As a result, the NOAEL has again been raised to the limit dose of the study of 250 ppm, and the LOAEL is unknown.

COMPLIANCE: A signed and undated Quality Assurance statement was presented in the report. A phase 3 summary (MRID 93194036) provides a statement of data correctness and certifies the availability of raw data and accuracy of summary and adequacy of the study, and provides a data confidentiality statement.

A.6.4 Carcinogenicity

870.4200b Carcinogenicity (feeding) – Mouse
MRID 00129570, 00151503, and 93194037
In a 24-month carcinogenicity study (MRIDs 00129570, 00151503, 00130844, and 93194037) propiconazole was administered to groups of CD-1 mice (52/sex/dose) in the diet at concentrations of 0, 100, 500, or 2500 ppm (10.0, 49.4, and 344.3 mg/kg/day for males and 10.8, 55.6 and 340.3 mg/kg/day for females, respectively). A satellite group (12 mice/sex/dose) was sacrificed at one year. Mice were provided drinking water and laboratory diet ad libitum, except for the fasting of animals the night before collection of samples for urinalysis. Control animals received normal diet, while for the first 51 weeks, the test material was ground directly into the diet as a premix prior to further dilution with the diet to attain desired concentrations. During the second year (week 52 onwards), the test substance was weighed out and dissolved in ethyl acetate before incorporation into the diet, to improve homogeneity. The EPA reviewers in the original DER questioned the use of the ethyl acetate and its impact on the study as an added variable separate from the dose compound. The results of analyses for purity (including identification of all impurities) and stability of the test material in the diet provided later by the registrant were found to be satisfactory (HED doc. No. 005352).

Parameters observed during the study included clinical signs, mortality, food consumption, hematology and clinical chemistry (measured at weeks 50 and 102), and urinalysis (measured at weeks 51 and 102). All surviving animals were necropsied at 53 weeks (satellite group) or 104 weeks (main group), with weighing of selected organs and gross/microscopic analysis of tissues.

There were no treatment-related effects on clinical signs. An increase in mortality for males in

the 2500 ppm group during the first six months is considered compound-related. Survival at 104 weeks for the control, 100, 500 and 2500 ppm groups was 46%, 38%, 40%, and 27% for males and 54%, 63%, 46% and 62% for females. However, a sufficient number of animals were alive at study termination to assess the carcinogenic potential of the test material. Body weights of males were first reduced to toxicologically significant values in the high-dose group relative to the control within the first week (↓10-21%) and remained at this level throughout the remainder of the study. Body weights of females remained at control levels in the high-dose group to ~day 63, then were reduced to toxicologically significant values (↓10-13%), and then were increased again from day 94 to the end of the study. Food consumption was increased in high-dose males only.

There were no treatment-related hematological effects observed. Glutamic pyruvate transaminase (GPT) and glutamic oxaloacetic transaminase (GOT) were significantly increased among males in the high-dose group relative to the control at weeks 52 (333% and 77% increase for GPT and GOT, respectively) and 100 (517% and 336% increase, respectively) and in females in the high dose group at week 52 (61% and 31% increase, respectively). The large standard deviation range for males at week 100 is recognized. Alkaline phosphatase (AP) was significantly increased in males of the high-dose group at week 100 (289% increase), although this was not seen in males at week 52 or in females at either time of sacrifice. These above changes are considered indicative of liver damage. Serum cholesterol was slightly altered in males and females in the high-dose group, though this effect was not consistent over time, and so is not considered toxicologically significant. Urinalysis results did not reveal any treatment-related effects. Amyloidosis occurred more frequently in treated animals compared to controls, but was not dose-related.

Significant increases in liver weight were seen for both sexes at the high dose relative to the control at week 53 (94% and 39% increase for males and females, respectively) and at termination (128% and 51% increase for males and females, respectively). Males treated with 500 ppm experienced liver weights that were marginally higher than those of control animals but were just at the threshold of statistical significance at week 53 (23% increase) and were not statistically significant at termination. A higher incidence of enlarged livers was also seen for both males and females in the high-dose group, with this effect observed to a lesser degree for males in the mid-dose group; this enlargement of livers correlates well with the increases in

liver weight for both sexes. Liver histopathology of low- and mid-dose mice was generally comparable to that of controls. Necropsy observations at the termination of the study indicated a treatment-related increase in liver lesions (masses/raised areas/swellings/nodular areas) among mid- and high-dose males relative to the control (50% and 40% increase, respectively) and in high-dose females (267% increase). Significant non-neoplastic findings were confined to the liver of mice in the high-dose group only and included hepatocyte enlargement (mostly in the centrilobular areas) and an increased incidence of hepatocellular fat deposition and hepatocyte vacuolation in females. A re-evaluation of pathology slides for this study allowed for providing both incidence and severity of these non-neoplastic lesions in male mice at terminal sacrifice and upon early death (E. Doyle, TXR 0009771, 09/11/1992). There were no differences from the control for the lowest dose. At 500 ppm, the incidence of minimal and mild hepatocyte enlargement was 2-3X that of the control. At 2500 ppm, moderate to severe hepatocyte

enlargement was noted in nearly half the livers. Mild to moderate hepatocyte vacuolation, chronic inflammation, and pigmented Kupffer cells were also seen in male livers at the highest dose. Treatment-related tumors were seen in the livers of male mice at the highest dose, while such tumors were not seen in female mice or at the two lowest dose groups.

The **LOAEL** is 2500 ppm (344.3 mg/kg/day and 340.3 mg/kg/day for males and females, respectively), based on decreased body weights, increased liver weights, and an accompanying increase in liver enzymes (GPT, GOT, and AP), non-neoplastic liver effects and histopathology (increased incidence and severity of centrilobular hepatocyte enlargement in males, increased fat deposition and vacuolation of hepatocytes in females, and enlarged livers in both sexes). The **NOAEL** is 500 ppm (49.4 mg/kg/d for and 55.6 mg/kg/d for males and females, respectively).

This Carcinogenicity study in the mouse is **Acceptable/Guideline** and satisfies the guideline requirement for a carcinogenicity study OCSPP 870.4200); OECD 451 in mice.

COMMENTS: This Executive Summary revises the previous LOAEL and NOAEL of 500 ppm and 100 ppm, respectively. These previous values were based on non-neoplastic liver effects that included increased liver weight in males and an increase in liver lesions. However, a high number of lesions, fat deposition, or swollen areas was also seen in control males at both times of sacrifice, and so these effects at the 500 ppm dose are likely of little toxicological significance. In addition, the changes in liver enzymes, which are more indicative of liver damage, were significant only at 2500 ppm. Body weight reductions below the guideline values of 10% seen in males throughout the majority of the study and in females at the end of the study, at this same dose, support the assumption of adversity only at the highest dose tested. This combined evidence has resulted in raising the LOAEL and NOAEL to 2500 ppm and 500 ppm, respectively. In addition to revising these values, this updated DER has included tables for clinical chemistry liver pathology, liver weights, and body weights of males and females.

COMPLIANCE: Signed and dated GLP, Quality Assurance and Data Confidentiality statements were provided.

MRID 44381401

This study was conducted to satisfy a Phase-4 data call-in for propiconazole from the U.S. EPA. The phase 4 memo called for an additional mouse oncogenicity study on the basis of the Agency's determination that the high dose (2500 ppm) in the original 2-year mouse oncogenicity Study was excessively toxic. A study design involving only the CD-1 males, histopathology of only the liver, and feeding levels of 0, 100, 500, and 850 ppm was accepted by the EPA in a final communication dated 5/10/94.

In an 18-month oncogenicity study (MRID 44381401), CGA 64250 technical (Batch No. OP.303011, Purity 92.4%) was administered to groups of 80 male Crl: CD-l (ICR) BR mice in the diet at concentrations of 0, 100, 500, or 850 ppm. These concentrations resulted in a nominal compound intake for each concentration level of 0, 11.0, 59.0, and 108 mg/kg/day for control, low-, mid-, and high-dose, respectively. Fifty animals per group were used for the main study, ten per group were used to investigate blood chemistry, and ten animals per group were designated for interim sacrifice at 9 weeks and twelve months. Blood chemistry was measured at

weeks -1 (pretest), 9, 14, 53, and 79.

No overt clinical signs were noted over the course of the study in any of the treated groups, and survival in all the treated groups was comparable to the control. While mean body weights and weight gain in the 850 ppm group were comparable to those of the control prior to treatment and for the first 3 months, they were significantly lower during weeks 18 to 50. During this latter part of the study (weeks 18-46), body weight gains in the 850 ppm group were significantly lower than the controls (11-19%). A non-significant decrease in weight gain (10%) was also noted in the 500 ppm group during this time. After week 50, mean body weights at this dose appeared to equilibrate and remain similar to controls throughout the remainder of the study. Food consumption was comparable in all groups.

Serum cholesterol was decreased throughout the treatment period in mice treated at ≥ 500 ppm. Significant reductions were seen at weeks 9, 14, and 53 in the 850 ppm group (↓24-32%) and at week 14 in the 500 ppm group (↓14%). Sorbitol dehydrogenase was significantly increased in the 850 ppm group at week 14 (↑44%). However, Both alanine aminotransferase and aspartate aminotransferase were significantly decreased at week 9 in the 500 ppm group but not at the highest dose. These transient changes in serum chemistry are not considered adverse.

The liver was identified as a target organ based on several toxic effects to this organ. Statistically significant concentration-effect increases in mean liver weight and mean liver to body weight ratios were observed in the high-dose group at interim and final sacrifice compared to the control (32% and 33%, 11% and 29%, and 19% and 20% for the interim sacrifices at weeks 9 and 53 and the terminal sacrifice, respectively). Increased liver weights were also seen in the mid-dose group, but these were not statistically significant (10-14% at any time of sacrifice). The high-dose group also was found to have significantly more (6 l%) incidences of enlarged livers compared to the control group. Increased incidences of masses and nodules were also observed in the 850 ppm treated animals compared to the controls, though these were not statistically significant. Hepatocellular hypertrophy was significantly increased by 86 and 93%, respectively in the mid- and high-exposure groups, with centrilobular hepatocytes being typically enlarged and with a very pale eosinophilic cytoplasm. Severity of hypertrophy was more pronounced at the highest dose. There was a concentration-effect relationship evident for the incidence of liver necrosis at ≥ 100 ppm only at the week 9 sacrifice; there were no differences from the control at other timepoints. There was an increase in the incidences of fatty change (vacuolation) and minimal lymphohistiocytic infiltration, with some evidence of necrosis in the livers of animals in the high-dose group only at the week 9 interim sacrifice. This increased incidence of these effects at only one timepoint is considered to be a spurious finding. At terminal sacrifice, Kupffer cell pigmentation and foci of cellular change were found to a greater degree in the high-dose group.

There was a treatment-related increase in the number of adenomas and total neoplasia (adenomas and carcinomas) of 2% and 4%, respectively and hepatotoxic effects seen at 500 and 850 ppm. The percentage adenomas and carcinomas were within the range of the inadequate historical control data submitted with the study report. In the 850 ppm dose group, the total incidence of hepatocellular neoplasia was slightly higher (24%) than the upper limit of the historical control range of 22.4% submitted, and the concurrent control (4%) was lower than of the lower range of

historical controls of 6.0% submitted. The historical controls submitted were inadequate because the collection dates were not specified and were not collected in the testing facility. The registrant later submitted additional control data for mice tested within the same time frame and at the same facility as mice in the current study (MRID 45215804), and the tumor incidence observed in male mice at the 850 ppm dose was within the range of the new historical control data.

The **LOAEL** is 850 ppm (108 mg/kg/day) based on a significant increase in absolute and relative liver weights, enlarged livers, and hypertrophy, accompanied by changes in clinical chemistry (decreased serum cholesterol and increased sorbitol dehydrogenase). The **NOAEL** is 500 ppm (59 mg/kg/day).

This carcinogenicity study in mice is **Acceptable/Guideline** and satisfies guideline requirements for a carcinogenicity study [OCSPP 870.4200; OECD 451] in mice.

