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WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

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The Health Effects Division (HED) of the Office of Pesticide Programs (OPP) is charged with estimating the risk to human health from exposure to pesticides. As part of Registration Review, the Pesticide Re-evaluation Division (PRD) of OPP has requested that HED evaluate the 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 registered uses of paclobutrazol.

HED has evaluated the toxicity and exposure databases for the active ingredient, paclobutrazol, and has conducted a human health risk assessment in support of Registration Review.

A summary of the findings and an assessment of human health risk resulting from the currently registered uses of paclobutrazol are provided in this document. The HED team members contributing to this risk assessment include Sheila Piper (risk assessment), Monica Hawkins (occupational and residential assessment), Nancy McCarroll (hazard assessment), and P. Yvonne Barnes (chemistry and dietary assessment). Faruque Khan of the Environmental Fate and Effects Division (EFED) performed the drinking water assessment.

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1.0 Executive Summary

Paclobutrazol is a plant growth regulator. Syngenta Crop Protection has registered labels for paclobutrazol with formulations including liquids, wettable powders, and granulars. It is currently registered for use as a foliar spray for turf (including parks, athletic fields, and golf courses); a foliar spray for ornamentals in greenhouses and nurseries; as a tree injection; as a tree root drench; and as a seed treatment. There are currently no registered food uses for paclobutrazol.

Paclobutrazol is one of several active ingredients that has triazole metabolites. The triazole metabolites produce a different toxic response than the parent compound; therefore separate risk assessments are performed for the parent compound and its triazole metabolites. In 2013, HED updated the aggregate human health risk assessments for 1,2,4-triazole and the conjugated triazole metabolites (D414952, T. Morton, 10/24/13), which addresses risks from triazole metabolites produced from all registered triazole producing active ingredients.

The toxicology database for paclobutrazol is complete, no additional data are required. In the subchronic feeding studies in rats and dogs, the target organ was the liver, based on increased organ weights and alterations in clinical chemistry parameters associated with liver function. In agreement with the subchronic findings, the liver was the target organ following chronic exposure via the diet in dogs, rats, and mice. Adverse effects included: increased liver weights, steatosis, and/or alterations in clinical chemistry parameters associated with liver function. A 21-day dermal study in rabbits showed a dose-related increase in the degree of hyperkeratosis, acanthosis, and inflammatory changes of the superficial dermis at higher doses. These effects are, however, local and no systemic effects were seen in the study.

Two rat pre-natal developmental toxicity studies were available. In both studies, there was increased evidence of quantitative susceptibility, in the form of delayed ossification of the 7th cervical vertebrae and an increased incidence of extra rib (14th rib). These effects were significantly altered for both fetuses and litters at a dose that was not maternally toxic. There was, however, no evidence (quantitative or qualitative) of increased susceptibility following *in utero* exposures to rabbit or following pre-and/or post natal exposure in rats for two generations in the reproduction study.

Food Quality Protection Act (FQPA) considerations do not apply to paclobutrazol since currently registered use patterns are all non-food uses. While there are potential exposures to infants and children from turf use patterns of paclobutrazol, there are adequate pre-and/or post natal toxicity studies that demonstrate no residual uncertainties to infants and children for pre-and/or post natal susceptibilities. The points of departure (PoDs) used for assessing risks to infants and children from dermal and inhalation exposures are based on the most sensitive developmental effects of concern. There is also no clear evidence of neurotoxicity in the database, and the negative findings from the acute neurotoxicity study support this conclusion.

Although carcinogenicity studies are not required for non-food use chemicals, carcinogenicity mouse and rat studies are available in the database. However, the Agency was unable to determine the potential carcinogenicity of paclobutrazol because the maximum tolerated dose

(MTD) was not achieved in the 2-year carcinogenicity/ chronic study in rats and the carcinogenicity/chronic study in mice. It is noted that paclobutrazol was not mutagenic in a comprehensive battery of acceptable/guideline genetic toxicology assays.

Residential post-application exposure is expected to be short-term in duration only. Since there is not intermediate-term residential exposure, an intermediate-term aggregate risk assessment is not appropriate. Paclobutrazol is not registered for homeowner use on residential lawns. A residential handler assessment was not conducted as part of the risk assessment. A residential post-application assessment was performed as use of paclobutrazol in parks and golf courses is expected to result in residential post-application exposure. Based on the turf use pattern in parks, the target population for incidental oral was identified as young (1-2 year old) children, because of hand-to-mouth activities. Quantification of incidental oral ingestion risks was performed using the 2-generation reproduction study. The offspring NOAEL was 23.2 mg/kg/day and the LOAEL from this study was 116.9 mg/kg/day. A target MOE of 100 is considered adequate for all exposure scenarios (10x for interspecies extrapolation, 10x for intraspecies variability).

The dermal (short-term) and inhalation risk for females 13-49 years old from paclobutrazol were estimated using a developmental oral toxicity study in rats. The NOAEL of 10 mg/kg/day was based on increases in partial ossification of the 7th cervical vertebra and increases in an extra rib (14) at the LOAEL of 40 mg/kg/day. A target MOE of 100 is considered adequate for all exposure scenarios (10x for interspecies extrapolation, 10x for intraspecies variability).

Paclobutrazol is a highly to moderately mobile chemical that is expected to be fairly persistent in the environment. Based on the environmental fate parameters, there is the potential for paclobutrazol to reach drinking water resources. The Environmental Fate and Effects Division (EFED) performed Tier 1 surface water and groundwater modeling using the highest application rates. The highest estimated drinking water concentrations were from groundwater. Since EFED completed their drinking water assessment prior to the Residue of Concern Knowledgebase Sub-committee (ROCKS) determination of the drinking water residues of concern; HED notes that EFED took a total residue approach which overestimates residues. However, since no dietary risks of concern were identified, a revised drinking water assessment, which included only the recommended residues of concern, was not conducted.

No exposure to food is expected. The acute drinking water risk estimates are below HED's level of concern (<100% of the acute population adjusted dose (aPAD) for the general U.S. population (17% of the aPAD) and all population subgroups. The most highly exposed population subgroup was all infants (<1 years old) with an estimated risk equivalent to 54% of the aPAD at the 95th percentile of exposure. The resulting drinking water chronic exposure estimates were less than HED's level of concern (<100% cPAD) for the general U.S. population (12% of the cPAD) and all population subgroups; the most highly exposed population subgroup was all infants (<1 years old) with an estimated risk of 31% of the cPAD.

Paclobutrazol is currently not registered for homeowner use on residential lawns. Therefore, a residential handler exposure assessment was not conducted. Paclobutrazol is applied commercially to parks and golf courses; therefore residential post-application exposure was assessed. Dermal post-application risks were assessed for adults, and children 11 to 16 years old.

All adult and older children golfing dermal risk estimates for both liquid and granular formulations are greater than HED's level of concern ($MOEs \geq 100$). All adults on treated turf dermal risk estimates for both liquid and granular formulations $MOEs$ range from 170 to 1,100. All children 1 – 2 years old oral non-dietary ingestion risk from hand-to-mouth activity on treated turf estimates for both liquid and granular formulations $MOEs$ range from 210 to 1,400,000.

A quantitative spray drift assessment for paclobutrazol is not required because the maximum application rate to a crop/target site multiplied by the adjustment factor for drift of 0.26 is less than the maximum direct spray residential turf application rate (0.75 lb ai/A)¹ for the paclobutrazol products. The turf post-application $MOEs$ are protective for any potential exposures related to spray drift for paclobutrazol.

An acute and chronic aggregate assessments are equivalent to the corresponding dietary risk estimates, which are not of concern. HED has conducted short-term aggregate assessments that includes residential post-application exposure and average dietary (water only) exposures. Short/intermediate-term aggregate $MOEs$ for adults (including females 13-49 years old) is 140 and children (1 to < 2 years old) is 780. Intermediate-term aggregate exposure is not expected; therefore an intermediate-term aggregate assessment was not conducted.

Occupational handler exposures to the existing turf, ornamental, and tree uses of paclobutrazol may occur via the dermal and inhalation route. The short- and intermediate-term risk estimates for the occupational handler scenarios are greater than HED's LOC ($MOEs \geq 100$) with the exception of mixing/loading/applying liquids via a backpack sprayer. The $MOEs$ range from 29 to 19,000,000. The backpack sprayer equipment scenario is still not greater than HED's LOC ($MOEs < 100$) even with the use of personal protective equipment PPE of a double layer and gloves ($MOE = 58$).

Occupational handler exposures to the existing seed treatment uses of paclobutrazol may occur via the dermal and inhalation route for both primary handlers (i.e., those who treat the seed in commercial seed treatment facilities) and secondary handlers (i.e., those who plant paclobutrazol treated seeds). The short- and intermediate-term risk estimates for all primary and secondary handler scenarios $MOEs$ range from 16,000 to 13,000,000.

Occupational post-application exposures to the existing uses of paclobutrazol may occur via the dermal route. The results indicate that occupational post-application risks $MOEs$ range from 110 to 2,800 on day zero after application for all post-application activities that were assessed.

2.0 HED Recommendations

2.1 Data Deficiencies

There are no data deficiencies relating to toxicology, residue chemistry, residential or occupational exposure associated with this registration review for paclobutrazol.

¹ $0.59 \text{ lb ai/A} \times 0.26 \leq 0.75 \text{ lb ai/A}$

2.2 Tolerance Considerations

Paclobutrazol has no food use registration; therefore, there are no tolerances established and a discussion of tolerances and enforcement methods is not pertinent to this risk assessment.

2.3 Label Recommendations

None.

3.0 Introduction

The most recent human health risk assessment for paclobutrazol was conducted 2013 (D394230, S. Piper, C. Smith, M. Hawkins, and N. McCarroll, 9/11/13). The document was revised to incorporate data from the acceptable/guideline acute neurotoxicity study and to account for the data waivers granted for the subchronic inhalation, the subchronic neurotoxicity, and the immunotoxicity studies by the Hazard and Science Policy Council on March 13, 2014 (TXR # 0056914). As a result of the meeting, the 10X database uncertainty factor was removed. In addition, the dermal absorption factor was updated to be consistent with current HED policy. The Toxicity Science Advisory Council (ToxSAC), held on October 02, 2014 approved these refinements.

Paclobutrazol ($\alpha R, \beta R$)-*rel*- β -[(4-chlorophenyl)methyl]- α -(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol is a plant growth regulator that is currently registered for application to turf grass and a number of ornamentals (trees, shrubs, bulbs). It is also registered for use as a seed treatment for broccoli, cabbage, cauliflower, cucurbits, peppers, and tomatoes. There are currently no registered food uses for paclobutrazol.

Paclobutrazol is one of several active ingredients that has triazole metabolites. The triazole metabolites produce a different toxic response than the parent compound; therefore separate risk assessments are performed for the parent compound and its triazole metabolites. In 2013, HED updated the aggregate human health risk assessments for 1,2,4-triazole and the conjugated triazole metabolites (D414952, T. Morton, 10/24/13), which addresses risks from triazole metabolites produced from all registered triazole producing active ingredients. The assessment include the contributions from all the registered uses of paclobutrazol. The findings of the 1,2,4-triazole and the conjugated triazole metabolites assessment were that risk estimates for all exposure scenarios were below HED's level of concern.

3.1 Chemical Identity

Table 3.1. Paclobutrazol Nomenclature	
Chemical Structure	($\alpha R, \beta R$)-isomer
Common Name	Paclobutrazol
IUPAC name	(2 <i>RS</i> ,3 <i>RS</i>)-1-(4-chlorophenyl)-4,4-dimethyl-2-(1 <i>H</i> -1,2,4-triazol-1-yl)pentan-3-ol
CAS Name	($\alpha R, \beta R$)- <i>rel</i> - β -[(4-chlorophenyl)methyl]- α -(1,1-dimethylethyl)-1 <i>H</i> -1,2,4-triazole-1-ethanol
CAS Registry Number	76738-62-0
Chemical Class	Triazole plant growth regulator

3.2 Physical/Chemical Characteristics

Paclobutrazol's vapor pressure (1.28×10^{-9} mm Hg @ 25.0°C) and Henry's Law Constant (8.09×10^{-10} atm m³/mol) indicate that the compound is relatively non-volatile under field conditions. The log *K*_{ow} of 3.2 indicates the potential for this chemical to bioaccumulate in aquatic organisms. Paclobutrazol has a low solubility (25.9 mg/L) in water; however, paclobutrazol is a highly to moderately mobile chemical that is expected to be fairly persistent in the environment. Based on the use pattern and environmental fate parameters, there is the potential for paclobutrazol to reach water resources.

Table 3.2. Paclobutrazol Physical and Chemical Properties	
Parameter	Value
Molecular Weight	293.8 g/mol
Water solubility (20°C)	25.9 mg/L
Solvent solubility (20°C)	2.8 g /L (n-Octanol) 79.8 g/L (methanol) 5.22 g/L (xylene)
Vapor pressure (20°C)	1.28×10^{-9} mmHg
Henry's Law Constant (25°C)	8.2×10^{-7} Pa M ³ mol ⁻¹

	(8.09 x 10 ⁻¹² atm M ³ mol ⁻¹)
Octanol/water partition coefficient (25°C)	log Kow = 3.18

3.3 Pesticide Use Pattern

There are a number of existing uses for paclobutrazol with formulations including liquids, wettable powders, and granulars. Paclobutrazol is currently registered for use as a foliar spray for turf (including parks, athletic fields, and golf courses), ornamentals in greenhouses and nurseries, as a drench treatment, as a bulb soak treatment, as a tree injection treatment, as a soil injection, as a pre-plant plug/liners treatment, and as a seed treatment for cucurbit, pepper, tomato, broccoli, cauliflower, and cabbage seeds. Table 3.3 provides more detail related to the currently registered uses of paclobutrazol.

Table 3.3. Paclobutrazol Use Patterns and Formulations

Formulation	Use Sites	Maximum Application Rate	Application Equipment	REI	Notes
Soluble Concentrate	Turf	0.75 lb ai/A	Ground and handheld	24 hrs or 12 hrs depending on label	
Granular	Turf	0.5 lb ai/A	Ground and handheld	12 hrs	
Soluble Concentrate	Tree Injection (Soil injection at base of tree)	0.352 lb ai/tree	Soil injection equipment	N/A	
Emulsifiable Concentrate	Pre-plant plugs/liners	0.0000051 lb ai/gal	Plug/liner soak	N/A	
Emulsifiable Concentrate	Bulbs	0.00255 lb ai/gal	Bulb soak	N/A	Application rate represents highest application rate for a bulb (freesia)
Emulsifiable Concentrate	Ornamental Plants in Greenhouses and Nurseries	0.59 lb ai/A	Ground and handheld	12 hours	Application rate represents highest application rate for an ornamental (chrysanthemums)
Soluble Concentrate	Tree Injection (8 inch tree)	0.0099 lb ai/tree	Pressurized injection system	N/A	Application rates on labels are presented for multiple diameter trees; two application rates were selected to be representative of those on the labels
	Tree Injection (35 inch tree)	0.07 lb ai/tree	Pressurized injection system		
Soluble Concentrate	Cucurbit Seed	0.00027 lb ai/lb seed	Commercial seed treatment equipment	N/A	On-farm seed treatment is prohibited
	Tomato Seed	0.00414 lb ai/lb seed			
	Pepper Seed	0.00247 lb ai/lb seed			
	Broccoli Seed	0.000661 lb ai/lb seed			
	Cauliflower Seed	0.000635 lb ai/lb seed			

Table 3.3. Paclobutrazol Use Patterns and Formulations

Formulation	Use Sites	Maximum Application Rate	Application Equipment	REI	Notes
	Cabbage Seed	0.000639 lb ai/lb seed			
Wettable Powder	Tree Injection (6-16 inches in diameter)	0.000059 lb ai/tree	Pressurized injection system	N/A	Application rates on labels are presented for multiple diameter trees; two application rates were selected to be representative of those on the labels
	Tree Injection (>16 inches in diameter)	0.00024 lb ai/tree	Pressurized injection system		

3.4 Anticipated Exposure Pathways

Exposure is not expected to occur through food because there are no registered agricultural uses of paclobutrazol. Residential handler exposure is not expected since paclobutrazol is currently not registered for homeowner use on residential lawns. There are residential post-application uses of paclobutrazol, so exposure to paclobutrazol is likely to occur in residential post-application settings. In an occupational setting, handlers may be exposed while handling the pesticide prior to application, as well as during application. There is also a potential for post-application exposure for workers re-entering treated sites.

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,” (<http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf>). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup’s food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the U.S. Department of Agriculture under the National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA). These food consumption patterns 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, season of the year, ethnic group, and region of the country. 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 children, youths, and adults entering or playing on treated areas post-application are evaluated. Exposure risk estimates were not of concern. Further considerations are currently in development, as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders 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 most recent risk assessment for paclobutrazol (D3944230, 9/11/2013) was conducted prior to the review of an acceptable/guideline acute neurotoxicity study, previously identified as a data gap; this study has been incorporated into the risk assessment. In addition, based on the weight of the evidence (WOE) approach used by HASPOC at the meeting, which was held February 27, 2014, it was recommended that the subchronic neurotoxicity, the subchronic inhalation and the immunotoxicity studies can each be granted data waivers (Leshin, 2014, TXR # 0056914). Data requirements for the non-food uses of paclobutrazol are listed in Table A.1 in Appendix A. The data from the following studies were used to evaluate the hazard potential of paclobutrazol (see Appendix A: Tables A.2 and A.3):

- Acute lethality studies (oral, dermal, inhalation, primary eye and dermal irritation, and dermal sensitization)
- Acute neurotoxicity study (rat)
- Subchronic oral toxicity studies [rat (with supplemental data) and dog]
- Developmental (2 rat and 2 rabbit) and reproductive toxicity (rat) studies (with supplemental data)
- Dermal toxicity (21-day dermal toxicity in rabbits)
- Chronic oral toxicity studies (rat and dog)
- Carcinogenicity studies [rat (chronic combined, with supplemental data) and mouse]
- Metabolism studies (rat and dog)
- Mutagenicity battery

Paclobutrazol hazard was previously reviewed by HED's RfD/Peer Review Committee in 1994 (Memo, G. Ghali, 06/21/1994). New data have been submitted since that review was completed. The registrant submitted a number of pieces of supplemental data (MRID 47338506) related to the 2-generation reproduction study. These data include the following: individual pup clinical observational signs; historical control data for these observations; and data for achieved dietary levels based on nominal dietary concentrations, food consumption, and body weight. Additional data for achieved dietary levels were also received for the 90-day feeding study in rats and for the 2-year chronic feeding study in rats (MRID 47078901). These supplemental data have recently been reviewed (TXR No. 0056158) as well as the acute neurotoxicity study (ToxSAC; October 2, 2014). The risk assessment team has incorporated these data into this risk assessment and reevaluated the points of departure and toxicity endpoints for the acute and chronic dietary and the occupational and residential scenarios using current policies on selecting endpoints and uncertainty factors.

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

The absorption, distribution, metabolism and excretion (ADME) of paclobutrazol was extensively characterized in a series of studies in rats and dogs. These studies were performed

using both low- and high-dose, single and repeated dosing protocols. Bile-cannulation was included as part of one of the studies. Estimation of absorption from the gastro-intestinal (GI) tract were based upon data from pharmacokinetic and excretion experiments.

Rats and dogs readily absorb low and high oral doses of paclobutrazol and excretion is rapid (70 to 80% of paclobutrazol is excreted within 72 hours). The major route of excretion is the urine but it is still present in the liver, kidneys, and gastrointestinal tract mostly as the parent compound after 72 hours. Paclobutrazol also does not bioaccumulate. It is included in the triazole alanine group of triazole derivatives. However, findings from a rat metabolism study indicate that the diol and carboxylic acid analogues of paclobutrazol are the major metabolites and that no triazole alanine was found. Details of these studies are found in Appendix 5.

