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

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

DATE: December-18-2020

SUBJECT: **Picarbutrazox.** Human Health Risk Assessment in Support of a New Active Ingredient for Use on Corn and Soybean Seed and Turf.

PC Code: 044200
Decision No.: 534473
Petition No.: 7F8623
Risk Assessment Type: Single Chemical/Aggregate
TXR No.: NA
MRID No.: NA

DP Barcode: D444137
Registration No.: 100-RAGL and 8033-RGT
Regulatory Action: Section 3 Registration
Case No.: NA
CAS No.: 500207-04-5
40 CFR: NA

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The HED of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. Nippon Soda Co. has requested registration of the new active ingredient (ai) picarbutrazox for the broad spectrum, fungicidal control of foliar and soil-borne plant diseases. The Registration Division (RD) of OPP has requested that HED evaluate hazard and exposure data and conduct dietary, occupational, residential, and aggregate exposure assessments, as needed, to estimate the risk to human health that will result from the proposed use of picarbutrazox. A summary of the findings and an assessment of human health risk resulting from the proposed uses of picarbutrazox on turf and seed treatment of corn and soybean seeds are provided in this document. There are no data deficiencies for the proposed uses. Additional studies may be required if the registrant proposes new uses that substantially increase human exposure. The registrant is encouraged to consult with EPA prior to submitting new uses.

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1.0 Executive Summary

Use Profile: Nippon Soda Co. has submitted a petition for registration of a new fungicidal ai, picarbutrazox. Picarbutrazox fungicide belongs to the tetrazolyloxime chemical class and is intended to control downy mildew, Pythium, and Phytophthora. This is a joint review with Canada's Pest Management Regulatory Agency (PMRA). The two proposed picarbutrazox end use products (Vayantis™ and Picarbutrazox 20WG) are intended for use on turf, as well as seed treatment uses on corn and soybeans. Picarbutrazox 20WG is formulated as wettable granule (WG) containing 20% ai. Vayantis™ is formulated as flowable concentrate containing 36.0% ai (3.3 lb ai/gallon of product). Picarbutrazox can be applied by ground, aerial, and chemigation equipment, or as a commercial seed treatment. The proposed labels require handlers to wear baseline attire (defined in this assessment as a long-sleeved shirt, long pants, shoes, and socks). The seed treatment label requires the use of chemical-resistant gloves. The restricted entry interval (REI) for the proposed Vayantis™ label is 12 hours and Picarbutrazox 20WG label is 4 hours.

Exposure Profile: Picarbutrazox is proposed for seed treatment application for corn (field, sweet, and popcorn) and soybean and for foliar application to turf. As a result of these uses, humans may be exposed to picarbutrazox in food and water. Non-dietary exposure to picarbutrazox may occur from occupational and residential exposure sources. Since all proposed labels require the use of personal protection equipment (PPE), residential handler exposures are not anticipated because the applications are not intended to be made by homeowner or residential applicators. However, there is a potential for adult dermal post-application exposure, as well as, child dermal and incidental oral post-application exposures to occur as a result of turf applications. 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.

Hazard Identification: The primary target organs for picarbutrazox are the liver and the thyroid gland, across species and durations (except acute). Both the liver and the thyroid showed increases in organ weights and histopathological changes. Disruption of thyroid hormones was also observed across the guideline studies, for the short-term and long-term durations in rats (alterations in triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH)). Thyroid follicular tumors were observed in rats following two years of oral exposure. No treatment-related effects were observed in mice following 78 weeks of exposure. There is no evidence of genotoxicity or mutagenicity in the picarbutrazox hazard database. There is no evidence of increased prenatal susceptibility in rats or rabbits or postnatal susceptibility in rats, with no adverse effects observed in the developmental toxicity studies. In the multi-generation reproductive study, adverse thyroid effects were observed in the parental animals and occurred at doses lower than offspring effects (thyroid hypertrophy and decreased body weight). No signs of neurotoxicity were observed, and no dermal toxicity was observed in rats up to the limit dose (1000 mg/kg/day). Picarbutrazox is categorized as having low acute lethality through the oral, dermal, and inhalation routes (Toxicity Categories III and IV). It is minimally irritating to the eye (Toxicity Category III) and is neither a dermal irritant nor sensitizer (Toxicity Category IV).

Food Quality Protection Act (FQPA) Safety Factor (SF) Decision: The picarbutrazox risk assessment team recommends that the 10X FQPA SF be reduced to 1X for all exposure scenarios. The toxicity database is complete, clear no-observed adverse-effect levels (NOAELs)/lowest-observed adverse-effect levels (LOAELs) have been established for the effects of concern, there is no evidence of neurotoxicity or increased susceptibility, and dietary exposure analyses are unlikely to underestimate exposure. There are no residual uncertainties in the exposure database.

Dose-Response Assessment: An acute dietary risk assessment is not required. There is no evidence in the picarbutrazox hazard database of adversity from a single-dose. The endpoint used for deriving the chronic population-adjusted dose (cPAD), as well as evaluating short- and intermediate-term incidental oral and inhalation exposures, was selected from the multigeneration reproductive toxicity study in rats with a parental NOAEL of 4 mg/kg/day. The LOAEL of 11.6/16.3 mg/kg/day [M/F] is based on changes in T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F_1 females. A total uncertainty factor (UF) of 30X (3X interspecies UF, 10X intraspecies UF, and 1X FQPA SF when applicable) was applied for chronic, incidental oral, and inhalation exposures. The interspecies UF can be reduced to 3X to account for the increased sensitivity of the adult rat to hypothyroidism compared to adult humans. A dermal endpoint was not selected. There were no adverse effects observed up to the limit dose in the dermal toxicity study and there is no evidence of increased quantitative or qualitative susceptibility. In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March 2005), the Cancer Assessment Review Committee (CARC) classified picarbutrazox as "Suggestive Evidence of Carcinogenic Potential" based on an increase in the incidence of thyroid follicular cell tumors, driven by adenomas in male and female rats and combined thyroid follicular adenomas/carcinomas in male rats. The Agency has determined that quantification of risk using a non-linear approach (i.e., chronic reference dose (cRfD)) will adequately account for all chronic toxicity, including potential carcinogenicity, that could result from exposure to picarbutrazox.

Dietary Exposure: A chronic dietary risk assessment was conducted using the Dietary Exposure Evaluation Model - Food Consumption Intake Database (DEEM-FCID, ver. 3.16) which incorporates food consumption data from the United States Department of Agriculture (USDA) National Health and Nutrition Examination Survey, What We Eat in America (NHANES/WWEIA; 2003-2008). Acute and cancer analyses were not conducted as toxicological effects attributable to a single dose were not identified and the chronic assessment adequately accounts for all chronic toxicity, including potential carcinogenicity. The conservative chronic analysis assumed 100% crop treated, tolerance-level residues adjusted to account for the residues of concern (ROC) for risk assessment, HED's 2018 default processing factors, and modeled drinking water estimates. The resulting chronic exposure estimates do not exceed HED's level of concern (LOC; 100% cPAD); all infants (<1 year old) were the most highly exposed subpopulation at <1% the cPAD.

Residential Exposure: Picarbutrazox is currently being proposed for use on residential lawns, as well as sod farms, sports fields, and golf courses. Residential handler exposure was not assessed because the proposed label requires the use of PPE and is not intended for application by homeowners. However, there is potential for post-application dermal and incidental oral exposures to occur. Dermal exposures were not assessed since a dermal point of departure (POD)

was not selected. Using picarbutrazox-specific turf transferrable residue (TTR) data, post-application incidental oral risk estimates for children (1 to <2 years old) are not of concern (i.e., margins of exposure (MOEs) ≥ the LOC of 30).

Aggregate Exposure:
An acute aggregate risk assessment was not necessary since an appropriate endpoint for the assessment of acute dietary risk was not identified. There are no long-term residential/non-occupational exposures expected based on the proposed use pattern. As a result, the chronic aggregate exposure is equivalent to chronic dietary risk (e.g., food and drinking water exposure) where the risk estimates are not of concern. An aggregate cancer risk assessment was not performed since the chronic assessment adequately accounts for all chronic toxicity, including potential carcinogenicity.

There is potential short-term aggregate exposure to picarbutrazox for adults from dietary exposure (which is considered background exposure) and residential dermal exposures from post-application activities on treated turf. However, since a dermal POD was not selected, short-term aggregate exposures were not conducted for adults.

The short-term aggregate exposure to picarbutrazox for children 1 to <2 years old is from dietary exposure (which is considered background exposure) and incidental oral exposure from hand to mouth activities on treated turf. The short-term aggregate MOE for children 1 to <2 years old is 950 and not of concern (LOC = 30).

Occupational Exposure: Only occupational handler inhalation exposure and risk estimates were calculated for the proposed uses of picarbutrazox since no dermal POD was selected. The occupational handler exposure and risk estimates indicate that the short- and intermediate-term inhalation MOEs are not of concern (i.e., inhalation MOEs ≥ 30) with baseline attire (i.e., no respirator).

Based on the Agency's current practices, a quantitative non-cancer occupational post-application inhalation exposure assessment was not performed for picarbutrazox at this time. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for picarbutrazox.

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. These data, which include studies from the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; Science Advisory Council for Exposure (ExpoSAC) Policy 14 (SOPs for Seed Treatment); and the Residential Standard Operating Procedures (SOPs Turf) are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. 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 http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-

handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure.

Environmental Justice Considerations: 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," (http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf).

2.0 HED Conclusions

Provided the petitioner submits revised Sections B (see Section 2.3.1) and F (see Section 2.2.2) and submits a picarbutrazox reference standard to the Analytical Chemistry Branch/Biological and Economics Analysis Division (ACB/BEAD; see below), HED concludes that the toxicological, residue chemistry, and exposure databases are adequate to support the proposed application scenarios.

Three grams of the picarbutrazox standard should be submitted in 30 aliquot vials of 100 mg each; the vials should be sealed and labeled with percent purity, lot number, and expiration date and mailed to the following address (full zip code is required).

USEPA; Theresa Cole
National Pesticide Standards Repository
Analytical Chemistry Branch/BEAD/OPP
701 Mapes Road
Fort George G. Meade, MD 20755-5350

2.1 Data Deficiencies

There are no data deficiencies for the proposed uses. Note that additional toxicity studies may be needed if the registrant requests uses in the future that substantially increase human exposure.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

The Association of Official Analytical Chemists (AOAC) Method 2007.1 and the Quick Easy Cheap Effective Rugged Safe (QuEChERS)-multimethod (BS EN 15662:2008) have been successfully validated (including independent laboratory validation) for the determination of picarbutrazox and the metabolites TZ-1E and TZ-5 in/on several crops (all analytes have different retention times). Although radiovalidation data were not provided, the extraction solvents are similar to those used in the metabolism studies, with the ROC identified in only the extracts. For the AOAC Official Method 2007.1, matrix-matched standards were required for picarbutrazox and TZ-1E in wheat straw and for TZ-5 in corn grain (matrix effects were >20%). Based on the requirements specified in the Analytical Chemistry Branch (ACB)/Biological and Economics Analysis Division (BEAD) Tolerance Method Validation Checklist (SOP No. 019, Revision 1.0), both methods are adequate for

enforcement of the tolerances recommended herein. The limit of quantitation (LOQ) for both methods is 0.005 ppm for each analyte. The following are brief summaries of these methods.

AOAC Official Method 2007.1: Samples are extracted with acetonitrile + 0.1% acetic acid. $MgSO_4$ and anhydrous sodium acetate are added to the extract and the mixture is shaken and centrifuged. The extract is collected, primary secondary amine (PSA) and $MgSO_4$ are added, and the mixture is again shaken and centrifuged. The resulting extract is collected and analyzed by liquid chromatography with tandem mass spectroscopy (LC/MS/MS).

QuEChERS-multimethod (BS EN 15662:2008): Samples are shaken by hand with acetonitrile followed by addition of the QuEChERS salt mixture (4 g $MgSO_4$, 1 g NaCl, 0.5 g Na_2H citrate x 1.5 H_2O, 1 g sodium citrate) and shaken by hand again. The extract is collected and cleaned up via PSA and $MgSO_4$ solid-phase extraction (SPE) followed by analysis via high-performance liquid chromatography (HPLC)/MS/MS.

2.2.2 Recommended Tolerances

Table 2.2.2 is a summary of the petitioner proposed and HED-recommended tolerance values. The proposed tolerance expression included parent and TZ-1E while the HED-recommended tolerance expression includes only parent. The recommended tolerance values are based on the available residue data. Following is the recommended tolerance expression:

> Tolerances are established for residues of the fungicide picarbutrazox, 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 picarbutrazox (1,1-dimethylethyl *N*-[6-[[[(*Z*)-[(1-methyl-1*H*-tetrazol-5-yl)phenylmethylene]amino]oxy]methyl]-2-pyridinyl]carbamate in or on the commodity

Table 2.2.2. Tolerance Summary (40 CFR 180.xxx(a)).

Commodity/**Correct Commodity Definition**	**Proposed Tolerance (ppm)**	**HED-Recommended Tolerance (ppm)**	**Comments**
180 xxx(a)(1):			
Corn, field, forage	--	**0.005**	commodity definition and tolerance value correction
corn, forage	0.01	--	
Corn, field, grain	--	**0.005**	commodity definition and tolerance value correction
corn, grain	0.01	--	
Corn, field, stover	--	**0.005**	commodity definition and tolerance value correction
corn, stover	0.01	--	
Corn, pop, grain	--	**0.005**	commodity definition and tolerance value correction
popcorn, grain	0.01	--	
Corn, pop, stover	--	**0.005**	tolerance on stover is required
Corn, sweet, forage	0.01	**0.005**	tolerance value correction
Corn, sweet, kernel plus cob with husks removed	0.01	**0.005**	tolerance value correction
Corn, sweet, stover	0.01	**0.005**	tolerance value correction
Soybean, forage	0.01	**0.005**	tolerance value correction
Soybean, hay	0.01	**0.005**	tolerance value correction
Soybean, seed	0.01	**0.005**	tolerance value correction

2.2.3 Revisions to Petitioned-For Tolerances

HED requests a revised Section F that specifies the tolerance expression, commodity definitions, and tolerance values in Section 2.2.2. HED is recommending changes to the tolerance expression and commodity definitions to conform to current practices. The HED recommended tolerance values are based on the submitted residue data. Note that the soybean and corn tolerances are recommended at 0.005 ppm rather than 0.01 ppm as parent is the only residue of concern rather than parent and TZ-1E as proposed by the petitioner (LOQ for each analyte is 0.005 ppm).

2.2.4 International Harmonization

Maximum residue limits (MRLs) for picarbutrazox have not been established by Codex or Mexico in/on any commodity; therefore, harmonization is not relevant. The current petition is a joint review with the Canadian Pest Management and Regulatory Agency (PMRA) and HED, with the crop tolerances harmonized (expression and value).

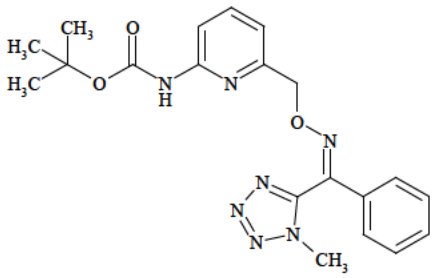
2.2.5 Label Recommendations

Based on the rotational crop data, residues in rotational crops are expected to be negligible provided the labels are revised to include the following rotational crop plant back restrictions: labeled crops - immediately; all other crops - 30 days.

3.0 Introduction

3.1 Chemical Identity

Table 3.1. Nomenclature for Picarbutrazox.

Common name	Picarbutrazox
Identity	CAS: 1,1-dimethylethyl *N*-[6-[[[(*Z*)-[(1-methyl-1*H*-tetrazol-5-yl)-phenylmethylene]amino]oxy]methyl]-2-pyridinyl]carbamate IUPAC: *tert*-butyl (6-{[(*Z*)-(1-methyl-1*H*-5-tetrazolyl)-(phenyl)methylene]aminooxymethyl]}-2-pyridyl)carbamate
CAS no.	500207-04-5
Company experimental name	ASF1073
Other synonyms (if applicable)	NF-171
Structure	

3.2 Physical/Chemical Characteristics

Tables 3.2 is a summary of the physicochemical properties for picarbutrazox. Picarbutrazox has low water solubility and low vapor pressure.

Table 3.2. Physicochemical Properties of Picarbutrazox.		
Molecular Weight	409.4 g	Administrative Materials; 26-Sep-2017
Melting range	136.6-138.7 °C	
Water solubility (20 °C)	0.333 mg/L	
Solvent solubility (20 °C)	*n*-hexane - 0.103 g/L, *n*-heptane - 0.106 g/L, *n*-octanol - 3.32 g/L, ethanol - 15.0 g/L, methanol - 34.8 g/L, xylene - 21.2 g/L, toluene - 49.8 g/L, ethyl acetate - 185 g/L, dichloromethane - >250 g/L, acetone- >250 g/L.	
Vapor pressure	$<9.00 \times 10^{-10}$ mm Hg	
Octanol/water partition coefficient; Log Kow (25 °C)	4.16	
Dissociation constant	not provided	
UV:visible absorption spectrum	not provided	

3.3 Pesticide Use Pattern

Picarbutrazox is a new ai being proposed for use as a fungicide formulated as a soluble concentrate and wettable granule. The proposed agricultural use of picarbutrazox is for the control of downy mildew for use as a seed treatment on corn and soybeans. Picarbutrazox is also proposed to be used on turf sites including golf courses, sports fields, residential and commercial lawns, sod farms, turf seed farms, cemeteries, recreational areas, and parks. Depending on the use site, it can be occupationally applied via aerial, ground, chemigation, and commercial seed treatment equipment with maximum application rates of 0.33 lb ai/acre and 0.00010 lb ai/lb seed. The proposed labels require handlers to wear baseline attire (long-sleeved shirt, long pants, shoes, and socks). The seed treatment label also requires the use of chemical-resistant gloves. Since all proposed labels require the use of PPE, applications are not intended to be made by homeowner or residential applicators.