COMMENTS: This Executive Summary revises the previous LOAEL of 500 ppm (59 mg/kg/day) and NOAEL of 100 ppm (11 mg/kg/day). These previous values were based on hepatotoxicity and body weight gain effects observed at the interim and terminal sacrifices. However, mean body weights for animals in the 100 and 500 ppm groups were similar to controls throughout the study. The study author attributes the lower body weight gain with little change in absolute body weight to the increase in liver weight. Both absolute body weight and body weight gain show significant reductions during the same period of 14-53 weeks, so there does appear to be a correlation between the two. If the increase in liver weight is driving the discrepancy between body weight gain and absolute body weight, then this should be seen during weight measurements prior to the 18-week timepoint, but at the mid-dose, the increase in both absolute and relative liver weight is fairly constant at 10-14% at all times of measurement.

There were no dose-related changes in serum clinical components, and the only effects seen were transient in nature. According to revised guidelines, hypertrophy and increases in liver weight or enlarged livers, in the absence of accompanying clinical chemistry effects (e.g., changes in liver enzymes) and corroborating histopathology, is not considered adverse. As a result, the LOAEL has been raised to 850 ppm (108 mg/kg/day), with the NOAEL now 500 ppm (59 mg/kg/day). It could be argued that even at this dose level, the pathological changes in the liver and changes in body and liver weights might still not be considered adverse. Even when reductions in body weight are statistically significant, they only decrease by 2-5%. Furthermore, the decrease in serum cholesterol and increase in sorbitol dehydrogenase are no longer apparent after week 14, and are not accompanied by changes in other liver enzymes. For the scope of this study, and based on the physiological parameters measured, however, the LOAEL has been set at the highest dose.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

A.6.6 Neurotoxicity

870.6200a Acute Neurotoxicity – Rat
MRID 46604601
In an acute neurotoxicity study (MRID 46604601), groups of fasted, 42-day old Alpk:APfSD (Wistar derived) rats (10/sex/dose) (167-206 g males and 147-173 g females) were given a single oral dose of CGA 64250 (95.2% a.i., Batch # P.802028) in corn oil by oral gavage at doses of 0, 30, 100, or 300 mg/kg and observed for the following 14 days. Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed one week prior to treatment, on day 1 approximately 5-6 hours after dosing, and on days 8 and 15 following the single dose. The bodyweight of each rat was also recorded at these same time points. Food consumption was recorded continuously throughout the study period for each cage of rats and calculated as the mean value (g food/rat/day) for each cage. At study termination, 5 animals/sex/group were euthanized and perfused [in situ] for neuropathological examination. Brain weights of the perfused animals were recorded at all doses, while histologic evaluation of brain and peripheral tissues was conducted only for those perfused animals from the control and high dose groups.

There were no treatment-related effects on body weight. Males at all dose levels had lower food consumption in week 2 (↓7-9%). However, lack of similar findings in the week following dose administration, no observation of differences in females, no evidence of a dose-response, and no body weight effects (<10%), indicate that these small differences in male food consumption in the second week are not related to treatment.

Single oral administration of 300 mg/kg propiconazole produced severe clinical signs of toxicity in male and female rats within 5- 6 hours (peak effect) of dosing. These effects were more pronounced in the females, where two females were sacrificed on the first day due to severe clinical toxicity, but after all testing had been completed for that day. Effects included: decreased activity, coldness, paleness, piloerection, subdued behavior, tip toe gait, staining around the nose, and stained with urine wet. A total of 5 males and 8 females of the 300 mg/kg dosed animals showed clinical signs of toxicity. These clinical observations were no longer evident on day 2. While a small number of animals in the 100 mg/kg dose group showed a limited number of clinical signs (piloerection in one male, diarrhea in one female, tip toe gait in 3 females), the majority were unaffected. A finding of reduced splay reflex was recorded for 1 male and 3 females in this dose group, but these incidences were similar in number to those of control animals at different time points (day 8 and 15) and were not correlated with any effect on quantitative measurement of landing foot splay. Therefore, this particular effect was not considered to be treatment-related, and the small number of clinical signs were no longer evident on day 2. The only effect seen in the 30 mg/kg dose group was reduced splay reflex in 1 male and 1 female, but again this was not considered treatment-related based on the explanation above for this same effect in the 100 mg/kg dose group.

No treatment-related differences were observed on landing foot splay measurements, fore-limb strength, or hind-limb strength in the FOB test conducted in animals 5-6 hours after dosing. Females dosed with 300 mg/kg had an increased time to tail flick (9.4 seconds vs 3.7 seconds for the controls) on day 1 only. Females dosed with 300 mg/kg also had reduced locomotor activity

on day 1 (time of peak effect) at each time interval (i.e., tested as five-minute scans with no food, water, or environmental enrichment for a total of ten times) and overall. Males treated at this dose had slightly reduced activity, with statistically significant reductions in minutes 11-15 and overall. Motor activity was not affected by treatment at 30 or 100 mg/kg on the first day. No treatment-related effects were observed on motor activity on days 8 and 15.

There were no differences in brain weight that were considered to be treatment-related. The slightly higher brain weights seen in males in the high dose group were attributed to a lower control group mean weight (1.94 g) than historical controls (1.90-2.11) and therefore normal variation in physiology. There were also no differences in gross or microscopic findings. A minor increase (2/5 versus 1/5 in the control group) of minimal distal tibial nerve demyelination in females in the high dose group fell within the historical control incidence for female Alpk:APfSD rats in acute neurotoxicity studies (0-40%).

The **LOAEL** is 300 mg/kg, based on reduced motor activity in males and females on Day 1 (time of peak effect), increased time to tail flick on Day 1 in females, and multiple clinical signs of toxicity (tip toe gait, piloerection, and decreased activity in both males and females; subdued behavior, coldness, paleness, and staining around the nose and with urine in females). The **NOAEL** is 100 mg/kg.

This neurotoxicity study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (OCSPP 870.6200; OECD 424).

COMMENTS: This revised Executive Summary updates the NOAEL/LOAEL. In the previous review, a LOAEL was set to 100 mg/kg, based on the limited clinical signs seen in animals (piloerection in one male, diarrhea in one female, and tip toe gait in 3 females); the NOAEL was 30 mg/kg. While the study report states that these clinical signs are transient in nature (having only been observed only on day 1), they did occur at the period of peak effect. However, this reviewer agrees with the original conclusion in the study report that the effects seen in the 100 mg/kg dose are limited to such a degree as to not be considered toxicologically significant (i.e., signs of piloerection or diarrhea in just one animal). The tip toe gait in 3 females offers a stronger argument, as this effect is first seen at the 100 mg/kg dose, but it remains 50% that of the incidence at the highest dose (3/10 verses 6/10). Additionally, only one observation was required to reveal tip toe gait in all six animals at the highest dose, whereas an extra observation was required to reveal this effect in the three animals at the middle dose. As a result, the LOAEL and NOAEL have been raised to 300 mg/kg and 100 mg/kg, respectively, based on reduced motor activity in both sexes on the day of peak effect, clinical signs in both sexes, and reduced time to tail flick and coldness/paleness in females.

COMPLIANCE: Signed and dated Data Confidentiality, GLP, Flagging, and Quality Assurance statements were provided.

870.6200 Subchronic Neurotoxicity Screening Battery
MRID 49300503
In a subchronic neurotoxicity study (MRID 49300503), propiconazole (95.2% a.i., batch/lot# P.802028) was administered to groups of ~6-week-old Crl-CD(SD) rats (12/sex/dose)

continuously in the diet for 13 weeks at concentrations of 0, 200, 600, or 1500 ppm (females) or 3500 ppm (males) (equivalent to 0,13, 38, and 222 mg/kg/day, respectively, in males and 0, 15, 45, and 111 mg/kg/day, respectively, in females). Dietary levels were chosen based on the findings of a 4-week dietary range-finding neurotoxicity study (MRID 49300502).

Neurobehavioral assessment (functional observational battery [FOB] and motor activity testing) was performed in 12 animals/sex/group during pretest (Week -1) and Weeks 1, 3, 7, and 12. Cholinesterase activity was not determined. At study termination (Week 13), 5 rats/sex/group were euthanized and perfused in situ for neuropathological examination. Of the perfused animals, the 5 rats/sex each from the control and high-dose groups were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

All animals survived to the scheduled necropsy, and no compound-related clinical findings were noted during weekly observations. No significant changes in body weight, body weight gain, or food consumption were noted in females at any dose level or in males at 200 ppm and 600 ppm. At 3500 ppm, males experienced a statistically significant decrease in mean body weight gain (83% of controls) during study days 0-7, which corresponded with a reduction in mean food consumption (88% of controls) during that period. Over the course of the study (Days 0-91), mean body weight gain for males at 3500 ppm was reduced to ~89% of controls, though this reduction was not statistically significant. At termination, the mean absolute body weight for males at 3500 ppm was 93% of the controls. While the male rats fed the high dose appeared to have not been able to fully recover from the reduction in body weight gain during the first week of treatment, body weights that were comparable to control animals at the end of the study suggest that at least some recovery had occurred over that time and that the reductions in overall body weight are not considered to be adverse.

There was no evidence of neurotoxicity associated with exposure to propiconazole based on FOB evaluations, motor activity assessments, mean brain weights and measurements, and macroscopic and microscopic findings. No treatment-related effects were noted during ophthalmoscopic examination, gross pathology, or in brain weight and brain dimension measurements. Positive control data were provided.

Based on the effects seen in this study, the **NOAEL** for male Sprague-Dawley rats was 3500 ppm (222 mg/kg bw/day), and the **NOAEL** for female rats was 1500 ppm (111 mg/kg bw/day). A **LOAEL** was not established for either sex.

The study is classified as **Acceptable/Guideline** and satisfies the guideline requirement for a subchronic neurotoxicity study in rats (OCSPP 870.6200b; OECD 424).

COMMENTS: This Executive Summary has revised the previous LOAEL of 3500 ppm (222 mg/kg/day) and NOAEL of 600 ppm (38 mg/kg/day) for male rats. The NOAEL and LOAEL for female rats has remained unchanged. The previous values for male rats were based on significant reductions in body weight gain and food consumption. The older DER states that “While these body weight data may appear to be of borderline significance, results of a 4-week study in male rats in which a dietary concentration of 6000 ppm produced a 15% lower mean absolute body weight and a 48% increase in liver weight at study termination support that the high-dose of

3500 ppm may be close to the threshold concentration producing notable toxicity." However, several dose levels between 3500 ppm and 6000 ppm are possible that might reveal toxicological effects that act as stronger evidence of an adverse response in male mice than those seen in the current study. Furthermore, the only significant change seen in body weight gain in males occurred during the first week of the study (an 18% decrease) and thereafter remained similar to control values, and the decrease in absolute body weight at this time was only 5%. Together with the lack of neuropathological effects, this suggests that the reductions in body weight during the first week of treatment were not adverse. As a result, the NOAEL has been raised to 3500 ppm (222 mg/kg/day) for males (the limit dose), with a LOAEL not established.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

A.6.7 Pharmacokinetics

870.7600 Dermal Absorption (*in vivo*) – Rat

MRID 42415701 and 45345901

In a dermal penetration study (MRIDs 42415701 and 45345901) triazole-[3,5-]14C- CGA-64250 (95% radioactive purity, specific activity 28.2 mCi/mg for low and mid-dose levels and 2.01 mCi/mg for the high-dose level, respectively) was administered to 4 young adult male Harlan Sprague-Dawley rats (200-250 g) per dose over a 10 cm^2 area (4.0 cm X 2.5 cm) of shaved skin in the dorso-lumbar region at dose levels of 0, 0.1, 1 and 10 mg/rat (equivalent to 0, 0.01, 0.1, and 1 mg/cm2). The radioactive test compound was added to the 3.6EC formulated product (45.8% active ingredient and 54.2% inert substances) and applied as an aqueous suspension. One group of four rats/dose were exposed for 24 hours, while two other groups of four rats each/dose were exposed for 10 or 24 hours followed by a 72-hour depletion phase. This study is an addendum to an earlier study where groups of four male rats each were treated similarly but exposed for 2, 4 or 10 hours prior to sacrifice (MRID 00164469). In both studies, following the exposure period, the test compound remaining on the skin was removed with a soap rinse. Fecal and urinary samples were collected at the end of the exposure periods and at 24-hour intervals (for the depletion groups) following the exposure.