4.2.1 Dermal Absorption

A dermal penetration study in rats (MRID 41048202) was available for paclobutrazol in which male rats were dermally exposed for 10 or 24 hours on an area of 10 cm²/rat. At the time this study was reviewed, the absorbed dose was calculated as the sum of the residues from the urine, feces, cage wash, and carcass (excluding the skin at the application site). The potentially absorbable dose included the residues in the skin at the application site. Previously, the most conservative value for total absorbable (sum of the absorbed dose and potentially absorbable dose) was used, which was 24.5% following a 24-hour exposure period. Currently, the policy is to use 8-hours exposure and to assume that residues found in the skin are potentially absorbable, unless data are provided to demonstrate otherwise. This policy reflects an 8-hour work day, and ongoing exposure is expected to cease at the end of the workday. Likewise, the Agency's position is to be protective; this is reflected in the assumption that residues found in the skin will eventually be absorbed, unless there are specific data which contradicts this assumption. Therefore, values following the 10-hour exposure period were used and the total absorbable dose was calculated to be 18.7%. The percentage of the dose absorbed and remaining on the washed application site (potentially absorbable) at 10 hours was 15.1% and 3.6% respectively, and 24.5% and 2.7% (24 hours), respectively. Since absorption rates were not measured beyond 24 hours, the percent absorbed plus the percent potentially absorbed (18.7%) for 10 hours was calculated. For risk assessment purposes, HED is using the conservative assumption that the dermal absorption factor (DAF) of paclobutrazol is 18.7% (See Appendix A.3.4).

4.3 Toxicological Effects

4.3.1 Toxicology Profile

In subchronic feeding studies in rats and dogs, the target organ was consistently the liver, based on increased organ weights and alterations in clinical chemistry parameters associated with liver function. In agreement with the subchronic findings, the liver was the target organ following chronic exposure via the diet in dogs, rats, and mice. Adverse effects consisted of: increased liver weights, steatosis, and/or alterations in clinical chemistry parameters associated with liver function. Following acute exposure, paclobutrazol exhibited only minimal signs indicative of neurotoxicity in rats.

A 21-day dermal study in rabbits showed a dose-related increase in the degree of hyperkeratosis, acanthosis, and inflammatory changes of the superficial dermis at higher doses. These effects are, however, local and no systemic effects were seen in the study.

Two rat pre-natal developmental toxicity studies were available. In both studies, there was increased evidence of quantitative susceptibility in the form of delayed ossification of the 7th cervical vertebra and an increased incidence of extra rib (14); these effects were significantly altered for both fetuses and litters. The finding of developmental defects and/or variations was seen in both studies at comparable doses, was dose-related, significantly altered and outside of the historical control ranges. These events occurred in the absence of maternal toxicity (maternal NOAELs of ≥ 100 mg/kg/day vs. developmental NOAELs of 10 mg/kg/day in one study and < 40 mg/kg/day in the 2nd study). There was, however, no evidence of susceptibility (quantitative or qualitative) following *in utero* exposures to rabbits or following pre-and/or post-natal exposure in rats for two generations in the reproduction study. Paclobutrazol was not mutagenic, immunotoxic, or neurotoxic. Although there is no evidence in the database that paclobutrazol is carcinogenic, chronic/carcinogenicity studies in rats and mice are insufficient to draw a definitive conclusion.

Paclobutrazol has low toxicity in the rat, rabbit, and guinea pig via the oral (category III) route of exposure, the dermal route (category III) in rats and rabbits, and via the inhalation route (category III to IV) in rats. It is slightly to mildly irritating to the skin and the eye and is negative for dermal sensitization.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)/ Lifestage Sensitivity

Food Quality Protection Act (FQPA) considerations do not apply to paclobutrazol as there are no current registered food/feed uses; therefore, paclobutrazol is not subject to the Food Quality Protection Act (1996). Accordingly, for the purposes of the forthcoming paclobutrazol risk assessment for Registration Review, an FQPA assessment is not included. However, after a thorough review of the database, there are potential exposures to infants and children from the turf use pattern for paclobutrazol were uncovered. There are adequate pre-and/or post-natal toxicity studies that show quantitative pre-natal susceptibility with clear NOAELs and LOAELs in the two rat developmental studies. Because of the concern for the developmental lifestage, the point of departure (PoD) used for assessing the incidental risks to infants and children from oral, dermal or inhalation exposures is based on offspring effects in these studies. Thus protecting the most sensitive lifestage in humans.

4.4.1 Completeness of the Toxicology Database

The toxicology database is complete for this non-food use chemical. The registrant has submitted an acceptable/guideline acute neurotoxicity study, which has been incorporated into this risk assessment. In addition, based on the weight of the evidence (WOE) approach used by HASPOC at the meeting, which was held March 13, 2014, it was recommended that the subchronic neurotoxicity, the subchronic inhalation and the immunotoxicity studies can each be granted data waivers (Leshin, 2014, TXR # 0056914).

4.4.2 Evidence of Neurotoxicity

As discussed in Section 4.4.1, an acceptable/guideline acute neurotoxicity study (ACN, MRID 49211902) has been conducted for paclobutrazol. Based on the weight of the evidence from this study and other studies in the database, there is no evidence of neurotoxicity for paclobutrazol. The findings of no treatment-related adverse effects on clinical signs, brain weight, gross pathology or neuropathology and the negative Functional Observation Battery (FOB) in the ACN study support this conclusion. For these reasons, the HASPOC concluded that a subchronic neurotoxicity study is not required at this time.

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

Quantitative evidence of susceptibility was observed in the rat developmental toxicity studies. The evidence consisted of delayed ossification of the 7th vertebra and an increased incidence of extra rib (14) in two developmental toxicity studies in rats at non-toxic doses in the dams. However, there was no evidence of qualitative or quantitative susceptibility in rabbits or in the rat two-generation reproduction toxicity study.

Although there is convincing evidence of increased susceptibility, the concern is low because: 1) the response was seen in one species (rat); 2) clear NOAELs and LOAELs were established for the developmental effects seen in the two rat studies conducted in this species; 3) there was no evidence of increased susceptibility in two developmental studies with rabbits; 4) there was no evidence of increased susceptibility in the offspring following exposures for two generations in the rat reproduction study; 5) the developmental endpoints are used as the PoD for assessing risk from oral, dermal and inhalation exposures; and 6) the database is complete. Thus, there are no residual uncertainties for pre-and/or post-natal susceptibility.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties with regard to dietary (drinking water only) and residential exposure. Conservative, upper-bound assumptions were used to determine exposure through drinking water and residential sources, such that these exposures have not been underestimated.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

The details for selecting toxicity endpoints and points of departure (PoDs) are presented in Appendix A2. Based on the existing use pattern for paclobutrazol, the exposure to paclobutrazol is expected to be via the oral, dermal, and inhalation routes.

Acute Dietary (General Population): Quantification of acute dietary (drinking water only) risks was performed using the acute neurotoxicity study in rats (MRID 49211902) with a NOAEL of 30 mg/kg, based on transient alterations in motor activity (i.e., decreased rearing counts (2 ♀) and decreased subsession distances) in females 3 to 4 hours after dosing at the LOAEL of 150

mg/kg. An Uncertainty Factor (UF) of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variability (10X). The acute reference dose (aRfD) for the general population was calculated to be 0.3 mg/kg/day.

Acute Dietary (Females 13-49): The most sensitive point of departure was 10 mg/kg/day from the developmental rat study (MRID 00143158), based on increased incidences of partial ossification of the 7th vertebra and 14th rib in fetuses at the LOAEL of 40 mg/kg/day. Both effects were dose-related, statistically significant, outside of the historical control ranges provided by the investigator, and reproducible at comparable doses (also seen MRID 00132693), which occurred in the absence of maternal toxicity. The study was specifically selected for this exposure scenario because increases in 14th rib may be the result of a single exposure. An Uncertainty Factor (UF) of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variability (10X). The acute reference dose (aRfD) for females 13-49 was calculated to be 0.1 mg/kg/day. The selection of this study and the PoD is protective of the pregnant female and the developing fetus.

Chronic Dietary: Quantification of chronic dietary (drinking water only) risks was performed using the 2-year chronic/carcinogenicity feeding study in rats with a NOAEL of 10.8 mg/kg/day based on increased liver weights (both sexes), hypertrophy, and steatosis (both sexes) and decreased triglycerides in the females at the LOAEL of 54.2 mg/kg/day. An Uncertainty Factor (UF) of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variability (10X). The chronic reference dose (cRfD) was calculated to be 0.11 mg/kg/day.

Short- and Intermediate-Term Incidental Oral (Young children, 1-2 years old): Based on the turf use pattern in parks. The target population for incidental oral (short and intermediate term) was identified as young (1-2 year old) children, because of hand-to-mouth activities. Quantification of incidental oral ingestion risks was performed using the 2-generation reproduction study, based on a revisit of the data and in consideration of supplemental data on achieved doses provided by the registrant (TXR No. 0056158). The offspring NOAEL for this study is 23.2 mg/kg/day. The LOAEL is 116.9 mg/kg/day, based on increased incidence of chromodacryorrhea, thickened eyelids and dental malocclusion; increased liver weights; mottling or accentuation of the lobular structure of the liver along with liver enlargement, pallor and discoloration in the male and female pups of both generations. This study was selected to protect the infants and small children. An MOE of 100 is required which includes interspecies extrapolation (10X) and intraspecies variability (10X).

Short-and Intermediate-term Dermal (Young children, 1-2 years old): A dermal assessment is not necessary because in a 3-week dermal toxicity test (MRID 00132688), paclobutrazol was not systemically toxic up to the limit dose. Additionally, there was no evidence suggesting that the young offspring was more susceptible than their parents to the toxic action of paclobutrazol.

Short-and Intermediate-term Dermal (Females 13-49): A 3-week dermal toxicity test was available for paclobutrazol (MRID 00132688); however, with the exception of local irritation, no systemic effects were recorded up to the limit dose. Consequently, quantification of the dermal risks was performed using the rat developmental study (MRID 00143158) with a developmental NOAEL of 10 mg/kg/day, based on increases in partial ossification of the 7th cervical vertebra

and increases in an extra rib (14) at the LOAEL of 40 mg/kg/day. Both effects were dose-related, statistically significant, outside of the historical control ranges provided by the investigator, and reproducible at comparable doses (MRID 00132693). The dermal absorption rate of 18.7% (MRID 41048202) was applied to the NOAEL (See Section 4.2.1). An MOE of 100 is required which includes interspecies extrapolation (10X) and intraspecies variability (10X). The selection of rat developmental study provides protection to the potentially pregnant worker and the developing fetuses but is equally protective for the general population.

Short- and Intermediate-term Inhalation (Young children, 1-2 years old): Based on the current use patterns, there is no exposure to young children via the inhalation route.

Short- and Intermediate-term Inhalation (Females 13-49): No inhalation study was available to establish this endpoint. Therefore, quantification of the inhalation risks was performed using the rat developmental study (MRID 00143158) with a developmental NOAEL of 10 mg/kg/day, based on increases in partial ossification of the 7th cervical vertebra and increases in an extra rib (14) at the LOAEL of 40 mg/kg/day. Both effects were dose-related, statistically significant, outside of the historical control ranges provided by the investigator, and reproducible at comparable doses (MRID 00132693). An inhalation absorption rate of 100% was applied to the NOAEL and an MOE of 100 is required which includes interspecies extrapolation (10X) and intraspecies variability (10X). The selection of rat developmental study provides protection to the potentially pregnant worker and the developing fetuses but is equally protective for the general population.

4.5.2 Recommendation for Combining Routes of Exposure for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major sources: oral, dermal and inhalation exposures, and determine whether the individual exposures can be combined if they have the same toxicological effects. For paclobutrazol, oral studies with the same toxicological effects were used to develop the risk assessment for oral, dermal, and inhalation exposures; accordingly, exposures can be combined, if appropriate for all three routes of exposure.

4.5.3 Cancer Classification and Risk Assessment Recommendations

There are no currently registered food uses for paclobutrazol and carcinogenicity studies are not required for non-food use chemicals. Carcinogenicity studies in mice and rats are, however, available for paclobutrazol and these studies were reviewed in 1994 by the RfD Peer Committee (TXR 0011081). At that time, the Agency determined that there was no evidence in the database of carcinogenicity. However, the maximum tolerated dose (MTD) was not achieved in the 2-year carcinogenicity/chronic study in rats and the carcinogenicity/chronic study in mice. Therefore, the carcinogenic potential of paclobutrazol will be re-evaluated if the use pattern changes (i.e., food uses are proposed). It is noted that paclobutrazol was not mutagenic in a comprehensive battery of acceptable/guideline genetic toxicology assays.

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

Table 4.5.4.1. Summary of Toxicological Points of Departure and Endpoints Used for Dietary Exposure to Paclobutrazol				
Exposure/Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary General Population	NOAEL = 30 mg/kg	UF _A =10x UF _H =10x	<u>30 mg/kg NOAEL</u> 100 (UF) aRfD = 0.3 mg/kg	Acute Neurotoxicity Study (Rats) MRID 49211902 LOAEL = 150 mg/kg, based on transient alterations in motor activity (decreased rearing and decreased subsession distances in females 3-4 hours after dosing)
Acute Dietary Females 13-49	NOAEL = 10 mg/kg/day	UF _A =10x UF _H =10x	<u>10 mg/kg/day NOAEL</u> 100 (UF) aRfD = 0.1 mg/kg	Developmental Toxicity in Rats MRID 00143158) Developmental LOAEL = 40 mg/kg/day, based on partial ossification of the 7 th vertebra and an increased incidence of 14 th rib on a fetal and litter basis at a dose that was not maternally toxic.
Chronic Dietary All Populations	NOAEL = 10.8 mg/kg/day	UF _A =10x UF _H =10x	<u>10.8 mg/kg/day NOAEL</u> 100 (UF) cRfD = 0.11 mg/kg/day	Chronic (2-Year Rat) Feeding Toxicity MRID 40734301 LOAEL = 54.2 mg/kg/day, based on increased liver weights (both sexes), hypertrophy, and steatosis (both sexes) and decreased triglycerides (females)
Cancer (oral, dermal, inhalation)	Not required for non-food use pesticides.			

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). aRfD = acute reference dose. cRfD = chronic acute reference dose. Note: A FQPA factor was not applied because the currently registered use patterns are all non-food uses.

Table 4.5.4.2. Summary of Toxicological Points of Departure and Endpoints Used for Non-Dietary Exposures to Paclobutrazol				
Exposure/Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Incidental Oral Short- and Intermediate-Term (Young children 1-2- years old)	NOAEL = 23.2 mg/kg/day	UF _A =10x UF _H =10x	Residential LOC = 100	Reproductive Toxicity in Rats MRID 40734303/47338506 Offspring LOAEL = 116.9 mg/kg/day, based on the increased incidence of chromodacryorrhea, thickened eyelids and dental malocclusion; increased liver weights; mottling or accentuation of the lobular structure of the liver along with liver enlargement; pallor and discoloration in male and female pups of both generations.
Dermal Short- and Intermediate-Term (Young Children 1-2 years old)	No dermal risk assessment because in a 3-week dermal toxicity test (MRID 00132688), paclobutrazol was not systemically toxic up to the limit dose.			

Table 4.5.4.2. Summary of Toxicological Points of Departure and Endpoints Used for Non-Dietary Exposures to Paclobutrazol				
Exposure/Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Inhalation Short- and Intermediate-Term (Young Children 1-2 years old)	There is no exposure to young children via the inhalation route.			
Dermal Short- and Intermediate-Term (Females 13-49)	Oral NOAEL = 10 mg/kg/day (Dermal Absorption Rate = 18.7%; (MRID 41048202)	UF _A =10x UF _H =10x	Residential/Occupational LOC = 100	Developmental Toxicity in Rats MRID 00143158) Developmental LOAEL = 40 mg/kg/day, based on partial ossification of the 7 th vertebra and an increased incidence of 14 th rib on a fetal and litter basis at a dose that was not maternally toxic.
Inhalation Short- and Intermediate-Term (Females 13-49)	Oral NOAEL = 10 mg/kg/day Inhalation Rate = 100%	UF _A =10x UF _H =10x	Residential/Occupational LOC = 100	Developmental Toxicity in Rats MRID 00143158) Developmental LOAEL = 40 mg/kg/day, based on partial ossification of the 7 th vertebra and an increased incidence of 14 th rib on a fetal and litter basis at a dose that was not maternally toxic.

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.

4.6 Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups.

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

At this time paclobutrazol is not subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP) as required by FFDCA section 408(p). For more information on the status of the EDSP, the policies and procedures, the list of 67 chemicals selected for Tier 1 testing, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: <http://www.epa.gov/endo/>.

5.0 Dietary Exposure and Risk Assessment

5.1 Food Residue Profile

There are no currently registered food uses for paclobutrazol. However, the registrant has registration of seed treatment uses for broccoli, cabbage, cauliflower, cucurbit, pepper and tomato for the active ingredient paclobutrazol to be classified as non-food uses. Based on the metabolism studies (D366305; D402767), the seed treatment use of paclobutrazol can be classified as non-food since total radioactive residues (TRR) were all below 1 ppb and no food tolerances are required.

5.2 Summary of Environmental Degradation

Available data suggest that paclobutrazol is stable to hydrolysis and photolysis. Under aerobic conditions, paclobutrazol appears to be generally quite persistent in acidic soils, with half-lives greater than 300 days. However in soils with neutral or higher pH, estimated half-lives were as short as 25 days. In anaerobic aquatic metabolism studies, paclobutrazol variably partitioned to the sediment and degraded with a half-life of more than one year in flood loam and silt loam soils. Since, the extrapolated half-lives were beyond the duration of experiment, paclobutrazol was considered stable in the anaerobic aquatic system. Paclobutrazol residues were persistent and mobile in terrestrial field dissipation studies. Paclobutrazol residues ranged from 450-950 days for orchard soils (CA, WV, and FL) and 175-252 days in agricultural soils (MS, NC, and IL). Two major environmental degradates, ketone analog of parent (CGA 149907, $\leq 40.0\%$) and 1H-1,2,4-triazol-3-ol (NOA457654, $\leq 25.1\%$) were identified in the environmental fate and terrestrial field dissipation studies.

5.3 Water Residue Profile

The estimated drinking water residues used in the dietary risk assessment were provided by the Environmental Fate and Effects Division (EFED) and were generated using computer modeling methods. The screening model FIRST (FQPA Index Reservoir Screening Tool, version 1.1, 01/01/07) was used to calculate the surface water EDWCs. Estimated groundwater EDWCs were calculated using the screening models SCI-GROW (Screening Concentrations in Ground Water, version 2.3, 07/29/03) and PRZM-GW (Pesticide Root Zone Model for Groundwater, version 1.0, August 31, 2012). The models and the descriptions are available at the EPA internet site: <http://www.epa.gov/oppefed1/models/water/>. The surface water and groundwater modeling were conducted with the highest application rate scenario which is 6.1 lbs/A for nursery production of container-grown ornamentals through soil drench method. This rate was

normalized with the lowest fraction (0.59) of paclobutrazol retained in the soil column leaching study which resulted in an effective modeled drinking water application rate of 2.5 lbs/A. The maximum ground water EDWCs were used in the human health risk assessment for paclobutrazol. See Table 5.3.