Table 3.3.1 is a summary of the proposed end-use products and Table 3.3.2 is a summary of the proposed application scenarios. The Vayantis™ label indicates that in the event of crop failure or harvest of a crop grown with treated seed, the treated field may be replanted immediately with any crop and indicates that bags containing treated seed should be labeled with the following statements: (1) this seed has been treated with picarbutrazox fungicide; (2) do not use for feed, food, or oil purposes; and (3) user is required to ensure that the seed bag meets all requirements under the Federal Seed Act.

Based on the available rotational crop data, HED requests a revised label indicating the following rotational crop restrictions: labeled crops - immediately; all other crops - 30 days.

Table 3.3.1. Proposed End-Use Products.					
Trade Name (EPA Reg. No.)	**Concentration**	**Formulation**	**Label Date**	**Proposed Target Crops**	**Target Pests**
Vayantis™ (100-RAGL)	3.3 lb ai/gal	Flowable concentrate	12-Dec-2017	-corn -soybean	-*Pythium spp.* -*Phytophthora spp.*
Picarbutrazox 20 WG (8033-RGI)	20% ai	Wettable granule	12-Dec-2017	-turf	

Table 3.3.2. Proposed Application Scenarios.						
App. Timing; Type	**Formulation**	**App. Rate**	**Max. No. Apps**	**Max. Rate**	**PHI[1] (days)**	**Use Directions and Limitations**
Corn						
Commercial Seed treatment	Vayantis™ (100-RAGL)	0.0010-0.010 lb ai/100 lb seed	--	0.010 lb ai/ 100 lb seed[2]	--	-The label also specifies rates of 0.00044-0.0044 lb ai/80,000 seeds and 0.0025-0.025 mg ai/seed based on 1,800 seed per pound. -For use in commercial seed treatment facilities. Do not use for at plant applications (e.g. hopper box, planter box, etc.). This product is to be used in liquid or slurry treaters only. PPE = long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves REI = 12 hrs
Soybean						
Commercial Seed treatment	Vayantis™ (100-RAGL)	0.0010-0.010 lb ai/100 lb seed	--	0.010 lb ai/ 100 lb seed[2]	--	-The label also specifies rates of 0.00046-0.0.0047 lb ai/140,000 seeds 0.0015-0.015 mg ai/seed based on 3,000 seed per pound. - For use in commercial seed treatment facilities. Do not use for at plant applications (e.g. hopper box, planter box, etc.). This product is to be used in liquid or slurry treaters only. PPE = long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves REI = 12 hrs
Turf (Golf courses, sports fields, residential and commercial lawns, sod farms, cemeteries, recreational areas and parks)						
Aerial Ground Chemigation	Picarbutrazox 20 WG (20% ai) 8033-RGI	0.33 lb ai/A 0.0075 lb ai/gal	4	1.32 lb ai/A	NA	PPE = long-sleeved shirt and long pants, socks, and shoes REI = 4 hrs

[1] PHI = preharvest interval.

[2] Based on seeding rates for sweet corn (33 lb seed/acre; worst-case for corn) and soybean (167 lb seed/acre), application rates of 0.0033 lb ai/acre and 0.017 lb ai/acre, respectively are calculated (seeding rates from ExpoSAC Policy 015.2).

3.4 Anticipated Exposure Pathways

RD has requested an assessment of human health risk associated with the new ai, picarbutrazox, to support the proposed uses listed above. Humans may be exposed to picarbutrazox in food and drinking water, since picarbutrazox may be applied to agricultural seed, and turf applications may result in picarbutrazox reaching surface and ground water sources of drinking water. The proposed product label with residential use sites (e.g., lawns/turf) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants). HED has made the assumption that these products are not for homeowner use, therefore, residential handler exposure is not anticipated. However, residential post-application exposures in residential or non-occupational settings are expected. 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.

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 USDA's 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 is also being considered whenever appropriate. 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 hazard database for picarbutrazox is complete. HED's Hazard Science and Policy Council (HASPOC) used a weight-of-evidence approach to recommend that a 90-day dermal toxicity, subchronic inhalation toxicity, subchronic neurotoxicity, and immunotoxicity studies, as well as a comparative thyroid assay (CTA) be waived at this time (TXR 0057873, R. Louden, 07-JUN-2019). The current database contains the following acceptable studies:

(1) Subchronic and chronic oral toxicity in rats, mice, and dogs;
(2) Subchronic (28-day) dermal toxicity in rats;
(3) Developmental toxicity in rats and rabbits;
(4) Reproductive and postnatal toxicity in rats;
(5) Carcinogenicity in mice and rats;
(6) Acute neurotoxicity in rats;
(7) Absorption, distribution, metabolism, and elimination (ADME) in rats;
(8) Dermal triple pack data (rat *in vivo*, rat *in vitro*, and human *in vitro*) and;
(9) Acute toxicity battery.

Several genetic toxicology studies were submitted for the parent and metabolites, including a bacterial reverse mutation test, an *in vitro* chromosome aberration test and an *in vivo* micronucleus test. Subchronic oral toxicity studies were also conducted and submitted for several metabolites which were generated in significant quantities in crop field trial studies. A series of *in vitro* and *in vivo* mechanistic studies were submitted to support the registrant's proposed mode of action (MOA) for thyroid tumors in rats.

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

The ADME of picarbutrazox was well characterized in two studies. The first study tested the phenyl-U-^{14}C-labeled parent compound at oral doses of 1 and 100 mg/kg. The second study tested the pyridine-4-^{14}C-labeled parent compound at 1 mg/kg oral dose and generated similar results. Since the results were similar, the following are the findings from the phenyl-U-^{14}C-label study.

In bile duct-cannulated rats, the extent of absorption was assessed as the sum of the total (mean) radioactivity measured in the bile, urine, feces, liver, and carcass following a single oral dose. Twenty-four hours after single oral doses of 1 mg/kg picarbutrazox, 80% and 77% of the administered dose (AD) was excreted in the bile of male and female rats, respectively. Most of the biliary excretion occurred during the first 12 hours post dosing, accounting for 78.55% and 73.95% of the AD in males and females, respectively. During the first 24 hours post-dosing, 9.79% and 8.36% of the AD was excreted in the urine for males and females, respectively. Fecal excretion from 0-24 hours post-dosing accounted for 4.26% and 9.25% of the AD in males and females, respectively.

Forty-eight hours after a 100 mg/kg single oral dose of picarbutrazox, 22.70% and 13.77% of the AD were excreted in the bile of male and female rats, respectively. Radioactivity was excreted in bile throughout the 48-hour collection period, with the majority being excreted during the first 24 hours. Urinary excretion from 0-48 hours accounted for 1.87% and 0.86% of the dose in males and females, respectively. Fecal excretion 0-48 hours accounted for 70.75% and 79.50% of the dose in males and females, respectively. The total absorbed was 85.90-90.63% of the AD at the 1-mg/kg dose level, and 14.68-24.72% of the dose at the 100-mg/kg dose level, indicating a saturation of absorption with a 100-fold increase in dose.

In terms of absorption kinetics, following administration of single oral doses of picarbutrazox at 1 mg/kg, a peak mean plasma concentration (Cmax) of radioactivity of 0.039 µg equiv./g (males and females) was reached at 1 hour (Tmax). At 100 mg/kg, peak mean plasma concentrations of radioactivity of 0.706 µg equiv./g (males) and 0.763 µg equiv./g (females) were reached at 4 and 6 hours post dosing, respectively. Concentrations of radioactivity in tissues were highest in the liver for both sexes and dose levels. There was no indication of tissue accumulation after single oral doses, with only low levels of radioactivity detected in tissues at 96 hours (<1% dose). Most of the identified metabolites were detected in fecal extracts for both the low- and high-dose groups. Unchanged parent compound accounted for 2.2-2.7% dose at the 1-mg/kg dose level and 66.9-78.3% dose at the 100-mg/kg dose level. Parent NF-171 was not detected in urine or bile. None of the metabolites identified were determined to be toxicologically relevant.

4.2.1 Dermal Absorption

Triple pack data (rat *in vivo*, rat *in vitro*, and human *in vitro*) are available for picarbutrazox. The doses for the *in vivo* study in rats were 0, 0.9348, 10.1 or 209.6 µg/cm^2. Dermal exposure was for eight hours, and the termination periods for analysis were 8, 24, 72, and 120 hours. The application site of all rats was washed at the end of the 8-hour exposure period. The rat *in vivo* data (MRID 50218589) demonstrated continued absorption from the *stratum corneum* with time

(8-72 hours). The estimate of dermal absorption from the *in vivo* study (MRID 50218589) was calculated as the amount absorbed + potentially absorbed (skin application site, adjacent skin, tape strips [excluding tape strips 1 and 2], cage wash, urine, feces, and carcass). Dermal absorption ranged from 1-5% across all dose groups and time points. An *in vivo* dermal absorption value of 5% based on results of the 0.9348 µg/cm^2 group sacrificed at 120 hours is considered appropriate and protective of dermal exposure to picarbutrazox.

The *in vitro* dermal absorption doses of picarbutrazox were 0.88, 10.2, and 203 µg ai/cm^2 in human and rat skin (MRID 50218587 and 50218588). The *in vitro* human study generated dermal absorption values of 6, 5 and 6% at the high, mid, and low doses, respectively, at 8 hours. For the same dilutions, the *in vitro* rat study generated dermal absorption values of 5, 10 and 55% at 8 hours. Taking the three absorption values based on the lowest dose tested, a refined dermal absorption factor (DAF) of 1% was derived:

In vivo rat * *In vitro* human/rat *In vitro* = 5% * (6%/ 55%) = 0.55% ≈ 1%.

4.3 Toxicological Effects

The primary target organs for picarbutrazox are the liver and the thyroid gland across species and durations (except acute). The rat was the most sensitive species is rat, followed by the mouse and the dog. Both the liver and the thyroid showed increases in organ weights and histopathological changes. In the liver, changes included hepatocyte hypertrophy, periportal vacuolation, cytoplasmic inclusions and portal inflammatory cell infiltration. In the thyroid, there were increased incidences of thyroid hypertrophy which corresponded with increased thyroid weights in both parental animals and neonates. Disruption of thyroid hormones was also observed across the guideline studies, for the short-term and long-term durations in rats (alterations in T3, T4, and TSH). Thyroid follicular tumors were observed in rats following two years of oral exposure. No treatment-related effects were observed in mice following 78 weeks of exposure. There is no evidence of genotoxicity or mutagenicity in the picarbutrazox hazard database.

There is no evidence of increased prenatal susceptibility in rats or rabbits or postnatal susceptibility in rats. There were no adverse fetal or maternal effects in the available developmental toxicity studies in rats or rabbits. Both studies tested up to the limit dose. In the multi-generation reproductive study, adverse thyroid effects were observed in the parental animals and occurred at doses lower than offspring effects. Pups were not culled so statistical significance and standard deviations could not be calculated for individual animals for body weights. However, there were trends for decreased pup weights in the F_2 generation from days 7-21 in addition to increased incidences of thyroid hypertrophy. There were no adverse reproductive effects up to the highest dose tested (46/63 mg/kg/day).

Subchronic studies in rats were performed for the numerous plant metabolites generated from parent picarbutrazox. All were less toxic than the parent molecule (see section 5.3.1 below). No signs of neurotoxicity were observed in the acute neurotoxicity study up to the limit dose (2,000 mg/kg/day). No dermal toxicity was observed in rats up to the limit dose (1000 mg/kg/day). Picarbutrazox is categorized as having low acute lethality through the oral, dermal, and

inhalation routes (Toxicity Categories III and IV). It is minimally irritating to the eye (Toxicity Category III) and is neither a dermal irritant nor sensitizer (Toxicity Category IV).

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)[1]

The picarbutrazox risk assessment team recommends that the 10X FQPA SF be reduced to 1X for all exposure scenarios. The toxicity database is complete, clear NOAELs/LOAELs have been established for the effects of concern, there is no evidence of neurotoxicity or increased susceptibility, and dietary exposure analyses are unlikely to underestimate exposure. There are no residual uncertainties in the exposure database.

4.4.1 Completeness of the Toxicology Database

The toxicology database for picarbutrazox is adequate for characterizing toxicity and quantification of risk. The toxicology database includes the following acceptable studies: developmental toxicity studies in rats and rabbits, a two-generation reproduction study in rats, and an acute neurotoxicity study in rats. The HASPOC recommended that the requirement for a guideline immunotoxicity, subchronic neurotoxicity study and a comparative thyroid assay (CTA) be waived at this time (TXR 0057873, R. Louden, 07-JUN-2019).

4.4.2 Evidence of Neurotoxicity

There is no evidence of neurotoxicity in the guideline acute neurotoxicity study, and there is no evidence of neurotoxicity in any of the other studies in the picarbutrazox hazard database. The HASPOC recommended that a guideline subchronic neurotoxicity study is not required at this time (TXR 0057873, R. Louden, 07-JUN-2019).

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

There is no evidence of an increased pre- or postnatal susceptibility in the picarbutrazox hazard database.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. Since the dietary and non-dietary exposure estimates were based on several conservative assumptions, HED does not believe that the exposure estimates are underestimated. The chronic dietary assessments conducted with DEEM-FCID were screening-level analyses. The assessments used tolerance residue values, default processing factors, and assumed that 100% of the proposed crops were treated with picarbutrazox. The dietary exposure analyses also assumed that all drinking water will contain picarbutrazox at the highest estimated drinking water concentration (EDWC) levels modeled by the Environmental Fate and Effects Division (EFED). Therefore, the dietary exposure analyses do not underestimate risk from chronic dietary exposure to picarbutrazox. Similarly, HED does not believe that the residential exposures are underestimated because they are also based on

[1] 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).

conservative assumptions, including maximum application rates, and standard values for exposure assumptions as described in the Residential SOPs.

4.5 Toxicity Endpoint and Point of Departure Selections

All of the endpoints selected for picarbutrazox are based on thyroid effects in rats. In accordance with EPA guidance[2] on the use of rat thyroid toxicity studies in human health risk assessment, the UF for extrapolation from animal to human (interspecies; UF_A) will be reduced to 3X. EPA considers toxicokinetic and toxicodynamic differences when determining the appropriate interspecies factor. When acceptable prenatal and postnatal data are available showing no increased sensitivities to fetuses or offspring compared to adults, the interspecies UF can be reduced to 3X to account for the increased sensitivity of the adult rat to hypothyroidism compared to adult humans. The 3X toxicodynamic component of the UF for interspecies differences can be removed because of several important quantitative dynamic differences between rats and humans with respect to thyroid function (Dohler *et al.,* 1979; McClain, 1992). The 3X interspecies toxicokinetic component is retained, in the absence of any additional information that would allow reducing this factor. With the remaining 3X toxicokinetic component of the interspecies UF, and the 10X intraspecies UF, the result is a total UF of 30X.

4.5.1 Dose-Response Assessment

Acute Dietary Endpoint for all Populations: An acute dietary risk assessment is not required. There is no evidence in the picarbutrazox hazard database of adversity from a single-dose effect for all populations including females of reproductive age.

Chronic Dietary Endpoint for All Populations: The endpoint used for deriving the cPAD was selected from the multigeneration reproductive toxicity study in rats (MRID 50218562). The cPAD of 0.13 mg/kg/day was derived from the parental NOAEL of 4 mg/kg/day and a 30-fold UF (3X for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF). The LOAEL of 11.6/16.3 mg/kg/day [M/F] is based on changes in T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F_1 females. This study is appropriate since the effects of concern were seen following repeated oral exposure via the diet. Based upon dose spacing, it is protective of the thyroid effects in the combined chronic/carcinogenicity study in rats which are seen at similar doses. The cRfD is further protective of all other effects seen following chronic exposure as well as the offspring effects observed in the reproduction toxicity study.

Short- (1-30 days) and Intermediate- (1-6 months) Term Incidental and Adult Oral Endpoints: The short- and intermediate-term incidental and adult oral endpoints were derived from the multigeneration reproductive toxicity study in rats (MRID 50218562). The parental NOAEL of 4 mg/kg/day and a 30-fold UF (3X for inter-species extrapolation, 10X for intra-species variation, and 1X for FQPA SF) was selected for the POD. The LOAEL of 11.6/16.3 mg/kg/day [M/F] is based on changes in T4, increased thyroid weights, and incidences of thyroid

[2] Thyroid Disrupting Pesticides: Use of Rat Thyroid Data and Application of Uncertainty Factors for RfD Derivation (https://www.epa.gov/sites/production/files/2020-02/documents/use-of-rat-thyroid-data-uncertainty-factors-rfd-derivation.pdf)

hypertrophy in the P and F_1 females. The LOC is 30 based on interspecies extrapolation (3X), intraspecies variation (10X), and the 1X FQPA SF. This study is protective of the offspring effects and all other subchronic rat and mouse effects observed across the database. Finally, it is appropriate for the short-/intermediate-term durations.