Upon sacrifice, rats were anesthetized and blood collected. The radioactivity present in excreta, blood, carcass, skin, skin washes and patch components was determined. The applied radioactivity was accounted for, with recoveries ranging from 82.8 to 108 % for MRID 42415701 and 86.6 to 112.6% for MRID 00164469.

The amount of test compound absorbed was inversely related and directly proportional to the applied dose. The rate of absorption appeared to be saturated at the highest dose level; at the low and mid dose levels, there generally was a time dependent increase in the amount of compound absorbed. After 24 hours, 57.1, 271 and 3010 µg/cm^2 (57.13, 27.14 and 30.10% of total dose were absorbed at the low, mid and high dose levels, respectively). During the 72-hour depletion phase essentially all of the compound was eliminated in the urine and feces; urinary elimination predominated at the mid and high dose levels. At the end of the 72-hour depletion phase, less than 2% of the test compound was still present in the carcass. The results of the earlier study (MRID 00164469) demonstrated that 26-35% of the applied radioactivity (at all dose levels) is

absorbed within the first two hours and remained fairly constant for the longer exposure periods of 4 and 8 hours except for the low dose of 0.01 mg/cm2 where it increased to 54%. The average dermal absorption, i.e., the dermal absorption factor (DAF), of propiconazole over a 10-hour period at an exposure level of 0.01 mg/cm2 is approximately 48% when including skin. The attached table provides a summary of both studies.

These two studies in the rat are **Acceptable/Guideline** and satisfy the guideline requirement for a dermal penetration study (870.7600) in rats.

COMMENTS: This revised Executive Summary updates a previous dermal absorption factor of 40%. In the previous review, the amount absorbed on the skin was not taken into consideration because the depletion study (MRID 42415701) demonstrated that a 72 hour depletion phase after a 10 hour exposure time resulted in less than 2% removed from the skin upon washing, with 4-6% remaining on the skin after washing, and because the authors of the study report concluded that this remaining radioactivity should be considered bound and not available for further absorption. As a result, the amount absorbed with skin not included was averaged between the two studies to give 41.02, which was rounded to approximately 40%. However, given the differences that could occur between both studies in regard to inherent variability among study factors, averaging the two may lead to errors. Because the amount absorbed in the depletion study is already above the previous DAF (42.37%), absorption percentage more likely falls between 42% and 48%, and so this is the reason for raising the DAF from 40% to 48%. Furthermore, there is evidence of additional absorption occurring across skin even after washing, which is why skin is included in the estimated absorption value.

COMPLIANCE: Signed and dated GLP and Quality Assurance statements were provided. Data Confidentiality and Flagging statements were not provided for MRID 00164469 and 42415701.

OECD 428 Dermal Absorption (*in vitro*) – Human Skin

MRID 51525101

In a dermal penetration study (MRID 51525101), the rate and extent of absorption of [14C]-Difenoconazole (99.1% a.i.; Batch # RDR-XX-90) and [14C]-Propiconazole (99.4% a.i.; Batch # RDR-XXI-2) following topical application as an emulsifiable concentrate (EC) formulation (A8122B) through human split-thickness skin (8 replicates with a total area of 2.25 cm2 and exposed area of 0.64 cm2) was determined in vitro. The concentration of difenoconazole and propiconazole in the concentrate EC formulation was 250 g/L, while the concentration in the in-use spray dilution was 0.42 g/L. Doses were applied at 10 µL/cm2 and left unoccluded for 24 hours, with an interim wash at 6 hours (gentle wash with hand soap) and final wash and processing (i.e., tape stripping, collection of skin samples, and collecting of samples from the donor and receptor chambers to account for mass balance) occuring at the 24-hour timepoint. Absorption was measured by collection of receptor fluid samples at recorded intervals of 2, 4, 6, 8, 12, and 24 hours, followed by liquid scintillation counting (LSC). Note that this DER discusses results only for propiconazole and refers to the original study report for data regarding the analyses and results for difenoconazole.

Mass balance for all individual samples exposed to the concentrate or spray dilution was 100 ± 10%, with mean total recoveries of 102.3% and 100.1%, respectively, of the administered dose

(AD). Absorption of propiconazole increased to 24 hours post-dose for both the concentrate and spray dilution, with similar profiles for all skin samples. Total absorption values took into consideration radioactivity recovered in the receptor fluid, the receptor chamber wash, the last several tape strips (i.e., all but the first two), and the exposed skin area; the latter two measurements were considered to be the potentially absorbable fraction. Penetration of the concentrate at 24 hours, as measured in the receptor fluid, was 0.29% of the AD, with a mean absorption rate of 0.30 µg equivalents/cm2/hour. For the spray dilution, penetration at 24 hours was 9.99% of the AD, with a mean absorption rate of 17.9 ng equivalents/cm2/hour. At the 6-hour wash, 99.3% of the administered concentrate and 78.6% of the spray dilution were removed from the skin; an additional 2.12% and 5.76% of the concentrate and spray dilution were removed at the 24-hour wash. Total absorption was 0.69% of the AD for the concentrate and 14.8% for the spray dilution.

This in vitro dermal penetration study is **Acceptable/Guideline**. While 8 hours is considered to be a typical workday for potentially exposed individuals, exposure times between 6-10 hours are considered acceptable for estimating dermal penetration.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

MRID 51525102

In a dermal penetration study (MRID 51525102), the rate and extent of absorption of [14C]-Azoxystrobin (99.2% a.i.; Batch # MJD-I-67) and [14C]-Propiconazole (98.1% a.i.; Batch # MJD-I-25) following topical application as a suspo-emulsion (SE) formulation (A15909D) through human split-thickness skin (8 replicates with a total area of 2.25 cm2 and exposed area of 0.64 cm2) was determined in vitro. The concentration of azoxystrobin and propiconazole in the concentrate EC formulation was ca 141.4 g/L and 122.4 g/l, respectively, while the highest concentration in the in-use spray dilution was ca 0.707 g/L and 0.612 g/L, respectively, and the lowest concentration in the in-use spray dilution was ca 0.236 g/L and 0.204 g/L, respectively. Doses were applied at 10 µL/cm2 and left unoccluded for 24 hours, with an interim wash at 6 hours (gentle wash with hand soap) and final wash and processing (i.e., tape stripping, collection of skin samples, and collecting of samples from the donor and receptor chambers to account for mass balance) occuring at the 24-hour timepoint. Absorption was measured by collection of receptor fluid samples at recorded intervals of 2, 4, 6, 8, 12, and 24 hours, followed by liquid scintillation counting (LSC). Note that this DER discusses results only for propiconazole and refers to the original study report for data regarding the analyses and results for azoxystrobin.

Mass balance for all individual samples exposed to the concentrate, high concentration spray dilution, or low concentration spray dilution was 100 ± 10%, with mean total recoveries of 96.4%, 99.7%, and 96.3%, respectively, of the administered dose (AD). Total absorption values took into consideration radioactivity recovered in the receptor fluid, the receptor chamber wash, the last several tape strips (i.e., all but the first two), and the exposed skin area; the latter two measurements were considered to be the potentially absorbable fraction. Penetration of the concentrate at 24 hours, as measured in the receptor fluid, was 0.74% of the AD, with a mean absorption rate of 0.39 µg equivalents/cm2/hour. For the high concentration spray dilution, penetration at 24 hours was 10.0% of the AD, with a mean absorption rate of 26.5 ng

equivalents/cm2/hour. For the low concentration spray dilution, penetration at 24 hours was 14.1% of the AD, with a mean absorption rate of 12.1 ng equivalents/cm2/hour. At the 6-hour wash, 93.3% of the administered concentrate, 79.3% of the high concentration spray dilution, and 69.2% of the low concentration spray dilution was removed from the skin; an additional 1.63%, 5.14%, and 6.12% of the concentrate and high and low spray dilutions was removed at the 24-hour wash. Total absorption was 1.15% of the AD for the concentrate, 14.4% for the high concentration spray dilution, and 20.0% for the low concentration spray dilution.

This in vitro dermal penetration study is **Acceptable/Guideline**. While 8 hours is considered to be a typical workday for potentially exposed individuals, exposure times between 6-10 hours are considered acceptable for estimating dermal penetration.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

MRID 51525103

In a dermal penetration study (MRID 51525103), the rate and extent of absorption of [14C]-Propiconazole (99.4% a.i.; Batch # RDR-XXI-2) following topical application as an emulsifiable concentrate (EC) formulation (A6780L) through human split-thickness skin (8 replicates with a total area of 2.25 cm2 and exposed area of 0.64 cm2) was determined in vitro. The concentration of propiconazole in the concentrate EC formulation was 161.6 g/L, while the highest concentration in the in-use spray dilution was ca 1.30 g/L, and the lowest concentration in the in-use spray dilution was ca 0.486 g/L. Doses were applied at 10 µL/cm2 and left unoccluded for 24 hours, with an interim wash at 6 hours (gentle wash with hand soap) and final wash and processing (i.e., tape stripping, collection of skin samples, and collecting of samples from the donor and receptor chambers to account for mass balance) occuring at the 24-hour timepoint. Absorption was measured by collection of receptor fluid samples at recorded intervals of 2, 4, 6, 8, 12, and 24 hours, followed by liquid scintillation counting (LSC).

Mass balance for all individual samples exposed to the concentrate, high concentration dilution, or low concentration dilution was 100 ± 10%, with mean total recoveries of 102.0%, 96.7%, and 96.6%, respectively, of the administered dose (AD). Absorption of propiconazole increased to 24 hours post-dose for both the concentrate and spray dilutions, with similar profiles for all skin samples. Total absorption values took into consideration radioactivity recovered in the receptor fluid, the receptor chamber wash, the last several tape strips (i.e., all but the first two), and the exposed skin area; the latter two measurements were considered to be the potentially absorbable fraction. Penetration of the concentrate at 24 hours, as measured in the receptor fluid, was 0.11% of the AD, with a mean absorption rate of 0.07 µg equivalents/cm2/hour. For the high concentration spray dilution, penetration at 24 hours was 5.67% of the AD, with a mean absorption rate of 0.03 µg equivalents/cm2/hour. For the low concentration spray dilution, penetration at 24 hours was 10.8% of the AD, with a mean absorption rate of 22 ng equivalents/cm2/hour. At the 6-hour wash, 101.6% of the administered concentrate, 85.1% of the high concentration spray dilution, and 78.4% of the low concentration spray dilution was removed from the skin; an additional 0.13%, 3.14%, and 3.86% of the concentrate and high and low spray dilutions was removed at the 24-hour wash. Total absorption was 0.17% of the AD for the concentrate, 7.72% for the high concentration spray dilution, and 13.5% for the low

concentration spray dilution.

This in vitro dermal penetration study is **Acceptable/Guideline**. While 8 hours is considered to be a typical workday for potentially exposed individuals, exposure times between 6-10 hours are considered acceptable for estimating dermal penetration.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

Appendix B. Physical/Chemical Properties

Table B.1. Physicochemical Properties of Technical Grade Propiconazole.		
Parameter	**Value**	**Reference**
Boiling point	120°C at 1.9 Pa, >250°C at 101.325 kPa	MRID No. 43698701
pH	4.9 at 25°C (1% aqueous dispersion)	MRID No. 43698701
Density	1.289 g/cm^3 at 20°C	MRID No. 43698701
Water solubility	0.10 g/L at 20°C	MRID No. 41720301
Solvent solubility (temperature not specified)	Completely miscible in ethanol, acetone, toluene and n-octanol. hexane = 47 g/L	MRID No. 42030201
Vapor pressure	4.2 x 10^{-7} mm Hg at 25°C	MRID No. 41720301
Dissociation constant (pK_a)	1.09	MRID No. 43698701
Octanol/water partition coefficient Log(Kow)	3.72 at pH 6.6 and 25°C	MRID No. 43698701
UV/visible absorption spectrum	Not available	MRID No.: 40583703

Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. It is HED policy to use the best available data to assess exposure. Several sources of generic data were used in this assessment as surrogate data in the absence of chemical-specific data, including Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the Outdoor Residential Exposure Task Force (ORETF) database; the Agricultural Reentry Task Force (ARTF) database; the Residential SOPs, other registrant-submitted exposure monitoring studies (MRIDs 45528801, 44658401, 44439901, 45519601, 45333401, 44433303, 44459801, 41054701, 44739301, 44433302, 44339801, 49602401, 45773201, 45250702, 45167201, 45250702, 43600102). Some of these data are proprietary and subject to the data protection provisions of the *Federal Insecticide, Fungicide, and Rodenticide Act (*FIFRA). For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[23].