Two major environmental degradates, CGA 149907 (maximum of 40.4%) and NOA 457654 (maximum of 25.1%) were identified in the environmental fate and terrestrial field dissipation studies, and were included into the drinking water exposure assessment. However, the Residues of Concern Knowledgebase Sub-committees (ROCKS) had determined the residues of concern in drinking water are the parent compound and its ketone analog CGA 149907. Since EFED completed their drinking water assessment prior to the ROCKS determination of the drinking water residues of concern; HED notes that EFED took a total residue approach which overestimates residues. However, since no dietary risks of concern were identified, a revised drinking water assessment, which included only the recommended residues of concern, was not conducted.

Table 5.3. Estimated Maximum Drinking Water Environmental Concentrations (EDWCs) for Paclobutrazol					
Drinking Water Source (model)	Use (modeled rate)	Application Method	Acute (µg/L)	Chronic (µg/L)	Average Simulation Breakthrough Time (days)
Total Residue (Paclobutrazol plus CGA 149907 and NOA 457654)					
Surface Water (FIRST)	<u>Nursery:</u> (1app. X 2.50 lbs ai/acre)	Drench	255.3	166.2	
Ground Water (SCIGROW)	<u>Nursery:</u> (1app. X 2.50 lbs ai/acre)	Drench	25.0	25.0	
Groundwater (PRZM-GW)	<u>Nursery:</u> (1app. X 2.50 lbs ai/acre)	Drench	945.0	622.0	868
High solubility (760000 mg/L) and very low K _d (0.16 L/kg) of NOA457654 are the drivers of high concentrations for total toxic residue Bolded values are recommended for human health concerns					

5.4 Dietary Risk Assessment

5.4.1. Description of Residue Data Used in Dietary Assessment

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

estimates provided by EFED are modeled estimates, and were generated using the most conservative model available for the existing uses. The unrefined acute and chronic approach to dietary risk exposure analysis will not underestimate risk to the general U.S. population or any population subgroup.

5.4.2 Percent Crop Treated Used in Dietary Assessment

Percent crop treated refinements were not used in this assessment.

5.4.3 Acute Dietary Risk Assessment

An unrefined acute dietary analysis for paclobutrazol was conducted that directly incorporated potential drinking water residues. The resulting acute drinking water risk estimates are below HED's level of concern (<100% acute population adjusted dose (aPAD)) at the 95th percentile of the exposure distribution for the general U.S. population 17% aPAD, and all population subgroups. The most highly-exposed population subgroup was all infants <1 year old which utilized 54% of the aPAD at the 95th percentile of exposure. The detailed results for the general population and all population subgroups are shown below in Table 5.4.6.

5.4.4 Chronic Dietary Risk Assessment

The unrefined chronic dietary (drinking water only) risk estimate utilizes 12% of the chronic population-adjusted dose (cPAD) for the U.S. population. The estimated risk for the most highly exposed population subgroup all infants <1 year is 31% of the cPAD. Thus, chronic dietary exposure to paclobutrazol for all population subgroups is not of concern. The detailed results for the general population and all population subgroups are shown below in Table 5.4.6.

5.4.5 Cancer Dietary Risk Assessment

Paclobutrazol currently has no registered food uses; carcinogenicity studies are not required for non-food use pesticides under the 40 CFR Part 158 Toxicology Data Requirements. However, carcinogenicity studies were reviewed by the RfD Peer Committee (TXR 0011081). At that time the Agency was unable to determine the potential carcinogenicity of paclobutrazol because the maximum tolerated dose (MTD) was not achieved in the 2-year carcinogenicity/chronic study in rats and in mice. The carcinogenic potential of paclobutrazol and the need for a cancer dietary assessment will be re-evaluated if the use pattern changes (i.e., food uses are proposed). Since the Agency has not classified the carcinogenic potential of paclobutrazol a cancer aggregate risk assessment was not conducted at this time.

5.4.6 Dietary Summary Table

The acute and chronic dietary exposure and risks for paclobutrazol are summarized below.

Table 5.4.6. Summary of Dietary (Drinking Water Only) Exposure and Risk for Paclobutrazol

Population Subgroup	aPAD (mg/kg/day)	Acute Results 95 th Percentile		Chronic Results		Cancer Results	
		Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD	Exposure (mg/kg/day)	% aPAD
General U.S. Population	0.3	0.051528	17	0.013024	12	Not Applicable	
All Infants (<1 year old)		0.161395	54	0.033582	31		
Children 1-2 years old		0.079458	27	0.018788	17		
Children 3-5 years old		0.064474	22	0.015829	14		
Children 6-12 years old		0.049263	16	0.011416	10		
Youth 13-19 years old		0.042913	14	0.009498	9		
Adults 20-49 years old		0.050707	17	0.012994	12		
Adults 50-99 years old		0.045169	15	0.012846	12		
Females 13-49 years old	0.1	0.051429	51	0.012947	12		

¹ Values for the population with the highest risk are **bolded**.

6.0 Residential Exposure and Risk Estimates

Paclobutrazol is currently registered for use as a foliar spray for turf (including parks, athletic fields, and golf courses). Paclobutrazol is currently not registered for homeowner use on residential lawns. Therefore, a residential handler exposure assessment was not conducted. A residential post-application assessment was performed as use of paclobutrazol in parks and golf courses is expected to result in residential post-application exposure. In assessing these exposures, *HED's 2012 Residential SOPs² for Residential Pesticide Exposure Assessment: Lawns/Turf* was used.

6.1 Residential Post-application Exposure/Risk Estimates

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with paclobutrazol. The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenarios:

- Physical activities on turf: adults (dermal) and children 1 < 2 years old (incidental oral)
- Golfing: adults (dermal), children 11 < 16 years old (dermal)

² Available: <http://www.epa.gov/pesticides/science/residential-exposure-sop.html>

Residential post-application exposure is expected to be short-term in duration.

The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) should be considered inter-related and it is likely that they occur interspersed amongst each other across time. However, combining these scenarios would be overly-conservative because of the conservative nature of each individual assessment. Therefore, the post-application exposure scenarios that represents the highest exposure for children 1 to < 2 years old is the hand-to-mouth scenario. This scenario should be considered a protective estimate of children's exposure to pesticides used outdoors. A summary of the adult and children short-term dermal exposure and risk estimates is shown in Table 6.1.1. All adult and children golfing dermal risk estimates for both liquid and granular formulations are greater than the LOC (MOEs ≥ 100). All adults on treated turf dermal risk estimates for both liquid and granular formulations are greater than the LOC (MOEs ≥ 100).

Table 6.1.1. Residential Post-application Non-cancer Exposure and Risk Estimates for Paclobutrazol						
Lifestage	Post-application Exposure Scenario		Application Rate ^a (lb ai/A)	TTR (ug/cm ²)	Dermal Dose ^b (mg/kg/day)	Dermal MOEs ^c
Liquid Formulations						
Adult	Dermal	Physical Activities on Turf	0.75	0.080 ^d	0.058	170
		Golfing			0.0046	2,200
Child 11 < 16 years old	Dermal	Golfing	0.75	0.080 ^d	0.0046	2,200
Granular Formulations						
Adult	Dermal	Physical Activities on Turf	0.5	0.01 ^e	0.01	1,100
		Golfing			0.0006	16,000
Child 11 < 16 years old					0.0006	16,000

a. Application rates = maximum application rates from labels.

b. Dose (mg/kg/day) equations provided in Appendix A.

c. Dermal MOE = NOAEL (10 mg/kg/day) / Dermal Dose (mg/kg/day)

d. Representative of California TTR data taken from MRID No.: 45214201; the site that resulted in the highest TTR values.

e. Turf Transferable Residues (TTR) = Application Rate x 0.2% x 11.2.

A summary of the children short-term oral non-dietary ingestion exposure and risk estimates is shown in Table 6.1.2. All children oral non-dietary ingestion risk estimates for both liquid and granular formulations do not exceed HED's level of concern (MOEs ≥ 100).

Table 6.1.2. Short-Term Oral Non-dietary Ingestion Residential Post-application Exposure and Risk Estimates for Paclobutrazol

Lifestage	Post-application Exposure Scenario		Application Rate ^a (lb ai/A)	TTR (ug/cm ²)	Oral Dose ^b (mg/kg/day)	Oral MOEs ^c
Liquids						
Child 1 < 2 year old	Oral	Hand-to-Mouth	0.75	0.080 ^d	0.011	2,100
		Object-to-Mouth			0.00033	70,000
		Soil Ingestion			0.000025	910,000
Granulars						
Child 1 < 2 year old	Oral	Hand-to-Mouth	0.5	0.01 ^e	0.0008	31,000
		Object-to-Mouth			0.00005	500,000
		Soil Ingestion			0.000017	1,400,000
		Episodic Granular Ingestion (1.4% ai)			0.05	210

a. Application rates = maximum application rates from labels.

b. Dose (mg/kg/day) equations provided in Appendix A.

c. Oral MOE = NOAEL (23.2 mg/kg/day) / Oral Dose (mg/kg/day).

d. Representative of California TTR data taken from MRID No.: 45214201; the site that resulted in the highest TTR values.

e. Turf Transferable Residues (TTR) = Application Rate x 0.2% x 11.2.

6.2 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.2 reflects the residential risk estimates that are recommended for use in the aggregate assessment for paclobutrazol.

- The recommended residential exposure for use in the adult short-term aggregate assessment reflects dermal exposure from post-application exposure from physical activities on turf.
- The recommended residential exposure for use in the children 1 to <2 years old short-term aggregate assessment reflects hand-to-mouth exposures from post-application exposure to turf applications.

Table 6.2. Recommendation for the Residential Exposures for the Paclobutrazol Aggregate Assessment

Lifestage	Exposure Scenario	Dose (mg/kg/day) ¹				MOE ²			
		Dermal	Inhalation	Oral	Total	Dermal	Inhalation	Oral	Total
Adult	Turf (Liquids)	0.058	N/A	N/A	0.058	170	N/A	N/A	170
Child 1 to <2 yrs old	Hand-to-Mouth (Liquids)	N/A	N/A	0.011	0.011	N/A	N/A	2,100	2,100

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).

2 MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental Oral MOE), where applicable.

6.3 Spray Drift

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.³ Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

Several paclobutrazol products have existing labels for use on turf, thus it was considered whether the risk assessment for that use may be considered protective of any type of exposure that would be associated with spray drift. The currently registered maximum single application rate of paclobutrazol for foliar sprays on ornamentals in nurseries is 0.59 lb ai/A which is less than the direct turf application rate of 0.75 lbs ai/A, therefore the registered residential uses on turf result in exposure greater than potential exposure from spray drift; and no new spray drift residential assessment needs to be completed. The turf post-application MOEs are protective for any potential exposures related to spray drift for paclobutrazol.

6.4 Residential Bystander Post-Application Inhalation Exposure

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 Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (<http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html>). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (<http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219>). 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 paclobutrazol.

³ This approach is consistent with the requirements of the EPA's Worker Protection Standard which, when included on all labels, precludes direct exposure pathways.

7.0 Aggregate Exposure/Risk Characterization

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

Acute aggregate risks is by definition acute exposures to food and water only. Since there are no food exposures, this assessment would address exposure from drinking water only. As a result, the acute aggregate risk assessment is equivalent to the acute dietary risk assessment discussed in Section 5.4.6 above. There are no acute aggregate risks of concern.

7.2 Short- -Term Aggregate Risk

There is a potential for short-term exposure to paclobutrazol. To estimate short-term aggregate risk, HED combined average dietary (water only) exposures (as a measure of average background dietary exposure) with short-term residential exposures.

The most conservative residential exposure scenario was chosen for the adult population which reflects dermal exposure from post-application exposure to turf (refer to Table 6.2). The residential exposure for use in the children 1 to <2 years old aggregate assessment reflects hand-to-mouth exposures from post-application high contact lawn activity exposure from turf applications.

Short-term aggregate margins of exposure for adults (including females 13-49 years old) and children (1 to < 2 years old) are above the LOC of 100 and do not exceed HED's level of concern (MOEs $\geq$ 100). Short-term aggregate risk estimates are shown below in Table 7.2.

Table 7.2. Short-Term Aggregate Risk Calculations							
Short -Term Scenario							
Population	NOAEL mg/kg/day	LOC ¹	Maximum Allowable Exposure mg/kg/day ²	Average Food and Water Exposure mg/kg/day ³	Residential Post- application Dermal Exposure mg/kg/day ⁴	Total Exposure mg/kg/day ⁵	Aggregate MOE (food, water, and residential) ⁶

Child 1-2 yrs old	23.2	100	0.232	0.018788	0.011	0.030	780
Adults (females 13-49 yrs old)	10	100	0.1	0.012947	0.058	0.071	140

¹ An UF of 100x was applied to account for interspecies extrapolation (10x) and intraspecies variation (10x) and no additional uncertainty factors/safety factors are required.

² Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC [23.2 mg/kg/day/100] child 1-2 yrs; [10 mg/kg/day/100] females 13-49 yrs. See Table 4.5.4.1

³ Average food and water exposure from chronic dietary exposure for child 1-2 yrs old and females 13-49 yrs old. See Table 5.4.6

⁴ Residential Exposure = Dermal exposure from treated turf (see Tables 6.1.1 and 6.1.2).

⁵ Total Exposure = Avg Food & Water Exposure + Residential Exposure

⁶ Aggregate MOE = [NOAEL/ (Avg Food & Water Exposure + Residential Exposure)]

7.3 Intermediate-Term Aggregate Risk

Residential post-application exposure is expected to be short-term in duration only. Since there is not intermediate-term residential exposure, an intermediate-term aggregate risk assessment is not appropriate.

7.4 Chronic Aggregate Risk

The chronic aggregate risk assessment is equivalent to the chronic dietary risk assessment (discussed in Section 5.4.6) as there are no residential scenarios that result in long-term exposure. All of the chronic dietary risk estimates do not exceed HED's level of concern.

7.5 Cancer Aggregate Risk

Paclobutrazol currently has no registered food uses and carcinogenicity studies are not required for non-food use pesticides under the 40 CFR Part 158 Toxicology Data Requirements. The Agency has not classified the carcinogenic potential of paclobutrazol and thus a cancer aggregate risk assessment was not conducted at this time.

8.0 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 paclobutrazol and any other substances. For the purposes of this assessment, therefore, EPA has not assumed that paclobutrazol has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

9.0 Occupational Exposure and Risk Estimates

9.1 Occupational Handler Exposure/Risk Estimates

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

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler dermal and inhalation exposure is expected from the existing uses.

The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Mixing/loading liquids for groundboom applications;
- Mixing/loading liquids for tree injection;
- Mixing/loading liquids for soil injection;
- Mixing/loading wettable powders for tree injections;
- Loading granules for open cab solid broadcast spreader applications;
- Mixing/loading liquid concentrations via dip (bulb soak)/liner soaks;
- Applying sprays for open cab groundboom equipment;
- Applying granules for open cab solid broadcast spreader;
- Loading/applying granules for belly grinder applications;
- Loading/applying granules for push type spreader applications;
- Mixing/loading/applying liquids for backpack sprayer applications;
- Mixing/loading/applying liquids for manually pressurized handwand applications; and
- Mixing/loading/applying liquids for mechanically pressurized handgun sprayer applications.

HED received written information from several paclobutrazol registrants that for occupational applicators, about 50 trees per day are treated for tree injection applications and soil injection applications. The data ranged from 10 trees per day to 70 trees per day. HED selected 50 trees per day for tree and soil injection applications because it was the most typical number from the available information.

Estimates of dermal and inhalation exposure were calculated for various levels of personal protective equipment (PPE). Results are presented for “baseline,” defined as a single layer of clothing consisting of a long sleeved shirt, long pants, shoes plus socks, no protective gloves, and no respirator, as well as baseline with various levels of PPE as necessary (e.g., gloves, respirator, etc). The paclobutrazol product labels direct mixers, loaders, applicators and other handlers to

wear long-sleeved shirt and long pants, chemical-resistant gloves, and shoes plus socks. In addition, some of the labels also state that chemical-resistant aprons should also be used.

The short- and intermediate-term risk estimates for occupational handlers are included in Table 9.1.1. The short- and intermediate-term risk estimates for the occupational handler scenarios are greater than HED's LOC ($\text{MOEs} \geq 100$) with the exception of mixing/loading/applying liquids via a backpack sprayer. The backpack sprayer equipment scenario is still not greater than HED's LOC ($\text{MOEs} < 100$) even with the use of PPE of a double layer and gloves ($\text{MOE} = 58$).

Table 9.1.1. Occupational Handler Exposures and Risks for Paclobutrazol Turf, Ornamental, and Tree Uses

Activity	Use Site	PPE-G Dermal Unit Exposure (mg/lb ai) ^a	Baseline Inhalation Unit Exposure (mg/lb ai) ^a	Application Rate ^b	Area Treated Daily ^c	PPE-G		Baseline Inhalation		Total MOE (PPE-G + Baseline Inhalation)
						Dermal Dose (mg/kg/day) ^d	MOE ^f	Dose (mg/kg/day) ^e	MOE ^g	
Mixer/Loader										
Mixing/Loading Liquids	Groundboom Applications on Ornamentals in Nurseries	0.0376	0.000219	0.59 lb ai/A	40 A	0.0024	4,200	0.000075	130,000	4,000
	Groundboom Applications on Golf Courses			0.75 lb ai/A	40 A	0.0031	3,300	0.000095	110,000	3,200
	Tree Injection (8 diameter Inch Trees)			0.0099 lb ai/tree	50 trees	0.00005	200,000	0.0000016	6,400,000	190,000
	Tree Injection (35 diameter Inch Trees)			0.07 lb ai/tree	50 trees	0.00036	28,000	0.000011	900,000	27,000
	Tree Soil Injection			0.352 lb ai/tree	50 trees	0.0018	5,600	0.000056	180,000	5,400
	Dips for Plug/Liner Soaks			0.000051 lb ai/gal	100 gals	0.00000052	19,000,000	1.60E-08	620,000,000	19,000,000
				0.000051 lb ai/gal	1000 gals	0.0000052	1,900,000	1.60E-07	62,000,000	1,900,000
				0.00255 lb ai/gal	100 gals	0.000026	380,000	8.1E-07	12,000,000	370,000
				0.00255 lb ai/gal	1000 gals	0.00026	38,000	0.0000081	1,200,000	37,000
Mixing/Loading Wettable Powders	Tree Injection (6-16 inches in diameter)	0.17	0.043	0.000059 lb ai/tree	50 trees	0.0000014	7,400,000	0.0000018	5,400,000	3,100,000

Table 9.1.1. Occupational Handler Exposures and Risks for Paclobutrazol Turf, Ornamental, and Tree Uses

Activity	Use Site	PPE-G Dermal Unit Exposure (mg/lb ai) ^a	Baseline Inhalation Unit Exposure (mg/lb ai) ^a	Application Rate ^b	Area Treated Daily ^c	PPE-G		Baseline Inhalation		Total MOE (PPE-G + Baseline Inhalation)
						Dermal Dose (mg/kg/day) ^d	MOE ^f	Dose (mg/kg/day) ^e	MOE ^g	
	Tree Injection (>16 inches in diameter)			0.00024 lb ai/tree	50 trees	0.0000055	1,800,000	0.0000075	1,300,000	770,000
Loading Granulars	Tractor Drawn Spreader Applications on Golf Courses	0.0069	0.0017	0.5 lb ai/A	40 A	0.00037	27,000	0.00049	20,000	12,000
Applicator										
Applying Liquid Sprays via Groundboom	Golf Courses	0.0161	0.00034	0.75 lb ai/A	40 A	0.0013	7,600	0.00015	68,000	6,900
	Ornamentals in Nurseries			0.59 lb ai/A	40 A	0.001	9,700	0.00012	86,000	8,700
Applying Granulars via Tractor Drawn Spreader	Golf Courses	0.0072	0.0012	0.5 lb ai/A	40 A	0.00039	26,000	0.00035	29,000	14,000
Mixer/Loader/Applicator										
Mixing/Loading/Applying Liquids via Backpack Sprayer	Turf	8.26	0.00258	0.75 lb ai/A	5 A	0.084	120	0.00014	71,000	120
	Golf Course			0.75 lb ai/A	5 A	0.084	120	0.00014	71,000	120
	Drench Tree Treatments (8 inch Tree)			0.07 lb ai/tree	50 trees	0.078	130	0.00013	76,000	130
	Drench Tree Treatments (35 inch Tree)			0.31 lb ai/tree	50 trees	0.35	29	0.00058	17,000	29
	Drench Tree Treatments (35 inch Tree)	4.12 (PPE G-DL)	0.00258	0.31 lb ai/tree	50 trees	0.17	58	0.00058	17,000	58 (PPE G-DL + baseline Inhalation)
	Foliar Sprays on Ornamentals in Nurseries and Greenhouses	11200	140	0.00423 lb ai/gallon	40 gallons	0.00515	1,900	0.000343	29,000	1,800