Short- (1-30 days) and Intermediate- (1-6 months) Term Dermal Endpoints: No dermal endpoints were selected. The dermal study conducted histopathological examination of the main target organs identified in oral studies (thyroid and liver) and collected organ weight information. No systemic effects were observed in the dermal study up to the limit dose. Dermal triple pack data are available indicating low dermal absorption potential (refined DAF =1%) and there is no evidence of increased quantitative susceptibility in the young. Finally, the offspring effects observed in the developmental and reproductive toxicity studies occurred only in the presence or at higher doses comparable maternal/parental toxicity.

Short- (1-30 days) and Intermediate- (1-6 months) Term Inhalation Endpoints: A route-specific inhalation study is not available for picarbutrazox. The HASPOC recommended that the study is not required at this time (TXR 0057873, R. Louden, 07-JUN-2019) based upon the chemical's current overall hazard and exposure profile. As a result, an oral endpoint was selected to evaluate inhalation exposures. The short- and intermediate-term inhalation endpoints were derived from the multigeneration reproductive toxicity study in rats (MRID 50218562). The parental NOAEL of 4 mg/kg/day and a 30-fold UF (3X for inter-species extrapolation, 10X for intra-species variation, and 1X for FQPA SF) was selected as the POD. The LOAEL of 11.6/16.3 mg/kg/day [M/F] based on changes in T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F_1 females. The LOC is 30 based on interspecies extrapolation (3X), intraspecies variation (10X), and the 1X FQPA SF (in residential settings). Inhalation exposure is assumed to be equivalent to oral. This study is protective for all other subchronic rat and mouse effects observed across the database. Finally, it is protective of the general population in residential settings, workers in occupational settings, and is appropriate for the subchronic duration.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

Based upon the same study/effects, the incidental oral and inhalation exposure scenarios can be combined. No dermal endpoint was selected.

4.5.3 Cancer Classification and Risk Assessment Recommendation

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March 2005), the CARC classified picarbutrazox as "Suggestive Evidence of Carcinogenic Potential" based upon thyroid follicular cell tumors, driven by adenomas in male and female rats, and combined thyroid follicular adenomas/carcinomas in male rats (TXR 0057877, R. Louden, 21-AUG-2020). The MOA data for thyroid tumors is not established by the data submitted. No treatment-related tumors were seen in mice. Both studies had adequate dosing, and there was no concern for genotoxicity or mutagenicity.

The Agency has determined that quantification of risk using a non-linear approach (i.e., cRfD) will adequately account for all chronic toxicity, including potential carcinogenicity, that could result from exposure to picarbutrazox.

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 Picarbutrazox for Use in Dietary and Non-Occupational Human Health Risk Assessments.

Exposure/ Scenario	POD	UFs	RfD, PAD, LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All Populations)	An acute dietary risk assessment is not required. There is no evidence in the picarbutrazox hazard database of a single-dose effect.			
Chronic Dietary (All Populations)	NOAEL = 4 mg/kg/day	UF_A = 3X UF_H = 10X FQPA SF = 1X	Chronic RfD = 0.13 mg/kg/day cPAD = 0.13 mg/kg/day	Reproduction and fertility effects (rat) (MRID 50218562) Parental LOAEL = 11.6 mg/kg/day based on changes T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F_1 females.
Incidental Oral Short-Term (1-30 days)	NOAEL = 4 mg/kg/day	UF_A = 3X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 30	Reproduction and fertility effects (rat) (MRID 50218562) Parental LOAEL = 11.6 mg/kg/day based on changes in T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F_1 females.
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	A dermal endpoint was not selected. There were no adverse effects observed up to the limit dose in the dermal toxicity study where the target organs were examined. There was further no evidence of an increased quantitative susceptibility in the picarbutrazox hazard database.			
Inhalation Short-Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 4 mg/kg/day	UF_A = 3X UF_H = 10X FQPA SF = 1X	Residential LOC for MOE = 30	Reproduction and fertility effects (rat) (MRID 50218562) Parental LOAEL = 11.6 mg/kg/day based on changes in T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F_1 females.
Cancer (oral, dermal, inhalation)	Classification: "*Suggestive Evidence of Carcinogenic Potential*" based upon thyroid follicular cell tumors, driven by adenomas in male and female rats and combined thyroid follicular adenomas/carcinomas in male rats. See CARC document (TXR 0057877, R. Louden, 21-AUG-2020).			

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.

Table 4.5.4.2. Summary of Toxicological Doses and Endpoints for Picarbutrazox for Use in Occupational Human Health Risk Assessments.				
Exposure/ Scenario	**POD**	**UFs**	**LOC for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short-Term (1-30 days) and Intermediate-Term (1-6 months)	A dermal endpoint was not selected. There were no adverse effects observed up to the limit dose in the dermal toxicity study where the target organs were examined. There was further no evidence of an increased quantitative susceptibility in the picarbutrazox hazard database.			
Inhalation Short- Term (1-30 days) and Intermediate-Term (1-6 months)	NOAEL = 4 mg/kg/day	UF_A = 3X UF_H = 10X	Occupational LOC for MOE = 30	Reproduction and fertility effects (rat) (MRID 50218562) Parental LOAEL = 11.6 mg/kg/day based on changes in T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F1 females.
Cancer (oral, dermal, inhalation)	Classification: "*Suggestive Evidence of Carcinogenic Potential*" based upon thyroid follicular cell tumors, driven by adenomas in male and female rats and combined thyroid follicular adenomas/carcinomas in male rats. See CARC document (TXR 0057877, R. Louden, 21-AUG-2020).			

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. N/A = not applicable.

5.0 Dietary Exposure and Risk Assessment

Residue of Concern Knowledgebase Subcommittee (ROCKS) decision memo - D447984, M. Negussie, 03-AUG-2020; residue chemistry memo - D446212, T. Bloem, 06-AUG-2020; dietary risk assessment memo - D446213, T. Bloem, 06-AUG-2020; EFED drinking water memo - D447897, K. Crews, 24-JUL-2020

5.1 Metabolite/Degradate Residue Profile

5.1.1 Summary of Plant and Animal Metabolism Studies

Primary Crops: Foliar (cucumber and leaf lettuce) and seed treatment (maize; 1.8-2.3x) metabolism studies were conducted with picarbutrazox radiolabeled in the [phenyl-U-^{14}C], [pyridine-4-^{14}C], and [tetrazole-5-^{14}C] rings. The cucumber and leaf lettuce samples were harvested at several PHIs up to a maximum of 14 days after the final application. Total radioactive residues (TRRs) were roughly the same for each radiolabel position and were highest in leaf lettuce and significantly lower in cucumber and maize. The majority of the radioactivity in the foliar studies was recovered in the initial solvent rinses and in the extracts. For maize, only the forage samples were analyzed (TRRs ≤0.003 ppm in the remaining matrices) with the majority of the TRRs found in the extracts. Picarbutrazox, TZ-1E (E-isomer of picarbutrazox), TZ-5, TT-1 (maize only), and/or TT-3 (maize only) were identified at significant concentrations (>10% TRR). The following compounds were identified at <10% TRR: TZ-2, TZ-4, TZ-5-Glc, and/or TY-1. It is noted that TZ-1E is present in the technical-grade ai at ~0.6% (Z-isomer present at 97.5%).

Rotational Crops: Picarbutrazox radiolabeled in the [phenyl-U-^{14}C], [pyridine-4-^{14}C], and [tetrazole-5-^{14}C] rings was applied to sandy loam soil at 0.91-1.00 lb ai/acre (≥54x). Rotational crops of radish, lettuce, and wheat were planted at plant-back intervals (PBIs) of ~30, ~120, and ~275 days. TRRs were ≥0.01 ppm in all rotated crop matrices with the TRRs highest in samples from the tetrazole radiolabel (0.107-5.165 ppm), followed by samples from the phenyl (0.029-1.832 ppm) and pyridine (0.010-0.674 ppm) radiolabels. For all labels, TRRs decreased with increasing PBI and were highest in wheat.

The samples were extracted with acetonitrile/water and acetonitrile with a greater percentage of the radioactivity released from the tetrazole samples (75-99% TRR) than from the phenyl (34-96% TRR) and pyridine (24-73% TRR) samples. Selected post extraction solids (PES) were further extracted with 0.1 M KOH, 24% KOH, 6 M HCl, and/or 72% sulfuric acid. Nonextractable residues remaining after all extractions were <10% or ≤0.015 ppm in all matrices except phenyl and pyridine label wheat straw at the 30-day PBI where 0.235 ppm (13% TRR) and 0.141 ppm (21% TRR), respectively, remained unextracted.

Picarbutrazox was a minor residue in all samples (<10% TRR). In the phenyl labeled samples, TZ-5 (free and conjugated) was the major identified residue with minor amounts of TZ-2, TZ-4, TZ-2E, TZ-2-β-Glc, and TZ-5-OH-Glc also identified. In the pyridine labeled samples, TZ-2-β-Glc was the only major residue with minor amounts of TZ-2, TZ-2E, and TY-2 also identified. It is noted that the concentrations of TZ-2-β-Glc was similar for both labels but was only a major residue (>10% TRR) following treatment with the pyridine label as the TRR was lower for these samples. In the tetrazole labeled samples, TT-1 and TT-3 were the major identified residues with minor amounts of TZ-5 and TZ-5-Glc also identified. The tetrazole labeled studies resulted in several unknowns at significant concentrations with the petitioner indicating that additional data concerning these unknowns is forthcoming. Based on the exaggerated rate the study was performed at, this information is unnecessary for the current action.

Poultry: Picarbutrazox radiolabeled in the [phenyl-U-^{14}C] or [pyridine-4-^{14}C] ring was orally administered to six laying hens via gelatin capsule once daily for 14 consecutive days at dietary burdens of 12.635 ppm and 11.018 ppm, respectively (1102-1264x maximum reasonable dietary burden (MRDB)). Eggs were collected twice daily, and excreta was collected once a day throughout the study period. Samples of muscle, fat, and liver were collected at sacrifice (11 hours following the last dose).

The majority of the AD was found in the excreta (94-100% of the AD). TRRs in egg (plateau by day 8) and tissue were as follows and represented <0.1% of the AD (TRRs similar for both labels): fat/muscle - ≤0.005 ppm, liver - 0.034-0.044 ppm, egg whites - 0.008-0.010 ppm, and egg yolks - 0.008-0.015 ppm. Due to the low TRR, fat and muscle were not analyzed further. The liver, egg white, and egg yolk samples were extracted with aqueous acetonitrile (+hexane for egg yolk) which released the majority of radioactivity.

The metabolite profile was similar for both labels. Unchanged picarbutrazox was not detected in either label. The major metabolite in liver was TZ-9. The major metabolites in egg white were TZ-7 and TZ-9. No metabolites were identified in the pyridine egg yolk samples, while in the phenyl egg yolk samples, the major metabolites were TZ-7 and TZ-9.

Ruminants: Picarbutrazox radiolabeled in the [phenyl-U-^{14}C] or [pyridine-4-^{14}C] ring was orally administered to lactating goats via gelatin capsule once daily for 7 consecutive days at dietary burdens

of 20.322 ppm and 22.580 ppm, respectively (1016-1129x MRDB). Milk was collected twice daily, and excreta collected once a day throughout the study period. Samples of muscle, fat, kidney, and liver were collected at sacrifice (11 hours following the last dose).

The majority of the AD was found in the feces (57-68% of the AD) and urine (8-12% of the AD). An additional 10-15% of the AD was recovered from the gastrointestinal (GI) tract and 1-3% of the AD from the cage wash. TRRs were as follows in milk (plateau reached by end of dosing) and tissue samples from the phenyl and pyridine samples, respectively (slightly lower levels found in the phenyl samples as compared to the pyridine samples; total of 0.9% of the AD): fat - 0.086-0.096 ppm and 0.113-0.138 ppm; muscle - 0.011-0.015 ppm and 0.032-0.035 ppm; liver - 0.280 and 0.619 ppm; kidney - 0.090 and 0.118 ppm; and milk - 0.019 ppm and 0.019 ppm. Milk samples collected on days 4-7 were processed into cream and skim milk; TRRs in skim milk and cream in comparison to milk were 0.59-0.90x and 5.8-9.6x, respectively.

Extraction with aqueous acetonitrile (+hexane for fat and milk) released the majority of the TRRs. The metabolite profile was similar in both labels; however, the major identified analytes (>10% TRR) varied among the matrices and were picarbutrazox, TZ-7, TZ-9, TZ-10, and/or TZ-1-2.

5.1.2 Summary of Environmental Degradation

The aerobic and anaerobic soil and aquatic dissipation studies resulted in the identification of significant residues of TZ-2, TZ-5, TT-3 (soil only), TY-2 (anaerobic aquatic only) and carbon dioxide (9-15% TRR) and minor residues of TZ-4, TZ-7, and TY-1. The aqueous photolysis studies indicated that picarbutrazox is rapidly isomerized to TZ-1E and also resulted in the identification of several compounds which contained only the pyridine ring; these pyridine-only compounds were not identified or were identified at minor concentrations in the remaining environmental fate studies. The aerobic soil and aquatic dissipation studies indicated a half-life for picarbutrazox of 31-105 days and 21-86 days, respectively. The estimated aerobic half-lives for TZ-2 and TZ-5 are as follows: TZ-2 soil - 191-307 days; TZ-2 aquatic - 77-97 days; and TZ-5, soil - 103 days to stable. Based on these data, the proposed soil and aquatic dissipation pathways (aerobic and anaerobic) are similar and proceed with picarbutrazox cleaved to produce tert-butyl formate and TZ-2. TZ-2 is then cleaved at the imine bond to produce TZ-4 and substituted pyridine followed by reduction of TZ-4 to TZ-5.

5.1.3 Comparison of Metabolic Pathways

The primary crop metabolism studies (foliar - cucumber and lettuce; seed treatment - corn) yielded a similar metabolic pathway and indicate that the picarbutrazox is isomerized to TZ-1E (foliar studies only) and cleaved at the imine bond to produce TZ-5 followed by conjugation of TZ-5 with glucose. The confined rotational crop studies also resulted in the identification of TZ-5 and TZ-5 Glc and demonstrated further degradation to TT-1, TT-3, and TZ-2 with TZ-2 conjugated with glucose to produce the glucosylamine TZ-2-β-Glc. TT-3 and TT-1 were also identified in the seed treatment primary crop metabolism studies (maize; ≤0.001 ppm) but were not identified the cucumber and leaf lettuce primary crop metabolism studies. Based on these results and the aerobic soil metabolism studies where TT-3 was identified (TT-1 was not identified), TT-3 most likely forms in the soil and is taken up by plants and metabolized to TT-1.

The ruminant and poultry metabolism studies demonstrated the following similar metabolic pathway: hydroxylation at the t-butyl group to yield TZ-1-2 (ruminant only); oxidation of TZ-1-2 to give the carboxylic acid metabolite TZ-9 or cyclization of the oxidized alkyl to give TZ-7; oxidation of TZ-7 or cyclization of TZ-9 to produce TZ-10 (ruminant only).

The metabolic pathway in rats was similar to that in ruminant and poultry with the identification of TZ-1-2, TZ-7, TZ-9, and TZ-10 at significant concentrations (>10% TRR) in tissue. It is noted that TZ-1E, TZ-2 (free or conjugated), TZ-5 (free or conjugate), TT-3, and TT-1 were not identified in the rat metabolism studies (technical-grade picarbutrazox is 97.5% the Z-isomer and ~0.6% the E-isomer). However, TZ-1E, TZ-5, and TT-3 were less toxic than the parent following subchronic oral exposure in rats; for the TT-3 subchronic toxicity studies, no toxicity was demonstrated at any dose (highest dose tested (male/female) of 1754/1805 mg/kg/day (acute) and 1263/1433 mg/kg/day (90-day)).

5.1.4 Residues of Concern Summary and Rationale

Table 5.1.4 and the following paragraphs are a summary of the HED ROCKS conclusions pertaining to the picarbutrazox ROC for tolerance enforcement and risk assessment (D447984, M. Negussie, 03-AUG-2020).

Primary Crops - Tolerance Expression and Risk Assessment: For the following reasons, HED concluded that parent is suitable for tolerance enforcement in the proposed primary crops and parent and TZ-1E are suitable for risk assessment (1) although TZ-5 and TZ-5-Glc were the major residues identified in the seed treatment metabolism studies and picarbutrazox and TZ-1E were not identified, TRRs were low (≤0.007 ppm) in the seed treatment metabolism study and the field trial studies resulted in all residues being <LOQ (picarbutrazox, TZ-1E, TZ-5, and TZ-5-Glc); (2) foliar application to several crops was initially proposed with picarbutrazox and TZ-1E being the principal residues in the field trial studies for these crops; the petitioner withdrew these uses due to the lack of rotational crop residue data for the free tetrazole compounds, but indicated that they will seek registration in the near future; and (3) including picarbutrazox and TZ-1E will adequately account for potential residue following seed treatment. HED notes that for future registrations that rely on the currently available primary crop metabolism data, residues of picarbutrazox, TZ-1E, TZ-5, and TZ-5-Glc should be monitored in the magnitude of the residue studies.