[23] https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

Appendix D. International Residue Limit Status Sheet

Propiconazole (PC Code 122101)

Table D.1. Summary of U.S. and International Tolerances and Maximum Residue Limits.

Residue Definition:

U.S. –
40 CFR 180.434(a)(1)[1]:
Plant/Livestock: Tolerances are established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only those propiconazole residues convertible to 2,4-dichlorobenzoic acid (2,4-DCBA), expressed as the stoichiometric equivalent of propiconazole, in or on the commodity in the table below:
40 CFR 180.434(a)(2)[1]:
Plant/Livestock: Tolerances are established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only propiconazole, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole, in or on the commodity.

Canada - Propiconazole: 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole

Codex - Propiconazole (160): For compliance with MRLs for plant and animal commodities: propiconazole. For estimation of dietary intake for plant and animal commodities: propiconazole plus all metabolite convertible to 2,4-dichloro-benzoic acid, expressed as propiconazole. The residue is fat soluble.

Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
40 CFR §180.378 (a)(1) General[1]				
Almond, hulls[5]	7.0	7		
Banana	0.2	0.2	0.2 Bananas; plantains	0.1 Banana
Barley, bran[5]	6.0	Remove		
Bean, dry seed[5]	0.40	0.4	0.1 Dry beans; dry adzuki beans; dry broad beans; dry kidney beans; dry lablab beans; dry lima beans; dry moth beans; dry mung beans; dry navy beans; dry pinto beans; dry rice beans; dry tepary beans; dry urd beans; dry chickpeas; dry cowpea seeds; dry guar seeds; dry lentils; dry blackeyed peas; dry catjang seeds	
Bean, snap, succulent[5]	--	0.7		
Bean, snap[5]	0.70	Remove		
Bean, succulent shelled[5]	0.10	0.1	0.05 Succulent shelled broad beans; succulent shelled lima beans; succulent shelled cowpeas; succulent shelled blackeyed peas	
Beet, garden, leaves[5, 7]	--	5.5	5.5 Garden beet tops	
Beet, garden, tops[5, 7]	5.5	Remove		
Beet, sugar, dried pulp[5]	1.0	1		
Beet, sugar, leaves[5]	--	10		
Beet, sugar, molasses	1.5	1.5		
Beet, sugar, roots	0.3	0.3	0.3 Sugar beet roots	
Beet, sugar, tops[5]	10	Remove		

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Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
Berry, low growing, subgroup 13-07G, except cranberry[5, 7]	--	1.3	1.3 Bearberries; bilberries; lowbush blueberries; cloudberries; lingonberries; muntries; partridgeberries; strawberries	
Brassica, leafy greens, subgroup 4-16B, except watercress	20	20		
Bushberry subgroup 13-07B[5]	--	1	1 Aronia berries; highbush blueberries; Chilean guavas; highbush cranberries; currants; buffalo currants; elderberries; European barberries; gooseberries; honeysuckle; huckleberries; jostaberries; Saskatoon berries (juneberries); native currants; salal berries; sea buckthorn 1.3 Lowbush blueberries	
Bushberry, subgroup 13-07B[5]	1.0	Remove		
Caneberry subgroup 13-07A[5]	--	1	1 Blackberries; loganberries; raspberries; wild raspberries	
Caneberry, subgroup 13-07A[5]	1.0	Remove		
Cattle, fat	0.05	0.05	0.05 Fat of cattle	0.01 Mammalian fats (except milk fats) (*)
Cattle, kidney[5]	2.0	2	2 Kidney of cattle	0.5 Edible offal (mammalian)

Table D.1. Summary of U.S. and International Tolerances and Maximum Residue Limits.

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Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
Cattle, liver[5]	2.0	2	2 Liver of cattle	0.5 Edible offal (mammalian)
Cattle, meat	0.05	0.05	0.05 Meat of cattle	0.01 Meat (from mammals other than marine mammals) (*) (fat)
Cattle, meat byproducts, except liver and kidney	0.05	0.05	0.05 Meat byproducts (except kidney and liver) of cattle	0.5 Edible offal (mammalian)
Celtuce	5	5	5 Celtuce	
Cilantro, fresh leaves[5, 7]	--	13	13 Fresh cilantro leaves	
Cilantro, leaves[5, 7]	13	Remove		
Citrus, oil[5]	1000	Remove		
Corn, field, forage[5]	12	15		
Corn, field, stover	30	30		
Corn, pop, stover	30	30		
Corn, sweet, forage[5]	6.0	6		
Corn, sweet, stover	30	30		
Dill, seed	15	15		
Dillweed, dried leaves	80	80		
Dillweed, fresh leaves[5]	30	Remove		
Dillweed[5]	--	30		
Fennel, Florence, fresh leaves and stalk	5	5	5 Fresh Florence fennel leaves and stalks	
Fruit, stone, group 12-12, except plum[5]	4.0	Remove		
Goat, fat	0.05	0.05	0.05 Fat of goats	0.01 Mammalian fats (except milk fats) (*)
Goat, kidney[5]	2.0	2	2 Meat byproducts of goats	0.5 Edible offal (mammalian)
Goat, liver[5]	2.0	2	2 Meat byproducts of goats	0.5 Edible offal (mammalian)

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Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
Goat, meat	0.05	0.05	0.05 Meat of goats	0.01 Meat (from mammals other than marine mammals) (*) (fat)
Goat, meat byproducts, except liver and kidney	0.05	0.05	2 Meat byproducts of goats	0.5 Edible offal (mammalian)
Grain, aspirated fractions[5]	110	150		
Grass, forage, fodder and hay, group 17, forage[5]	--	0.5		
Grass, forage, fodder and hay, group 17, hay[5]	--	0.5		
Grass, forage, fodder and hay, group 17, straw[5]	--	40		
Grass, forage[5]	0.5	Remove		
Grass, hay[5]	0.5	Remove		
Grass, straw[5]	40	Remove		
Hog, kidney	0.2	0.2	0.1 Meat byproducts of hogs	0.5 Edible offal (mammalian)
Hog, liver	0.2	0.2	0.1 Meat byproducts of hogs	0.5 Edible offal (mammalian)
Horse, fat	0.05	0.05	0.05 Fat of horses	0.01 Mammalian fats (except milk fats) (*)
Horse, kidney[5]	2.0	2	2 Meat byproducts of horses	0.5 Edible offal (mammalian)
Horse, liver[5]	2.0	2	2 Meat byproducts of horses	0.5 Edible offal (mammalian)
Horse, meat	0.05	0.05	0.05 Meat of horses	0.01 Meat (from mammals other than marine mammals) (*) (fat)
Horse, meat byproducts, except liver and kidney	0.05	0.05	2 Meat byproducts of horses	0.5 Edible offal (mammalian)
Leaf petiole vegetable subgroup 22B	5	5	5 Cardoon; celery; Chinese celery; rhubarb	

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Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
Low growing berry subgroup 13-07G, except cranberry[5]	1.3	Remove		
Milk	0.05	0.05	0.03 Milk	0.01 Milks (*)
Mushroom	0.1	0.1	0.1 Mushrooms	
Nut, tree, group 14-12[5]	0.10	0.1	0.1 Chinquapin nuts; coconuts; Japanese horse-chestnuts; African tree nuts; almond nuts; beechnuts; Brazil nuts; Brazillian pine nuts; bunya nuts; bur oak nuts; butternuts; cajou nuts; candlenuts; cashew nuts; chestnuts; coquito nuts; dika nuts; ginkgo nuts; guiana chestnuts; hazelnuts; heartnuts; hickory nuts; macadamia nuts; mongongo nuts; monkey puzzle nuts; monkey-pot nuts; okari nuts; pachira nuts; peach palm nuts; pecan nuts; pequi nuts; pili nuts; pine nuts; pistachio nuts; sapucaia nuts; tropical almond nuts; black walnuts; English walnuts; yellowhorn nuts	0.02 Pecan (*)
Onion, bulb subgroup 3-07A[5]	0.2	Remove		
Onion, bulb, subgroup 3-07A[5]	--	0.2	0.2 Daylilies; fritillaria bulbs; garlic; great headed garlic; serpent garlic; lilies; dry bulb onions; Chinese onions; pearl onions; potato onions; shallot bulbs	

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Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
Onion, green, subgroup 3-07B[5]	9.0	9	9 Fresh Chinese chive leaves; fresh chive leaves; elegans hosta; fritillaria leaves; kurrats; lady's leeks; leeks; wild leeks; Beltsville bunching onions; fresh onions; green onions; macrostem onions; tree onion tops; Welsh onion tops; shallot leaves	
Parsley, dried leaves[7]	35	35	35 Dried parsley leaves	
Parsley, fresh leaves[7]	13	13	13 Fresh parsley leaves	
Peanut	0.2	0.2	0.2 Peanuts	
Peanut, hay	20	20	20 Peanut hay	
Peppermint, fresh leaves[5]	--	10	10 Peppermint tops	
Peppermint, tops[5]	10.0	Remove		
Pineapple[7]	4.5	4.5	4.5 Pineapples	2 Pineapple (Po)
Pineapple, process residue[5]	7.0	7		
Plum[5]	0.60	Remove		
Radish, tops[5]	0.20	Remove		
Rice, bran	15	15		
Rice, grain[5]	7.0	7	7 Rice	
Rice, hulls	20	20		
Sheep, fat	0.05	0.05	0.05 Fat of sheep	0.01 Mammalian fats (except milk fats) (*)
Sheep, kidney[5]	2.0	2	2 Meat byproducts of sheep	0.5 Edible offal (mammalian)
Sheep, liver[5]	2.0	2	2 Meat byproducts of sheep	0.5 Edible offal (mammalian)
Sheep, meat	0.05	0.05	0.05 Meat of sheep	0.01 Meat (from mammals other than marine mammals) (*) (fat)

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Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
Sheep, meat byproducts, except liver and kidney	0.05	0.05	2 Meat byproducts of sheep	0.5 Edible offal (mammalian)
Sorghum, grain, forage[5, 7]	12	15		
Sorghum, grain, grain[7]	3.5	3.5	3.5 Sorghum	
Sorghum, grain, stover	15	15		
Soybean, forage[5, 7]	11	15		
Soybean, hay	30	30		5 Soya bean fodder
Spearmint, fresh leaves[5]	--	10	10 Spearmint tops	
Spearmint, tops[5]	10.0	Remove		
Swiss chard	5	5	5 Swiss chard	
Ti palm, leaves	10	10		
Ti palm, roots[5]	0.30	0.3		
Vegetable, foliage of legume, except soybean, subgroup 7A[5]	--	30		
Vegetable, foliage of legume, group 7[5]	30	Remove		
Vegetable, root, except sugar beet, subgroup 1B	0.3	0.3	0.3 Garden beet roots 0.25 Carrot roots	
Watercress[5]	6.0	6		
40 CFR §180.378 (a)(2) General[1]				
Avocado[5]	0.2	0.015		
Barley, grain[5]	3.0	2	2 Barley	2 Barley
Barley, hay[5]	30	7		
Barley, straw[5]	20	10		8 Barley straw and fodder, dry
Cherry subgroup 12-12A[5]	--	3	4 Sweet cherries; tart cherries	3 Cherries (Po)
Corn, field, grain[5]	0.2	0.05	0.2 Field corn	0.05 Maize
Corn, pop, grain[5]	0.2	0.05	0.2 Popcorn grain	0.05 Popcorn
Corn, sweet, kernel plus cob with husks removed[5]	0.1	0.05	0.2 Sweet corn kernels plus cob with husks removed	0.05 Sweet corn (corn-on-the-cob)
Fruit, citrus, group 10-10, oil[5]	--	1000		1850 Orange oil, edible

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Plant/Livestock: Tolerances are established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only propiconazole, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole, in or on the commodity.