Table 9.1.1. Occupational Handler Exposures and Risks for Paclobutrazol Turf, Ornamental, and Tree Uses

Activity	Use Site	PPE-G Dermal Unit Exposure (mg/lb ai) ^a	Baseline Inhalation Unit Exposure (mg/lb ai) ^a	Application Rate ^b	Area Treated Daily ^c	PPE-G		Baseline Inhalation		Total MOE (PPE-G + Baseline Inhalation)
						Dermal Dose (mg/kg/day) ^d	MOE ^f	Dose (mg/kg/day) ^e	MOE ^g	
Mixing/Loading/Applying Liquids via Manually Pressurized Handwand	Foliar Sprays on Ornamentals in Nurseries and Greenhouses	0.43	30	0.00423 lb ai/gallon	40 gallons	0.000197	51,000	0.0000736	140,000	37,000
	Drench Tree Treatments (8 inch Tree)			0.07 lb ai/tree	50 trees	0.0041	2,500	0.0015	6,600	1,800
	Drench Tree Treatments (35 inch Tree)			0.31 lb ai/tree	50 trees	0.018	550	0.0067	1,500	400
Loading/Applying Granulars via Push-type Spreader	Turf	0.24	0.01	0.5 lb ai/A	5 A	0.0016	6,100	0.00036	28,000	5,000
	Golf Course			0.5 lb ai/A	5 A	0.0016	6,100	0.00036	28,000	5,000
Mixing/Loading/Applying Liquids via Mechanically Pressurized Handwand	Turf	0.88	0.0019	0.75 lb ai/A	5 A	0.0089	1,100	0.0001	97,000	1,100
	Golf Course			0.75 lb ai/A	5 A	0.0089	1,100	0.0001	97,000	1,100
	Foliar Sprays on Ornamentals in Nurseries	390	3.9	0.00423 lb ai/gallon	1,000 gallons	0.00447	2,200	0.000239	42,000	2,100
	Foliar Sprays on Ornamentals in Greenhouses	2,500	120	0.00423 lb ai/gallon	1,000 gallons	0.0287	350	0.00736	1,400	280

a. Unit Exposures taken from Occupational Pesticide Handler Unit Exposure Surrogate Reference Table” (<http://www.epa.gov/opp00001/science/handler-exposure-table.pdf>)

b. Application rates = maximum application rates from labels.

c. Exposure Science Advisory Council Policy #9.1.

d. Dermal Dose (mg/kg/day) = Dermal Unit exposure (mg/lb ai) × Conversion Factor (0.001 mg/μg) x Application Rate x Area Treated or Amount Handled x % Dermal Absorption Factor (18.7%) /Body weight (69 kg).

e. Inhalation Dose (mg/kg/day) = Inhalation Unit Exposure (mg/lb ai) x Conversion Factor (0.001 mg/μg) x Application Rate x Area Treated x %Absorption (100% inhalation) / Body weight (69 kg).

f. Dermal MOE = Dermal NOAEL (10 mg/kg/day) / Dermal Dose (mg/kg/day). LOC = 100.

g. Inhalation MOE = Inhalation NOAEL (10 mg/kg/day) / Inhalation Dose (mg/kg/day). LOC = 100

Short-/Intermediate-Term Handler Risk for Seed Treatments

Paclobutrazol is currently registered for commercial seed treatment use on tomato, pepper, and cucurbit, broccoli, cauliflower, and cabbage seeds. The paclobutrazol labels do not permit on-farm seed treatment. Based on the existing seed treatment use pattern, there is a potential for exposure to paclobutrazol to primary handlers (i.e., activities related to treating the seed) and secondary handlers (i.e., planting treated seed). Primary and secondary handler exposure is expected to be short- or intermediate-term in duration based on the information provided on the existing labels. The short- and intermediate-term toxicological endpoints are the same for the respective routes of exposure; therefore, the estimates of risk for short-term duration exposures are protective of those for intermediate-term durations.

Primary Handler (Treating Seed)

Potential primary occupational handler exposure scenarios from the use of paclobutrazol as a commercial seed treatment include:

- Mixing, loading, applying liquid formulations;
- Bagging treated seed;
- Sewing bags; and
- Multiple activities.

Typically, for large-scale commercial seed treatments, workers perform only those specific individual tasks listed above; however, it is assumed that workers also may perform multiple activities throughout the day. As a result a “multiple activities” scenario (i.e. where one worker performs all seed treatment tasks such as loading/applying, sewing, bagging, cleaning, calibration, repair, forklift driver, etc.) was addressed. No assessment was performed for on-farm seed treatment as the paclobutrazol labels do not permit on-farm seed treatment.

Secondary Handler (Planting Treated Seed)

Potential secondary occupational handler exposure scenarios from the use of paclobutrazol as a commercial seed treatment include planting treated seed. Summaries of the risk estimates for primary and secondary handlers are included in Tables 9.1.2 and 9.1.3. The short- and intermediate-term risk estimates for all primary and secondary handler scenarios are greater than HED's LOC (MOEs ≥ 100).

Table 9.1.2 Summary of Short- and Intermediate-Term Handler Exposures and Risks for Paclobutrazol Seed Treatment								
Seed Type	Max Application Rate ^a	Unit Exposure ^b (mg/lb ai)		Amount of Seed Treated ^c	Absorbed Dose (mg/kg/day) ^d		MOE ^e	
	lb ai/lb seed	Dermal	Inhal.	lb seed/day	Dermal	Inhal.	Dermal	Inhal.
LOADER/APPLICATOR (single layer, gloves)								
Cucurbit (Cucumber)	0.000229	0.00023	0.00034	3,000	0.000043	0.000003	230,000	3,000,000
Cucurbit (Cantaloupe)	0.00027				0.000050	0.000004	200,000	2,500,000
Cucurbit (Pumpkin)	0.000107				0.000020	0.000002	500,000	6,300,000
Cucurbit (Squash)	0.000172				0.000032	0.000003	310,000	3,900,000
Cucurbit (Watermelon)	0.000157				0.000029	0.000002	340,000	4,300,000
Pepper	0.00247				0.000462	0.000037	22,000	270,000
Tomato	0.00414				0.000774	0.000061	13,000	160,000
Broccoli	0.000661				0.000124	0.000010	81,000	1,000,000
Cauliflower	0.000635				0.000119	0.000009	84,000	1,100,000
Cabbage	0.000639				0.000119	0.000009	84,000	1,100,000
SEWER (single layer, no gloves)								
Cucurbit (Cucumber)	0.000229	0.0062	0.00023	3,000	0.000012	0.000002	870,000	4,400,000
Cucurbit (Cantaloupe)	0.00027				0.000014	0.000003	730,000	3,700,000
Cucurbit (Pumpkin)	0.000107				0.000005	0.000001	1,900,000	9,300,000
Cucurbit (Squash)	0.000172				0.000009	0.000002	1,200,000	5,800,000
Cucurbit	0.000157				0.000008	0.000002	1,300,000	6,400,000

Table 9.1.2 Summary of Short- and Intermediate-Term Handler Exposures and Risks for Paclobutrazol Seed Treatment								
Seed Type	Max Application Rate ^a	Unit Exposure ^b (mg/lb ai)		Amount of Seed Treated ^c	Absorbed Dose (mg/kg/day) ^d		MOE ^e	
	lb ai/lb seed	Dermal	Inhal.	lb seed/day	Dermal	Inhal.	Dermal	Inhal.
(Watermelon)								
Pepper	0.00247				0.000125	0.000025	80,000	400,000
Tomato	0.00414				0.000209	0.000041	48,000	240,000
Broccoli	0.000661				0.000033	0.000007	300,000	1,500,000
Cauliflower	0.000635				0.000032	0.000006	310,000	1,600,000
Cabbage	0.000639				0.000032	0.000006	310,000	1,600,000
BAGGER (single layer, no gloves)								
Cucurbit (Cucumber)	0.000229	0.0091	0.00016	3,000	0.000017	0.000002	590,000	6,300,000
Cucurbit (Cantaloupe)	0.00027				0.000020	0.000002	500,000	5,300,000
Cucurbit (Pumpkin)	0.000107				0.000008	0.000001	1,300,000	13,000,000
Cucurbit (Squash)	0.000172				0.000013	0.000001	790,000	8,400,000
Cucurbit (Watermelon)	0.000157				0.000012	0.000001	860,000	9,200,000
Pepper	0.00247				0.000183	0.000017	55,000	580,000
Tomato	0.00414				0.000306	0.000029	33,000	350,000
Broccoli	0.000661				0.000049	0.000005	200,000	2,200,000
Cauliflower	0.000635				0.000047	0.000004	210,000	2,300,000
Cabbage	0.000639				0.000047	0.000004	210,000	2,200,000
MULTIPLE ACTIVITIES (combination of loader/applicator with gloves and no coveralls, sewer without gloves, stacker without gloves)								
Cucurbit (Cucumber)	0.000229	0.042	0.0016	3,000	0.000078	0.000016	130,000	630,000
Cucurbit	0.00027				0.000092	0.000019	110,000	530,000

Table 9.1.2 Summary of Short- and Intermediate-Term Handler Exposures and Risks for Paclobutrazol Seed Treatment								
Seed Type	Max Application Rate ^a	Unit Exposure ^b (mg/lb ai)		Amount of Seed Treated ^c	Absorbed Dose (mg/kg/day) ^d		MOE ^e	
	lb ai/lb seed	Dermal	Inhal.	lb seed/day	Dermal	Inhal.	Dermal	Inhal.
(Cantaloupe)								
Cucurbit (Pumpkin)	0.000107				0.000037	0.000007	270,000	1,300,000
Cucurbit (Squash)	0.000172				0.000059	0.000012	170,000	840,000
Cucurbit (Watermelon)	0.000157				0.000054	0.000011	190,000	920,000
Pepper	0.00247				0.000843	0.000172	12,000	58,000
Tomato	0.00414				0.001414	0.000288	7,100	35,000
Broccoli	0.000661				0.000226	0.000046	44,000	220,000
Cauliflower	0.000635				0.000217	0.000044	46,000	230,000
Cabbage	0.000639				0.000218	0.000044	46,000	220,000

a Application Rates based on existing labels for paclobutrazol.

b Unit Exposures from HED Exposure Science Advisory Council Policy 14.

c HED default for lb seed treated per day from HED Exposure Science Advisory Council Policy 15.

d Dermal Dose (mg/kg/day) = dermal unit exposure (mg/lb ai) x application rate (lb ai/lb seed) x amount treated (lb seed/day) x absorption factor (18.7%) / body weight (69 kg adult). Dermal MOE = NOAEL (10.0 mg/kg/day for short- and intermediate-term exposure) / Dermal Dose (mg/kg/day). Level of concern = 100.

e Inhalation Dose (mg/kg/day) = inhalation unit exposure (mg/lb ai) x application rate (lb ai/lb seed) x amount treated (lb seed/day) x absorption factor (100%) / body weight (69 kg adult). Inhalation MOE = NOAEL (10.0 mg/kg/day for short- and intermediate-term exposure) / Inhalation Dose (mg/kg/day). Level of concern = 100.

Table 9.2.3. Summary of Secondary Handler (Planter) Exposures and Risks for Paclobutrazol (Single Layer, Gloves during Loading Only)

Seed Type	Max Application Rate ^a (lb ai/lb seed)	Dermal Unit Exposure ^b (mg/lb ai)	Inhalation Unit Exposure ^b (mg/lb ai)	Amount of Seed Planted Per Day ^c (lb seed/day)	Absorbed Dermal Dose ^d (mg/kg/day)	Absorbed Inhalation Dose ^d (mg/kg/day)	Dermal MOE ^e	Baseline Inhalation MOE ^e
Cucurbit Seed (Cucumber)	0.000229	0.25	0.0034	3,000	0.00046547	0.0000339	21,000	300,000
Cucurbit Seed (Cantaloupe)	0.00027	0.25	0.0034	3,000	0.00054880	0.0000399	18,000	250,000
Cucurbit Seed (Pumpkin)	0.000107	0.25	0.0034	3,000	0.00021749	0.0000158	46,000	630,000
Cucurbit Seed (Squash)	0.000172	0.25	0.0034	3,000	0.00034961	0.0000254	29,000	390,000
Cucurbit Seed (Watermelon)	0.000157	0.25	0.0034	3,000	0.00031912	0.0000232	31,000	430,000
Pepper	0.00247	0.25	0.0034	3,000	0.00502054	0.0003651	2,000	27,000
Tomato	0.00414	0.25	0.0034	3,000	0.00841500	0.0006120	1,200	16,000
Broccoli	0.000661	0.25	0.0034	3,000	0.00134355	0.0000977	7,400	100,000
Cauliflower	0.000635	0.25	0.0034	3,000	0.00129071	0.0000939	7,700	110,000
Cabbage	0.000639	0.25	0.0034	3,000	0.001298837	0.0000945	7,700	110,000

a Application Rates based on existing labels for paclobutrazol.

b Unit Exposures from HED Exposure Science Advisory Council Policy 14: Standard Operating Procedures for Seed Treatment.

c HED default for lb seed planted per day from HED Exposure Science Advisory Council Interim Policy 15 and the BEAD memo "Acres Planted Per Day and Seeding Rates of Crops Grown in the United States" (J. Becker, March 2011).

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- d Daily Absorbed Dose (mg/kg/day) = daily unit exposure (mg/lb ai) x application rate (lb ai/lb seed) x amount treated (lb seed/day) x absorption factor (18.7% for dermal, 100% for inhalation) / body weight (69 kg adult). Level of concern = 100.
- e MOE = NOAEL (dermal and inhalation = 10.0 mg/kg/day for short- and intermediate-term exposure) /Absorbed Dose (mg/kg/day). Level of concern = 100.

9.2 Occupational Post-application Exposure/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.

9.2.1 Occupational Post-application Inhalation Exposure/Risk Estimates

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.

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.

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

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.

9.2.2 Occupational Post-application Dermal Exposure/Risk Estimates

Occupational Post-application Dermal Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational post-application risk assessments. Each assumption and factor is detailed below on an individual basis. HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. For paclobutrazol, based on the currently registered use, short- and intermediate-term exposures are expected. The short- and intermediate-term PODs are the same; therefore, short-term risk estimates are protective of longer-term exposures.

Table 9.2.2.1. provides a summary of the transfer coefficients and activities associated with turf and ornamentals in greenhouse and nurseries.

Table 9.2.2.1. Post-application Activities and Dermal Transfer Coefficients.				
Crops	Crop Height	Foliage Density	Transfer Coefficients (cm ² /hr)	Activities
Turf	Low	Full	2,500	Golf course maintenance, greens only
Turf	Low	Full	3,700	Maintenance
Ornamentals in Nurseries	Low	Min	230	Grafting, Propagating, Transplanting
	Low	Full	230	Hand harvesting, Hand pruning, Scouting, Hand Weeding, Transplanting, Pinching, Tying/Training
	High	Min	230	Hand harvesting, Hand pruning, Transplanting
	High	Full	230	Hand harvesting, Hand pruning, Scouting, Container Moving, Hand weeding, Transplanting, Pinching
	Low/High	Full	1900	Hand set irrigation
Ornamentals in Greenhouses	Low	Min	230	Grafting, Propagating, Transplanting
	Low	Full		Hand harvesting, Hand pruning, Scouting, Hand weeding, Transplanting, Pinching, Tying/Training
	High	Min		Hand harvesting, Hand pruning, Transplanting
	High	Full		Hand harvesting, Hand pruning, Scouting, Container Moving, Hand weeding, Transplanting, Pinching

A summary of the estimated occupational post-application risks are provided in Table 9.2.2.2. The short- and intermediate-term risk estimates for golf course maintenance activities are greater than HED's LOC (MOEs ≥ 100) using predicted Day 0 residue values from the TTR study. The short- and intermediate-term risk estimates for ornamentals in greenhouses and nurseries are greater than HED's LOC (MOEs ≥ 100) using predicted Day 0 residue values from either the Chrysanthemum or Poinsettia DFR data for all activities.

Table 9.2.2.2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Paclobutrazol.

Crop/Site	Activities	Transfer Coefficient (cm ² /hr)	DFR/TTR ¹	Dermal Dose (mg/kg/day) ²	MOE ³
Short- and Intermediate-term					
Turf ⁴	Golf course maintenance, greens only	2,500	0.080	0.004	2,300
Turf ⁴	Maintenance	3,700	0.080	0.006	1,600
Ornamentals in Nurseries using Chrysanthemum DFR Data ⁵	Hand harvesting, Hand pruning, Scouting, Container moving, Hand Weeding, Transplanting, Grafting, Propagating, Pinching, Tying/Training	230	0.73	0.004	2,800
	Hand set irrigation	1,900	0.73	0.030	330
Ornamentals in Greenhouse using Chrysanthemum DFR Data ⁵	Hand harvesting, Hand pruning, Scouting, Container moving, Hand Weeding, Transplanting, Grafting, Propagating, Pinching, Tying/Training	230	0.73	0.004	2,800

Table 9.2.2.2. Occupational Post-application Non-Cancer Exposure and Risk Estimates for Paclobutrazol.

Crop/Site	Activities	Transfer Coefficient (cm ² /hr)	DFR/TTR ¹	Dermal Dose (mg/kg/day) ²	MOE ³
Short- and Intermediate-term					
Ornamentals in Nurseries using Poinsettia DFR Data ⁶	Hand harvesting, Hand pruning, Scouting, Container moving, Hand Weeding, Transplanting, Grafting, Propagating, Pinching, Tying/Training	230	2.20	0.011	910
	Hand set irrigation	1,900	2.20	0.091	110
Ornamentals in Greenhouse using Poinsettia DFR Data ⁶	Hand harvesting, Hand pruning, Scouting, Container moving, Hand Weeding, Transplanting, Grafting, Propagating, Pinching, Tying/Training	230	2.20	0.011	910

1 (See MRID 45214201, MRID 45310801, MRID 45336601).

2 Daily Dermal Dose = [DFR or TTR (µg/cm²) × Transfer Coefficient × 0.001 mg/µg × 8 hrs/day × dermal absorption (18.7 %)] ÷ BW (69 kg).

3 MOE = POD (mg/kg/day) / Daily Dermal Dose. Daily Dermal Dose = [DFR/TTR (µg/cm²) × TC × 0.001 mg/µg × 8 hrs/day × dermal absorption factor (18.7 %)] ÷ BW (69 kg).