Rotational Crops: The following field rotational crop data were submitted: (1) soil treatment at ≥15x the seed treatment rate planted with lettuce, radish, and wheat 30, 120, and 365 days after application; the crops were harvested at maturity and analyzed for residues of picarbutrazox, TZ-2-β-Glc, TZ-5, and TZ-5-Glc and (2) soil treatment at ≥1x the seed treatment rate planted with lettuce or spinach, radish or turnip, and wheat 30 days after application; the harvested samples were analyzed for residues of TT-1 and TT-3. Residues were <LOQ in all samples excluding TT-1 and TT-3 in wheat hay and straw which were found at 0.006-0.013 ppm.

Although TT-3 and TT-1 were the principal residue in rotational crops, based on toxicological considerations they are not of concern. Based on the results of the rotational crop studies and provided the labels are revised as indicated in Section 2.3, residues in rotational crops are expected be insignificant. If in the future, additional field rotational crop data are submitted, then residues of

picarbutrazox, TZ-5, TZ-5-Glc, and TZ-5-Glc2 should be monitored. It is noted that additional data concerning the identity of unknowns from the tetrazole labeled confined rotational crop study are forthcoming; however, based on the seed treatment application rate, these additional data are unnecessary for the current petition.

Poultry: A poultry feeding study has not been submitted. Based on the results of the poultry metabolism study, HED is preliminarily concluding that the ROC in poultry for tolerance enforcement and risk assessment are picarbutrazox, TZ-7, and TZ-9; only these compounds were found at >10% the TRR. A final decision will be made once a feeding study monitoring for the indicated compounds has been submitted. Based on the results of the metabolism study and the current MRDB (0.01 ppm), residues in poultry are expected to be insignificant (≤0.00004 ppm; 180.6(a)(3)).

Ruminants: A ruminant feeding study has not been submitted. Based on the results of the ruminant metabolism study, HED is preliminarily concluding that the ROC in ruminants for tolerance enforcement and risk assessment are picarbutrazox, TZ-1-2, TZ-7, TZ-9, and TZ-10; only these compounds were found at >10% the TRR. A final decision will be made once a feeding study monitoring for the indicated compounds has been submitted. Based on the results of the metabolism study and the current MRDB (0.02 ppm), residues in ruminants are expected to be insignificant (≤0.0006 ppm; 180.6(a)(3)).

Drinking Water: Based on the aerobic and anaerobic soil and aquatic dissipation studies and the terrestrial field study, HED concludes that the residues of concern in drinking water are picarbutrazox, TZ-1E, TZ-2, and TZ-5. Although TT-3 was a significant residue in the aerobic soil metabolism study, based on toxicological considerations, it is not of concern. TY-2 was not included as a residue of concern as it was only found at significant concentrations in the anaerobic aquatic dissipation studies with drinking water not derived from anaerobic sources. The aqueous photolysis studies resulted in the identification of several compounds which contained only the pyridine ring with these compounds not included as residues of concern as they were not identified or were identified at minor concentrations in the remining environmental fate studies.

Toxicity of Metabolites/Degradates: The major residues identified in the livestock metabolism studies, TZ-1-2, TZ-7, TZ-9, and TZ-10, were also identified in the rat metabolism study. Therefore, these compounds are assumed to have similar toxicity to parent. TZ-1E, TZ-2 (free or conjugated), and TZ-5 (free or conjugate) were identified as significant residues in the primary crop, rotational crop and fate studies. Although these compounds were not identified in the rat metabolism studies, they are considered to have similar toxicity to parent based on the similar structure to parent and the subchronic toxicity studies for TZ-1E and TZ-5 which indicate that these compounds are not more toxic than parent. TT-3 and/or TT-1, which contain only the tetrazole ring, were identified at significant concentrations in the rotational crop and environmental fate studies but were excluded as residues of concern based on the TT-3 subchronic oral toxicity study which showed no toxicity at doses exceeding 1000 mg/kg/day as well as the structure activity analysis.

Table 5.1.4. Residues of Concern.			
Matrix		Residues of Concern	
		Risk Assessment	Tolerance
Plants	Primary crops[1] - leafy vegetables (foliar), cucurbit vegetables (foliar), and cereal grains (seed treatment)	picarbutrazox and TZ-1E	picarbutrazox
	Rotational crops[2]	picarbutrazox, TZ-5, TZ-5-Glc, and TZ-5-Glc2	
Livestock	Ruminant[2]	Picarbutrazox, TZ-1-2, TZ-7, TZ-9, and TZ-10	
	Poultry[2]	Picarbutrazox, TZ-7, and TZ-9	
Drinking water		Picarbutrazox, TZ-1E, TZ-2, and TZ-5	Not Applicable

[1] For future registrations which rely on the currently available primary crop metabolism data, HED advises that the petitioner monitor for picarbutrazox, TZ-1E, TZ-5, and TZ-5-Glc in the magnitude of the residue studies.
[2] These are preliminary decisions. A final decision will be made upon submission of magnitude of the residue studies that monitor for the indicated compounds (these data are unnecessary for the current request). It is noted that additional data concerning the identity of unknowns from the tetrazole labeled confined rotational crop study are forthcoming; however, based on the seed treatment application rate, these additional data are unnecessary for the current petition.

5.2 Food Residue Profile

Based on the field trial and metabolism data and the proposed use, residues in corn (field, sweet, and popcorn) and soybean commodities are anticipated to be <LOQ. Residues in livestock are anticipated to be insignificant (180.6(a)(3)) and residues in rotational crops are also expected to be insignificant provided the label is revised as indicated in Section 2.3.

5.3 Water Residue Profile

Table 5.3 is a summary of the modeled surface water EDWCs provided by EFED (Pesticide in Water Calculator (PWC); ver. 1.52; ground water estimates were significantly lower). The estimates were generated using the total toxic residue approach and assumed a percent cropped area of 1 since both crop and non-crop uses are proposed. The turf surface water estimate provides the worst case EDWC and was incorporated into the dietary risk assessment.

Table 5.3. Summary of Estimated Surface Water and Ground Water Concentrations.[1]		
Crop (Rate)	Surface Water EDWC (µg/L; PWC Ver. 1.52)	
	1-day average (ppb)	1-in-10-year Chronic (ppb)
sweet corn (0.0066 lb ai/acre)	0.020	0.004
field corn (0.0044 lb ai/acre)	0.010	0.002
soybean (0.017 lb ai/acre)	0.058	0.01
turf (1.31 lb ai/acre)	8.63	**2.56**

[1] Value in bold was used in the dietary risk assessment.
[2] Ground water estimates for corn (sweet and field) and soybean were not provided.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

Acute and cancer analyses were not conducted as toxicological effects attributable to a single dose were not identified and the chronic assessment adequately accounts for all chronic toxicity, including potential carcinogenicity. The chronic analysis assumed 100% crop treated, tolerance-

level residues adjusted to account for the ROC for risk assessment, HED 2018 default processing factors, and modeled drinking water estimates.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The analysis assumed 100% crop treated.

5.4.3 Acute Dietary Risk Assessment

An acute dietary risk assessment is not required. There is no evidence in the picarbutrazox hazard database of a single-dose effect.

5.4.4 Chronic Dietary Risk Assessment

A chronic dietary risk assessment was conducted using DEEM-FCID (ver. 3.16) which incorporates food consumption data from the USDA NHANES/WWEIA (2003-2008). The chronic exposure estimates do not exceed HED's level of concern (100% cPAD); all infants (<1 year old) were the most highly exposed subpopulation at <1% cPAD. Table 5.4.6 is a summary of the chronic exposure and risk estimates.

5.4.5 Cancer Dietary Risk Assessment

A cancer analysis was not conducted as the chronic assessment adequately accounts for all chronic toxicity, including potential carcinogenicity.

5.4.6 Summary Table

Table 5.4.6. Summary of Dietary (Food and Drinking Water) Exposure and Risk.

Population Subgroup	Chronic Dietary[1]	
	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population	0.000075	<1.0
All Infants (<1 year old)	**0.000181**	**<1.0**
Children 1-2 years old	0.000127	<1.0
Children 3-5 years old	0.000115	<1.0
Children 6-12 years old	0.000082	<1.0
Youth 13-19 years old	0.000062	<1.0
Adults 20-49 years old	0.000071	<1.0
Adults 50-99 years old	0.000065	<1.0
Females 13-49 years old	0.000070	<1.0

[1] Subgroup in bold had the highest dietary exposure.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

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The proposed product label with residential use sites (e.g., lawns/turf) require that handlers wear specific clothing (e.g., long sleeve shirt/long pants). HED has made the assumption that these products are not for homeowner use and therefore, has not conducted a quantitative residential

handler assessment. However, there is a potential for adults and children to have post-application exposures following turf treatments made by professional applicators. The quantitative exposure/risk assessment for residential post-application exposures is based on turf/lawn scenarios.

6.1 Residential Post-Application Exposure and Risk Estimates

There is the potential for post-application exposure for individuals as a result of contact with turf that has been previously treated with picarbutrazox. A dermal exposure assessment was not quantitatively conducted because a dermal POD was not selected. The quantitative exposure/risk assessment for residential post-application exposures is based only on incidental oral scenarios for children 1 to <2 years old.

Picarbutrazox TTR data were used in the residential post-application exposure assessment. The TTR study (MRID No. 50218724) was conducted to characterize the dissipation of picarbutrazox turf transferable residues when applied to turf at three sites in California, Georgia, and New York (MRID No. 50218724, 2017). Using the chemical-specific TTR data, the children's (1 to <2 years old) post-application exposure and risk estimates indicate that the short-term incidental oral MOEs, ranging from 970 to 360,000, are not of concern (i.e., MOEs ≥ 30).

Table 6.1.2. Residential Post-Application Non-Cancer Exposure and Risk Estimates for Picarbutrazox.

Lifestage	Post-application Exposure Scenario		TTR[1] (ug/cm^2)	Dose (mg/kg/day)[2]	MOEs[3] (LOC = 30)
	Use Site	Route of Exposure and Activity			
Child 1 to < 2 years	Turf/lawn	Hand to Mouth	0.03	0.0041	970
		Object to Mouth		0.00012	32,000
		Soil ingestion		0.000011	360,000

1 Based on TTR study conducted at the labeled application rate of 0.325 lb ai/A/application.
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 (mg/kg/day) ÷ Dose (mg/kg/day).

6.2 Residential Risk Estimates for Use in Aggregate Assessment

The recommended residential exposure for use in the children 1<2 years old aggregate assessment is incidental oral exposures from hand to mouth activities on treated turf.

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.

7.1 Acute Aggregate Risk

A quantitative acute aggregate risk assessment was not conducted since an appropriate acute POD was not established for picarbutrazox.

7.2 Short-Term Aggregate Risk

There is potential short-term exposure to picarbutrazox via the dietary pathway (which is considered background exposure) and the residential pathway (which is considered the primary pathway). The short-term aggregate exposure assessment for adults was not conducted since residential handler or post-application exposures were not assessed as a dermal POD was not selected. The short-term aggregate exposure assessment for children 1 to <2 years old includes dietary (food and drinking water) and incidental oral exposure from hand-to-mouth activities from post-application exposure to turf applications.

For picarbutrazox, the child lifestage with the highest dietary exposure (all infants <1 year old) does not match the child lifestage with the highest residential exposure (children 1 to <2 years old). The lifestages selected for each residential post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs. This analysis provides a quantitative and qualitative basis for why children 1 to <2 years old are the representative lifestage for most residential post-application scenarios involving young children, as well as reasons why a residential assessment is not conducted for infants. For children, therefore, the metaldehyde aggregate assessment only combines the residential exposure estimates for children 1 to <2 years old with the dietary exposure estimates for that same lifestage, children 1-2 years old

Table 7.2. Short-Term Aggregate Risk Calculations.

Population	Short-Term Scenario						
	NOAEL mg/kg/day	LOC[1]	Max Allowable Exposure[2] mg/kg/day	Average Food and Water Exposure[3] mg/kg/day	Residential Exposure mg/kg/day[4]	Total Exposure mg/kg/day[5]	Aggregate MOE (food, water, and residential)[6]
Children 1 to <2	4.0	30	7.5	0.000127	0.0041	0.00423	950

[1] LOC = standard inter- and intra- species UFs totaling 30.
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC.
[3] See Table 5.4.6
[4] Residential Exposure = Incidental Oral Exposure via Hand-to-Mouth for Children 1 to <2. Table 6.1.2.
[5] Total Exposure = Avg Food & Water Exposure + Residential Exposure.
[6] Aggregate MOE = [NOAEL ÷ (Avg Food & Water Exposure + Residential Exposure)].

7.3 Chronic Aggregate Risk

Chronic aggregate exposure is equivalent to chronic dietary risk (e.g., food and drinking water exposure) where the estimates are not of concern.

7.4 Cancer Aggregate Risk

A cancer aggregate analysis was not conducted as the chronic assessment adequately accounts for all chronic toxicity, including potential carcinogenicity.

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 picarbutrazox. 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).[3] 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.

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 its Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://archive.epa.gov/scipoly/sap/meetings/web/pdf/120309meetingminutes.pdf). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2014-0219-0003&disposition=attachment&contentType=pdf). 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 picarbutrazox.

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 picarbutrazox and any other substances and picarbutrazox does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that picarbutrazox has a common mechanism of toxicity with other substances. In 2016,

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

EPA's Office of Pesticide Programs released a guidance document entitled, *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)[1] and conducting cumulative risk assessments (CRA)[2]. During Registration Review, the agency will utilize this framework to determine if the available toxicological data for picarbutrazox 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.

11.0 Occupational Exposure/Risk Characterization

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

Occupational exposures are expected to occur from the proposed turf and seed-treatment uses of picarbutrazox. Dermal risks were not assessed since a dermal POD was not selected. Additionally, for inhalation exposures, the POD selected is considered protective of both short- and intermediate-term durations.

The quantitative exposure/risk assessment developed for occupational handlers is based on the scenarios presented in Table 11.1. Inhalation results are presented for "baseline," defined as no respirator. The proposed picarbutrazox labels require handlers to wear baseline attire (long-sleeved shirt, long pants, shoes, and socks), while chemical-resistant gloves are required for seed treatment uses. All handler scenarios resulted in MOEs greater than the LOC (MOEs $\geq$ 30) for baseline inhalation exposures, and therefore are not of concern.

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Picarbutrazox.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure[1] (µg/lb ai)	Maximum Application Rate[2]		Area Treated or Amount Handled Daily[3]		Inhalation	
							Dose[4] (mg/kg/day)	MOE[5] (LOC =30)
Mixer/Loader								
Dry Flowable, Aerial, Broadcast	Sod	8.96	0.33	lb ai/acre	350	acres	0.013	310
Dry Flowable, Chemigation, Broadcast	Sod	8.96	0.33	lb ai/acre	350	acres	0.0123	310
Dry Flowable, Groundboom, Broadcast	Golf course (tees and greens only)	8.96	0.33	lb ai/acre	5	acres	0.00019	22,000
Dry Flowable, Groundboom, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	8.96	0.33	lb ai/acre	5	acres	0.00019	22,000
Dry Flowable, Groundboom, Broadcast	Golf course (fairways, tees, greens)	8.96	0.33	lb ai/acre	40	acres	0.00145	2,700
Dry Flowable, Groundboom, Broadcast	Sod	8.96	0.33	lb ai/acre	80	acres	0.0030	1,400
Applicator								
Spray (all starting formulations), Aerial, Broadcast	Sod	0.0049	0.33	lb ai/acre	350	acres	0.0000071	560,000
Spray (all starting formulations), Groundboom, Broadcast	Golf course (tees and greens only)	0.34	0.33	lb ai/acre	5	acres	0.00000088	4,500,000
Spray (all starting formulations), Groundboom, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	0.34	0.33	lb ai/acre	5	acres	0.0000070	570,000
Spray (all starting formulations), Groundboom, Broadcast	Golf course (fairways, tees, greens)	0.34	0.33	lb ai/acre	40	acres	0.000056	71,000
Spray (all starting formulations), Groundboom, Broadcast	Sod	0.34	0.33	lb ai/acre	80	acres	0.00011	36,000
Flagger								
Spray (all starting formulations), Aerial, Broadcast	Sod	0.35	0.33	lb ai/acre	350	acres	0.00051	7,900

Table 11.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Picarbutrazox.