Canada - Propiconazole: 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole

Codex - Propiconazole (160): For compliance with MRLs for plant and animal commodities: propiconazole. For estimation of dietary intake for plant and animal commodities: propiconazole plus all metabolite convertible to 2,4-dichloro-benzoic acid, expressed as propiconazole. The residue is fat soluble.

Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
Fruit, citrus, group 10-10[5]	8.0	8	8 Calamondins; citrus hybrids; citrus citrons; tangerines; grapefruits; kumquats; lemons; limes; Australian desert limes; Australian finger limes; Australian round limes; Brown River finger limes; Mount White limes; New Guinea wild limes; Russell River limes; sweet limes; Tahiti limes; Mediterranean mandarins; Satsuma mandarins; tangelos; Japanese summer grapefruits; oranges; tachibana oranges; trifoliate oranges; pummelos; tangors; uniq fruits	10 Mandarins (including mandarin-like hybrids) (subgroup) (Po); oranges, sweet, sour (including orange-like hybrids (Subgroup) (Po); lemons and limes (including citron) (subgroup) (Po) 4 Pummelo and grapefruits (including Shaddock-like hybrids, among others Grapefruit) (subgroup) (Po)
Oat, forage[5]	4.0	3		
Oat, grain[5]	3.0	0.7	0.7 Oats	0.7 Oats
Oat, hay[5]	15	7		
Oat, straw[5]	10	2		8 Oat straw and fodder, dry
Peach subgroup 12-12B[5]	--	5	4 Apricot; nectarines; peaches	5 Peach (Po)
Plum subgroup 12-12C[5]	--	0.4	4 Fresh prune plums; plumcots 1 Plums	0.4 Plums (including fresh prunes) (Po)

Table D.1. Summary of U.S. and International Tolerances and Maximum Residue Limits.

Residue Definition:

U.S. –
40 CFR 180.434(a)(1)[1]:
Plant/Livestock: Tolerances are established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only those propiconazole residues convertible to 2,4-dichlorobenzoic acid (2,4-DCBA), expressed as the stoichiometric equivalent of propiconazole, in or on the commodity in the table below:
40 CFR 180.434(a)(2)[1]:
Plant/Livestock: Tolerances are established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only propiconazole, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole, in or on the commodity.

Canada - Propiconazole: 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole

Codex - Propiconazole (160): For compliance with MRLs for plant and animal commodities: propiconazole. For estimation of dietary intake for plant and animal commodities: propiconazole plus all metabolite convertible to 2,4-dichloro-benzoic acid, expressed as propiconazole. The residue is fat soluble.

Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
Quinoa, grain[5]	3.0	0.09		
Rapeseed subgroup 20A[5]	0.30	0.02	0.02 Borage seeds; cuphea seeds; echium seeds; flaxseeds; Gold of Pleasure seeds; hare's ear mustard seeds; milkweed seeds; mustard seeds (oilseed type); oil radish seeds; poppy seeds; rapeseeds (canola); sesame seeds; sweet rocket seeds	0.02 Rape seed
Rye, bran[5]	0.6	0.15		
Rye, forage[5]	9.0	4		
Rye, grain[5]	0.3	0.09	0.05 Rye	0.09 Rye
Rye, straw[5]	10	1.5		15 Rye straw and fodder, dry
Soybean, seed[5]	2.0	0.07	0.25 Dry soybeans	0.07 Soya bean (dry)
Sugarcane, cane[5]	0.4	0.3		0.02 Sugar cane (*)
Tea, dried[6, 8]	--	4	4 Tea (dried leaves)	
Tea[6, 8]	4.0	Remove		
Tomato[5]	3.0	3	3 Tomatoes	3 Tomato (Po)
Wheat, bran[5]	0.6	0.15		
Wheat, forage[5]	15	6		
Wheat, grain[5]	0.3	0.09	0.05 Triticale 0.09 Wheat	0.09 Triticale; wheat
Wheat, hay[5]	30	15		
Wheat, straw[5]	20	7		15 Wheat straw and fodder, dry; triticale straw and fodder, dry
40 CFR §180.434 (c)(1) Tolerances with regional registrations[1]				
Rice, wild, grain	0.5	0.5	0.5 Wild rice	
40 CFR §180.434 (c)(2) Tolerances with regional registrations[1]				

Table D.1. Summary of U.S. and International Tolerances and Maximum Residue Limits.

Residue Definition:

U.S. –
40 CFR 180.434(a)(1)[1]:
Plant/Livestock: Tolerances are established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only those propiconazole residues convertible to 2,4-dichlorobenzoic acid (2,4-DCBA), expressed as the stoichiometric equivalent of propiconazole, in or on the commodity in the table below:
40 CFR 180.434(a)(2)[1]:
Plant/Livestock: Tolerances are established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only propiconazole, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole, in or on the commodity.

Canada - Propiconazole: 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole

Codex - Propiconazole (160): For compliance with MRLs for plant and animal commodities: propiconazole. For estimation of dietary intake for plant and animal commodities: propiconazole plus all metabolite convertible to 2,4-dichloro-benzoic acid, expressed as propiconazole. The residue is fat soluble.

Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
Cranberry[5]	1.0	0.3	1.3 Cranberries	0.3 Cranberry
40 CFR §180.434 (d) Indirect or inadvertent residues				
Alfalfa, forage	0.1			
Alfalfa, hay	0.1			
MRLs with no U.S. Tolerance Equivalent				
Asparagus			0.1	
Buckwheat			0.05	
Coffee beans				0.02
Dry field peas			0.1	
Dry pigeon peas			0.1	
Dry southern peas			0.1	
Edible-podded dwarf peas			0.25	
Edible-podded jackbeans			0.25	
Edible-podded moth beans			0.25	
Edible-podded pigeon peas			0.25	
Edible-podded runner beans			0.25	
Edible-podded snap beans			0.25	
Edible-podded snow peas			0.25	
Edible-podded soybeans			0.25	
Edible-podded sugar snap peas			0.25	
Edible-podded sword beans			0.25	
Edible-podded wax beans			0.25	
Edible-podded yardlong beans			0.25	
Eggs			0.05	0.01 Eggs (*)
Fat of hogs			0.05	
Fat of poultry			0.05	
Grain lupin			0.1	
Liver of poultry			0.1	
Meat byproducts (except liver) of poultry			0.05	
Meat of hogs			0.05	
Meat of poultry			0.05	0.01 Poultry meat (*) (fat)
Pearl millet			0.05	
Proso millet			0.05	

Table D.1. Summary of U.S. and International Tolerances and Maximum Residue Limits.

Residue Definition:

U.S. –
40 CFR 180.434(a)(1)[1]:
Plant/Livestock: Tolerances are established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only those propiconazole residues convertible to 2,4-dichlorobenzoic acid (2,4-DCBA), expressed as the stoichiometric equivalent of propiconazole, in or on the commodity in the table below:
40 CFR 180.434(a)(2)[1]:
Plant/Livestock: Tolerances are established for residues of propiconazole, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only propiconazole, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole, in or on the commodity.

Canada - Propiconazole: 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]methyl]-1*H*-1,2,4-triazole

Codex - Propiconazole (160): For compliance with MRLs for plant and animal commodities: propiconazole. For estimation of dietary intake for plant and animal commodities: propiconazole plus all metabolite convertible to 2,4-dichloro-benzoic acid, expressed as propiconazole. The residue is fat soluble.

Commodity[2]	*Tolerance (ppm)/Maximum Residue Limit (mg/kg)*			
	U.S. Established	U.S. Recommended[3]	Canada	Codex
Succulent shelled English peas			0.05	
Succulent shelled garden peas			0.05	
Succulent shelled green peas			0.05	
Succulent shelled pigeon peas			0.05	
Succulent shelled souther peas			0.05	
Teosinte			0.05	

Completed: J. Camp; 6/22/2020 using Global MRL

[1] Tolerance expression reflects HED recommendations.
[2] Commodities with different tolerance levels between the US, Canada, and Codex are in **bold text**.
[3] Tolerance values reflect HED recommendations. See Table 2.2.2.1 for further details.
[4] Po = The MRL accommodates post-harvest treatment of the commodity.
(fat) = (for meat) The MRL/EMRL applies to the fat of meat.
(*) = At or about the limit of determination.
[5] Commodity definitions and/or tolerance levels reflect HED recommendations. See Table 2.2.2.1 for further details.
[6] There are no United States registrations for use of propiconazole on tea as of December 24, 2015.
[7] Although the recommended tolerance level is not consistent with OECD Rounding Class Practice, HED is recommending retaining the established tolerance level to be consistent with Canadian MRLs to avoid trade irritant potential.
[8] The currently established tolerance for residues in/on tea is established under 40 CFR §180.434(a)(2). HED is recommending amending the tolerance expression to include only propiconazole. Therefore, 40 CFR §180.434(a)(1) should be revised to 40 CFR §180.434(a), including only propiconazole. The recommended tolerance for residues in/on Tea, dried should be moved to 40 CFR §180.434(a).

Banana: Banana data reviewed by the 2007 JMPR: 10 supervised trials on banana (bagged and non-bagged) from Honduras conducted in 1981 to 1982 (GAP in Honduras: 8-10 applications at 0.1 kg ai/ha/application (0.09 lb ai/A/application) every 18-21 days; 0-day PHI). The JMPR noted that the use pattern is the same for Belize, Dominican Republic, Guatemala, Honduras, and Panama. Parent propiconazole was measured in peel and pulp separately. The peel/pulp weight ratio was not reported.

From bagged bananas, the pulp contained non-detectable residues in all samples (10 x <0.02 mg/kg) regardless of the PHI and number of applications. Two peel samples out of 10 total samples from bagged bananas contained detectable residues (0.024, 0.03 mg/kg).

From non-bagged bananas, two pulp samples out of 14 total samples contained detectable residues (0.025, 0.029 mg/kg). Residues of propiconazole (parent only) following treatment in/on non-bagged banana peel were (n=13): <0.02, <0.02, <0.02, 0.021, 0.026, 0.032, 0.044, 0.045, 0.046, 0.07, <0.072, 0.075, 0.1 mg/kg.

The Meeting took into account that the peel amounts to approximately 30% of the weight of the whole banana. Thus, the Meeting

calculated the maximum residue in/on whole banana as (0.3 x 0.1+0.7 x 0.029=0.052): 0.02, 0.021, 0.021, 0.022, 0.027, 0.028, 0.044, 0.052 mg/kg. The Meeting estimated a STMR of 0.06 mg/kg, and a HR of 0.087 (3 x 0.029) mg/kg for propiconazole in/on banana pulp.

A U.S. tolerance has been established for residues of propiconazole in/on bananas based on data from Honduras, Martinique and Belize. The U.S. tolerance level was determined based on residues analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes.

For determination of the currently established tolerance level, the U.S. also considered residue data from banana field trials conducted in Martinique and Belize (n=3). Residues of total propiconazole in/on non-bagged banana pulp and peel were non-detectable in all samples from these trials. See MRID Nos. 00137150 & 93194071. 16 field trials were conducted on bananas at the 1X and 2X the currently registered maximum use rate (0.67 lb ai/A/year total application rate; max. 8 applications every 21-25 days; bananas must be bagged); six of the 16 field trials were conducted with an exaggerated number of applications at intervals less than what is specified on the label. See MRID No. 00137150. Given the different use patterns, HED is not recommending to harmonize with Codex.

Barley, straw: Barley data reviewed by the 2014 JMPR: nine supervised trials on barley from the U.S. conducted in 2009 and 2010. Residues of propiconazole (parent only) in/on barley hay following GAP treatment were (n=9): 0.19, 0.44, 0.73, 0.78, 0.81, 1.7, 2.2, 3.0, and 4.2 mg/kg. The Meeting estimated a maximum residue level of 8 mg/kg for propiconazole in barley straw and fodder, dry.

A U.S. tolerance is established for residues of total propiconazole in/on Barley, straw at 20 ppm based on the same field trial data that Codex used, but the U.S. tolerance level was determined using residue data from barley straw samples analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. Nine field trials were conducted on barley straw at the currently registered maximum use rate (0.22 lb ai/A total application rate; 14-day PHI (7 for forage and hay)). See MRID No. 48681702. Using OECD tolerance calculation procedures, the recommended tolerance using current practices is 10 ppm for residues of propiconazole (parent only) in/on Barley, straw. A separate tolerance is established for residues in/on Barley, hay. See Appendix E.