4 TTR data represents CA which was the test site with the highest residues (MRID 45214201).

5 Chrysanthemum DFR data represents use in a greenhouse in Oregon (MRID 45310801).

6 Poinsettia DFR data represents use in a shade house in Florida (MRID 45336601).

Restricted Entry Interval

Paclobutrazol is classified as Toxicity Category III via the dermal route and or skin irritation potential based on studies submitted in 2012. It is not a skin sensitizer. Short- and intermediate-term post-application risk estimates were not a concern on day 0 (12 hours following application) for all post-application activities. Under 40 CFR 156.208 (c) (2) (iii), ai's classified as Acute Toxicity Category III chemicals require a 12- REI. The occupational post-application assessment, dermal risk estimates do not exceed HED's level of concern (MOEs ≥100). Based on the acute dermal toxicity, the 12-hour REI that appears on the current paclobutrazol labels is supported by the acute toxicity data.

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 PHED 1.1; the AHETF database; the Outdoor Residential Exposure Task Force (ORETF) database; the ARTF database; ExpoSAC Policy 14 (SOPs for Seed Treatment); the Residential SOPs (Lawns/Turf); a chemical-specific turf transferable residue study (MRID 45214201), and a chemical-specific dislodgeable foliar residue study (MRID 45310801 and 45336601) 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 the Agency website⁴.

Review of Incident Report

Paclobutrazol incidents were analyzed in 2007 (M. Hawkins and H. Allender, 02/27/2007, D335541). There were 2 incidents identified in IDS from 1999 to 2007; there were no incidents identified in Poison Control Center Data from 1993 to 2005; and there were no incidents identified in NIOSH SENSOR data from 1998 to 2003. An updated incident analyses of the Main and Aggregate Incident Data System (IDS) from January 1, 2010 to January 20, 2015, and the National Institute of Occupational Safety and Health Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR-Pesticides) from 1998 to 2011 are consistent with the previous analyses (S. Recore, via email dated 1/20/2015).

10.0 References

Hawkins, M., McCarroll, N., Piper, S., and Smith, C. (2013). Paclobutrazol. Preliminary Human Health Risk Assessment for Registration Review. DP Number: D394230, dated September 11, 2013.

Khan, F. (2014). Revised Tier 1 Drinking Water Assessment for the Registration Review of Paclobutrazol on Turf (commercial, ornamental and golf courses), Ornamental and Shade Trees, and Seed Treatment of Tomato, Pepper and Cucurbit. DP Number: D418301, dated March 13, 2014.

Barnes, Y. (2014). Paclobutrazol. Acute and Chronic Dietary (Drinking Water Only) Exposure and Risk Assessment. DP Number: D419143, dated 1/21/2015.

Smegal, D. (2012). Paclobutrazol: Summary of Hazard and Science Policy Council (HASPOC) meeting of December 8, 2011: Recommendations on the need for immunotoxicity and acute and subchronic neurotoxicity studies for paclobutrazol, TXR 0056149.

⁴ <http://www.epa.gov/pesticides/science/handler-exposure-data.html> and <http://www.epa.gov/pesticides/science/post-app-exposure-data.html>

Smith, C. (2012). Paclobutrazol: Non-food Use for Seed Treatment on Broccoli. DP Number: D402767, dated September 13, 2012.

Morton, T. (2013). Common Triazole Metabolites: Updated Aggregate Human Health Risk Assessment to Address The New Section 3 Registrations For Use of Propiconazole on Rapeseed Crop Subgroup 20A; Use of Difenoconazole on Rapeseed Crop Subgroup 20A; and Use of Tebuconazole on Imported Oranges. DP Number: D414952, dated October 24, 2013.

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Available for Paclobutrazol

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food vs. non-food for Paclobutrazol are in Table A.1 below. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1 Test Required for Nonfood Use Pesticides		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 (rat)	yes	yes
870.3150	Oral Subchronic (dog)	no	no
870.3200	21/28-Day Dermal (rat)	yes	yes
870.3250	90-Day Dermal	yes	yes
870.3465	28-Day Inhalation	yes	no ^a
870.3700a	Developmental Toxicity (rat)	yes	yes
870.3700b	Developmental Toxicity (rabbit)	yes	yes
870.3800	Reproduction (rat)	yes	yes
870.4100a	Chronic Toxicity (rat)	yes	yes
870.4100b	Chronic Toxicity (dog)	yes	yes
870.4200a	Carcinogenicity (rat)	yes	no
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Chronic/Carcinogenicity (rat)	yes	yes ^b
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations....	yes	yes
870.5395	Mutagenicity—Mammalian Erythrocyte Micronucleus .	yes	yes
870.5450	Mutagenicity—Rodent dominant lethal assay	no	yes
870.5500	Mutagenicity— Bacterial DNA Damage or Repair Test	no	yes
870.5550	Mutagenicity—Unscheduled DNA Synthesis	no	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)	yes	no ^a
870.6300	Developmental Neurotoxicity (rat)	no	no
870.7485	General Metabolism (rat)	yes	yes
870.7600	Dermal Penetration, <i>in vivo</i> (male rat)	yes	yes
870.7800	Immunotoxicity (rat and mouse)	yes	no ^a

<u>Non-Guideline</u> : Comparative dermal absorption, <i>in vitro</i> (rat and human skin)	No	no
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^a Data waivers granted by HASPOC March 13, 2014 (TXR 0056914).

^b Only the chronic portion of the Chronic/Carcinogenicity (rat) study is acceptable.

Table A2.1: Acute Toxicity of Paclobutrazol Technical Grade

Guideline No/Study Type	MRIDs	Results	Toxicity Category
870.1100 Acute Oral (97% ai) Alderley Park Rat	00117478 (1983)	LD ₅₀ = 1954 mg/kg (M) 1336 mg/kg (F)	III
870.1100 Acute Oral (97% ai) Alderley Park Mouse	00117478 (1982)	LD ₅₀ = 490 mg/kg (M) 1219 mg/kg (F)	II
870.1100 Acute Oral (97% ai) Dunkin Hartley Albino Guinea pig	00117478 (1982)	LD ₅₀ = 542 mg/kg (M) >400 and <640 mg/kg (F)	III
870.1100 Acute Oral (97% ai) NZW Rabbit	00117478 (1982)	LD ₅₀ = 835 mg/kg (M) 937 mg/kg (F)	III
870.1200 Acute Dermal (97% ai) Alderley Park Rat	00117478 (1982)	LD ₅₀ = >1000 mg/kg (M F)	II
870.1200 Acute Dermal (97% ai) NZW Rabbit	00117478 (1982)	LD ₅₀ = >1000 mg/kg (M F)	II
870.1300 Acute Inhalation (97% ai) 50% ai Alderley Park Rat	00117482 (1982)	LC ₅₀ = >766 mg/m ³ (M) 359-766 mg/m ³ (F)	III
870.2400 Primary Eye Irritation (97% ai) NZW Rabbit	00117479 (1982)	5/6 rabbits with unwashed eyes had slight corneal opacity, which cleared within 7 days; 3/6 rabbits with washed eyes had slight redness of the conjunctiva, with some chemosis and discharge, which was not apparent by 3 days.	III ^a
870.2500 Primary Skin Irritation (97% ai) NZW Rabbit	00117479 (1982)	Mild irritation that persisted for 72 hours	III
870.2500 Primary Skin Irritation (97% ai) Alderley Park Albino Rat	00117479 (1982)	3/5 M showed erythema; 2/5 (F) showed desquamation and scabbing. Effects did not persist in either sex.	III
870.2600 Dermal Sensitization (Guinea pig) Dunkin Hartley Albino	00117479 (1982)	Not a skin sensitized	

^a Reclassified in 1995, based on additional data provided by the registrant (HED Document 011460).

The Toxicity Profile Table is presented below in Table A.2.2

Table A.2.2: Toxicity Profile of Paclobutrazol Technical		
Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.3100 90-Day oral toxicity rodents (rat)	00132689 (1983)/ 47338506 (2007) Acceptable/guideline 0, 50, 250 or 1250 ppm [equivalent to 0, 3.7, 18.8 or 93.0 mg/kg/day (M) 0, 4.4, 21.6 or 106.5 mg/kg/day (F)] ^a .	NOAEL =18.8 mg/kg/day for both sexes LOAEL = 93.0 mg/kg/day, based on elevated liver weights, serum cholesterol, hepatic aminopyrene-N- demethylase activity and alanine transaminase levels in females.
870.3150 6-Week oral toxicity in dogs	00132690 (1983) Unacceptable 0, 15, 75, or 225 mg/kg/day (M & F).	NOAEL = 15 mg/kg/day (LDT) LOAEL = 75 mg/kg/day, based on increased liver weights and serum alkaline phosphatase levels. Only 1 M and 1 F tested at each level.
870.3200 21/28-Day dermal toxicity (rabbit)	00132688 (1980) Acceptable/guideline 0, 10, 100, or 1000 mg/kg/day, 6 hrs/day for 5 d/week during a 21-day period.	NOAEL =10 mg/kg/day (intact skin) LOAEL = 100 mg/kg/day, based on irritation at all doses with abraded skin and at 100 and 1000 mg/kg/day with intact skin. Irritation began to appear during 2 nd week of application. Degree increased with increasing dose. Hyperkeratosis, acanthosis and inflammatory changes of superficial dermis. No systemic toxicity seen at any dose.
870.3465 28-Day inhalation toxicity (rat)	Data waiver granted by HASPOC March 13, 2014 (TXR 0056914)	
870.3700a Prenatal developmental toxicity in rodents (Wistar rats, derived from Alderley Park strain)	00132693 (1983) Acceptable/guideline 0, 40, 100, or 250 mg/kg/day from days 6 through 15 of gestation Oral gavage; solvent = corn oil.	Maternal NOAEL = 100 mg/kg /day LOAEL =250 mg/kg /day, based on mortality, significantly decreased body weight gain and food efficiency, and gross liver effects (pallor and enlargement). Developmental NOAEL was not established. LOAEL = 40 mg/kg/day (lowest dose tested), based on significant and dose-related increases in fetuses with bilateral partial ossification of the 7 th cervical bone at 40, 100 and 250 mg/kg/day and in bilateral significant increases in the number of fetuses with an extra rib (15). Increases in the number of litters affected with these defects were also seen but not analyzed statistically. Cleft palate was also seen in 3 fetuses from 2 litters at 250 mg/kg/day.
870.3700a Prenatal developmental toxicity in rodents	00143158 (1984) Acceptable/guideline	Maternal NOAEL =>100 mg/kg /day (HDT).

Table A.2.2: Toxicity Profile of Paclobutrazol Technical

Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
(Wistar rats, derived from Alderley Park strain)	0, 2.5, 10, 40, or 100 mg/kg/day from days 7 through 16 of gestation. Oral gavage; solvent = corn oil.	Developmental NOAEL = 10 mg/kg /day LOAEL = 40 mg/kg/day, based on significant and dose-related increases in fetuses and litters with unilateral partial ossification of the 7 th vertebra and with significant and dose-related bilateral increases in fetuses and litters with extra rib (14). (See TXR No. 0056512)
870.3700b Prenatal developmental toxicity in nonrodents (NZW rabbit)	00132692 (1983) Unacceptable 0, 25, 75, or 125 mg/kg/day from days 6 through 18 of gestation. Oral gavage; solvent = corn oil.	Maternal NOAEL = 75 mg/kg /day LOAEL = 125 mg/kg/day, based on decreased body weight gain during dosing. Low fertility; only low and mid-dose groups had > minimum number of litters at sacrifice. Developmental NOAEL = None observed
870.3700b Prenatal developmental toxicity in nonrodents (NZW rabbit)	40734302 (1986) Acceptable/guideline 0, 25, 75, or 125 mg/kg/day from days 7 through 19 of gestation.	Maternal NOAEL = 75 mg/kg /day LOAEL = 125 mg/kg/day, based on decreased body weights and food consumption during dosing. Developmental NOAEL = 75 mg/kg/day LOAEL = 125 mg/kg/day, based on the increased incidence of extra ribs in pups.
870.3800 Reproduction and fertility effects (rat)	40734303 (1987)/ 47338506 (2007) Acceptable/guideline 0, 50, 250 and 1250 ppm in the diet [equivalent to 0, 4.8, 24.4, and 121.2 mg/kg/day (F ₀ M); 0, 5.1, 25.9 and 126.2 (F ₀ F); 0, 4.7, 23.2 and 116.9 (F ₁ M); and 0, 5.1, 24.8 and 124.1 mg/kg /day (F ₁ F)] ^a	Parental systemic NOAEL = 23.2 mg/kg /day LOAEL = 116.9 mg/kg/day, based on the increases in liver weights and fatty changes and thickening of the urinary bladder walls in females Reproductive NOAEL = 116.9 mg/kg/day (HDT) LOAEL = N/A Offspring NOAEL = 23.2 mg/kg /day ^b LOAEL = 116.9 mg/kg/day, based on the increased incidence of chromodacryorrhea, thickened eyelids and dental malocclusion, increased liver weights, mottling or accentuation of the lobular structure of the liver, along with liver enlargement, pallor and discoloration.
870.4100a Chronic toxicity (rat)	40734301 (1986)/ 47078901 (2007) Acceptable/guideline 0, 50, 250 or 1250 ppm [equivalent to 0, 2.2, 10.8, 54.2 mg/kg/day (M) & 0, 2.8, 14.0, 72.1 mg/kg/day (F) for 2 years] ^a	NOAEL = 10.8 mg/kg/day LOAEL. = 54.2 mg/kg/day based on an increase in hypertrophy/steatosis of the liver (both sexes), and increased absolute and relative liver weights (both sexes). Possible borderline increase in uterine stromal polyps in high and mid-dose females.
870.4100b Chronic toxicity (dog)	00132691/00143166 (1986) Acceptable/guideline 0, 15, 75 or 300 mg/kg/day) for 1 year.	NOAEL = 15 mg/kg/day LOAEL = 75 mg/kg/day, based on elevated serum alkaline phosphatase and triglycerides levels, enlarged hepatic cells, increased liver weights, and increased hepatic aminopyrine N-demethylase activity.

Table A.2.2: Toxicity Profile of Paclobutrazol Technical

Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.4200a Carcinogenicity (rat)	See 870.4100a 40762501 (1986) Unacceptable	Maximum tolerated dose (MTD) was not achieved and possible positive response for uterine stromal polyps.
870.4200b Carcinogenicity (mouse)	40762501 (1986) Acceptable/guideline (Chronic phase) 0, 25, 125, or 750 ppm (equivalent to 0, 3.75, 18.75 or 112.5mg/kg /day for 104 weeks. Unacceptable (Carcinogenicity phase)	NOAEL =125 ppm (18.85 mg/kg/day both sexes). LOAEL = 750 ppm (112.5 mg/kg/day both sexes), based on increased severity of steatosis of the liver in males, decreased triglycerides and cholesterol (males) and increased absolute & relative liver weights (M & F). Borderline increase in Leydig cell tumors in high dose males with a significant (p<0.05) pairwise comparison and a significant (p<0.05) trend. However, the high dose is considered inadequate because of the minimal toxicity at this level
870.5100 Bacterial reverse mutation (Ames Assay)	00017480 (1982) 1.6-5000 µg/plate +/-S9 Acceptable/guideline	Negative up to 5,000 µg/plate.
870.5300 <i>In vitro</i> mammalian cell gene mutation (mouse lymphoma cells)	00132695 (1983) 1.0-100 µg/mL -S9; 60- 140 µg/mL +S9 Acceptable/guideline	Negative up to cytotoxic doses.
870.5375 <i>In vivo</i> chromosome aberration (rat bone marrow)	00143156 (1984) 0, 30, 150 or 300 mg/kg/ oral gavage Acceptable/guideline	Negative; no clastogenic effects at any dose tested.
870.5395 Mammalian erythrocyte micronucleus assay (mouse)	00132694 (1983) 0, 87.5 or 140 mg/kg /ip Acceptable/guideline	Negative up to 50 or 80% of the LD ₅₀ via ip injection.
870.5450 Rodent dominant lethal test (mouse)	00143155 (1983) 0, 25, 1000 or 300 mg/kg/day X 5 days/oral gavage Acceptable/guideline	Negative for dominant lethal mutations.
870.5550 <i>In vivo</i> unscheduled DNA synthesis (UDS, rat hepatocytes)	40734304 (1986) 0, 40, 200 or 400 mg/kg Acceptable	Negative, no induction of UDS

Table A.2.2: Toxicity Profile of Paclobutrazol Technical

Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.6200a Acute neurotoxicity screening battery (rat)	49211902 (2013) 0, 30, 150 or 500 mg/kg 10/sex/dose; solvent = 0.5% CMC Acceptable/guideline	NOAEL = 30 mg/kg LOAEL = 150 mg/kg, based on transient alterations in motor activity (i.e., decreased rearing counts and decreased subsession distances) in females 3-4 hours after dosing in motor rearing counts and decreased subsession distances in females 3-4 hours postdosing. activity in motor activity (decrease rearing counts and decreased subsession distances) in females 3-4 hours after dosing. The NOAEL was 30 mg/kg bw.
870.6200b 90 Day neurotoxicity screening battery (rat)	Data waiver granted by HASPOC March 13, 2014 (TXR 0056914)	
870.7485 General Metabolism (rat)	00132696 (1983) Nonguideline M&F: 10 mg/kg single gavage dose	During the 4 days following administration, 39.18 and 52.6 % of the dose was recovered in the urine of male and female rats, respectively. Fecal recoveries were 53.49% in the males and 37% in females. Approximately 60% of the administered dose was accounted for in feces and urine of males and females during the first 24 hours of dosing. Residue concentrations in tissues 3 or 4 days after dosing did not indicate accumulation, and urinary excretion along with slow fecal excretion indicated a significant gastrointestinal absorption of the dose.
870.7485 General Metabolism (rat)	00143161 (10/1983) Acceptable/guideline 5 mg/kg (single oral gavage)	70-80% of the 5 mg/kg dose was excreted during 72 hours after dosing. Approximately 55% of the dose was recovered in the urine of both sexes, and 32% or 24% was recovered in the feces of males and females, respectively. 7 days after dosing, liver tissue contained 0.017 to 0.028 ppm; gastrointestinal tract contained 0.012-0.025 ppm. No other tissue levels were detectable.
870.7485 General Metabolism (rat)	00143162 (2/1984) Acceptable/guideline 250 mg/kg	70-80% of the 250-mg/kg dose was excreted during first 72 hours after dosing. Approximately 40% of the dose was excreted in urine from males and 30% from females. Approximately 30% and 40% of the dose was recovered in the feces of males and females, respectively after 72 hours. Gastrointestinal contents had 0.303 (♂) and 1.461 ppm (♀); liver samples contained from 0.444 to 0.848 ppm.
870.7485 General Metabolism (rat)	EPA Accession No. 254865 Acceptable/guideline 5 and 250 mg/kg (dose selection study for MRID 00143160	A single dose of 250 mg/kg increased the liver weight, and the 5 mg/kg dose had no effect. These results were used as the basis for doses selection.