Exposure Scenario	Crop or Target	Inhalation Unit Exposure[1] (µg/lb ai)	Maximum Application Rate[2]		Area Treated or Amount Handled Daily[3]		Inhalation	
							Dose[4] (mg/kg/day)	MOE[5] (LOC =30)
Mixer/Loader/Applicator								
Dry Flowable, Backpack, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	69.1	0.0075	lb ai/gallon solution	40	gallons solution	0.00026	15,000
Dry Flowable, Backpack, Spot	Landscaping, turf (lawns, athletic fields, parks, etc.)	2.58	0.0075	lb ai/gallon solution	40	gallons solution	0.000010	410,000
Dry Flowable, Manually-pressurized Handwand, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	30	0.0075	lb ai/gallon solution	40	gallons solution	0.00011	35,000
Dry Flowable, Mechanically-pressurized Handgun, Broadcast	Golf course (tees and greens only)	42	0.33	lb ai/acre	5	acres	0.00087	4,600
Dry Flowable, Mechanically-pressurized Handgun, Broadcast	Golf course (fairways, tees, greens)	42	0.33	lb ai/acre	5	acres	0.00087	4,600
Dry Flowable, Mechanically-pressurized Handgun, Broadcast	Landscaping, turf (lawns, athletic fields, parks, etc.)	42	0.33	lb ai/acre	5	acres	0.00087	4,600
Seed Treatment								
Loader/Applicator	Corn	0.34	0.000099	lb ai/lb seed	339,500	lb seed	0.00014	28,000
	Soybean	0.34	0.000099	lb ai/lb seed	281,250	lb seed	0.00012	34,000
Sewer	Corn	0.23	0.000099	lb ai/lb seed	339,500	lb seed	0.000097	41,000
	Soybean	0.23	0.000099	lb ai/lb seed	281,250	lb seed	0.000080	50,000
Bagger	Corn	0.16	0.000099	lb ai/lb seed	339,500	lb seed	0.000067	59,000
	Soybean	0.16	0.000099	lb ai/lb seed	281,250	lb seed	0.000056	72,000
Multiple Activities	Corn	1.6	0.000099	lb ai/lb seed	339,500	lb seed	0.00067	5,900
	Soybean	1.6	0.000099	lb ai/lb seed	281,250	lb seed	0.00056	7,200
Planter	Corn, sweet	3.4	0.000099	lb ai/lb seed	6,638	lb seed	0.000011	360,000
	Corn, field	3.4	0.000099	lb ai/lb seed	5,915	lb seed	0.000025	160,000
	Soybean	3.4	0.000099	lb ai/lb seed	33,333	lb seed	0.000141	28,000

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 mitigation: Baseline (no respirator).

2 Based on proposed labels as summarized in Table 3.3.2.

3 ExpoSAC Policy #9.1 and Policy 14.
4 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 Daily (A or gal/day) or Amount of Seed treated or Planted per day ÷ BW (80kg).
5 Inhalation MOE = Inhalation NOAEL (4 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

11.2 Dermal Post-Application Exposure and Risk Estimates

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure. Although, there is potential for dermal post-application exposures to occur for workers entering picarbutrazox treated areas, dermal exposures were not assessed since dermal toxicity was not observed in the dermal toxicity study.

Restricted Entry Interval

Picarbutrazox is classified as Toxicity Category III via the dermal route and Toxicity Category IV for skin irritation potential. Picarbutrazox is not irritating to the eye and is not a skin irritant or sensitizer. Under 40 CFR 156.208 (c) (2), ai's classified as Acute III or IV for acute dermal, eye irritation and primary skin irritation are assigned a 12-hour REI.

Based on the acute toxicity categories and post-application assessment for picarbutrazox, the Worker Protection Standard (WPS) Interim REI is 12-hours. REIs may be further reduced if certain criteria are met in accordance with the Pesticide Registration (PR) Notice 95-3 [Reduction of WPS Interim REIs for Certain Low Risk Pesticides][4]. In PR Notice 95-3, there are a set of criteria listed for the ai that must be met for chemicals to be eligible for a reduced REI. These criteria include:

1. The ai is in Toxicity Category III or IV based upon data for acute dermal toxicity, acute inhalation toxicity, primary skin irritation, and primary eye irritation. Acute oral toxicity data were used if no acute dermal data were available. If EPA lacked data on primary skin irritation, acute inhalation, or primary eye irritation of the ai, the Agency reviewed data on that end-point for similar ai's (analogs), and excluded such ai's from consideration for the reduced REI, if the analog is in Toxicity Category I or II for that endpoint.
2. The ai is not a dermal sensitizer (or in the case of biochemical and microbial ai's, no known reports of hypersensitivity exist).
3. The ai is not a cholinesterase inhibitor (*N*-methyl carbamate and organophosphate) as these chemicals are known to cause large numbers of pesticide poisonings and have the potential for serious neurological effects.
4. No known reproductive, developmental, carcinogenic, or neurotoxic effects have been associated with the ai. If ai's did not have data available for these chronic health effects, EPA considered data on appropriate chemical and biological analogs. Ai's that have been classified as carcinogenic in Category B (probable human carcinogen) or Category

[4] Available: https://www.epa.gov/pesticide-registration/prn-95-3-reduction-worker-protection-standard-wps-interim-restricted-entry

C with a potency factor, Q* (possible human carcinogen, for which quantification of potential risk is considered appropriate), or are scheduled for HED's cancer peer review process, were omitted from consideration.

5. EPA does not possess incident information (illness or injury reports) that are "definitely" or "probably" related to post-application exposures to the ai.

Upon review of the criteria for the ai only, it appears that picarbutrazox is consistent with the criteria in PRN 95-3 that allow for a 4-hour REI. It should be noted that EPA Cancer Classifications were most recently updated in 2005, which differs in terminology as referenced above (i.e., Category B or Category C). Due to that change, the current classifications that would result in exclusion from reduced REI consideration are "Carcinogenic to Humans" and "Likely Carcinogenic to Humans." Picarbutrazox is currently classified as **"**Suggestive**"** and therefore meets the criteria for chemicals to be eligible for a reduced REI.

11.3 Inhalation 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 its FIFRA SAP in December 2009, and received the SAP's final report on March 2, 2010 (http://archive.epa.gov/scipoly/sap/meetings/web/pdf/120309meetingminutes.pdf). The Agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2014-0219-0003&disposition=attachment&contentType=pdf). 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 picarbutrazox.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the ARTF. 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.

For seed treatments, a post-application inhalation exposure assessment is not required as exposure is expected to be negligible. Seed treatment assessments provide quantitative inhalation exposure assessments for seed treaters and secondary handlers (i.e., planters). It is expected that these exposure estimates would be protective of any potential low-level post-application inhalation exposure that could result from these types of applications.

12.0 References

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Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.500) for food vs. nonfood uses for picarbutrazox 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	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	28-Day Dermal	yes	yes
870.3250	90-Day Dermal	yes[1]	-
870.3465	90-Day Inhalation	no[1-]	-
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	yes	yes
870.4100a	Chronic Toxicity (rodent)	no	-
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	no	-
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5xxx	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotoxicity (hen)	no	-
870.6100b	90-Day Neurotoxicity (hen)	no	-
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90-Day Neurotoxicity Screening Battery (rat)	no[1]	-
870.6300	Develop. Neurotoxicity	CR	-
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	yes	yes
870.7800	Immunotoxicity	no[1]	-
Non-guideline	Comparative Thyroid	no[1]	-

1- HED's Hazard Science and Policy Council (HASPOC) used a weight of evidence approach to recommend that a 90-day dermal toxicity, subchronic inhalation toxicity, subchronic neurotoxicity, immunotoxicity studies, as well as a comparative thyroid assay (CTA) are not required at this time (TXR 0057873, R. Louden, 07-JUN-2019).

A.2 Toxicity Profiles

Note: The submitted acute toxicity data are registered under TXR 5017272 (B. Backus, 20-AUG-2018) and TXR 5018148 (B. Backus, 26-AUG-2020).

Table A.2.1.A. Acute Toxicity Profile - Test Substance.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute Oral (rat)	50218527	LD_{50} > 2000 mg/kg (M & F)	III
870.1200	Acute Dermal (rat)	50218536	LD_{50} > 2000 mg/kg (M & F)	III
870.1300	Acute Inhalation (rat)	50218537	LC_{50} > 5.20 mg/L (M & F)	IV
870.2400	Primary Eye Irritation (rabbit)	50218538	Minimally irritating	IV
870.2500	Primary Skin Irritation (rabbit)	50218539	Not irritating	IV
870.2600	Dermal Sensitization (guinea pig)	50218540	Non-sensitizer (Maximization Test)	N/A

Table A.2.1.2.B. Acute Toxicity Profile – Metabolites.

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral (rat), TZ-1E	50218528	LD_{50} > 2000 mg/kg (F)	III
870.1100	Acute oral (rat), TZ-2*	50218529	LD_{50} > 300 mg/kg (F)	II
870.1100	Acute oral (rat), TZ-2*	50218530	LD_{50} > 2000 mg/kg (F)	III
870.1100	Acute oral (rat), TZ-2E	50218531	LD_{50} > 2000 mg/kg (F)	III
870.1100	Acute oral (rat), TZ-2-ß-Glc	50218532	LD_{50} > 2000 mg/kg (F)	III
870.1100	Acute oral (rat), TZ-4	50218533	LD_{50} > 2000 mg/kg (F)	III
870.1100	Acute oral (rat), TZ-5	50218534	LD_{50} > 300 mg/kg (F)	II
870.1100	Acute oral (rat), TY-2	50218535	LD_{50} > 300 mg/kg (F)	II
870.1100	Acute oral (rat), BPOH-NF-171	50218729	LD_{50} > 2000 mg/kg (F)	III
870.1100	Acute oral (rat), Me-NF-171	50218730	LD_{50} > 2000 mg/kg (F)	III
870.1100	Acute oral (rat), TT-1	51046510	LD_{50} > 2000 mg/kg (F)	III
870.1100	Acute oral (rat), TT-3	51046501	LD_{50} > 2000 mg/kg (F)	III

* Two studies were conducted on TZ-2. One study (MRID 50218529) a single rat died after dosing with 2000 mg TZ-2/kg and then a rat was dosed at 300 mg/kg. After this rat survived, an additional 5 rats were dosed at 300 mg/kg and all survived. In the second study (MRID 50218530) all 6 rats dosed with 2000 TZ-2/kg survived.

Note: The submitted guideline and mechanistic non-guideline studies are registered under TXR 0058004 (A. Dunbar, 20-NOV-2020).

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile.