Beet, sugar, roots: Sugar beet data reviewed by the 2007 JMPR: 12 supervised trials on sugar beets from France, Germany, and the UK conducted in 1982 to 1992. Residues of propiconazole (parent only) in/on sugar beet roots following GAP treatment were <LOQ (<0.01 to <0.05 mg/kg) for all samples. Based on the Danish and German GAP, the Meeting estimated a maximum residue level of 0.02 mg/kg for sugar beet roots. Using the default conversion factor of 3, the Meeting estimated a median residue of 0.06 mg/kg.

A U.S. tolerance is established for residues of total propiconazole in/on Beet, sugar, roots at 0.3 ppm based on U.S. field trial data. The U.S. tolerance level was determined based on residues analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. However, sugar beet samples were not analyzed for residues of parent propiconazole only. A total of 15 field trials were conducted on sugar beets at the currently registered maximum use rate 0.24 lb ai/A total application rate; 21-day PHI). See MRID Nos. 44757207 & 45080807. Given the different use patterns, HED is not recommending to harmonize with Codex.

Cherry subgroup 12-12A; Peach Subgroup 12-12B; Plum Subgroup 12-12C: Cherry data reviewed by the 2013 and 2017 JMPR: five supervised trials on cherries from the U.S. conducted in 2012 and 2014. Residues of propiconazole (parent only) in/on cherries following GAP treatment were (n=5): 0.67, 0.73, 0.85, 1.3, and 1.4 mg/kg. The Meeting estimated a maximum residue level of 3 mg/kg (Po), an STMR of 1.0 mg/kg, and an HR of 1.8 mg/kg for cherries (Subgroup) with post-harvest treatment.

A U.S. tolerance is established for residues of total propiconazole in/on Fruit, stone, group 12-12, except plum at 4.0 ppm based on U.S. cherry and peach field trial data. A U.S. tolerance is established for residues of total propiconazole in/on Plum at 0.60 ppm based on U.S. plum field trial data. Four peach post-harvest trials, two plum post-harvest trials, and three sweet cherry post-harvest trials were conducted at the currently registered maximum use rate (1 post-harvest dip application at 0.11 lb ai/100 gal; 1 post-harvest spray application at 0.11 lb ai/250,000 lb fruit). See MRID No. 48438206.

The recommended tolerances resulting from representative crop residue data for crop subgroup 12-12 (peach, plum, cherry) are not within 5X, so HED is recommending to establish separate tolerances for residues in/on Cherry subgroup 12-12A, Peach subgroup 12-12B, and Plum subgroup 12-12C. Using OECD tolerance calculation procedures, the recommended tolerances for residues of propiconazole (parent only) are 4 ppm in/on peach, 0.6 ppm in/on plum, and 2 ppm in/on cherry. See Appendix E. However, HED is recommending to harmonize with Codex since the Codex MRLs for residues in/on Cherries at 3 mg/kg, Peach

at 5 mg/kg, and Plums at 0.4 mg/kg are based on field trial residue data reflecting currently registered U.S. use patterns.

Corn, field, grain: Field corn data reviewed by the 2007 JMPR: 19 supervised trials on field corn from the U.S. conducted in 1984 and 1999. Residues of propiconazole (parent only) in/on field corn grain following GAP treatment and treatment at 1.5X the maximum seasonal rate were <LOQ (<0.05 mg/kg) except in two trials (0.05 and 0.06 mg/kg), regardless of PHI and application rate. The Meeting estimated a maximum residue level and an STMR value of 0.05 mg/kg for field corn.

A U.S. tolerance is established for residues of total propiconazole in/on Corn, field, grain at 0.2 ppm based on U.S. field trial data. The U.S. tolerance level was determined based on residues analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. However, field corn grain samples were not analyzed for residues of parent propiconazole only. A total of 24 field trials were conducted on field corn at the currently registered maximum use rate (0.45 lb ai/A total application rate; 30-day PHI). See MRID Nos. 45080809 and 45080810. HED is recommending to decrease the tolerance level from 0.2 ppm to 0.05 ppm to reflect the revised tolerance expression and harmonize with Codex since the Codex MRL for residues in/on Mazie at 0.05 mg/kg is based on field trial residue data reflecting currently registered U.S. use patterns.

Corn, pop, grain: Popcorn data reviewed by the 2007 JMPR: 11 supervised trials on popcorn from the U.S. conducted in 1998 and 1999. Residues of propiconazole (parent only) in/on popcorn grain following GAP treatment were <LOQ (<0.05 mg/kg) except in two trials (0.06 and 0.065 mg/kg). The Meeting estimated a maximum residue level and an STMR value of 0.05 mg/kg for popcorn.

A U.S. tolerance is established for residues of total propiconazole in/on Corn, pop, grain at 0.2 ppm based on U.S. field trial data. The U.S. tolerance level was determined based on residues analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. However, popcorn grain samples were not analyzed for residues of parent propiconazole only. A total of four field trials were conducted on field corn at the currently registered maximum use rate (0.45 lb ai/A total application rate; 30-day PHI). See MRID Nos. 45080809 and 45080810. HED is recommending to decrease the tolerance level from 0.2 ppm to 0.05 ppm to reflect the revised tolerance expression and harmonize with Codex since the Codex MRL for residues in/on Popcorn at 0.05 mg/kg is based on field trial residue data reflecting currently registered U.S. use patterns.

Corn, sweet, kernel plus cob with husks removed: Sweet corn data reviewed by the 2007 JMPR: four supervised trials on sweet corn from the U.S. conducted in 1994. Residues of propiconazole (parent only) in/on sweet corn ears following GAP treatment were <LOQ (<0.05 mg/kg) in all samples. The Meeting estimated a maximum residue level and an STMR value of 0.05 mg/kg for sweet corn.

A U.S. tolerance is established for residues of total propiconazole in/on Corn, sweet, kernel plus cob with husks removed at 0.1 ppm based on U.S. field trial data. The U.S. tolerance level was determined based on residues analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. However, sweet corn kernel plus cob with husks removed (K+CWHR) samples were not analyzed for residues of parent propiconazole only. A total of four field trials were conducted on sweet corn at the currently registered maximum use rate (0.45 lb ai/A total application rate; 30-day PHI). See MRID No. 43655612. HED is recommending to decrease the tolerance level from 0.1 ppm to 0.05 ppm to reflect the revised tolerance expression and harmonize with Codex since the Codex MRL for residues in/on Sweet corn at 0.05 mg/kg is based on field trial residue data reflecting currently registered U.S. use patterns.

Fruit, citrus, group 10-10, oil: Orange processing data reviewed by the 2013 JMPR. In one processing study conducted in the U.S., oranges were processed into oil, juice, and dried pomace. Residues of propiconazole (parent only) in oranges were 0.94 mg/kg and 174 mg/kg in oil, giving a processing factor of 185 for orange oil.

The 2018 JMPR recommended a maximum residue level of 1850 mg/kg for orange oil, based on the maximum residue level of 10 mg/kg for orange (Subgroup) and processing factor of 185 for orange oil.

A U.S. tolerance is established for residues of propiconazole in/on Citrus, oil at 1000 ppm based on the same data that Codex used. The U.S. tolerance level was determined using the HAFT from orange residue data (4.91 ppm) and processing factor for orange oil (185x). See MRID No. 48438205. Due to different tolerance calculation procedures, HED is not recommending to harmonize with Codex.

Fruit, citrus, group 10-10: Citrus fruit data reviewed by the 2013, 2017, and 2018 JMPR. Propiconazole is registered for post-harvest treatment on citrus fruits in the U.S. The U.S. critical GAP is for two applications at a rate of 52.7 g ai/100L by dip/drench. Residue trials from the U.S., matching the GAP, were submitted. The previously submitted residue information on citrus fruits that was evaluated by the 2013 JMPR was also considered. Residues of propiconazole (parent only) following GAP

treatment were:
Whole orange (n=8): 2.2, 2.3, 2.5, 2.5, 3.4, 3.6, 3.7, and 3.7 mg/kg. Total residues (measured parent x 1.2) in orange pulp were (n=4): 0.11, 0.16, 0.17, and 0.35 mg/kg.
Whole mandarin (n=4): 3.1, 3.6, 4.8, and 5.9 mg/kg. Total residues (measured parent × 1.2) in mandarin pulp were (n=4): 0.070, 0.19, 0.34, and 0.38 mg/kg.
Whole lemon (n=4): 3.1, 3.2, 5.6, and 6.6 mg/kg. Total residues (measured parent × 1.2) in lemon pulp were (n=4): 0.20, 0.23, 0.36, and 0.43 mg/kg.
Whole grapefruit (n=4): 1.6, 1.6, 2.2, and 2.3 mg/kg. Total residues (measured parent × 1.2) in grapefruit pulp were (n=4); 0.07, 0.080, 0.13, and 0.16 mg/kg.

The residue distributions among the citrus fruits were considered similar by Kruskal-Wallis test, except for grapefruit. Therefore, the Meeting decided to combine the residue values for orange, mandarin and lemon.
The combined data set for parent in whole orange, mandarin, and lemon was (n=16): 2.2, 2.3, 2.5, 2.5, 3.1, 3.1, 3.2, 3.4, 3.6, 3.6, 3.7, 3.7, 4.8, 5.6, 5.9, and 6.6 mg/kg.
The combined data set for total residues (measured parent × 1.2) in whole orange, mandarin, and lemon was (n=16): 2.6, 2.8, 3.0, 3.0, 3.7, 3.7, 3.8, 4.1, 4.3, 4.3, 4.4, 4.5, 5.7, 6.8, 7.1, and 8.0 mg/kg.
The combined data set for total residues (measured parent × 1.2) in pulp of orange, mandarin, and lemon was (n=12); 0.070, 0.11, 0.16, 0.17, 0.19, 0.20, 0.23, 0.34, 0.35, 0.36, 0.38, 0.43 mg/kg.

The 2017 JMPR estimated a maximum residue level of 15 mg/kg (Po), an STMR of 0.22 mg/kg, and an HR of 0.43 mg/kg for orange (Subgroup), mandarin (Subgroup), and lemon (Subgroup) based on a post-harvest treatment. The 2017 JMPR estimated a maximum residue level of 6 mg/kg (Po), an STMR of 0.11 mg/kg and an HR of 0.16 mg/kg for pummelo and grapefruits (Subgroup) based on a post-harvest treatment.

The 3*mean is used to ensure the coefficient of variance is at least 0.5, given small data sets can underestimate the standard deviation (SD). The SD of the data sets for the post-harvest uses of propiconazole were low. However, the 2018 JMPR considered that as more homogenous residues are expected for post-harvest uses it is not appropriate to account for the low SD when estimating the maximum residue level and therefore base it on the CF*3 Mean. The 2018 Meeting agreed that more refined maximum residue levels are possible for the post-harvest uses considered by the 2017 JMPR using the mean + 4SD.

The 2018 JMPR subsequently recommended a maximum residue level of 10 mg/kg (Po) for orange (Subgroup), mandarin (Subgroup), and lemon (Subgroup); and 4 mg/kg (Po) for pummelo and grapefruits (Subgroup) for the post-harvest uses of propiconazole.

A U.S. tolerance is established for residues of propiconazole in/on Fruit, citrus, group 10-10 at 8.0 ppm based on the same data that Codex used, but the U.S. tolerance level was determined for each of the citrus fruit representative crops. 12 trials reflecting post-harvest applications were conducted on citrus fruits (eight orange, two grapefruit, and two lemon trials) at the currently registered maximum use rate (1 post-harvest dip/drench application at 0.45 lb ai/100gal; 1 post-harvest spray application at 0.45 lb ai/250,000 lb fruit). See MRID No. 48438205. Given the different tolerance calculations, HED is not recommending to harmonize with Codex.