Table A.2.2: Toxicity Profile of Paclobutrazol Technical

Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.7485 General Metabolism (Bioaccumulation in rat)	00143160 (5/1984) Acceptable/guideline 250 mg/kg (single oral gavage)	Autoradiographs indicated that the liver, kidneys, and gastrointestinal tract contained the administered radiolabel. Similarly, the disposition of the ¹⁴ C label after a single oral dose of 250 mg/kg is limited to the gastrointestinal contents and to a lesser extent to the liver and kidneys.
870.7485 General Metabolism (rat)	00143164 (5/1984) Acceptable/guideline 5 mg/kg (oral gavage)	Concentrations of radiolabel plateaued in livers and kidneys after 28 days consecutive daily 5 mg/kg doses. Maximum levels: 2.22-2.55 ppm in liver and approx. 1 ppm in kidney. Blood levels rose throughout the 49-day dosing period (max. level = 0.158 ppm). Levels in fat were below the limit of detection (0.081 ppm) at most observations, and ranged from 0.046-0.148 ppm at other observations. Elimination of radioactivity from the livers and kidneys occurred in a biphasic manner. Half times for the first phase were 1.36 & 1.56 days for liver & kidney, respectively. Times for the 2 nd phase were 6.69 and 9.26 days, respectively.
870.7485 General Metabolism (rat)	00143165 (5/1984) Acceptable/guideline 5 or 250 mg/kg (single oral gavage)	A single oral gavage dose (5 or 250 mg/kg) paclobutrazol was absorbed almost completely by male and female rats. Triazole and halogenated phenyl moieties not affected in rat. Pentanol moiety oxidized to a diol or carboxylic acid & excreted in free or conjugated forms. Males excreted more of carboxylic acid metabolites than females but proportion of acid metabolites excreted by females increased as dose decreased. Two male and 2 female rats received a single dose of 250 mg/kg paclobutrazol and were allowed a 24-hour recovery period. The bile duct of these rats was cannulated and the rats were given a second dose of 250 mg/kg paclobutrazol, and samples of the bile, urine and feces were collected over a 4-day interval and measured. The highest percentage of radioactivity was general recovered after 48 hours in bile (46%, ♂ and 24% ♀), urine (12%, ♂ and ♀), and feces (0.9%, ♂ and 0.3% ♀).
870.7485 General Metabolism (dog)	00143163 (1984) Acceptable/guideline 5 mg/kg (single oral gavage)	80-85% of 5 mg/kg dose extracted during first 24 hours after dosing. Approx. 50% of dose recovered in urine of both sexes, & 35-40% recovered in feces. Peak blood levels at 1 hour after dosing (4.1-4.4 ppm in plasma) declined to pre-dose levels 24-48 hours after treatment. No detectable levels in tissue & no sex differences were observed.
870.7600 Dermal penetration (Rat)	41048202 0.011 mg/kg on an area 10 cm ² /rat Acceptable/guideline	The % dose absorbed and remaining on the washed application site (potentially absorbable) at 10 hours was 15.1% and 3.6% respectively. (10 hours) and 24.5 % and 2.7% (24 hours), respectively. Since absorption rates were not measured beyond 24 hours, the percent absorbed + the percent potentially absorbed = 18.7% for 10 hours.

Table A.2.2: Toxicity Profile of Paclobutrazol Technical		
Guideline No./ Study Type	MRID No. (year)/ Classification/Doses	Results
870.7800 Immunotoxicity	Data waiver granted by HASPOC March 13, 2014 (TXR 0056914)	

^a Based on new supplemental data on achieved doses (TXR no. 0056158).

^b Based on new supplemental data on individual and historical control pup data submitted by the registrant in MRID 47338506 (TXR no. 0056158).

Appendix A.3. Hazard Identification and Endpoint Selection

A.3.1 Acute Reference Dose (aRfD) –General Population

Study Selected: Acute Neurotoxicity in rats 870.6200a [§81-8]

MRID No. 49211902

Dose and Endpoint for Risk Assessment: NOAEL = 30 mg/kg

Comments about Study/Endpoint/Uncertainty Factors: For the acute dietary risk assessment, the acute neurotoxicity study in rats, with a NOAEL of 30 mg/kg, was selected because it was the appropriate exposure duration of concern (effects were seen within 3-4 hours of dosing) and it occurred in the most sensitive species. An Uncertainty Factor (UF) of 100 was applied to account for both the interspecies extrapolation (10X) and intraspecies variability (10X). On this basis, the aRfD was calculated to be 0.30 mg/kg.

$$\text{Acute RfD (general population)} = \frac{30 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}} = 0.30 \text{ mg/kg}$$

A.3.2. Acute Reference Dose (aRfD) –Females 13-49

Study Selected: Prenatal developmental study in rats 870.3700a [§83-3]

MRID No. 00143158

Dose and Endpoint for Risk Assessment: Developmental NOAEL = 10 mg/kg

Comments about Study/Endpoint/Uncertainty Factors: The most sensitive point of departure was 10 mg/kg/day from the developmental rat study (MRID 00143158), based on increased incidences of partial ossification of the 7th vertebra and 14th rib in fetuses at the LOAEL of 40 mg/kg/day. Both effects were dose-related, statistically significant, outside of the historical control ranges provided by the investigator, and reproducible at comparable doses (also seen MRID 00132693), which occurred in the absence of maternal toxicity. The study was specifically selected for this exposure scenario because increases in 14th rib may be the result of a single

exposure. An Uncertainty Factor (UF) of 100 was applied to account for interspecies extrapolation (10X) and intraspecies variability (10X). The acute reference dose (aRfD) for females 13-49 was calculated to be 0.1 mg/kg/day. The selection of this study and the PoD is protective of the pregnant female and the developing fetus.

$$\text{Acute RfD (general population)} = \frac{10 \text{ mg/kg (NOAEL)}}{100 \text{ (UF)}} = 0.10 \text{ mg/kg}$$

A.3.3. Chronic Reference Dose (cRfD)

Study Selected: Two-year chronic/carcinogenicity feeding study in rats 870.4300a [§83-5]

MRID No. 40734301

Dose and Endpoint for Risk Assessment: NOAEL = 10.8 mg/kg/day

Comments about Study/Endpoint/Uncertainty Factors: For the chronic dietary risk assessment, the 2-year chronic/carcinogenicity feeding study in rats, with a NOAEL of 10.8 mg/kg/day, was selected because it was near the lowest NOAEL in the most sensitive species and more appropriately covers the exposure duration of concern. An Uncertainty Factor (UF) of 100 was applied to account for both the interspecies extrapolation (10X) and intraspecies variability (10X). On this basis, the cRfD was calculated to be 0.11 mg/kg/day.

$$\text{Chronic RfD} = \frac{10.8 \text{ mg/kg/day (NOAEL)}}{100 \text{ (UF)}} = 0.11 \text{ mg/kg/day}$$

A.3. 4 Incidental Oral Exposure (Young children, 1-2 years old): Short- (1-30 days) and Intermediate-term (1-6 months)⁶⁹

Study Selected: Reproductive Toxicity (Rats)

870.3800 [§83-3]

MRID No. 40734303/47338506

Dose and Endpoint for Risk Assessment: Offspring NOAEL = 23.2 mg/kg/day

Comments about Study/Endpoint/Uncertainty Factors: Based on the turf use pattern in parks. The target population for incidental oral (short and intermediate term) was identified as young (1-2 year old) children, because of hand-to-mouth activities. Quantification of incidental oral ingestion risks was performed using the 2-generation reproduction study, based on a revisit of the data and in consideration of supplemental data on achieved doses provided by the registrant (TXR

No. 0056158). The offspring NOAEL for this study is 23.2 mg/kg/day. The LOAEL is 116.9 mg/kg/day, based on increased incidence of chromodacryorrhea, thickened eyelids and dental malocclusion; increased liver weights; mottling or accentuation of the lobular structure of the liver along with liver enlargement, pallor and discoloration in the male and female pups of both generations. This study was selected to protect the infants and small children. An MOE of 100 is required which includes interspecies extrapolation (10X) and intraspecies variability (10X).

A.3.5. Dermal Exposure (Females 13-49): Short- (1-30 days) and Intermediate-term (1-6 months) Occupational

Study Selected: Prenatal developmental study in rats

870.3700a [§83-3]

MRID No. 00143158

Dose and Endpoint for Risk Assessment: NOAEL = 10 mg/kg/day

Comments about Study/Endpoint/Uncertainty Factors: The original study considered for these exposure scenarios was the 21-day dermal study in rabbits with a NOAEL of 10 mg/kg/day. However, the LOAEL (100 mg/kg/day) was based solely on irritation, which is not considered an appropriate endpoint for occupational or residential exposure. The Agency prefers to mitigate irritation through product labeling and the use of gloves and/or other protective clothing, which minimizes dermal contact. To safeguard the pregnant female and the developing fetus, the most sensitive point of departure was 10 mg/kg/day from the developmental rat study (MRID 00143158), based on increased incidences of partial ossification of the 7th vertebra and 14th rib in fetuses at the LOAEL of 40 mg/kg/day. Both effects were dose-related, statistically significant, outside of the historical control ranges provided by the investigator, and reproducible at comparable doses (also seen MRID 00132693), which occurred in the absence of maternal toxicity. The study was specifically selected for this exposure scenario because increases in 14th rib may be the result of a single exposure. The dermal absorption factor (DAF) of 18.7 is applied to the NOAEL (See A.3.7). An MOE of 100 which accounts for interspecies extrapolation (10X) and intraspecies variability (10X). The selection of this study and the PoD is protective of the pregnant female and the developing fetus.

A.3.6. Inhalation Exposure (Young children, 1-2 years old): Short- (1-30 days) and Intermediate-term (1-6 months)

There is no exposure of young children to paclobutrazol via the inhalation route.

A.3.5. Inhalation Exposure (Females 13-49): Short- (1-30 days) and Intermediate-term (1-6 months) Occupational

Study Selected: Prenatal developmental study in rats

870.3700a [§83-3]

MRID No. 00143158

Dose and Endpoint for Risk Assessment: NOAEL = 10 mg/kg/day

Comments about Study/Endpoint/Uncertainty Factors: Since a repeated dose inhalation study was not available, an oral NOAEL was selected for this risk assessment. See Section A.3.4. Since an oral dose was selected absorption via inhalation is presumed to be equivalent to oral absorption. An MOE of 100 is required which includes the interspecies extrapolation (10X) and intraspecies variability (10X).

A.3.7 Dermal Absorption

A dermal penetration study in rats (MRID 41048202) was available for paclobutrazol in which male rats were dermally exposed on an area of 10 cm²/rat. At the time this study was reviewed, the absorbed dose was calculated as the sum of the residues from the urine, feces, cage wash, and carcass (excluding the skin at the application site). The potentially absorbable dose included the residues in the skin at the application site. Previously, the most conservative value for total absorbable (sum of the absorbed dose and potentially absorbable dose) was used, which was 24.5% following a 24-hour exposure period. Currently, the policy is to use 8-hours exposure and to assume that residues found in the skin are potentially absorbable, unless data are provided to demonstrate otherwise. This policy reflects an 8-hour work day, and ongoing exposure is expected to cease at the end of the workday. Likewise, the Agency's position is to be conservative to insure public safety, and this is reflected in the assumption that residues found in the skin will be absorbed, unless there are data which contradicts this assumption. Therefore, values following the 10-hour exposure period were used and the total absorbable dose was calculated to be 18.5%. The percentage of the dose absorbed and remaining on the washed application site (potentially absorbable) at 10 hours was 15.1% and 3.6% respectively, and 24.5 % and 2.7% (24 hours), respectively. Since absorption rates were not measured beyond 24 hours, the percent absorbed plus the percent potentially absorbed (18.7%) for 10 hours was calculated. For risk assessment purposes, HED is using the conservative assumption that the **dermal absorption factor (DAF) of 18.7% for paclobutrazol**.

A.4 Executive Summaries

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity- Rat

In a 90-day feeding study (MRID 00132689/47338506), groups of 20 Wistar rats/sex/group received diets containing 0, 50, 250, or 1250 ppm paclobutrazol (91.9%) for 90 days. The actual doses were 0, 3.7/4.4, 18.8/21.6 or 93.0/106.5 mg/kg/day (M/F).

No deaths or clinical signs of toxicity were seen. Body weight was unaffected by treatment. However, at 1250 ppm, increased liver weights (16%) and a 2-fold increase in aminopyrene-N-demethylase activity was seen in the females. These effects were noted to a lesser extent in the females given diets containing 250 ppm. Without concomitant histological changes, however, the effects at the mid dose are unlikely to be toxicologically significant.

Accordingly, the NOAEL is 250 ppm [18.8/21.6 mg/kg/day (M/F)] and the LOAEL is 1250 ppm [93.0/106.5 mg/kg/day (M/F)], based on elevated liver weights in females, serum

cholesterol in females, hepatic aminopyrene-N- demethylase activity in both sexes and alanine transaminase levels in males.

The study is classified as Acceptable guideline and satisfies the guideline requirements of a 90-day oral toxicity study (OPPTS 870.3100; OECD 408).

COMMENT: This is an updated Executive Summary. The original Executive Summary was revised to include the actual dose levels on a mg/kg/day basis and provides table correcting the previous one and making it consistent with the risk assessment of March 2012.

870.3200 21/28-Day Dermal Toxicity- Rabbit

In a 21-day dermal toxicity study (MRID 00132688), groups of 10 male and 10 female New Zealand white rabbits were treated with paclobutrazol at rates of 0, 10, 100, or 1000 mg per kg for 21 days. Twenty-four hours prior to the first application of the test substance, hair was clipped from the mid dorsal region of each rabbit. About 10% of each animal's surface area was clipped; clipped treatment sites were abraded. The treatment sites on the remaining animals in each group were left intact. Hair clipping was repeated as needed during the 21-day treatment period, and abrasion was done on a weekly basis during the test. The test substance was suspended in 1% aqueous carboxymethyl cellulose and applied to the prepared skin sites bodyweight. After each application the treated areas were covered with an occlusive dressing for 6 hours. At the end of that time the bandages were removed, and each test site was washed with warm tap water and blotted dry. This procedure was followed once each day 5 days each week for 3 consecutive weeks. During the study the animals were observed daily for the appearance of toxic signs, mortality, and behavioral changes.

All dose levels (10, 100, or 1000 mg/kg/day) caused irritation of the abraded skin of test animals but only the 100 and 1000 mg/kg/day doses irritated the intact skin sites of test animals. The irritation began to appear during the second week of dermal applications, and the degree of irritation increased with dose. Histologically, treated skin exhibited hyperkeratosis, acanthosis, and inflammatory changes of the superficial dermis. The NOAEL for intact skin with respect to these effects is 10 mg/kg/day, and the LOAEL is 100 mg/kg/day. The 1000 mg/kg/day dose (highest dose tested) caused severe irritation after two weeks of application to the skin of rabbits. The study is classified as Acceptable/guideline

A.4.2 Prenatal Developmental Toxicity**870.3700a Prenatal Developmental Toxicity- Rat (#1)**

In a prenatal developmental toxicity study (MRID 00132693), paclobutrazol (92.4%) suspended in corn oil was administered to pregnant Wistar derived Alderley Park strain rats (24/dose) via gavage at concentrations of 0, 40, 100, or 250 mg/kg/day on gestation days (GD) 6 through 15. All dams were sacrificed on GD 21 and their uterine contents examined.

Maternal effects: The highest dose tested (250 mg/kg/day) caused mortality (5/24 animals) as well as significant decreases in body weight gain, decreased food consumption and food

utilization. Staining of the genital and ventral areas and grossly observable liver effects (pallor and enlargement) were also noted at the high dose. Toxic effects at 100 mg/kg/day were decreased food consumption and food utilization. **Based on a revisit of the data, the decreased food consumption and food efficiency reported at 100 mg/kg/day are not considered toxicologically relevant because neither observation was significant and no adverse effects were reported on body weight.**

Accordingly, the revisited maternal NOAEL is 100 mg/kg/day and the LOAEL is 250 mg/kg/day, based on mortality, significantly decreased body weight gain and food efficiency during dosing, and gross liver effects (pallor, accentuated lobulation, and enlargement).

Developmental effects: In the previous DER, a NOEL was not established. Therefore, the data were revisited and the following conclusions were reached:

As summarized in Table 1, the incidence of total skeletal defects and/or variations in the fetuses was dose-related and significant ($p < 0.01$) at 40, 100 and 250 mg/kg/day. The major contributors to the increased incidence of defects and variations were partial ossification of the transverse process of the 7th cervical vertebra, which is classified as a minor defect and extra rib (14), which is considered a variant. As further shown in Table 1, the dose-related increase in the incidence of unilateral partial ossification of the 7th vertebra was significant ($p < 0.01$) at ≥ 100 mg/kg while the incidence of this effect bilaterally was dose-related and significantly ($p < 0.01$) increased at ≥ 40 mg/kg. These increases, which were all outside of the historical control ranges, generally resulted from the occurrence of multiple fetuses in the affected litters of all treatment groups. However, the combined number and frequency of litters affected was not appreciably higher than control at any dose (e.g., 79% at 250 mg/kg/day vs. 54% for controls); the litter data were not evaluated statistically.

Similarly, the incidence of fetuses with bilateral extra ribs (14th) was dose-related and significantly increased at all doses, with the majority or 100% of the treated litters demonstrating this effect in multiple fetuses per litter. These values were also outside of the historical control range. Nevertheless, the frequency of unilateral extra rib (14) was lower or comparable to control for all treatment groups. It is of note that these findings were reproduced in a subsequent study (MRID 00143158).

The only external/visceral defect of note was cleft palate, which was only observed at a low frequency (3 fetuses from 2 litters) at a maternally toxic dose (250 mg/kg/day).

The developmental NOAEL was not established. The LOAEL is 40 mg/kg/day, based on a significant and dose-related increase in fetuses with the incidence of bilateral partial ossification of the 7th cervical bone and in bilateral significant increases in the number of fetuses with an extra rib (14). These incidence rates were outside of the historical control ranges. Increases in the number of litters affected with these defects were also seen but not analyzed statistically. Cleft palate was reported in 3 fetuses from 2 litters at 250 mg/kg/day.

This developmental toxicity study is classified **acceptable/guideline** (OPPTS 870.3700; §83-

3[a]) and satisfies the guideline requirement for a developmental toxicity study in the rat.

COMMENTS: This is a revised Executive Summary, which provides a discussion of changes made to the original DER (revised NOAEL/LOAEL) and data tables to support the conclusions.

Table 1. Summary of the incidence of fetuses/litters with most frequently observed skeletal defects or variations following exposure to paclobutrazol in the rat developmental study (MRID 00132693).

Observation	Dose of Paclobutrazol (mg/kg/day)			
	0	40	100	250
	Total Skeletal Defects/Variations			
No. Fetuses Examined	204	198	190	153
No. Fetuses Showing Effect	84	110	117	111
% Fetuses Affected	41%	56% **	61% **	73% **
No. Litters	24	24	24	19
Partial Ossification of 7th Cervical Vertebra				
Unilateral	Fetal Historical control Range: 2.5-13%			
No. Fetuses Showing Effect/% Fetuses Affected	12/6%	20/10%	33**/17%	29**/19%
Bilateral	Fetal Historical Control Range : 0.6 -3.4%			
No. Fetuses Showing Effect/% Affected	1/0.5%	12**/6%	16**/ 8%	18**/12%
Combined No. Litters Affected/% Affected	13/54%	10/42%	14/58%	15/79%
Increased Incidence of 14th Rib				
Unilateral Extra Rib (14)	Fetal Historical Control Range: 8 – 16%			
No. Fetuses Showing Effect/% Affected	32/16%	18/9%	34/18%	21/14%
No. Litters Affected/% Affected	14/58%	17/71%	20/83%	16/84%
Bilateral Extra Rib (14)	Fetal Historical Control Range: 8 – 14%			
No. Fetuses Showing Effect/% Affected	22/11%	36*/18%	101**/53%	104**/68%
No. Litters Affected/% Affected	12/50	14/58%	24/100%	19/100%

Note: Two-thirds of the fetuses were examined for skeletal defects

*Significantly altered $p < 0.05$

**Significantly altered $p < 0.01$

870.3700a Prenatal Developmental Toxicity- Rat (#2)

In a prenatal developmental toxicity study (MRID 00143158), paclobutrazol (92.4%) suspended in corn oil was administered to pregnant Wistar derived Alderley Park strain rats (24/dose) via gavage at concentrations of 0, 2.5, 10, 40, or 100 mg/kg/day on gestation days (GD) 7 through 16. All dams were sacrificed on GD 21 and their uterine contents examined.

Maternal effects: There were no treatment-related effects on the dams at any dose.

Consequently, the maternal NOAEL is > 100 mg/kg/day.