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100	28-Day oral toxicity (mouse)	50218543 (2009) Acceptable/non-guideline 0, 70, 700, 7000 ppm M: 0, 9.86, 95.63, 1009.89 mg/kg/day F: 0, 14.11, 125.19, 1233.33 mg/kg/day	The NOAEL > 7,000 ppm (1009.89/1233.33 mg/kg/day [M/F]). Based on the lack of adverse effects at the highest dose tested. The LOAEL was not established.
870.3100	28-Day oral toxicity (CD rat)	50218542 (2009) Acceptable/non-guideline 0, 200, 2000, 20000 ppm M: 0, 15.1, 150.3, 1443.5 mg/kg/day F: 0, 16.5, 162.7, 1572.9 mg/kg/day	NOAEL = 200 ppm (15.1/16.5 mg/kg bw/day [M/F]). LOAEL = 2000 ppm (150.3/162.7 mg/kg bw/day [M/F]) based on alterations in hematology and clinical chemistry parameters, increases in liver and thyroid weights and histopathological lesions in the liver, thyroid and pituitary glands.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	28-Day oral toxicity (rat), TT-3 Metabolite	51046502 (2019) Acceptable/non-guideline 0, 800, 4000, or 20,000 ppm M: 0, 67.3, 339, or 1754 mg/kg/day F: 0, 69.9, 363, or 1805 mg/kg/day	NOAEL = 20,000 ppm (1754/1805 mg/kg/day [M/F]). The LOAEL was not determined.
870.3100	90-Day oral toxicity (mouse)	50218547 (2011) Acceptable/guideline 0, 200, 2000, 8000 ppm M: 0, 24.8, 254.0, 1088.3 mg/kg/day F: 0, 33.4, 347.0, 1327.5 mg/kg/day	NOAEL = 2000 ppm (254/347 mg/kg bw/day [M/F]). LOAEL = 8000 ppm (1088.3/1327.5 mg/kg bw/day [M/F]) based on increased liver weights and histopathological changes (focal inflammatory cell infiltration, generalized hepatocyte vacuolation, generalized hepatocyte hypertrophy and cytoplasmic inclusions).
870.3100	90-Day oral toxicity (CD rat)	50218545 (2014) Acceptable/guideline 0, 10, 150, 500, and 1,000 ppm M: 0, 3.5, 10.5, 34.5, and 68.1 mg/kg/day F: 0, 3.9, 12.0, 40.3, and 77.5 mg/kg/day	NOAEL = 150 ppm (10.5/12.0 mg/kg bw/day [M/F]). LOAEL is 500 ppm (34.5 mg/kg bw/day in males and 40.3 mg/kg bw/day [M/F]) based on increases in thyroid weights and thyroid hypertrophy (M/F).
870.3100	90-Day oral toxicity (SD rat)	50218546 (2010) Acceptable/guideline 0, 10, 20, 200, 1000 ppm (F only) M: 0, 0.3, 0.6, 1.2, 11.5 mg/kg/day F: 0, 0.7, 1.4, 14.1, 69.8 mg/kg/day	NOAEL = 200 ppm (11.5 mg/kg bw/day [M]). A LOAEL was not established. NOAEL = 200 ppm (14.1 mg/kg bw/day [F]). LOAEL = 1000 ppm (69.8 mg/kg bw/day [F]) based on increases of GGT level, increases in liver and thyroid weights, and histopathological lesions of the liver, thyroid and pituitary glands.
870.3100	90-Day oral toxicity (SD rat), TZ-1E Isomer	50218546 (2010) Acceptable/guideline 0, 50, 150, 500, 1000 ppm M: 0, 0.3, 0.6, 1.2, 11.5 mg/kg/day F: 0, 3.9, 11.6, 39.1 and 77.4 mg/kg/day	NOAEL > 1000 ppm (68.0/39.1 mg/kg bw/day [M/F]). No LOAEL was established in either sex. *There were no alterations in thyroid hormone levels
870.3100	90-Day oral toxicity (rat), TT-3 Metabolite	51046503 (2019) Acceptable/non-guideline 0, 800, 4000, or 20,000 ppm M: 0, 50.0, 242, and 1263 mg/kg/day F: 0, 55.8, 283, and 1433 mg/kg/day in males/females)	NOAEL = 20,000 ppm (1263/1433 mg/kg/day [M/F]). The LOAEL was not determined.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (SD rat), TZ-5 Isomer	50218549 (2017) Acceptable/guideline 0, 15, 150, 600, 2000, and 6000 ppm (females) M: 0, 0.9, 9.0, 36.3, and 121.7 mg/kg/day F: 11.3, 46.1, 153.5 and 457.8 mg/kg/day	NOAEL = 600 ppm (equivalent to 46.1 mg/kg bw/day [F]) and 2000 ppm (121.7 mg/kg bw/day [M]). The LOAEL = 2000 ppm (152.5 mg/kg/day [F]) based on decreases in body weight and food consumption. A LOAEL for males was not established.
870.3150	28-Day oral toxicity (dog)	50218550 (2012) Acceptable/non-guideline 0, 400, 4,000, or 20,000 ppm M: 0, 27.47, 110.05, 742.35 mg/kg/day F: 0, 25.27, 115.32, 581.18 mg/kg/day	The NOAEL > 20,000 ppm (742.35/581.18 mg/kg/day [M/F]). Based on the lack of adverse effects at the highest dose tested. The LOAEL was not established.
870.3150	90-Day oral toxicity (dog)	50218551 (2013) Acceptable/guideline 0, 400, 4,000, or 40,000 ppm M: 0, 13.3, 133.1, 1506 mg/kg/day F: 0, 13.5, 129.7, 1787.9 mg/kg/day	The NOAEL > 40,000 ppm (1506.0/1787.9 mg/kg/day [M/F]). Based on the lack of adverse effects at the highest dose tested. The LOAEL was not established.
870.3200	28-Day dermal toxicity (rat)	50218552 (2016) Acceptable/guideline 0, 100, 300, 1000 mg/kg/day	Dermal NOAEL = 1000 mg/kg/day. A LOAEL was not established. Systemic NOAEL = 1000 mg/kg/day. A LOAEL was not established.
870.3700a	Prenatal developmental in (rat)	50218558 (2011) Acceptable/guideline 0, 10, 100, 1000 mg/kg/day	**Maternal** NOAEL = 1000 mg/kg/day. **Maternal** LOAEL was not established. **Developmental** NOAEL = 1000 mg/kg/day. **Developmental** LOAEL was not established.
870.3700b	Prenatal developmental in (rabbit)	50218560 (2013) Acceptable/guideline 0, 10, 100, 500, 1000 mg/kg/day	**Maternal** NOAEL = 1000 mg/kg/day. **Maternal** LOAEL was not established. **Developmental** NOAEL = 1000 mg/kg/day. **Developmental** LOAEL was not established.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800	Reproduction and fertility effects (rat)	50218562 (2014) Acceptable/guideline 0, 20, 50, or 200, and 800 ppm P-M: 0, 1.2, 2.9, 11.6, and 46.4 mg/kg/day P-F: 0, 1.6, 4.0, 16.3, 62.6 mg/kg/day	**Parental/Systemic** NOAEL = 2.9/4.0 mg/kg/day. LOAEL = 11.6/16.3 mg/kg/day based on changes in T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F_1 females. **Reproductive** NOAEL = 46.4/62.6 mg/kg/day A LOAEL is not established. **Offspring** NOAEL = 11.6/16.3 mg/kg/day LOAEL = 46.4/62.6 mg/kg/day based on an increased incidence of thyroid hypertrophy in male and female F_2 pups and decreased body weight in F_2 pups.
870.4100b	Chronic toxicity (dog)	MRID 50218554 (2013) Acceptable/Guideline 0, 200, 1,500, or 10,000 ppm (0,5.1/5.2, 40.5/43.4, and 327/297.6 mg/kg/day [M/F])	NOAEL = 327/297.6 mg/kg/day. A LOAEL was not observed.
870.4200	Carcinogenicity (mouse)	MRID 5021855 (2013) Acceptable/Guideline 0, 30, 180 and 1,000 ppm (0,3.38/3.87, 21.1/23.2, and 116.8/133.5 mg/kg/day [M/F])	NOAEL = 180 ppm (21.1 mg/kg bw/day [M]). NOAEL = 1000 ppm (133.5 mg/kg/day [F]). LOAEL = 1000 ppm (116.8 mg/kg bw/day [M]) based on increases in liver weight and hepatotoxicity (portal inflammatory cell infiltration) in both sexes. A LOAEL in females was not established. **No evidence of carcinogenicity See CARC document (TXR 0057877, R. Louden, 21-AUG-2020).**
870.4300	Combined Chronic Carcinogenicity (rat)	MRID 5021856 (2013) Acceptable/Guideline 0, 60, 200 and 660 ppm 30 ppm was tested only in the toxicity phase (0,2.34/3.01, 7.82/10.16, and 26.90/34.6 mg/kg/day [M/F])	NOAEL = 60 ppm (2.34/3.01 mg/kg bw/day [M/F]). LOAEL = 200 ppm (7.82/10.16 mg/kg bw/day [M/F]) based on increased thyroid weights in males and thyroid hypertrophy in both sexes. **Evidence of carcinogenicity; treatment-related thyroid follicular cell tumors, driven by adenomas in male and female rats, and combined thyroid follicular adenomas/carcinomas in male rats See CARC document (TXR 0057877, R. Louden, 21-AUG-2020).**
Gene Mutation 870.5100	*In vitro* Bacterial Gene Mutation (Genotoxicity w/ Parent)	MRID 5021870 (2009) Acceptable/Guideline 0, 313, 625, 1,250, 2,500, and 5,000 µg/plate	There was no evidence of induced mutant colonies over background.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Gene Mutation 870.5100	*In vitro* Bacterial Gene Mutation (Genotoxicity w/ TZ-1E)	MRID 5021871 (2010) Acceptable/Guideline 0, 313, 625, 1,250, 2,500, and 5,000 µg/plate	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5100	*In vitro* Bacterial Gene Mutation (Genotoxicity w/ TZ-2)	MRID 5021872 (2013) Acceptable/Guideline 0, 313, 625, 1,250, 2,500, and 5,000 µg/plate	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5100	*In vitro* Bacterial Gene Mutation (Genotoxicity w/ TZ-2E)	MRID 5021873 (2013) Acceptable/Guideline 0, 156, 313, 625, 1,250, 2,500, and 5,000 µg/plate	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5100	*In vitro* Bacterial Gene Mutation (Genotoxicity w/ TY-2)	MRID 5021875 (2013) Acceptable/Guideline 0, 156, 313, 625, 1,250, 2,500, and 5,000 µg/plate	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5100	*In vitro* Bacterial Gene Mutation (Genotoxicity w/ TZ-4)	MRID 5021876 (2010) Acceptable/Guideline 0, 156, 313, 625, 1,250, 2,500, and 5,000 µg/plate	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5100	*In vitro* Bacterial Gene Mutation (Genotoxicity w/ TZ-5)	MRID 5021876 (2010) Acceptable/Guideline 0, 313, 625, 1,250, 2,500, and 5,000 µg/plate	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5100	*In vitro* Bacterial Gene Mutation (Genotoxicity w/ TT-1)	MRID 51046511 (2013) Acceptable/Guideline 313, 625, 1250, 2500, or 5000 µg/plate	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5100	*In vitro* Bacterial Gene Mutation (Genotoxicity w/ TT-1)	MRID 51046504 (2013) Acceptable/Guideline 313, 625, 1250, 2500, or 5000 µg/plate	There was no evidence of induced mutant colonies over background.
Mouse Lymphoma Assay 870.5300	*In vitro* mammalian cell gene mutation assay (TT-3)	MRID 51046505 (2018) Acceptable/Guideline 13.0, 25.9, 51.9, 104, 208, 415, 830, or 1660 µg/mL	There was no evidence of induced background gene mutations *in vitro*.
Gene Mutation 870.5375	*In Vitro* Microbial Gene Mutation (Impurity of Picarbutrazox)	MRID 5021876 (2013) Acceptable/Guideline 0, 313, 625, 1,250, 2,500, and 5,000 µg/plate	There was no evidence of induced mutant colonies over background.
Gene Mutation 870.5375	*In Vitro* Mammalian Cytogenetics Chromosome Aberration	MRID 5021879 (2014) Acceptable/Guideline 0, 31, 63, 125, 250, 500, and 1000 µg/ml with S9 metabolic activation 0, 16, 31, 63, 125, 250, and 500 µg/ml without S9 metabolic activation	NF-171 did not induce chromosomal aberrations with or without metabolic activation.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Gene Mutation 870.5375	*In vitro* mammalian clastogenicity (micronucleus) (TT-3)	-MRID 51046506 (2018) Acceptable/Guideline 0, 104, 208, 415, 830, or 1660 µg/mL for continuous 24 hour treatment.	Under the conditions tested in this study, there was no evidence of micronuclei induction *in vivo*.
Cytogenetics 870.5395	*In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus Assay in CD1 Mice (Parent)	MRID 5021880 (2013) Acceptable/Guideline 0, 500, 1,000, and 2,000 mg/kg bw/day	There was not a significant increase in the frequency of micronucleated polychromatic erythrocytes in bone marrow after 24 hours following two daily treatments.
Cytogenetics 870.5395	*In Vivo* Mammalian Cytogenetics - Erythrocyte Micronucleus Assay in CD1 Mice (TZ-4)	MRID 5021880 (2013) Acceptable/Guideline 0, 500, 1,000, and 2,000 mg/kg bw/day	Under the conditions tested in this study, there was no evidence of micronuclei induction *in vitro*.
Cytogenetics 870.5395	In vitro mammalian micronucleus assay (TT-1)	MRID 51046512 (2019) Acceptable/Guideline 0, 105, 210, 421, or 841 µg/mL with or without S9 metabolic activation	Under the conditions tested in this study, there was no evidence of micronuclei induction *in vivo*.
870.6200a	Acute neurotoxicity screening battery	MRID 50218541 (2014) Acceptable/Guideline 0, 125, 500, or 2,000 mg/kg bw/day	Neurotoxicity NOAEL = 2,000 mg/kg bw/day. Neurotoxicity LOAEL was not established based on the lack of toxicological findings. Systemic NOAEL = 2,000 mg/kg bw/day. Systemic LOAEL was not established based on the lack of toxicological findings.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7485	Metabolism and pharmacokinetics (rat), [phenyl-U-^{14}C]NF-171	MRID 50218585 (2013) Acceptable/Guideline 1 and 100 mg/kg bw/day MRID 50218586 (2013) Acceptable/Guideline 1 mg/kg bw/day	In bile duct-cannulated rats, 24 hours after single oral doses of 1 mg/kg picarbutrazox, 80.10% and 76.88% dose were excreted in the bile of male and female rats, respectively. Most of the biliary excretion occurred during the first 12 hours post dosing, accounting for 78.55% and 73.95% of the AD in males and females, respectively. During the first 24 hours post-dosing, 9.79% and 8.36% of the AD was excreted in the urine for males and females, respectively. Fecal excretion from 0-24 hours post-dosing accounted for 4.26% and 9.25% of the AD in males and females, respectively. Forty-eight hours after of a 100 mg/kg single oral dose of picarbutrazox, 22.70% and 13.77% AD were excreted in the bile of male and female rats, respectively. Radioactivity was excreted in bile throughout the 48-hour collection period, with the majority being excreted during the first 24 hours. Urinary excretion from 0-48 hours accounted for 1.87% and 0.86% dose in males and females, respectively. Fecal excretion from 0-48 hours accounted for 70.75% and 79.50% dose in males and females, respectively for non-bile-cannulated rats. The total absorbed was 85.90-90.63% AD at the 1 mg/kg dose level and 14.68-24.72% dose at the 100 mg/kg dose level, indicating a saturation of absorption with increasing dose. In terms of absorption kinetics, at 1 mg/kg, a peak mean plasma concentration (Cmax) of radioactivity of 0.039 µg equiv./g (males and females) was reached at 1 hour. At 100 mg/kg, peak mean plasma concentrations of radioactivity of 0.706 µg equiv./g (males) and 0.763 µg equiv./g (females) were reached at 4 and 6 hours post dosing, respectively. Concentrations of radioactivity in tissues were highest in the liver for both sexes and dose levels. There was no indication of tissue accumulation after single oral doses, with only low levels of radioactivity detected in tissues at 96 hours (<1% dose). Unchanged parent compound accounted for 2.2-2.7% dose at the 1 mg/kg dose level and 66.9-78.3% dose at the 100 mg/kg dose level.

Table A.2.2. Subchronic, Chronic, and Other Toxicity Profile.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.7600	Dermal penetration – *in vivo* rat	50218589 (2017) Acceptable/Guideline 0, 0.9348, 10.1 or 209.6 µg/cm^2 in males	The absorption of picarbutrazox following an 8-hour exposure period to either a Picarbutrazox 20 WG formulation (200 g NF-171/kg) or to one of the two aqueous spray strength dilutions (1/200: 1 g NF-171/L; 1/2000: 0.1 g NF-171/L) was low (i.e., approximately 1-5%, for the concentrate, 1/200 dilution and 1/2000 dilution, respectively). For all formulations, the small proportions of absorbed materials were excreted in urine and feces with no discernible accumulation in tissues or residual carcasses.
870.7600	Dermal penetration – *in vitro* human	50218587 Acceptable/Non-Guideline 0, 0.203, 0.0102, and 0.00088 mg ai/cm^2	The absorption rate of picarbutrazox through human dermatomed skin is limited and the vast majority of the total applied picarbutrazox is washed off the skin after 8 hours for all 3 dose levels with 95, 94, and 92% of the applied dose for the formulation concentrate, the 1/200 (w/v) dilution and the 1/2000 (w/v) dilution, respectively. The total picarbutrazox absorbed, including all tape strips, the remaining skin and the receptor fluid represented 6, 5, and 6% of the total applied dose for the formulation concentrate, the 1/200 (w/v) dilution and the 1/2000 (w/v) dilution, respectively.
870.7600	Dermal penetration – *in vitro* rat	50218588 Acceptable/Non- Guideline 0, 0.203, 0.0102, and 0.00088 mg ai/cm^2	The absorption rate of picarbutrazox through rat dermatomed skin is generally limited and that the vast majority of the applied picarbutrazox is washed off the skin after 8 hours from the formulation concentrate and the 1/200 (w/v) dilution with 96 and 89% of the applied dose, respectively. With the 1/2000 (w/v) dilution, that fraction was smaller with 35%. The total picarbutrazox absorbed, including all tape strips, the remaining skin and the receptor fluid represented approximately 5, 10, and 55% of the applied dose for the formulation concentrate, the 1/200 (w/v) dilution and the 1/2000 (w/v) dilution, respectively.

Table A.2.3. Mode-of-Action Studies.			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
Non-Guideline	NF-171 – Hepatic Drug-Metabolizing Enzyme Induction Study in Rats (7 and 14 days, and 14 days of recovery)	50218582 (2013) Acceptable/non-guideline 0, 60, 660, or 2,000 ppm 0, 5.6, 62.4 and 191.1 mg/kg bw/day (7-days [M]) 0, 5.3, 56.3, and 169.6 mg/kg bw/day (14-days [M]) 176.6 mg/kg bw/day (recovery period group [M])	NF-171 caused alterations in liver UDPGT expression and activities at 660 and 2000 ppm which led to marginal alterations in TSH, T3, and T4, increases in liver and thyroid weights, and increases in liver and thyroid hypertrophy. The effects subsided following cessation of treatment.
Non-Guideline	Influence of NF-171 on the Thyroid Peroxidase Activity Using Rat Thyroid Microsomal Fractions	50218583 (2015) Acceptable/non-guideline 0, 0.01, 0.1, 1, and 10 µM (NF-171) 0, 1, 10, and 100 µM (PTU)	NF-171 is not an inhibitor of rat thyroid peroxidase activity *in vitro*, based on the lack of any effect on relative TPO activity in the presence of NF-171.

A.3 Hazard Identification and Endpoint Selection

A.3.1 Acute Reference Dose (aRfD) – All Populations

An acute dietary risk assessment is not required. There is no evidence in the picarbutrazox hazard database of adversity from a single-dose effect.

A.3.2 Acute Reference Dose (aRfD)

An acute dietary risk assessment is not required. There is no evidence in the picarbutrazox hazard database of adversity from a single-dose effect for all populations including females of reproductive age.

A.3.3 Chronic Reference Dose (cRfD) `

Study Selected: Two-Generation (One Litter per Generation) Reproduction Study of NF-171 in Rats

MRID No.: 50218562

Executive Summary: In a two-generation reproduction study (OECD IIA 5.6.1/02, MRID 50218562) NF-171 [picarbutrazox (96.9% ai, Lot No. T3G-OK-P01)] was administered to 30 Crl:CD (Sprague- Dawley) rats/sex/dose in the diet at dose levels of 0, 20, 50, 200, and 800 ppm (equivalent to 0, 1.2/1.4, 2.9/4.0, 11.6/16.3, and 46.4/62.6 mg/kg bw/day [M/F] precohabitation through to termination of P males and females) in the P generation. For the F1 generation, the average daily consumed NF-171 for males (PPD 29 – 148)/females (PPD29 – 99, pre-mating period) was 1.3/2.0, 3.2/5.0, 13.0/19.9, and 52.8/75.0 mg/kg bw/day. Exposure began at

approximately six weeks of age, at least 70 days before cohabitation, and continuing until euthanasia for the P generation. For the F_1 generation, 30 male and 30 female pups were selected at PD21 (weaning) and exposed through the feed to the same test diets for at least 70 days before cohabitation until euthanasia.

In the P and F1 parental groups, no deaths related to NF-171 occurred. No test substance-related adverse clinical observations occurred in the exposure groups. Absolute body weights, body weight gains, absolute and relative food consumption values, mating, fertility, estrous cycling, sperm motility, sperm count, sperm morphology, pregnancy, natural delivery, litter observations, and gross necropsy observations were unaffected by exposure to NF-171 up to 800 ppm.

MRID 59018501 was submitted to account for the quality of the data and potential experimental difficulties in quantifying thyroid hormone levels. The registrant had difficulties with consistent quantification of TSH levels resulting in concurrent controls that were below the LLOQ of 4.00 ng/ml, making the data inconclusive and unreliable. All the T3 data were within the historical LLOQ of 25 ng/dL and the ULOQ of 800 ng/dL. All values were further within the historical control range presented in MRID 59018501. From 0 to 800 ppm, there was no change in T3 in either sex. All T4 measurements were within the LLOQ and ULOQ of 1.20 µg/dL and 24 µg/dL, respectively, though some samples were very near the LLOQ. The concurrent control measurements were all within the historical control ranges presented in MRID 59018501. For the P and F1 females, there were treatment-related decreases in T4 at 200 and 800 ppm (↓28%-↓47%). Though not robust, there were also decreases in the high dose P and F1 males (↓15% and ↓8%).

The absolute weight of the liver in the 800 ppm exposure groups were all statistically significantly increased compared to the carrier control group values (↑26% and ↑27%). At 200 ppm in the F1 males, absolute liver weights were statistically significantly increased (↑13%). In the P and F1 males, thyroid weights were increased at 800 ppm (↑13% and ↑58%). In the F1 males at 200 ppm, thyroid weights were statistically significantly increased (↑21%). The absolute weight of the liver in the 50 ppm exposure groups were all statistically significantly increased compared to the carrier control group values (↑5% and ↑10%). The absolute weight of the liver in the 200 ppm exposure groups were all statistically significantly increased compared to the carrier control group values (↑22% and ↑24%). The absolute weight of the liver in the 800 ppm exposure groups were all statistically significantly increased compared to the carrier control group values (↑58% and ↑67%). The absolute weight of the thyroid (with parathyroid) and ratio of this organ weight to the terminal body weight was statistically significantly reduced in the 20 ppm (~↓30%) and higher exposure groups compared to the carrier control group value (0.066 g). In the F1 females, thyroid weights were increased at 200 ppm and 800 ppm (↑18% and ↑61%). In the F1 males at 200 ppm, thyroid weights were statistically significantly increased (↑21%). In the P males, dietary administration of 200 or 800 ppm NF-171 resulted in test substance-related hypertrophy of the thyroid gland (37% and 83% vs. 0% in the control). Hepatocellular hypertrophy in the 800-ppm dose group was test substance-related (47% vs. 0% in the control). Dietary administration of 200 or 800 ppm NF-171 resulted in test substance-related hypertrophy of the thyroid gland (48% and 74% vs. 0% in the control). Follicular cells were columnar with the nucleus occupying about one third of the cell height. Hepatocellular hypertrophy in the 800-ppm exposure group was test substance related (22% vs. 0% in the control). The number of rats

with minimal periportal hypertrophy was significantly increased in the 800-ppm exposure group compared to the control group value.