Nut, tree, group 14-12: Pecan data reviewed by the 2007 JMPR: eight supervised trials on pecans from the U.S. conducted in 1980-1984. Residues of propiconazole (parent only) in/on pecan nut following treatment at 1.5-3X the registered rate were <LOQ (<0.1 mg/kg) in all samples. The Meeting concluded that the registered use of propiconazole does not lead to detectable residues, and estimated a maximum residue level of 0.02 mg/kg, and an HR and STMR of 0.02 mg/kg for pecan nuts.

A U.S. tolerance is established for residues of total propiconazole in/on Nut, tree, group 14-12 at 0.1 ppm based on U.S. pecan and almond field trial data. Since the U.S. tolerance level is based on representative commodities for crop group 14-12, HED is not recommending to harmonize with Codex.

Oat, straw: Oat data reviewed by the 2014 JMPR: 11 supervised trials on oat from the U.S. conducted in 2009 and 2010. Residues of propiconazole (parent only) in/on oat hay following GAP treatment were (n=11): 0.18, 0.24, 0.35, 1.1, 1.2, 1.4, 2.0, 2.4, 3.6, 4.2, and 4.5 mg/kg. The Meeting estimated a maximum residue level of 8 mg/kg for propiconazole in oat straw and fodder, dry.

A U.S. tolerance is established for residues of total propiconazole in/on Oat, straw at 10 ppm based on the same field trial data that Codex used, but the U.S. tolerance level was determined using residue data from oat straw samples analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. 12 field trials were conducted on oat straw at the currently registered maximum use rate (0.22 lb ai/A total application rate; 14-day PHI (7 for forage and hay)). See MRID No. 48681703. Using OECD tolerance calculation procedures, the recommended tolerance using current practices is 2 ppm for residues of propiconazole (parent only) in/on Oat, straw. A separate tolerance is established for residues in/on Oat, hay.

See Appendix E.

Pineapple: Pineapple data reviewed by the 2017 JMPR: four supervised trials on pineapple from the U.S. conducted in 2013. Residues of propiconazole (parent only) in/on pineapples following GAP treatment were (n=4): 0.92, 0.97, 1.1, and 1.2 mg/kg. The Meeting estimated a maximum residue level of 4 mg/kg (Po) for pineapples, an STMR of 0.16 (1.3 × Pf, < 0.12) mg/kg, and an HR of 0.19 (1.6 × Pf, < 0.16) mg/kg for pineapple flesh.

The 3*mean is used to ensure the coefficient of variance is at least 0.5, given small data sets can underestimate the standard deviation (SD). The SD of the data sets for the post-harvest uses of propiconazole were low. However, the 2018 JMPR considered that as more homogenous residues are expected for post-harvest uses it is not appropriate to account for the low SD when estimating the maximum residue level and therefore base it on the CF*3 Mean. The 2018 Meeting agreed that more refined maximum residue levels are possible for the post-harvest uses considered by the 2017 JMPR using the mean + 4SD.

The 2018 JMPR subsequently recommended a maximum residue level of 2 mg/kg (Po) for pineapple for the post-harvest uses of propiconazole.

A U.S. tolerance is established for residues of total propiconazole in/on Pineapple at 4.5 ppm, based on the same data that Codex used as well as additional data reflecting registered U.S. use patterns. The U.S. tolerance level was determined using residue data from pineapple samples analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. Three trials reflecting post-harvest dip applications were conducted on pineapple at the currently registered maximum use rate (1 post-harvest dip application at 0.113 lb ai/100gal). See MRID No. 47297204. Four trials reflecting post-harvest dip + spray and drench + spray applications were conducted on pineapple at the currently registered maximum use rate (1 post-harvest dip/drench + spray application at 0.215 lb ai/100 gal). See MRID No. 49179603. Given the different use patterns, HED is not recommending to harmonize with Codex.

Rapeseed subgroup 20A: Rape and canola seed data reviewed by the 2007 JMPR: five supervised trials on rape and canola seed from Canada conducted in 1992 and 1993. Residues of propiconazole (parent only) in/on rape and canola seed following Canadian GAP treatment (0.125 kg ai/ha; 60-day PHI) were <LOQ (<0.02 mg/kg) in all samples. The Meeting estimated a maximum residue level of 0.02 mg/kg and an STMR residue of 0.06 (3 x 0.02) mg/kg for canola and rape seed.

A U.S. tolerance is established for residues of total propiconazole in/on Rapeseed subgroup 20A at 0.30 ppm, based on canola field trials conducted in Canada. The U.S. tolerance level was determined using residue data from rapeseed samples analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. 13 field trials were conducted on canola at the currently registered maximum use rate (0.113 lb ai/A; 30-day PHI). See MRID No. 48604486. Using OECD tolerance calculation procedures, the recommended tolerance using current practices is 0.015 ppm for residues of propiconazole (parent only) in/on Rapeseed subgroup 20A. See Appendix E. However, HED is recommending to decrease the tolerance level from 0.30 ppm to 0.02 ppm to reflect the revised tolerance expression and harmonize with Canada and Codex.

Rye, straw: Wheat data reviewed by the 2014 JMPR: 15 supervised trials on wheat from the U.S. conducted in 2009-2010. Residues of propiconazole (parent only) in/on wheat hay following GAP treatment were (n=15): 0.44, 0.75, 1.1, 1.3, 1.6, 1.9, 2.0 (2), 2.2, 2.8. 3.0, 3.3, 4.2, 5.4, and 9.6 mg/kg. Taking into account the trial conditions, the Meeting concluded that the residues measured in hay are applicable for straw and fodder, and recommended a maximum residue level of 15 mg/kg for propiconazole in wheat straw and fodder, dry, and extended this estimation for rye and straw and fodder, dry. The Meeting also estimated a medium and highest residue of 5.3 and 22 mg/kg, respectively, for propiconazole in wheat hay.

A U.S. tolerance is established for residues of total propiconazole in/on Rye, straw at 10 ppm based on the same field trial data that Codex used, but the U.S. tolerance level was determined using residue data from rye straw samples analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. Four field trials were conducted on rye straw at the currently registered maximum use rate (0.22 lb ai/A total application rate; 14-day PHI (7 for forage and hay)). See MRID No. 48681701. Using OECD tolerance calculation procedures, the recommended tolerance using current practices is 1.5 ppm for residues of propiconazole (parent only) in/on Rye, straw. A separate tolerance is established for residues in/on Rye, forage. See Appendix E.

Soybean, hay: Soybean hay data reviewed by the 2007 JMPR: 16 supervised trials on soybean from the U.S. conducted in 2004 and 2005. Residues of propiconazole (parent only) in/on soybean hay following GAP treatment (2 × 0.12 – 0.18 kg ai/ha; 14-day PHI) were (n=16): 0.12, 0.15, 0.17, 0.335, 0.4, 0.48, 0.65, 0.65, 0.7, 0.77, 1.1, 1.15, 1.2, 1.4, 1.5, and 3.2 mg/kg. The Meeting estimated a maximum residue level of 5 mg/kg, and using the default conversion factor of 3 a highest residue of 9.6 (3 x 3.2) mg/kg, and an STMR of 2.025 (3 x 0.675) mg/kg for propiconazole in soybean fodder.

A U.S. tolerance is established for residues of total propiconazole in/on Soybean, hay at 30 ppm. The U.S. tolerance level was determined using residue data from soybean hay samples analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. 14 field trials were conducted on soybean at the currently registered maximum use rate (0.34 lb ai/A total application rate; application up to Stage R6). See MRID No. 43386502. 20 additional field trials were conducted on soybean at 0.75X the currently registered maximum use rate. See MRID No. 46576301. The U.S. used soybean hay data reflecting a 30-day PHI to calculate the tolerance level, while Codex used data reflecting a 14-day PHI. Therefore, given the different use pattern, HED is not recommending to harmonize with Codex.

Soybean, seed: Soybean data reviewed by the 2007 JMPR: 19 supervised trials on soybean seed from the U.S. conducted in 2003-2005. Residues of propiconazole (parent only) in/on dried seed following GAP treatment were (n=19): <0.01 (12), 0.01 (3), 0.02 (3), 0.04, and 0.05 mg/kg. The Meeting estimated a maximum residue level of 0.07 mg/kg and an STMR of 0.03 (3 × 0.01) mg/kg.

A U.S. tolerance is established for residues of total propiconazole in/on Soybean, seed at 2 ppm. The U.S. tolerance level was determined using residue data from soybean seed samples analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. 20 field trials were conducted on soybean at 0.75X the currently registered maximum use rate (0.34 lb ai/A total application rate; application up to Stage R6). See MRID No. 46576301. Four additional field trials were conducted on soybean at the currently registered maximum use rate. See MRID No. 46473001. HED is recommending to decrease the tolerance level from 2 ppm to 0.07 ppm to reflect the revised tolerance expression and harmonize with Codex since the Codex MRL for residues in/on Soya bean (dry) at 0.07 mg/kg is based on field trial residue data reflecting currently registered U.S. use patterns.

Sugarcane, cane: Sugarcane data reviewed by the 2007 JMPR. A radio-label study indicated that following treatment of seed pieces at 5X and 10X rate, there were no measurable residues in cane six months after planting. Furthermore, no TRR (<0.01 mg/kg) was detected in any plant parts (chopped cane, bagasse, raw sugar, molasses) grown from the seed treated at 5X, 10X, and 20X rates. The Meeting concluded that the registered use of propiconazole does not lead to detectable resides, and estimated a maximum residue level of 0.02 mg/kg and an STMR of 0 mg/kg in sugar.

A U.S. tolerance is established for residues of total propiconazole in/on Sugarcane, cane at 0.4 ppm based on foliar field trial data. The tolerance level was determined using residue data from sugarcane samples analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. Eight field trials were conducted on sugarcane at the currently registered maximum use rate (0.701 lb ai/A total application rate; 30-day PHI). See MRID No. 48497001. Using OECD tolerance calculation procedures, the recommended tolerance using current practices is 0.3 ppm for residues of propiconazole (parent only) in/on Sugarcane, cane. See Appendix E. Given the different use patterns, HED is not recommending to harmonize with Codex.

Wheat, straw: Wheat data reviewed by the 2014 JMPR: 15 supervised trials on wheat from the U.S. conducted in 2009-2010. Residues of propiconazole (parent only) in/on wheat hay following GAP treatment were (n=15): 0.44, 0.75, 1.1, 1.3, 1.6, 1.9, 2.0 (2), 2.2, 2.8. 3.0, 3.3, 4.2, 5.4, and 9.6 mg/kg. Taking into account the trial conditions, the Meeting concluded that the residues measured in hay are applicable for straw and fodder, and recommended a maximum residue level of 15 mg/kg for propiconazole in wheat straw and fodder, dry. The Meeting also estimated a medium and highest residue of 5.3 and 22 mg/kg, respectively, for propiconazole in wheat hay.

A U.S. tolerance is established for residues of total propiconazole in/on Wheat, straw at 20 ppm based on the same field trial data that Codex used, but the U.S. tolerance level was determined using residue data from wheat straw samples analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer being recommended for inclusion in the tolerance expression for enforcement purposes. 15 field trials were conducted on wheat straw at the currently registered maximum use rate (0.22 lb ai/A total application rate; 14-day PHI (7 for forage and hay)). See MRID No. 48681704. Using OECD tolerance calculation procedures, the recommended tolerance using current practices is 7 ppm for residues of propiconazole (parent only) in/on Wheat, straw. A separate tolerance is established for residues in/on Wheat, hay. See Appendix E.

Cranberry: Cranberry data reviewed by the 2006 JMPR: three supervised trials on cranberry from the U.S. conducted in 1995 and 1999. Residues of propiconazole (parent only) in/on cranberry following GAP treatment were (n=3): 0.2, 0.23, and 0.53 mg/kg. The Meeting estimated a maximum residue level of 0.3 mg/kg, an HR of 0.13 mg/kg, and an STMR of 0.058 mg/kg.

A regional U.S. tolerance is established for residues of total propiconazole in/on Cranberry at 1.0 ppm based on the data that Codex used, but the U.S. tolerance level was determined using residue data from cranberry samples analyzed with a common moiety method. Therefore, the established U.S. tolerance level takes into account the 2,4-DCBA metabolite, which is no longer

being recommended for inclusion in the tolerance expression for enforcement purposes. Three field trials were conducted on cranberry at the currently registered maximum use rate (0.67 lb ai/A; 45-day PHI). See MRID Nos. 44338101 & 45778901. HED is recommending to decrease the tolerance level from 1.0 ppm to 0.3 ppm to reflect the revised tolerance expression and harmonize with Codex since the Codex MRL for residues in/on Cranberry is based on the same residue data.