Developmental effects: In the previous DER, the NOEL was listed as 10 mg/kg/day and the LOEL was 40 mg/kg/day, based on dose-related fetal effects (renal dilatation, hydroureter, and minor skeletal defects or variations). The data were revisited and the following conclusions were reached:

The numbers of corpora lutea, implantations, and live fetuses were comparable among the groups, and fetal body weights were comparable among the groups.

As summarized in Table 1, the incidence of total skeletal defects and/or variations in the fetuses was dose-related and significantly increased at 40 ($p<0.05$) and 100 mg/kg/day ($p<0.01$). The major contributors to the increased incidence of defects and variations were partial ossification of the transverse process of the 7th cervical vertebra, which is classified as a minor defect and an extra rib, which is considered a variant. As further shown in Table 1, the increased incidence of fetuses with unilateral partial ossification of the 7th vertebra was dose-related and significantly increased at 10 mg/kg/day ($p<0.05$) and at ≥ 40 mg/kg ($p<0.01$) while the incidence of this effect bilaterally was only significant ($p<0.05$) at 100 mg/kg. Although the incidence of this effect was significant for affected fetuses, no significant increase was seen in the number of litter affected. Since the number of affected litters is considered the critical indicator of developmental toxicity, the findings at 10 mg/kg/day are insufficient to conclude developmental toxicity. It is also of note that the above values were outside of the historical control ranges. The significant increases generally result from the occurrence of multiple fetuses in the affected litters of all treatment groups. These data are in good agreement with similar findings in an earlier rat developmental study performed by the same laboratory on paclobutrazol (MRID 00132693). With the exception of a significant increase ($p<0.05$) in the number of fetuses showing bilateral partial ossification of the 7th vertebra, the response was limited to the high dose.

The incidence of fetuses with bilateral extra ribs (14th) and the percentage of litters showing this effect were dose-related and significantly increased at 40 and 100 mg/kg/day paclobutrazol. As previously observed for skeletal effects in this and the earlier studies, the majority or 100% of the treated litters demonstrated these effects in multiple fetuses per litter. These values were also outside of the historical control ranges. Nevertheless, the frequency of unilateral extra rib (14) was unaffected by treatment.

Table 2 summarized the incidence data for external and/or visceral defects. As shown, the incidence of fetuses with external and/or visceral defects was significantly ($p<0.01$) increased at 40 and 100 mg/kg/day. The most frequently observed effects were slight to moderate renal dilation, increased hydroureter and unilateral kinked ureter. Significant increases in slight renal

dilation were noted at 40 and 100 mg/kg/day but the number of litters affected was not significant. Significant hydroureter was seen in 3% of the fetuses of the high dose group in 4 of 24 litters. However, information from the open literature (Woo and Hoar, 1972; NTP-CERHR, 2004) indicates that hydroureter is more appropriately classified as a variation and not as a defect or a malformation. Likewise, the significant increase in unilateral kinked ureter at 40 and 100 mg/kg/day may be resolved at weaning since Woo and Hoar (1972) also observed that the rate of development of the renal system in normal rats occurs very late and may not be completed until several weeks after birth.

Based on a revisit of the data, the developmental NOAEL is 10 mg/kg/day. The LOAEL is 40 mg/kg/day, based on the significant and dose-related increases in fetuses and litters with unilateral partial ossification of the 7th cervical vertebra and significant and dose-related bilateral increases in fetuses and litters with an extra rib (14).

This developmental toxicity study is classified **acceptable/guideline (OPPTS 870.3700; §83-3[a])** and satisfies the requirement for a developmental toxicity study in the rat.

REFERENCES

Woo, DC and Hoar, RM. (1972). "Apparent hydronephrosis" as a normal aspect of renal development in late gestation of rats: The effect of methyl salicylate. *Teratology* 6: 191-196.

NTP-CERHR, 2004. National Toxicology Program-Center for evaluation of Risks to Human Reproduction. NTP-CERHR Monograph on the potential human reproductive and developmental effects of ethylene glycol. NIH Publication No. 04-4481. U.S. Department of Health and Human Services.

COMMENTS: This is a revised Executive Summary. The original review NOEL (10 mg/kg/day) was based on dose-related fetal effects (renal dilatation, hydroureter, and minor skeletal defects or variations) at the LOEL of 40 mg/kg/day. Based on a reassessment of the data, the NOAEL and LOAEL have been revised to reflect new information and to make it consistent with the risk assessment of October 2014. Additionally, data tables have been added to provide support for these conclusions.

Table 1. Summary of the incidence of fetuses/litters with skeletal defects or variations following exposure to paclobutrazol in the rat developmental study (MRID 00143158).

Observation	Dose of Paclobutrazol (mg/kg/day)				
	0	2.5	10	40	100
	Total Skeletal Defects/Variations				
No. Fetuses Examined	176	213	199	200	202
No. Fetuses Showing Effect	61	80	75	89	106
% Fetuses Affected	35%	38%	38%	44%*	52.5%**
No. Litters	22	24	24	24	24
Partial Ossification of 7th Cervical Vertebra					
Unilateral	Fetal Historical Control Range 2.5-13%				
No. Fetuses Showing Effect/% Affected	7/4%	16/7.5%	18*/9%	35**/17%	40**/20%
No. Litters Affected/% Affected	6/27%	10/42%	11/46%	15*/62.5%	20**/83%
Bilateral	Fetal Historical Control Range 0.63-3.4%				
No. Fetuses Showing Effect/% Fetuses Affected	3/2%	4/2%	1/0.5%	7/3%	14*/7%
No. Litters Affected	3/14%	3/12.5%	1/4%	5/21%	7/29%
Increased Incidence of 14th Rib					
Bilateral Extra Rib (14)	Fetal Historical Control Range 9.7-14.2				
No. Fetuses Showing Effect/% Affected	24/14%	31/15%	25/13%	57**/29%	86**/43%

Observation	Dose of Paclobutrazol (mg/kg/day)				
	0	2.5	10	40	100
	Total Skeletal Defects/Variations				
No. Litters Affected/% Affected	11/50%	12/50%	9/37.5%	19**/79%	23**/96%

Note: Two-thirds of the fetuses were examined for skeletal defects

*Significantly altered $p < 0.05$

**Significantly altered $p < 0.01$

870.3700b Prenatal Developmental Toxicity- Rabbit

In a developmental toxicity study (MRID 407343020), Paclobutrazol was tested in New Zealand White rabbits at the following dose levels: 0, 25, 75 or 125 mg/kg/day. The maternal toxicity NOEL is 75 mg/kg/day and the maternal LEL is 125 mg/kg/day based on decreases in body weights and body weight gain and food consumption during dosing. The developmental toxicity NOEL is 75 mg/kg/day and the LEL is 125 mg/kg/day based on the increased incidence of extra ribs in pups.

The study is reclassified as Acceptable/Guideline

A.5.3 Reproduction and Fertility Toxicity

870.3800 Reproduction and Fertility Effects – Rat

In a multigenerational reproduction study (MRIDs 40734303, 47338506), paclobutrazol (technical, 92.4%) was tested in Alpk:AP (Wistar derived) rats at the following dose levels: 0, 50, 250 and 1250 ppm (0, 2.5, 12.5 or 62.5 mg/kg/day) in the diet. Each generation began with 17 males and 34 females for each control and high does group and 15 males and 30 females for each low and mid-dose group. One male was mated with 2 females from the same test group until sperm plugs were observed in vaginal smears. The F_0 parental animals were given test diets for 12 weeks before they were mated, and the F_1 parental animals were not mated until 11 weeks after they were selected from the F_{1A} litters. Selection of parents for the F_1 generation was made when the pups were 36 days of age, and the mated animals in the study were between 16 and 20 weeks of age at mating.

Supplemental information (MRID 47338506) was provided by the registrant on individual pup data and achieved doses of paclobutrazol. Based on an evaluation of these data, the overall doses administered were as follows:

Overall Average Dose Received (mg/kg/day) of Paclobutrazol During the Pre-mating Period in the 2-Generation Reproduction Study (MRID 40734303)^a

Generation/Sex	Dietary Concentrations of Paclobutrazol (mg/kg/day)		
	50 ppm	250 ppm	1250 ppm
F ₀ Parents: Male	4.8	24.4	121.2
Female	5.1	25.9	126.2
F ₁ Parents: Male	4.7	23.2	116.9
Female	5.1	24.8	124.1

^a Data were extracted from the Study Report, p. 10, MRID 47338506, Supplemental data

In the previous DER at 250 ppm and above, an increased incidence of chromodacryorrhea and thickened eyelids was observed in both generations. This was observed in both the prenatal animals and in the pups. In the parental animals, the incidences were within the historical control range. At 1250 ppm, increased liver weights were observed in females in both generations (23% absolute, 26% relative F₀; 7% absolute, 14% relative F₁) and fatty change in the liver was observed in F₀ females (23/30 versus 0/30 for the controls). Increased liver weights, mottling or accentuation of the lobular structure, liver enlargement and pallor and discoloration were observed in male and female pups from both generations. In addition to the changes in the liver, dental malocclusion was observed in both generations (parental animals and pups; incidence in the parental animals was within the historical control range) and thickening of the urinary bladder wall was observed in 1 F₀ and in 3 F₁ high dose females. The reproductive/systemic LOEL is 250 ppm (12.5 mg/kg/day) based on increased liver weights and on fatty change in the liver of parental females; and on an increased incidence of chromodacryorrhea, and thickened eyelids, dental malocclusion, increased liver mottling or accentuation of the lobular structure, liver enlargement and pallor and discoloration in male and female pups. The reproductive/systemic NOEL is 50 ppm (2.5 mg/kg/day).

From a revisit of the data, the following was seen:

Parental animals: There were no treatment-related deaths in the parental animals, and body weights were not adversely affected in either sex/generation. The maternal body weights were also not adversely affected (< 10% reduction) during gestation or lactation, although statistical significance was sometimes attained. Although there was a slight increase in the incidence of chromodacryorrhea, thickened eyelids, and twisted snout in the F₁ adult animals, the incidence at 250 ppm was within the historical control incidence and not considered adverse. There were no adverse effects on mating, fertility, or gestation interval in either generation. There were no treatment-related effects on litter size, pup body weights, or pup survival, although pup survival (F₁A litters) was reduced compared to the control at 250 ppm and 1250 ppm. However, the survival rate was within the historical control, and survival was not reduced in the F₁B litters or in the F₂ generation.

Based on a revisit of the parental data, the following observational signs observed in the parental animals are presented in Table 1:

Table 1. Observational Signs Observed in the Parental Animals				
Parameter/dose	0 ppm	50 ppm	250 ppm	1250 ppm
F0 generation (males/females)				
Chromodacryorrhea	0/1	0/1	0/2	1/1
Thickened eyelid	0/1	0/1	0/2	0/1
Twisted snout	0/1	0/0	0/0	1/0
F1 generation (males/females)				
Chromodacryorrhea	0/0	0/0	2/3	3/7
Thickened eyelid	0/2	0/0	2/2	1/8
Twisted snout	0/0	0/0	1/1	0/1

n= 15/30

Based on these data, the parental NOAEL for the two-generation reproduction study should be 250 ppm (equivalent to 23.2 mg/kg/day) because the response noted at 250 ppm (an increased incidence of chromodacryorrhea and thickened eyelids observed in both generations) was generally within the provided historical control ranges, and, therefore, is not considered a treatment-related effect. Consequently, the parental LOAEL should be 1250 ppm (equivalent to 116.9 mg/kg/day; the highest dose tested), based on an increased incidence of chromodacryorrhea and thickened eyelids in F1 females and increases in liver weight and fatty changes in the liver and thickening of the urinary bladder wall in the females.

Reproductive effects: Since there were no consistent effects on reproductive performance, the reproductive NOAEL is 1250 ppm (equivalent to 116.9 mg/kg/day); an LOAEL was not established.

Offspring: Table 2 presents the incidence of chromodacryorrhea in the offspring. As shown, the number of pups affected with chromodacryorrhea and the number of litters affected is generally within the historical control for all generations at 250 ppm. Only the pups and litters of the 1250-ppm group show increases beyond the historic control for these observations. Similarly, the number of pups affected with thickened eye lids and the number of litters affected is generally within the historical control for all generations at 250 ppm (Table 3). Only the pups and litters of the high dose group show increases beyond the historic control for these observations. Likewise, the incidence of dental malocclusions was only increased in all generations of pups in the high-dose groups.

The offspring NOAEL is 250 ppm (equivalent to 23.2 mg/kg/day), and the LOAEL is 1250 ppm (equivalent to 116.9 mg/kg/day), based on the increased incidence of dental malocclusions, chromodacryorrhea, thickened eyelids, increased liver weights, mottling or accentuation of the lobular structure of the liver, along with liver enlargement, pallor and discoloration in the male and female pups of both generations.

This study is classified **acceptable/guideline (OPPTS 870.3800; §83-4)** and satisfies the guideline requirement for a two-generation reproductive study in the rat.

COMMENTS: This is a revised Executive Summary. The original review considered the findings at 250 ppm as the basis for an adverse effect (LOAEL) for the entire study (reproductive and systemic). Based on a reassessment of the data, the NOAEL and LOAEL have been revised

to reflect the new information and to make it consistent with the risk assessment of October 2014. Additionally, separate NOAELs/LOAELs for offspring and reproductive toxicity have been identified, and data tables have been added to provide support for these conclusions.

Table 2. Summary of the incidence of pups with chromodacryorrhea following exposure to paclobutrazol in the rat developmental study (MRID 40734303).

Dose	No. of pups	No. of pups affected	% pups affected	No. of litters	No. of litters affected	% litters affected
F _{1A}						
0	303	5	2	25	4	16
50	320	-	-	27	-	-
250	279	10	4	28	5	18
1250	305	37	12	28	16	57
F _{1B}						
0	237	2	1	24	1	4
50	262	1	0.4	26	1	4
250	223	6	3	27	4	15
1250	250	7	3	26	5	19
F ₂						
0	282	-	-	27	-	-
50	295	4	1	27	2	7
250	334	10	3	30	7	23
1250	266	13	5	27	8	30

Historical control = 1-22 pups affected; 0-6 litters affected (MRID 47338506).

Table 3. Summary of the incidence of pups with thicken eye lids following exposure to paclobutrazol in the rat developmental study (MRID 40734303).

Dose	No. of pups	No. of pups affected	% pups affected	No. of litters	No. of litters affected	% litters affected
F _{1A}						
0	303	4	1	25	4	16
50	320	-	-	27	-	-
250	279	8	6	28	4	14
1250	305	38	12	28	17	61
F _{1B}						
0	237	2	1	24	1	4
50	262	1	0.4	26	1	0.4
250	223	6	3	27	4	15
1250	250	12	5	26	8	31
F ₂						
0	282	-	-	27	-	-
50	295	-	-	27	-	-
250	334	5	1.5	27	4	13
1250	266	17	6	30	8	30

Historical control = 1-8 pups affected; 0-4 litters affected (MRID 47338506).

A.4.4 Chronic Toxicity

870.4100a Chronic Toxicity – Rat

In a combined chronic feeding/oncogenicity study (MRIDs 40734301, 47078901), Sprague-Dawley Crl:CD(SD)BR rats (50/sex/dose group) were fed 0, 50, 250 or 1250 ppm technical Paclobutrazol (92.4% pure) in the diet (males 0, 2.2, 10.8, or 54.2 mg/kg/day; females 0, 2.8, 14.0, or 72.1 mg/kg/day) for 2 years. An additional ten animals/sex/group were placed in the control and high dose groups as microbiological sentinels. Another 10 animals/sex were added

that were sacrificed at 52 weeks. Based on new information provided by the registrant (MRID 47078901) actual achieved doses were as follows:

Dose	Dietary Concentrations of Paclobutrazol (mg/kg/day)		
	50 ppm	250 ppm	1250 ppm
Male	2.2	10.8	54.2
Female	2.8	14.0	72.1

For more details see TXR 0056158.

There were no treatment-related effects on mortality or any clinical signs of toxicity in either sex. Body weight was not adversely affected in males, but females at the high dose showed a progressive decrease in body weight, which was not statistically significant ($\downarrow$ 10% by week 20; $\downarrow$ 15% by week 52, and $\downarrow$ 16% by week 104).

Results show that at 1250 ppm, there was an increase in hypertrophy/steatosis of the liver (both sexes) and increased liver weights (14 and 13% in males and 9 and 24% in females for absolute and relative liver weights over control values, respectively).

There appeared to be a borderline increase in uterine stromal polyps in the high dose and possibly mid—dose females (0/50, 4/50, 5/50 and 7/50 for the control, low dose, mid—dose and high dose groups, respectively). Pairwise comparisons were statistically significant at all dose levels ($p < 0.05$, $p < 0.01$ and $p < 0.01$ for the low dose, mid-dose and high dose groups, respectively), and a positive trend was observed with increasing dose ($p < 0.05$). Although the authors stated that this was due to the 0 frequency in the controls, which is unusual, it is considered to be a possible positive response. However, the study is considered to be inadequate for classification of the chemical for carcinogenicity. Although these chronic effects are considered to be sufficient to establish a NOAEL and an LOAEL for chronic toxicity, they are not considered adequately severe to assure that the animals were tested at a sufficiently high dose for an acceptable oncogenicity study.

The LOAEL is 1250 ppm (54.2 /72.1 mg/kg/day) based upon an increase in hypertrophy/steatosis of the liver (both sexes), increased absolute and relative liver weights (both sexes) and possible borderline increase in uterine stromal polyps (females). The NOAEL for chronic effects is 250 ppm (10.8/14.0 mg/kg/day).

This study is classified as **Acceptable/guideline** as a chronic feeding study. The adequacy of the oncogenicity phase of testing is questionable because the low dose levels evaluated may not be sufficient to assess the relevance of the increased incidence of uterine stromal polyps. If the use pattern for the chemical changes a repeat carcinogenicity study may be warranted.

COMMENTS: This is a revised Executive Summary that includes the actual dose levels (on a mg/kg/day basis) attained in the study.

Based on new information provided by the registrant (MRID 47078901) actual achieved doses were as follows:

Dose	Dietary Concentrations of Paclobutrazol (mg/kg/day)		
	50 ppm	250 ppm	1250 ppm
Male	2.2	10.8	54.2
Female	2.8	14.0	72.1

For more details see TXR 0056158.

This supplemental DER provides an updated Executive Summary correcting the previous one and making it consistent with the risk assessment of October 2014.

870.4100b Chronic Toxicity – Dog

In a one-year chronic toxicity study (MRID 00132691/00143166), groups of four groups of six male and female beagles received daily doses of paclobutrazol (92.4%) at 0, 15, 75 and 300 mg/kg/day for 1 year. Doses were administered in capsules.

Elevated serum alkaline phosphatase and triglyceride levels, the enlarged hepatic cells, increased liver weights, and increased hepatic aminopyrine N-demethylase activity indicate that the two highest doses (75 and 300 mg/kg/day) have definite effects. However, no toxicologically significant effects were observed at the .15 mg/kg/day dose level. The NOEL is 15 mg/kg/day, and the LEL is 75 mg/kg/day in beagle dogs.

This study is classified as Core Minimum.

A.4.5 Carcinogenicity

870.4200a Carcinogenicity - Rat

See MRID 40734301

870.4200b Carcinogenicity – Mouse

In a combined chronic feeding/oncogenicity study (MRID 40762501) in Crl:CD-1 (ICR)BR albino mice. Fifty-one animals/sex/group were fed 0, 25, 125 or 750 ppm technical Paclobutrazol (92.4% pure) in the diet for 2 years (0, 3.75, 18.75 or 112.5 mg/kg/day). Two control groups of 51 animals/sex were utilized. Nine additional animals/sex in the first control and high dose groups were kept as microbiological sentinels.