In the F1 males, hypertrophy of the thyroid gland in the F_1 generation male rats was considered related to NF-171 in the 200 ppm and 800 ppm exposure groups (23% and 52% vs. 0% in the control). All findings were noted as minimal. The overall incidence was statistically significantly increased in the 200 and 800 ppm exposure groups. Hypertrophy in the liver was test substance related in males fed NF-171 at 200 and 800 ppm (30% and 59%). The number of rats with periportal hypertrophy was statistically significantly increased in the 200 and 800 ppm exposure groups compared to the control group value. Hypertrophy of the thyroid gland in the F_1 generation female rats was considered related to NF-171 in the 200 and 800 ppm exposure groups. All findings were noted as minimal (43% and 63% vs. 0% in the control). Hypertrophy in the liver was considered to be related to NF-171 in female rats exposed to NF-171 at 800 ppm (33% vs. 0% in the control).

For parental/systemic toxicity, the LOAEL is 200 ppm (11.6/16.3 [M/F]). The LOAEL is based on decreased T4 levels in females, increased thyroid weights in both sexes, and increased incidences of thyroid hypertrophy in both sexes. The NOAEL is 50 ppm (2.9/4.0 mg/kg/day [M/F]).

In the F_1 pups, the number of pups that had purple, black and or pale areas on the head, body (chest, lower midline) or tail was significantly increased in the 800-ppm exposure group. No other adverse clinical observations or necropsy observations in the F_1 generation pups from birth to Day 21 postpartum were attributable to maternal exposure to NF-171 at concentrations up to and including 800 ppm. The absolute weight of the brain, spleen, thymus, and uterus was comparable among the groups for the male and female pups. The absolute weight of the liver was statistically significantly increased in the 800 ppm exposure group male pups and increased in the female pups compared to the carrier control group value but was not considered adverse since it did not correlate with any histopathological findings

In F_2 pups, no adverse clinical or necropsy observations in the F_2 generation pups from birth to Day 21 postpartum were attributable to maternal exposure to NF-171 at concentrations up to and including 800 ppm. Pup body weight was slightly decreased (7%-9%) on lactation days 14 and 21. The absolute weight of the brain, thymus and thyroid was comparable among the groups for the F_2 generation male and female pups. The absolute weight of the liver was statistically significantly increased in the 200-ppm exposure group male pups and in the 200 and 800 ppm exposure group female pups compared to the carrier control group value. In addition, the weight of the spleen in the 800-ppm exposure group female pups was statistically significantly reduced compared to the carrier control group value. Oral (lactational) administration of NF-171 to F_2 generation rats resulted in a test substance-related increased incidence of a microscopic finding in the thyroid gland (hypertrophy) at 800 ppm (15% in males and 22% in females vs. 0% in the control) and at 200 ppm (7% in females only, not statistically significant).

For offspring toxicity, the LOAEL is 800 ppm based on an increased incidence of thyroid hypertrophy in male and female F_2 pups and decreased body weight in F_2 pups. The

NOAEL is 200 ppm. These values are analogous to the parental/systemic NOAEL and LOAEL.

There were no treatment-related effects on fertility or reproductive parameters in either generation.

For reproductive toxicity, the NOAEL is 800 ppm, the highest dose tested (P generation: 46.4 mg/kg bw/day in males and 62.6 mg/kg bw/day in females; F_1 generation: 52.8 mg/kg bw/day in males and 75.0 mg/kg bw/day in females). A LOAEL is not established.
Deficiencies: There were no significant deficiencies.

This reproduction and fertility effects study in the rat is **acceptable/guideline** and satisfies the guideline requirement for a reproduction and fertility effects toxicity study (OCSPP 870.3800; OECD 416) in rats.

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

Dose and Endpoint for Risk Assessment: For parental/systemic toxicity, the LOAEL is 200 ppm (11.6/16.3 [M/F]). The LOAEL is based on decreased T4 levels in females, increased thyroid weights in both sexes, and increased incidences of thyroid hypertrophy in both sexes. The NOAEL is 50 ppm (2.9/4.0 mg/kg/day [M/F]).

Comments about Study/Endpoint/Uncertainty Factors: The cPAD of 0.13 mg/kg/day was derived from the parental NOAEL of 4 mg/kg/day and a 30-fold UF (3X for inter-species extrapolation, 10X for intra-species variation, and 1X for FQPA SF). The LOAEL of 11.6/16.3 mg/kg/day [M/F] is based on changes in T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F1 females. This study is appropriate since the effects of concern were seen following repeated oral exposure via the diet. Based upon dose spacing, it is protective of the thyroid effects in the combined chronic/carcinogenicity study which are seen at similar doses. It is further protective of all other effects seen following chronic exposure as well as the offspring effects observed in the reproduction toxicity study.

A.3.4 Incidental Oral Exposure (Short-Term)

Study Selected: Two-Generation (One Litter per Generation) Reproduction Study of NF-171 in Rats
MRID No.: 50218562
Executive Summary: Same as for chronic dietary endpoint
Comments about Study/Endpoint/Uncertainty Factors: The short-term incidental oral endpoints were derived from the multigeneration reproductive toxicity study in rats. The parental NOAEL of 4 mg/kg/day and a 30-fold UF (3X for inter-species extrapolation, 10X for intra-species variation, and 1X for FQPA SF) was selected for the POD. The LOAEL of 11.6/16.3 mg/kg/day [M/F] is based on changes in T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F1 females. The LOC is 30 based on interspecies extrapolation (3X), intraspecies variation (10X), and the 1X FQPA SF. This study is protective

for all other subchronic rat and mouse effects observed across the database. Finally, it is protective of the general population in residential settings, workers in occupational settings, and is appropriate for the subchronic duration.

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

No dermal endpoints were selected. The dermal study conducted histopathological examination of the main target organs identified in oral studies (thyroid and liver) and collected organ weight information. No systemic effects were observed in the dermal study up to the limit dose. Dermal triple pack data are available indicating low dermal absorption potential (refined DAF =1%) and there is no evidence of increased quantitative susceptibility in the young. Finally, the offspring effects observed in the developmental and reproductive toxicity studies occurred only in the presence or at higher doses comparable maternal/parental toxicity.

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

Study Selected: Two-Generation (One Litter per Generation) Reproduction Study of NF-171 in Rats
MRID No.: 50218562

Executive Summary: Same as for chronic dietary endpoint

Comments about Study/Endpoint/Uncertainty Factors: A route-specific inhalation study is not available for picarbutrazox. The HASPOC recommended that the study is not required at this time (TXR 0057873, R. Louden, 07-JUN-2019) based upon the chemical's current overall hazard and exposure profiles. As a result, an oral endpoint was selected to evaluate inhalation exposures. The short- and intermediate-term inhalation endpoints were derived from the multigeneration reproductive toxicity study in rats. The parental NOAEL of 4 mg/kg/day and a 30-fold UF (3X for inter-species extrapolation, 10X for intra-species variation, and 1X for FQPA SF) was selected as the POD. The LOAEL of 11.6/16.3 mg/kg/day [M/F] based on changes in T4, increased thyroid weights, and incidences of thyroid hypertrophy in the P and F1 females. The LOC is 30 based on interspecies extrapolation (3X), intraspecies variation (10X), and the 1X FQPA SF in residential settings. Inhalation exposure is assumed to be equivalent to oral. This study is protective for all other subchronic rat and mouse effects observed across the database. Finally, it is protective of the general population in residential settings, workers in occupational settings, and is appropriate for the subchronic duration.

A.3.7 Carcinogenicity (All Routes)

In accordance with the EPA's *Final Guidelines for Carcinogen Risk Assessment* (March 2005), the CARC classified picarbutrazox as "Suggestive Evidence of Carcinogenic Potential" based upon thyroid follicular cell tumors, driven by adenomas in male and female rats, and combined thyroid follicular adenomas/carcinomas in male rats (TXR 0057877, R. Louden, 21-AUG-2020). The MOA data for thyroid tumors is not established by the data submitted. No treatment-related

tumors were seen in mice. Both studies had adequate dosing, and there was no concern for genotoxicity or mutagenicity.

The Agency has determined that quantification of risk using a non-linear approach (i.e., cRfD) will adequately account for all chronic toxicity, including potential carcinogenicity, that could result from exposure to picarbutrazox.

13.0 Appendix B. Metabolism Summary Table

Table B.1. Tabular Summary of Metabolites and Degradates.

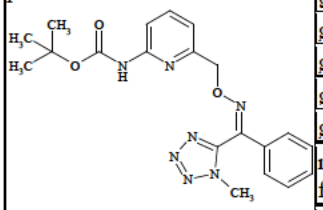
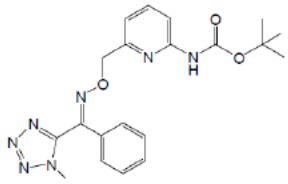
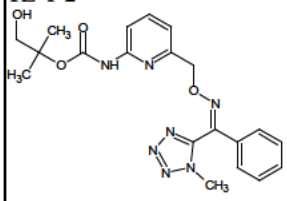
Chemical Name and Structure (see D447984 for IUPAC chemical name)	Matrix	Percent TRR (ppm)	
		Major Residue (>10% TRR)	Minor Residue (<10% TRR)
picarbutrazox 	maize - forage	--	--
	maize -grain (not analyzed (NA); TRR = 0.001 ppm)	--	--
	maize - stalk (NA; TRR = ≤0.003 ppm)	--	--
	leaf lettuce	42-99 (0.841-4.104)	--
	cucumber	6-87 (<0.001-0.127)	
	poultry	--	--
	goat - fat	<47 (<0.041)	--
	goat - muscle	≤25 (≤0.008)	--
	goat - kidney	--	2 (≤0.003)
	goat - liver	--	3 (≤0.016)
	goat - milk	≤16 (≤0.003)	--
	rotational crop - leaf lettuce, radish top/root, wheat forage/hay/straw/grain (~30-, ~120-, ~275-day PBI)	--	≤3 (≤0.009)
	rat - bile and urine	--	--
	rat - plasma	--	≤5 (≤0.002)
	rat - liver	≤13 (≤0.121)	--
	rat - kidney	--	≤9 (≤0.011)
	rat - fat	≤17 (≤0.056)	--
	rat feces	high dose - 67-78	low dose - 2-6
TZ-1E 	poultry, ruminant, rotational crops, rat	--	--
	maize - forage	--	--
	maize -grain (NA; TRR = 0.001 ppm)	--	--
	maize - stalk (NA; TRR = ≤0.003 ppm)	--	--
	leaf lettuce	ND-55 (≤3.143)	--
	cucumber	7-64 (0.001-0.028)	--
TZ-1-2 	primary crops, rotational crops, poultry	--	--
	goat - fat	--	<2 (<0.002)
	goat - muscle	≤16 (≤0.003)	--
	goat - kidney	--	≤3 (≤0.003)
	goat - liver	--	≤8 (≤0.036)
	goat - milk	--	--
	rat - bile	--	--
	rat - plasma	--	--
	rat - liver	≤24 (≤0.357)	--
	rat - kidney	≤35 (≤0.069)	--
	rat- fat	≤48 (≤0.155)	--
	rat - urine	--	--
	rat -feces	--	--

Table B.1. Tabular Summary of Metabolites and Degradates.

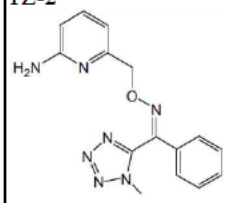
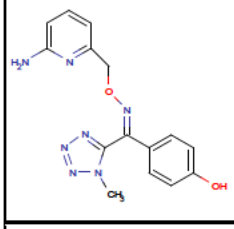
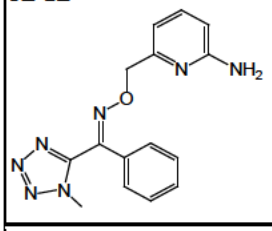
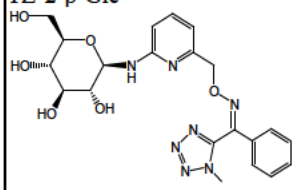
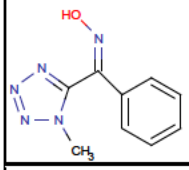
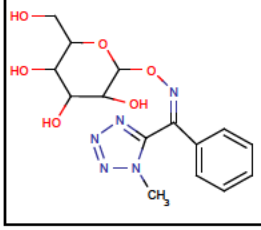
Chemical Name and Structure (see D447984 for IUPAC chemical name)	Matrix	Percent TRR (ppm)	
		Major Residue (>10% TRR)	Minor Residue (<10% TRR)
TZ-2 	poultry, ruminant, rat	--	--
	maize - forage	--	--
	maize -grain (NA; TRR = 0.001 ppm)	--	--
	maize - stalk (NA; TRR = ≤0.003 ppm)	--	--
	leaf lettuce	--	--
	cucumber	--	<1 (<0.001)
	rotational crop - leaf lettuce, radish top/root, wheat forage/hay/grain (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	--	≤1 (≤0.005)
TZ-2-3 	primary crops, rotational crops, poultry, ruminant	--	--
	rat - bile	--	<6
	rat - plasma	--	≤7 (≤0.002)≤
	rat - liver	--	≤3 (≤0.041)
	rat - kidney	≤11 (≤0.016)	--
	rat - fat	--	--
	rat - urine	--	--
	rat -feces	--	≤4
TZ-2E 	primary crops, poultry, ruminant, rat	--	--
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	--	≤1 (≤0.001)
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	--	<1 (<0.001)
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	--	≤1 (≤0.001)
	rotational crop - wheat hay (~30-, ~120-, ~275-day PBI)	--	≤1 (≤0.009)
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	--	≤1 (≤0.008)
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	--	--
TZ-2-β-Glc 	primary crops, poultry, ruminant, rat	--	--
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)	≤34 (≤0.015)	--
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	≤37 (≤0.030)	--
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	--	≤1 (≤0.001)
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	≤39 (≤0.069)	
	rotational crop - wheat hay (~30-, ~120-, ~275-day PBI)	≤14 (≤0.090)	
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	--	≤4 (≤0.024)
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	--	--
TZ-3 	primary crops, rotational crops, poultry, ruminant	--	--
	rat - urine	--	<1
	rat -feces, bile, plasma, liver, kidney, fat	--	--
TZ-3 Glu 	primary crops, rotational crops, poultry, ruminant	--	--
	rat - urine	--	≤5
	rat -feces, bile, plasma, liver, kidney, fat	--	--

Table B.1. Tabular Summary of Metabolites and Degradates.

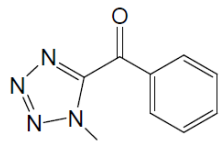
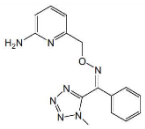
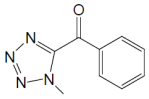
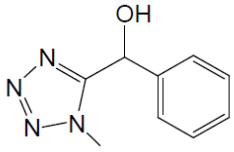
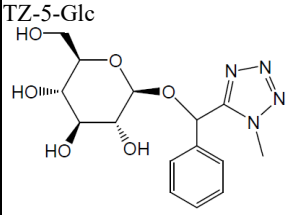
Chemical Name and Structure (see D447984 for IUPAC chemical name)	Matrix	Percent TRR (ppm)	
		Major Residue (>10% TRR)	Minor Residue (<10% TRR)
TZ-4 	poultry, ruminant, rotational crops, rat	--	--
	maize - forage	--	--
	maize -grain (NA; TRR = 0.001 ppm)	--	--
	maize - stalk (NA; TRR = ≤0.003 ppm)	--	--
	leaf lettuce	--	--
	cucumber	--	ND-0.5 (<0.001)
TZ-2  and TZ-4 	primary crops, poultry, ruminant, rat	--	--
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)	--	≤1 (≤0.001)
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	--	≤1 (≤0.005)
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	--	≤2 (≤0.002)
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	--	<1 (≤0.002)
	rotational crop - wheat hay (~30-, ~120-, ~275-day PBI)	--	≤3 (≤0.058)
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	--	≤2 (≤0.024)
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	--	--
TZ-5 	poultry, ruminant, rat	--	--
	maize - forage	21-53 (≤0.004)	--
	maize -grain (NA; TRR = 0.001 ppm)	--	--
	maize - stalk (NA; TRR = ≤0.003 ppm)	--	--
	leaf lettuce	--	ND-1 (≤0.066)
	cucumber	ND-18 (≤0.003)	--
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)	≤43 (≤0.126)	--
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	≤70 (≤0.571)	--
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	≤22 (≤0.013)	--
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	≤27 (≤0.293)	--
	rotational crop - wheat hay (~30-, ~120-, ~275-day PBI)	≤26 (≤0.366)	--
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	≤23 (≤0.369)	--
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	≤10 (≤0.006)	--
TZ-5-Glc 	poultry, ruminant, rat	--	--
	maize - forage (PH)	43 (0.003)	--
	maize -grain (NA; TRR = 0.001 ppm)	--	--
	maize - stalk (NA; TRR = ≤0.003 ppm)	--	--
	leaf lettuce	--	ND-0.6 (≤0.032)
	cucumber	--	ND-6 (≤0.001)
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)	≤32 (≤0.070)	--
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	≤10 (≤0.090)	--
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	--	2 (≤0.003)
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	≤35 (≤0.389)	--
	rotational crop - wheat hay (~30-, ~120-, ~275-day PBI)	≤18 (≤0.298)	--
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	≤19 (≤0.343)	--
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	--	--

Table B.1. Tabular Summary of Metabolites and Degradates.