Livestock fat, kidney, liver, meat, meat byproducts, and milk: The dietary burdens for livestock to combined propiconazole residues were previously recalculated in conjunction with a request to establish tolerances on various crops (Y. Donovan, 7/31/2006, D238458). At that time, the maximum theoretical dietary burdens (MTDBs) for combined propiconazole residues were calculated to be 29.0 ppm for beef and 18.5 ppm for dairy cattle, 2.3 ppm for swine and 2.0 ppm for poultry. These calculated MTDBs were used in conjunction with data from ruminant and poultry feeding studies to estimate maximum combined residues in livestock commodities and establish the current tolerances in/on livestock commodities. With subsequent petitions, the MTDBs were recalculated when necessary, but were found to be lower than the aforementioned dietary burdens. Therefore, there has been no changes to the established livestock tolerances. For Registration Review, HED is recommending several tolerance changes to livestock feed items; however, these recommendations are all decreases due to the recommended tolerance expression change. Therefore, the previously calculated dietary burdens are not expected to increase with the recommended tolerance changes and no changes to livestock tolerances are necessary at this time.

Appendix E. OECD Tolerance Calculations

Compound	Propiconazole	Propiconazole	Propiconazole
Crop	Avocado	Barley Grain	Barley Hay
Region / Country	Parent Only	Parent Only	Parent Only
GAP	MRID 50454601 (Flare Root Infusion; 6.18-8.80 g ai/inch tree diameter; 2 apps; 7-day PHI)	MRID 48681702 (0.2213-0.2290 lb ai/A; 16-49-day PHI)	MRID 48681702 (0.2188-0.2311 lb ai/A; 7-day PHI)
Total number of data (n)	6	9	9
Percentage of censored data	83%	44%	0%
Number of non-censored data	1	5	9
Lowest residue	0.010	0.010	0.436
Highest residue	0.011	1.120	4.190
Median residue	0.010	0.010	1.700
Mean	0.010	0.170	1.766
Standard deviation (SD)	0.000	0.363	1.250
Correction factor for censoring (CF)	0.444	0.704	1.000
Proposed MRL estimate			
- Highest residue	0.011	1.120	4.190
- Mean + 4 SD	0.012	1.622	6.765
- CF x 3 Mean	0.014	0.358	5.299
Unrounded MRL	0.014	1.622	6.765
Rounded MRL	0.015	2	7
	High uncertainty of MRL estimate due to small dataset and high level of censoring.		

Residues (mg/kg)		Residues (mg/kg)		Residues (mg/kg)	
0.010	*	0.141		0.814	
0.010	*	0.010	*	0.436	
0.010	*	0.010		0.732	
0.010	*	0.010	*	1 930	
0.010	*	0.010	*	4 190	
0.011		0.010	*	2 270	
		0.195		0.785	
		1.120		3.040	
		0.020		1.700	

Compound	Propiconazole	Propiconazole	Propiconazole
Crop	Barley Straw	Oat Forage	Oat Grain
Region / Country	Parent Only	Parent Only	Parent Only
GAP	MRID 48681702 (0.2213-0.2290 lb ai/A; 16-49-day PHI)	MRID 48681703 (0.2156-0.2290 lb ai/A; 7-day PHI)	MRID 48681703 (0.2188-0.2331 lb ai/A; 25-48-day PHI)
Total number of data (n)	9	11	11
Percentage of censored data	0%	0%	9%
Number of non-censored data	9	11	10
Lowest residue	0.082	0.154	0.010
Highest residue	4 990	1.170	0.370
Median residue	0 287	0.818	0.050
Mean	1.497	0.689	0.115
Standard deviation (SD)	1 911	0.379	0.135
Correction factor for censoring (CF)	1.000	1.000	0.939
Proposed MRL estimate			
- Highest residue	4 990	1.170	0.370
- Mean + 4 SD	9 143	2.203	0.656
- CF x 3 Mean	4.491	2.068	0.325
Unrounded MRL	9 143	2.203	0.656
Rounded MRL	10	3	0.7

Residues (mg/kg)		Residues (mg/kg)		Residues (mg/kg)	
3.020		1.170		0.010	*
0.120		0.820		0.020	
0.181		0.200		0.020	
0.719		0.843		0.030	
0.245		0.156		0.040	
0.082		1.160		0.050	
4.990		0.596		0.060	
3.830		1.010		0.080	
0.287		0.818		0.260	
		0.654		0.330	
		0.154		0.370	

Compound	Propiconazole	Propiconazole	Propiconazole
Crop	Oat Hay	Oat Straw	Canola Seed
Region / Country	Parent Only	Parent Only	Parent Only
GAP	MRID 48681703 (0.2156-0.2290 lb ai/A; 7-day PHI)	MRID 48681703 (0.2188-0.2331 lb ai/A; 25-48-day PHI)	MRID 48604486 (0.105-0 123 lb ai/A; 29-35-day PHI)
Total number of data (n)	11	11	16
Percentage of censored data	0%	0%	94%
Number of non-censored data	11	11	1
Lowest residue	0.184	0.019	0.010
Highest residue	4.260	1.210	0.013
Median residue	1.380	0.089	0.010
Mean	1.664	0.309	0.010
Standard deviation (SD)	1.342	0.383	0.001
Correction factor for censoring (CF)	1.000	1.000	0.375
Proposed MRL estimate			
- Highest residue	4.260	1.210	0.013
- Mean + 4 SD	7.032	1.841	0.013
- CF x 3 Mean	4.991	0.928	0.011
Unrounded MRL	7.032	1.841	0.013
Rounded MRL	7	2	0.015
			High uncertainty of MRL estimate due to high level of censoring.

Residues (mg/kg)		Residues (mg/kg)		Residues (mg/kg)	
2.050		0.800		0.010	*
1.270		0.089		0.013	
0.354		0.052		0.010	*
1.080		0.054		0.010	*
0.184		0.019		0.010	*
4.260		1.210		0.010	*
1.390		0.048		0.010	*
2.440		0.342		0.010	*
3.650		0.040		0.010	*
1.380		0.379		0.010	*
0.242		0.371		0.010	*
				0.010	*

						0.010	*
						0.010	*
						0.010	*
						0.010	*

Compound	Propiconazole	Propiconazole	Propiconazole
Crop	Rye Straw	Rye Forage	Sugarcane Cane
Region / Country	Parent Only	Parent Only	Parent Only
GAP	MRID 48681701 (0.2216-0.2288lb ai/A; 34-50-day PHI)	MRID 48681701 (0.2222-0.2263 lb ai/A; 6-8-day PHI)	MRID 48497001 (0.6636-1.3064 lb ai/A; 26-32-day PHI)
Total number of data (n)	4	4	7
Percentage of censored data	0%	0%	14%
Number of non-censored data	4	4	6
Lowest residue	0.043	0.895	0.010
Highest residue	0.551	1.520	0.156
Median residue	0.160	1.105	0.054
Mean	0.228	1.156	0.075
Standard deviation (SD)	0.225	0.263	0.056
Correction factor for censoring (CF)	1.000	1.000	0.905
Proposed MRL estimate			
- Highest residue	0.551	1.520	0.156
- Mean + 4 SD	1.129	2.210	0.298
- CF x 3 Mean	0.685	3.469	0.204
Unrounded MRL	1.129	3.469	0.298
Rounded MRL	1.5	4	0.3
	High uncertainty of MRL estimate due to small dataset.	High uncertainty of MRL estimate due to small dataset.	High uncertainty of MRL estimate due to small dataset.

Residues (mg/kg)		Residues (mg/kg)		Residues (mg/kg)	
0.205		1.140		0.021	
0.043		0.895		0.102	
0.114		1.070		0.156	
0.551		1.520		0.054	
				0.132	
				0.010	*
				0.051	

Compound	Propiconazole	Propiconazole	Propiconazole
Crop	Wheat Forage	Wheat Grain	Wheat Hay
Region / Country	Parent Only	Parent Only	Parent Only
GAP	MRID 48681704 (0.2190-0.2306 lb ai/A; 7-day PHI)	MRID 48681704 (0.2140-0.2308 lb ai/A; 24-64-day PHI)	MRID 48681704 (0.2190-0.2306 lb ai/A; 7-day PHI)
Total number of data (n)	15	15	15
Percentage of censored data	0%	80%	0%
Number of non-censored data	15	3	15
Lowest residue	0.271	0.010	0.444
Highest residue	4.790	0.078	9.570
Median residue	1.280	0.010	2.010
Mean	1.442	0.015	2.754
Standard deviation (SD)	1.128	0.018	2.304
Correction factor for censoring (CF)	1.000	0.467	1.000
Proposed MRL estimate			
- Highest residue	4.790	0.078	9.570
- Mean + 4 SD	5.952	0.086	11.970
- CF x 3 Mean	4.326	0.021	8.263
Unrounded MRL	5.952	0.086	11.970
Rounded MRL	6	0.09	15
		High uncertainty of MRL estimate due to high level of censoring.	

Residues (mg/kg)		Residues (mg/kg)		Residues (mg/kg)	
1.420		0.010	*	2.010	
0.664		0.010	*	1.550	
0.459		0.010	*	1.110	
0.271		0.010	*	0.444	
1.350		0.010	*	3.280	
4.790		0.010	*	9.570	
0.915		0.010	*	2.960	
1.280		0.010	*	2.240	
1.560		0.010	*	4.230	
1.740		0.010	*	1.970	
0.772		0.078		0.570	
2.270		0.010		2.770	
2.520		0.022		5.380	

	1.070		0.010	*	1.910	
	0.550		0.010	*	1.320	

Compound	Propiconazole	Propiconazole	Propiconazole
Crop	Wheat Straw	Cherry	Peach
Region / Country	Parent Only	Parent Only	Parent Only
GAP	MRID 48681704 (0.2190-0.2306 lb ai/A; 24-64-day PHI)	MRID 48438206 (0 11208-0.11265 lb ai/A; post-harvest)	MRID 48438206 (0.11252-0.11861-0.11265 lb ai/A; post-harvest)
Total number of data (n)	15	3	8
Percentage of censored data	0%	0%	0%
Number of non-censored data	15	3	8
Lowest residue	0.046	0.170	0.140
Highest residue	4.040	0.850	2.110
Median residue	0.455	0.670	0.835
Mean	1.157	0.563	0.961
Standard deviation (SD)	1.405	0.352	0.736
Correction factor for censoring (CF)	1.000	1.000	1.000
Proposed MRL estimate			
- Highest residue	4.040	0.850	2.110
- Mean + 4 SD	6.778	1.973	3.906
- CF x 3 Mean	3.470	1.690	2.884
Unrounded MRL	6.778	1.973	3.906
Rounded MRL	7	2	4
		High uncertainty of MRL estimate due to small dataset.	

Residues (mg/kg)		Residues (mg/kg)		Residues (mg/kg)	
3.510		0.170		0.140	
1.310		0.670		0.200	
0.046		0.850		0.490	
0.059				0.500	
0.526				1.170	
0.455				1.350	
0.373				1.730	
0.830				2.110	
0.139					
0.155					
3.210					
2.370					
4.040					

	0.281					
	0.048					

Compound	**Propiconazole**
Crop	**Plum**
Region / Country	**Parent Only**
GAP	**MRID 48438206 (0.11265-0.11596 lb ai/A; post-harvest)**
Total number of data (n)	4
Percentage of censored data	0%
Number of non-censored data	4
Lowest residue	0.160
Highest residue	0.200
Median residue	0.185
Mean	0.183
Standard deviation (SD)	0.017
Correction factor for censoring (CF)	1.000
Proposed MRL estimate	
- Highest residue	0.200
- Mean + 4 SD	0.251
- CF x 3 Mean	0.548
Unrounded MRL	0.548
Rounded MRL	0.6

High uncertainty of MRL estimate due to small dataset.

Residues (mg/kg)	
0.160	
0.180	
0.190	
0.200	