At 112.5 mg/kg/day, there was an increase in the severity of steatosis of the liver (males). There were also minor increases in relative and absolute liver weights (21% greater than controls for both absolute and relative, liver weights in males and 18 and 19% greater than controls for absolute and relative liver weights, respectively for females) the LOEL is 750 ppm (112.5

mg/kg/day) based on increases in severity of steatosis of the liver in males. The NOEL for chronic effects is 125 ppm (18.85 mg/kg/day).

There appeared to be a borderline increase in Leydig cell tumors in high dose males (2/53, 0/50, 2/51, 1/52 and 5/52 for the control 1, control 2, low, mid- and high-dose groups, respectively). A pairwise comparison was statistically significant at the highest dose level ($p < 0.05$)*. In addition, a positive trend was observed with increasing dose ($p < 0.05$). Although the authors stated that this was not considered to be biologically significant because the control values were low, it is considered to be a possible positive response. However, the study is considered to be inadequate for classification of the chemical for carcinogenicity for the following reason: although the chronic effects are considered to be sufficient to establish a NOEL and an LEL for chronic toxicity, they are not considered to be severe enough to indicate that the animals were tested at a sufficiently high dose level for an adequate carcinogenicity study.

This study is classified as core Minimum as a chronic feeding study and Core Supplementary as oncogenicity study (see discussion). It does not satisfy the regulatory requirement for an oncogenicity study. Due to the low dose levels tested and to the possible positive response for Leydig cell tumors, a repeat study will be needed if the use pattern for the chemical requires it.

A.4.6 Mutagenicity

Gene Mutation

Guideline 870.5100 Bacterial reverse mutations (Ames assay) MRID 00017480 Classification: Acceptable/guideline	Paclobutrazol was negative for the induction of reverse gene mutations in <i>Salmonella typhimurium</i> TA1535, TA1537, TA1538, TA98, and TA100 at concentrations of 0, 1.6, 8.0, 40, 200, 500, 1000, 2500 or 5000 µg/plate +/-S9 activation. Cytotoxicity and compound precipitation was reported at 5000 µg/plate.
Guideline 870.5300 In vitro mammalian cell gene mutation (mouse lymphoma L5178Y cells) MRID 00132695 Classification: Acceptable/guideline	Paclobutrazol was negative for the induction of forward gene mutations in mouse lymphoma L5178Y cells at the TK locus at concentrations 0, 0.1, 12.0, 10.3, and 102.5 µg/mL +/-S9. Severe cytotoxicity ($\leq 6\%$ cell survival) was seen at 102.5 µg/mL +/-S9

In Vivo Chromosomal Aberrations

Guideline 870.53.75 <i>In vivo</i> bone marrow chromosome aberration (Rat) MRID 00143156 Classification: Acceptable/guideline	Paclobutrazol was negative for the induction of chromosome aberrations in the bone marrow of Alderly Park male and female rats at doses of 0, 30, 150, or 300 mg/kg/day, once daily for 5 consecutive days via oral gavage.
Guideline 870.5300 Mouse Micronucleus Assay MRID 00132694 Classification: Acceptable/guideline	Paclobutrazol was negative for the induction of micronucleated polychromatic erythrocytes in the bone marrow of mice at 0, 87.5 or 140 mg/kg. The doses represent 50 and 80%, respectively of the LD ₅₀ when delivered via intraperitoneal injection.
Guideline 870.5450 Rodent Dominant Lethal Test (Mouse) MRID 00143155 Classification: Acceptable/guideline	Paclobutrazol was negative for the induction of dominant lethal mutations in the spermatocytes of CD-1 mice administered 0, 30, 150 or 300 mg/kg/day, once daily for 5 consecutive days via oral gavage.

Other In Vivo Studies

Guideline 870.550 <i>In vivo</i> Unscheduled DNA Synthesis assay (UDS, rat hepatocytes) MRID 00017480 Classification: Acceptable/guideline	Paclobutrazol was negative for the induction of UDS in hepatocytes harvested from Alderly Park rats treated with 0, 40, or 400 mg/kg of the test material.
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A.4.7 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery –

In an acute neurotoxicity study (MRID 49211902), four groups of unfasted 7-week-old RccHan™: WIST(SPF) rats (ten/sex/dose) were given single oral doses of paclobutrazol (99.6% a.i; Batch no. 680195) in 0.5% (w/v) aqueous carboxymethylcellulose at doses of 0, 30, 150, or 500 mg/kg bw. Dosing was on day 1, and the animals were observed for 14 days, until termination on day 16. Neurobehavioral assessments [functional observational battery (FOB) and motor activity testing] were performed on all animals pre-test, on day 1 (3-4 hours after dosing), and on days 8 and 15. At study termination, five animals per sex per dose were perfused *in situ* for collection of tissues, and fixed brain weights were also recorded. The tissues from all of the perfused control and high-dose animals were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

No deaths or other clinical signs of toxicity or were observed at any dose. Effects on food consumption and body weight gain were seen in high-dose animals of both sexes. Relative to controls, high-dose males had transiently decreased mean body weight gain (-84%; p<0.05) and a correlated slight decrease in food consumption (-16%) over days 1-2. High-dose females had decreased food consumption over days 1-2 and 2-3 (24-30% less than controls), with a corresponding decrease in body weight gain over days 2-3 (-74%). Treatment-related effects on motor activity were seen on day 1 in mid- and high-dose females. Relative to controls, mid- and high-dose females had significantly decreased rearing counts for bins 1-2 (53-67% less than

controls) and bins 1-3 (60-83% less than controls), respectively, which in both cases were of sufficient magnitude to result in decreased total rearing counts for the session overall (mid-dose: -54%, $p < 0.05$; high-dose: -78%, $p < 0.01$). Mid- and high-dose females also had decreased mean subsession distances during bins 1-2 (14-31% and 31-58% less than controls for mid- and high-dose, respectively; not significant at the mid dose during bin 1), but total distance for the overall session was only decreased in high-dose females (-32%; $p < 0.05$). Decreased subsession center time was seen during bin 2 in high-dose females (-78%; $p < 0.01$), only, without a corresponding effect on total center time for the session overall. On day 1 (3-4 hours after dosing), treatment-related statistically significant decreases in mean body temperature were seen in high-dose males (37.3 vs. 37.8 °C for controls; $p < 0.05$) and high-dose females (37.0 vs. 38.0 °C for controls; $p < 0.05$); this effect is of equivocal biological significance as these body temperatures are still within the normal range. There were no treatment-related effects on mortality, clinical signs, brain weight, gross pathology, or neuropathology. FOB testing revealed no treatment-related effects on home cage, handling, or open field parameters, grip strength, or landing foot splay. **In this study, the lowest-observed-adverse-effect level (LOAEL) for paclobutrazol in Han-Wistar rats was 150 mg/kg bw, based on transient alterations in motor activity (i.e., decreased rearing counts and decreased subsession distances) in females 3-4 hours after dosing. The NOAEL was 30 mg/kg bw.**

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

870.6200 Subchronic Neurotoxicity Screening Battery – Data waiver granted by HASPOC March 13, 2014 (TXR 0056914)

870.6300 Developmental Neurotoxicity Study – not required at this time

A.4.8 Metabolism

870.7485 Metabolism – Rat

In a metabolism study (MRID 00132696), male and female Wistar rats received a single oral gavage dose of 10 mg/kg of paclobutrazol (99%) or 10 mg/kg paclobutrazol radiolabeled with ^{14}C on the triazole ring for 4 days. Single rats/sex were subjected to autoradiography 24 hours after dosing and 3 rats per sex were sacrificed 72 hours after dosing and autoradiography. Urine, feces, cage washings and tissues (adipose tissue, gonads, kidneys, and liver were analyzed.

During the 4 days following administration, 39.18 and 52.6 % of the dose was recovered in the urine of male and female rats, respectively. Fecal recoveries were 53.49% in the males and 37% in females. Approximately 60% of the administered dose was accounted for in feces and urine of males and females during the first 24 hours of dosing. Residue concentrations in tissues 3 or 4 days after dosing did not indicate accumulation, and urinary excretion along with slow fecal excretion indicated a significant gastrointestinal absorption of the dose.

The study is Acceptable/guideline.

In a metabolism study (MRID 00143160), 1 male and 1 female rat received a single oral gavage dose of 250 mg/kg of paclobutrazol (99%) mixed with radiolabeled paclobutrazol (specific activity = 1.68 GBq/mM 32.16 μ Ci/mg) for 48 hours. Urine, feces and expired air samples were collected for analysis at 24 and 48 hours. Animals were sacrificed at 48 hours and subjected to autoradiography.

Autoradiographs indicated that the liver, kidneys, and gastrointestinal tract contained the administered radiolabel. Similarly, the disposition of the 14 C label after a single oral dose of 250 mg/kg is limited to the gastrointestinal contents and to a lesser extent to the liver and kidneys.

The study is Acceptable

In a metabolism study (MRID 00143161), 4 male and 4 female Wistar rats received a single oral gavage dose of 5 mg/kg of paclobutrazol (99%) or 5 mg/kg paclobutrazol radiolabeled (specific activity = 32.16 μ Ci/mg) for 7 days. Urine and feces samples were collected for analysis at 24 hour intervals for 7 days. Animals were sacrificed at 7 days post-treatment and organ samples were taken.

Most of the 5 mg/kg dose was excreted within 72 hours (70-80%). Approximately 55% of the dose was recovered in the urine of both sexes, and 32% or 24% was recovered in the feces of males and females, respectively. 7 days after dosing, liver tissue contained 0.017 to 0.028 ppm; gastrointestinal tract contained 0.012-0.025 ppm. No other tissue levels were detectable.

The study is Acceptable/guideline.

In a metabolism study (MRID 00143165), male and female rats received a single oral gavage dose of 5 or 250 mg/kg of radiolabeled paclobutrazol (specific activity = 1.68 GBq/mM 32.16 μ Ci/mg) for 3 days. The animals were placed in metabolism cages and urine and feces samples were collected for analysis at 24-hour intervals for 3 days. A second series of animals (2 males and 2 females) were cannulated and given 250 mg/kg paclobutrazol by oral gavage. Urine, bile and feces samples were collected for analysis at 24-hour intervals for 4 days. Animals were sacrificed and samples of the bile, urine and feces were collected over a 4-day interval and measured. The highest percentage of radioactivity was general recovered after 48 hours in bile (46%, ♂ and 24% ♀), urine (12%, ♂ and ♀), and feces (0.9%, ♂ and 0.3% ♀).

A single oral gavage dose (5 or 250 mg/kg) paclobutrazol was absorbed almost completely by male and female rats. Triazole and halogenated phenyl moieties not affected in rat. Pentanol moiety oxidized to a diol or carboxylic acid & excreted in free or conjugated forms. Males excreted more of carboxylic acid metabolites than females but proportion of acid metabolites excreted by females increased as dose decreased. Approx. 75% of dose was recovered in bile during first 48 hours after dosing in males, and 50% is recovered from females during first 72 hours.

The study is Acceptable.

870.7485 Metabolism – Dog

In a metabolism study (MRID 00143163) in dogs, three male and three female beagle dogs were given single oral doses of 5mg/kg radiolabeled (specific activity = 32.16 $\mu\text{Ci}/\text{mg}$) and unlabeled paclobutrazol. Blood samples were drawn prior to dosing, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours after treatment. Urine and feces samples were collected for analysis at 24 hour intervals for 7 days. Animals were sacrificed at 7 days post-treatment and organ samples were taken.

Paclobutrazol was rapidly absorbed in the dog after a single oral dose of 5 mg/kg is administered. Peak plasma and blood levels were observed 1.5 hours after dosing. During the 24 hours following dosing, approximately 80-85% of 5 mg/kg dose extracted during first 24 hours after dosing. Approx. 50% of dose recovered in urine of both sexes, & 35-40% recovered in feces. Peak blood levels at 1 hour after dosing (4.1-4.4 ppm in plasma) declined to pre-dose levels 24-48 hours after treatment. No detectable levels in tissue & no sex differences were observed.

The study was classified as Acceptable/guideline

A.4.9 Dermal penetration**870.7600 Dermal penetration – Rat**

In a dermal penetration study (MRID 41048202), groups of five adult male Alpk:APfsd rats received dermal applications of 0, 0.011, 0.025, 0.125, 1.23 or 12.49 mg/rat [^{14}C]-triazole labeled paclobutrazol, prepared in sterile deionized water. Approximately 24 hours before exposure, test sites were shaved and undamaged skin was washed with acetone and fitted with two 22.5 x 3 mm nitrile rubber “O” rings that were held in place using cyano-acrylate glue. The internal surface area of skin within each “O” ring was $\sim 5 \text{ cm}^2$ (total defined skin application area = $\sim 10 \text{ cm}^2$). A Queen Anne plastic collar was secured around the neck of each rat and rats were individually housed in metabolism cages for an overnight acclimatization. Each animal was doses with 25 μl of the appropriate dosing solution spread over the $\sim 5 \text{ cm}^2$ test site within each “O” ring. Application sites were dried, and protected. At 10 hours after dosing, “O” rings were detached and the “O” rings and application sites were rinsed. Samples of washes were collected from the skin, “O” rings, and gauze and analyzed for radioactivity. In addition to following the same procedures at 24 hours, carcasses, urine, feces and cage wash were measured for radioactivity.

The percent of dose absorbed and remaining on the washed application site for the 10- and 24-hour exposures are shown in Table 1, and were as follows:

Table 1. Absorbed Dose Remaining on the Intact Skin of Male Rats 10 or 24 Hours after Receiving Paclobutrazol Dermally over a Total Area of 10 cm²/Rat

Dose (mg/rat)	Absorbed (%)		Potentially Absorbable (%)		Total Absorbable (%)	
	10 hours	24 hours	10 hours	24 hours	10 hours	24 hours
12.48	1.12	2.8	2.6	2.4	3.7	5.2
1.23	3.3	3.2	1.6	0.8	4.9	4.0
0.125	11.6	10.4	0.8	1.6	12.4	12.0
0.025	16.0	20.8	2.4	2.4	18.4	23.2
0.011	15.1	24.5	3.6	2.7	18.7	27.2

At the time this study was reviewed, the absorbed dose was calculated as the sum of the residues from the urine, feces, cage wash, and carcass (excluding the skin at the application site). The potentially absorbable dose included the residues in the skin at the application site. Previously, the most conservative value for total absorbable (sum of the absorbed dose and potentially absorbable dose) was used, which was 24.5% following a 24-hour exposure period. Currently, the policy is to use 8-hours exposure and to assume that residues found in the skin are potentially absorbable, unless data are provided to demonstrate otherwise. This policy reflects an 8-hour work day, and ongoing exposure is expected to cease at the end of the workday. Likewise, the Agency's position is to be conservative to insure public safety, and this is reflected in the assumption that residues found in the skin will be absorbed, unless there are data which contradicts this assumption. Therefore, values following the 10-hour exposure period were used and the total absorbable dose was calculated to be 18.5%. The percentage of the dose absorbed and remaining on the washed application site (potentially absorbable) at 10 hours was 15.1% and 3.6% respectively, and 24.5 % and 2.7% (24 hours), respectively. Since absorption rates were not measured beyond 24 hours, the percent absorbed plus the percent potentially absorbed (18.7%) for 10 hours was calculated. For risk assessment purposes, HED is using the conservative assumption that the **dermal absorption factor (DAF) of 18.7% for paclobutrazol.**

COMMENTS:

This supplemental DER provides an updated Executive Summary correcting the previous one and making it consistent with the risk assessment of March 2014. The original DER is attached.

This study is classified Acceptable/Guideline, and it satisfies the guideline requirement (870.7600) for a dermal penetration study.

870.7800 Immunotoxicity – Rat

Data waiver granted by HASPOC March 13, 2014 (TXR #0056914).

A.5 Absorption, Distribution, Metabolism, and Elimination (ADME)

The absorption, distribution, metabolism and excretion (ADME) of paclobutrazol was extensively characterized in a series of studies in rats and dogs. These studies were performed using both low- and high-dose, single and repeated dosing protocols. Bile-cannulation was included as part of one of the studies. Estimation of absorption from the gastro-intestinal (GI) tract were based upon data from pharmacokinetic and excretion experiments.

In two guideline studies, rats readily absorbed low (5 mg/kg) and high (250 mg/kg) doses of paclobutrazol and excretion was rapid (70-80% within 72 hours). For the 5 mg/kg dosing (MRID 00143161), approximately 55% of paclobutrazol was recovered in the urine of both sexes in addition to 32 or 24% that was recovered in the feces of male or female rats, respectively. Seven days after dosing, livers contained 0.017 to 0.028 µg equivalents/g of tissue for males and females and the gastrointestinal tract content was 0.012-0.025 µg equivalents/g, respectively. Radioactivity was not detected in other tissues.

For the 250 mg/kg dosing (MRID 00143162), approximately 33% F/43%M of the dose was recovered in the urine after 72 hours and approximately, 30% or 40% of the dose was recovered in the feces of male or female rats, respectively. Seven days after dosing, the respective amount of test material found in the liver was 0.848 and 0.444 µg equivalents/g of tissue for males and females.

Excretion was more rapid in dogs administered a single gavage dose of 5 mg/kg (MRID 00143163). Approximately 80 to 85% of the doses were excreted within the first 24 hours; 50% of the dose was recovered in the urine of both sexes and 35-40% was recovered in the feces. Peak blood levels at 1 hour (T_{max}) after dosing ranged from 4.1-4.4 ppm in plasma (C_{max}) for both sexes and declined to baseline 24-48 hours after treatment. There were no detectable levels in any tissues.

In a guideline bioaccumulation study (MRID 00143164), male rats received daily oral administrations of radiolabeled 5 mg/kg paclobutrazol for 28 or 49 days. Concentrations of radiolabel plateaued in the liver and kidneys after 28 days. From 28 to 49 days, maximum levels were 2.22-4.76 ppm in the liver and 1-2.7 ppm in the kidney. Blood levels rose throughout the 49-day period (maximum = 0.158 ppm); levels in fat were below the level of detection. Elimination from the livers and kidney occurred in a biphasic manner: half-lives ($T_{1/2}$) for phase 1 (α -phase) were 1.36 and 1.56 days for liver and kidney, respectively. Half times for phase 2 (β -phase) were 6.69 and 9.26 days, respectively. After dosing was stopped, tissue levels declined below detectable levels after 28 days. Three days after dosing was halted, 15 and 8% of radioactivity was recovered from liver and kidney samples. By day 7, only 2% of the dose remained in the liver or kidney. It was concluded, therefore, that paclobutrazol does not bioaccumulate. In another guideline bioaccumulation study (MRID 00143160) lasting 48 hours, disposition of the single oral doses of radiolabeled 250 mg/kg paclobutrazol to rats was limited and generally confined to the gastrointestinal tract and to a lesser extent in the liver and kidneys. The finding that paclobutrazol does not bioaccumulate is supported by database and illustrated by the points of departure (PoDs) selected for the risk assessment. Regardless of the duration of

the study from acute to repeated exposures, the LOAELS range from 40 mg/kg (acute dietary, females 13-49) to 117 mg/kg/day (incidental oral, young children, 1-2 years old).

Paclobutrazol is included in the triazole alanine group of triazole derivatives. However, major metabolites found in another metabolism study (MRID 00143165) were the diol and carboxylic acid analogues of paclobutrazol; triazole alanine was not found. As part of this study, 2 male and 2 female rats received a single dose of 250 mg/kg paclobutrazol and were allowed a 24-hour recovery period. The bile duct of these rats was cannulated and the rats were given a second dose of 250 mg/kg paclobutrazol, and samples of the bile, urine and feces were collected over a 4-day interval and measured. The highest percentage of radioactivity was generally recovered after 48 hours in bile.