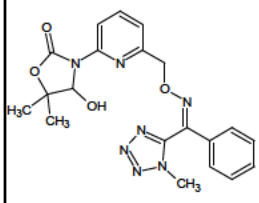
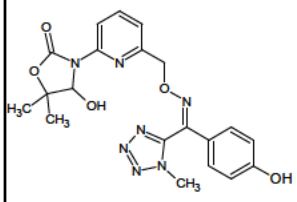
Chemical Name and Structure (see D447984 for IUPAC chemical name)	Matrix	Percent TRR (ppm)	
		Major Residue (>10% TRR)	Minor Residue (<10% TRR)
TZ-5-Glc2 (different sugar from TZ-5-Glc)	primary crops, poultry, ruminant, rat	--	--
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)	<26 (<0.062)	--
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - wheat hay (~30-, ~120-, ~275-day PBI)	--	≤6 (≤0.016)
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	--	--
TZ-5-OH-Glc (TZ-5-Glc hydroxylated on the phenyl ring)	primary crops, poultry, ruminant, rat	--	--
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)		--
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	≤11 (≤0.060)	--
	rotational crop - wheat hay (~30-, ~120-, ~275-day PBI)	--	≤4 (≤0.071)
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	--	≤7 (≤0.112)
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	--	≤8 (≤0.005)
TZ-7 	primary crops and rotational crops	--	--
	poultry - egg white	≤79 (≤0.008)	--
	poultry - egg yolk	≤19 (≤0.002)	--
	poultry - liver	--	--
	poultry - muscle (NA; TRR = ≤0.002 ppm)	--	--
	poultry - fat (NA; TRR = ≤0.005 ppm)	--	--
	goat - fat	<35 (<0.043)	--
	goat - muscle	38 (≤0.013)	--
	goat - kidney	--	≤8 (≤0.010)
	goat - liver	≤30 (≤0.184)	--
	goat - milk	≤16 (≤0.003)	--
	rat - bile	--	--
	rat - plasma	≤18 (≤0.007)	--
	rat - liver	--	≤8 (≤0.121)
	rat - kidney	≤11 (≤0.023)	--
	rat- fat	≤28 (≤0.022)--	--
	rat - urine	--	--
	rat - feces	--	≤6
TZ-7-3 	primary crops, poultry, rotational crops	--	--
	goat - fat	--	--
	goat - muscle	--	--
	goat - kidney	--	--
	goat - liver	--	≤2 (≤0.014)
	goat - milk	--	--
	rat - bile	--	<2
	rat - plasma	--	≤8 (≤0.003
	rat - liver	≤26 (≤0.241)	--
	rat - kidney	≤16 (≤0.018)	--
	rat- fat	--	≤6 (≤0.005)
	rat - urine	--	<1
	rat - feces	low dose - 25	high dose - 4-6

Table B.1. Tabular Summary of Metabolites and Degradates.

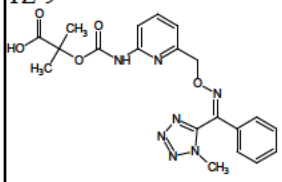
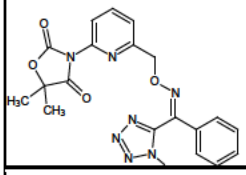
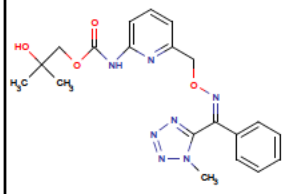
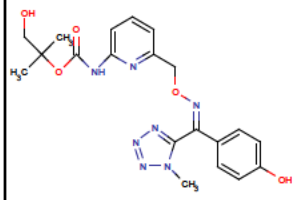
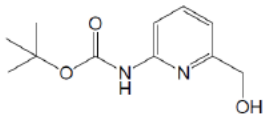
Chemical Name and Structure (see D447984 for IUPAC chemical name)	Matrix	Percent TRR (ppm)	
		Major Residue (>10% TRR)	Minor Residue (<10% TRR)
	primary crops, rotational crops	--	--
	poultry - egg white	≤23 (≤0.002)	--
	poultry - egg yolk	≤11 (≤0.001)	--
	poultry - liver	≤44 (≤0.020)	--
	poultry - muscle (NA; TRR = ≤0.002 ppm)	--	--
	poultry - fat (NA; TRR = ≤0.005 ppm)	--	--
TZ-9 	goat - fat	--	<8 (<0.009)
	goat - muscle	--	--
	goat - kidney	≤27 (≤0.024)	--
	goat - liver	≤21 (≤0.060)	--
	goat - milk	≤87 (≤0.015)	--
	rat - bile	--	--
	rat - plasma	≤9 (≤0.003)	--
	rat - liver	≤14 (≤0.203)	--
	rat - kidney	≤16 (≤0.019)	
	rat- fat	--	--
	rat - urine	--	≤1
	rat - feces		≤6
TZ-10 	primary crops, poultry, rotational crops, rat	--	--
	goat - fat	--	<8 (<0.009)
	goat - muscle	≤15 (≤0.005)	--
	goat - kidney	--	2 (≤0.003)
	goat - liver	≤16 (≤0.096)	--
	goat - milk	≤10 (≤0.002)	--
TZ-8 	primary crops, rotational crops, poultry, ruminant	--	--
	rat - bile	--	≤2
	rat - plasma	≤26 (≤0.010)	
	rat - liver	≤10 (≤0.092)	
TZ-1-23 	rat - kidney	≤12 (≤0.014)	
	rat- fat		≤6 (≤0.019)
	rat - urine	--	--
	rat -feces	low dose - 10-13	high dose - 2-5
TY-1 	poultry, ruminant, rotational crops, rat	--	--
	maize - forage	--	--
	maize -grain (NA; TRR = 0.001 ppm)	--	--
	maize - stalk (NA; TRR = ≤0.003 ppm)	--	--
	leaf lettuce	--	--
	cucumber	--	ND-0.5 (<0.001)

Table B.1. Tabular Summary of Metabolites and Degradates.

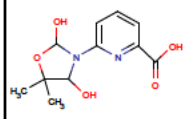
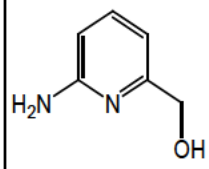
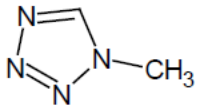
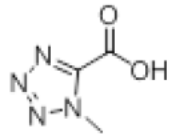
Chemical Name and Structure (see D447984 for IUPAC chemical name)	Matrix	Percent TRR (ppm)	
		Major Residue (>10% TRR)	Minor Residue (<10% TRR)
TY-7 	primary crops, rotational crops, poultry, ruminant	--	--
	rat - urine	--	4
	rat -feces, rat -feces, bile, plasma, liver, kidney, fat	--	--
TY-2 	primary crops, poultry, ruminant, rat	--	--
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	≤10 (≤0.007)	--
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - wheat hay (~30-, ~120-, ~275-day PBI)	--	≤5 (≤0.033)
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	--	≤3 (≤0.018)
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	--	--
TT-1 	poultry, ruminant, rat	--	--
	maize - forage	10 (<0.001)	--
	maize -grain (NA; TRR = 0.001 ppm)	--	--
	maize - stalk (NA; TRR = ≤0.003 ppm)	--	--
	leaf lettuce	--	--
	cucumber	--	--
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)	--	--
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	≤16(≤0.042)	--
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	--	≤2(≤0.007)
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	--	≤7(≤0.105)
	rotational crop - wheat hay (~30-, ~120-, ~275-day PBI)	≤41(≤1.306)	--
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	≤21(≤0.686)	--
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	≤(16≤0.356)	--
TT-3 	poultry, ruminant, rat, primary crops	--	--
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)	≤52(≤0.319)	≤(≤)
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	≤55(≤0.378)	≤(≤)
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	≤28(≤0.113)	≤(≤)
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	≤64(≤1.686)	≤(≤)
	rotational crop - wheat hay (~30-, ~120, ~275-day PBI)	≤63(≤2.806)	≤(≤)
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	≤45(≤2.248)	≤(≤)
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	≤29(≤0.641)	≤(≤)
TZ-5-Glc/TT-3; compounds were not resolved in the maize metabolism study (51046518.der)	poultry, ruminant, rotational crops, rat	--	--
	maize - forage	67 (0.001)	
	maize -grain (NA; TRR = 0.001 ppm)	--	--
	maize - stalk (NA; TRR = ≤0.003 ppm)	--	--
	leaf lettuce	--	--
	cucumber	--	--

Table B.1. Tabular Summary of Metabolites and Degradates.

Chemical Name and Structure (see D447984 for IUPAC chemical name)	Matrix	Percent TRR (ppm)	
		Major Residue (>10% TRR)	Minor Residue (<10% TRR)
unknown	maize - forage	ND-102 (≤0.003)	--
	maize -grain (NA; TRR = 0.001 ppm)	--	--
	maize - stalk (NA; TRR = ≤0.003 ppm)	--	--
	leaf lettuce	--	≤3 (≤0.074 ppm)
	cucumber	≤38 (≤0.004)	--
	poultry - egg white	--	--
	poultry - egg yolk	≤26 (≤0.004)	--
	poultry - liver	≤13 (≤0.004)	--
	poultry - muscle (NA; TRR = ≤0.002 ppm)	--	--
	poultry - fat (NA; TRR = ≤0.005 ppm)	--	--
	goat - fat	--	≤5 (≤0.004)
	goat - muscle	--	≤7 (≤0.001)
	goat - kidney	--	≤8 (≤0.009)
	goat - liver	--	≤7 (≤0.045)
	goat - milk	--	≤7 (0.001)
	rotational crop - leaf lettuce (~30-, ~120-, ~275-day PBI)	≤18 (≤0.009; PH&PY) ≤18(≤0.020 T)	--
	rotational crop - radish top (~30-, ~120-, ~275-day PBI)	≤12 (≤0.101; PH&PY) ≤19(≤0.133; T)	--
	rotational crop - radish root (~30-, ~120-, ~275-day PBI)	≤27(≤0.090; T)	≤7 (≤0.007; PH&PY)
	rotational crop - wheat forage (~30-, ~120-, ~275-day PBI)	≤28(≤0.196; T)	≤7 (≤0.034; PH&PY)
	rotational crop - wheat hay (~30-, ~120-, ~275-day PBI)	≤12(≤0.510; T)	≤7 (≤0.056; PH&PY)
	rotational crop - wheat straw (~30-, ~120-, ~275-day PBI)	≤14 (≤0.043; PH&PY) ≤10(≤0.378; T)	--
	rotational crop - wheat grain (~30-, ~120-, ~275-day PBI)	≤21(≤0.468; T)	≤7 (≤0.002; PH&PY)
	rat - bile	20-36 (1 unknown)	≤10 (12 unknowns)
	rat - plasma	<1-49 (1 unknown)	≤11 (5 unknowns)
	rat - liver	≤1-27 (1 unknown)	≤7 (5 unknowns)
	rat - kidney	--	≤9 (7 unknowns)
	rat- fat	--	--
	rat urine	--	≤6
	rate feces	≤16	--

The plant (primary and rotational) metabolism studies used phenyl (PH), pyridine (PY), and tetrazole (T) radiolabeled picarbutrazox and the livestock metabolism studies used PH and PY radiolabeled picarbutrazox. The following is a summary of application and dosing scenario.

maize - 50218702.der and 51046518.der; seed treatment at 17.8-23.3 g ai/100 kg seed (1.8-2.3x); corn forage harvested 35 days after planting and mature corn stalks, cobs, and grain were harvested 131-168 days after planting.

lettuce - 50218699.der and 51046514.der; three broadcast foliar applications at 0.090-0.101 lb ai/acre; RTI = 5-7 days; samples were harvested just prior to the second application and 2, 7, and/or 14 days after the third application.

cucumbers - 50218701.der and 51046513.der; three broadcast foliar applications at 0.084-0.106 lb ai/acre; RTI = 5-7 days; samples were harvested just prior to the second application and 0 and 1, 7, and/or 14 days after the third application.

poultry - 50218703.der; dosed orally by gelatin capsule daily for 14 consecutive days at a dietary burden of 11.018-12.635 ppm (1102-1264x MRDB).

goat - 50218704.der; dosed orally by gelatin capsule daily for 7 consecutive days at a dietary burden of 20.322-22.580 ppm (1016-1129x MRDB).

confined rotational crops - 50218705.der and 51046517.der; single application to bare soil at 0.91-1.00 lb ai/acre (≥54x).

rat - MRIDs 50218585 and 50218586; phenyl radiolabeled picarbutrazox dosed orally at 1 and 100 mg/kg; pyridine radiolabeled dosed orally at 1 mg/kg. Residue identification was performed in urine and feces samples from both studies and doses and in plasma and tissue samples from the phenyl study (1 mg/kg dose).

14.0 Appendix C. Residue Summary Table

Table C.1. Summary of Field Trial Residues.

Crop Matrix	Analyte	Total App. Rate	PHI (days)[2]	n[3]	Residues[1] (ppm)						
					Min.	Max.	LAFT	HAFT	Median	Mean	SD
Sweet Corn, Field Corn, and Popcorn (Proposed Use = 10 g ai/100 kg seed)											
K+CWHR, Forage, Grain, and/or Stover	NF-171[4]	8.9-11.1 g ai/100 kg seed	NCH[2]	16	<0.005	<0.005	<0.005	<0.005	0.005	0.005	NA
	TZ-1E				<0.005	<0.005	<0.005	<0.005	0.005	0.005	NA
	Combined NZ-171[4] + TZ-1E				<0.010	<0.010	<0.010	<0.010	0.010	0.010	NA
	TZ-5				<0.011	<0.011	<0.011	<0.011	0.011	0.011	NA
	TZ-5-Glc				<0.006	<0.006	<0.006	<0.006	0.006	0.006	NA
	Total[4]				<0.027	<0.027	<0.027	<0.027	0.027	0.027	NA
Field Corn Grain	NF-171[4]	28.0-32.8 g ai/100 kg seed	NCH[2]	2	<0.005	<0.005	<0.005	<0.005	0.005	0.005	NA
	TZ-1E				<0.005	<0.005	<0.005	<0.005	0.005	0.005	NA
	Combined NZ-171[4] + TZ-1E				<0.010	<0.010	<0.010	<0.010	0.010	0.010	NA
	TZ-5				<0.011	<0.011	<0.011	<0.011	0.011	0.011	NA
	TZ-5-Glc				<0.006	<0.006	<0.006	<0.006	0.006	0.006	NA
	Total[4]				<0.027	<0.027	<0.027	<0.027	0.027	0.027	NA
Soybean (Proposed Use = 10 g ai/100 kg seed)											
Forage, Hay, and Seed	NF-171[4]	8.9-13.0 g ai/100 kg seed	NCH[2]	21	<0.005	<0.005	<0.005	<0.005	0.005	0.005	N/A
	TZ-1E				<0.005	<0.005	<0.005	<0.005	0.005	0.005	N/A
	Combined NZ-171[4] + TZ-1E				<0.010	<0.010	<0.010	<0.010	0.010	0.010	N/A
	TZ-5				<0.011	<0.011	<0.011	<0.011	0.011	0.011	N/A
	TZ-5-Glc				<0.006	<0.006	<0.006	<0.006	0.006	0.006	N/A
	Total[4]				<0.027	<0.027	<0.027	<0.027	0.027	0.027	N/A
Seed	NF-171[4]	29.4-30.2 g ai/100 kg seed	NCH[2]	2	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	N/A
	TZ-1E				<0.005	<0.005	<0.005	<0.005	<0.005	<0.005	N/A
	Combined NZ-171[4] + TZ-1E				<0.010	<0.010	<0.010	<0.010	0.010	0.010	N/A
	TZ-5				<0.011	<0.011	<0.011	<0.011	0.011	0.011	N/A
	TZ-5-Glc				<0.006	<0.006	<0.006	<0.006	0.006	0.006	N/A
	Total[4]				<0.027	<0.027	<0.027	<0.027	0.027	0.027	N/A

[1] Expressed in parent equivalents; min. and max. values based on total number of samples; remaining values based on per-trial averages. LAFT = lowest average field trial, HAFT = highest average field trial, SD = standard deviation. For computation of the LAFT, HAFT, median, mean, and standard deviation, values < LOQ are assumed to be at the LOQ (0.005 ppm for picarbutrazox and TZ-1E, 0.011 ppm for TZ-5, and 0.006 ppm for TZ-5-Glc). NA = not applicable.

[2] NCH = normal crop harvest.

[3] n = number of field trials.

[4] NF-171 = picarbutrazox; total = picarbutrazox + TZ-1E + TZ-5 + TZ-5-Glc.