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OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

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This document provides the Health Effects Division's Draft Risk Assessment for the active ingredient tebuthiuron. A summary of the findings and an assessment of potential human health risk resulting from the currently registered uses of tebuthiuron are provided in this document. The HED team members contributing to this risk assessment include Bridgett Bobowiec (risk assessment and occupational risk assessment), P. Yvonne Barnes (chemistry and dietary exposure assessments) and Christopher Schlosser (hazard assessment). Ibrahim Abdel-Saheb of the Environmental Fate and Effects Division (EFED) performed the drinking water assessment for tebuthiuron.

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1.0 Executive Summary

Introduction

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. The HED Tebuthiuron Registration Review Team has evaluated the current databases to support the Registration Review of the active ingredient (ai), tebuthiuron. Tebuthiuron is a relatively nonselective substituted urea herbicide that acts by inhibiting photosynthesis. It is used to control broadleaf, grassy weeds, and woody plants. Use sites include pastureland, rangeland, and a variety of non-food sites including airports/landing fields, outdoor industrial areas, non-agricultural rights-of-way, fencerows, hedgerows, uncultivated areas/soils, and under paved roads and sidewalks in areas where no future landscaping is planned. Tebuthiuron is not registered for agricultural crops or for residential use. End use products are formulated as dry flowable (DF), water dispersible granulars (WDG), pellets (P), and granulars (G). Applications are conducted by aerial, ground, and handheld equipment.

Updated points of departure (POD) and safety factors (SF) were used for the dietary and occupational exposure risk assessments, as well as for the spray drift assessment. No changes to the current tolerances for meat and milk are recommended at this time. Tebuthiuron is not registered for residential uses; however residential bystander exposure may be possible through spray drift. Therefore, HED has conducted a spray drift assessment and there are risks of concern identified from exposures to both adults (dermal only) and children 1 to < 2 years old (dermal and incidental oral). There are no dietary (food and drinking water) or aggregate risks of concern associated with tebuthiuron. There are several occupational dermal and inhalation risks of concern for scenarios including mixing/loading for aerial application, and ground application, and mixing/loading/applying using handheld equipment.

Hazard Identification

The most consistent toxicological effect across the tebuthiuron database is decreased body weight, occurring in rats, rabbits and dogs. No evidence of reproductive, neurological or immunological toxicity were identified in the database. No evidence of qualitative/quantitative susceptibility was observed in the rabbit or rat database. Decreased fetal body weights and increased number of litters with early resorptions in the rabbit developmental study were observed at the same dose. In rats, decreases in pup body weights were observed on post natal day (PND) 21 in the first and second (F1 and F2) generation pups occurred in the presence of maternal toxicity (decreases in F1female adult bodyweights).

The acute toxicity studies indicate that tebuthiuron is more toxic following oral (Toxicity Category II) exposure than either dermal (Toxicity Category IV) or inhalation (Toxicity Category III) exposure. Tebuthiuron is not an eye or skin irritant and not a skin sensitizer. In the 2002 Preliminary Human Health Risk Assessment (P. Deschamp, D274580, April 22, 2002) tebuthiuron was classified as a Group D compound “not classifiable as to human carcinogenicity.”

Dose Response Assessment

Acute Dietary
No appropriate acute toxicological endpoint attributable to a single exposure was identified for the general population. An acute reference dose (aRfD) was selected for females 13 – 49 years old based on an increase in early resorptions at the lowest observed adverse effect level (LOAEL) of 25 mg/kg/day in the developmental toxicity study in rabbits with a no adverse effect level (NOAEL) of 10 mg/kg/day.

Chronic Dietary
The chronic reference dose (cRfD) was selected from the 2-generation reproductive toxicity study in rats based on decreased body weights in parents and pups at the LOAEL of 26 mg/kg/day. The study NOAEL was 14 mg/kg/day.

Non-Dietary Endpoints for Occupational and Spray Drift Analysis

Incidental Oral
The 2-generation reproductive toxicity study in rats was selected with a NOAEL of 14 mg/kg/day for the short-term (1-30 days) incidental oral endpoint. The LOAEL is 26 mg/kg/day based on decreased body weights in F1 females and decreased pup body weights on PND 21 in the F1 and F2 generation.

Dermal and Inhalation
A dermal toxicity study is available for tebuthiuron, however, the short- and intermediate-term dermal endpoints were selected from the 2-generation reproductive toxicity study in rats because the dermal study conducted is not protective of the adverse outcome (resorptions) of concern for pregnant females. Since the endpoint is derived from an oral study, HED would typically apply a dermal absorption factor, however because no dermal absorption data are available and the physical properties of the chemical support the potential for dermal absorption this risk assessment assumes 100% dermal absorption for tebuthiuron. There are no route-specific inhalation studies available for tebuthiuron. The Hazard and Science Policy Council, (HASPOC) determined that a guideline 90-day inhalation study is required for this route of exposure. In the absence of an inhalation study, HED has selected short- and intermediate-term endpoints from the 2-generation rat study discussed above and has retained an additional 10X database uncertainty factor for the inhalation risk assessments to account for the missing data. Long-term exposures are not anticipated from the occupational use of tebuthiuron.

Uncertainty/Safety Factors
For acute and chronic dietary, incidental oral, and dermal risk assessments, a 100X uncertainty factor is applied (interspecies factor of 10X and intraspecies factor of 10X). Acute and chronic risk estimates are expressed as a percent of the population adjusted dose (PAD) and risks which do not exceed 100% of the acute PAD (aPAD) or chronic PAD (cPAD) are not of concern. Incidental oral or dermal risk estimates resulting in MOEs greater than or equal to 100 do not exceed HED's level of concern (LOC).

The total uncertainty/safety factor for the inhalation risk assessments is 1000 and includes a 10X for interspecies extrapolation, 10X for intraspecies variation, and a 10X database uncertainty

factor to account for the missing inhalation study. Inhalation risk estimates resulting in MOEs greater than or equal to 1000 are not of concern.

There is no evidence of increased qualitative or quantitative susceptibility in the rat 2-generation reproduction study or the rat and rabbit developmental studies. Furthermore, there is no evidence of neurotoxicity in any of the submitted studies for tebuthiuron and there is no residual uncertainty in the exposure database. Therefore, the FQPA safety factor (for the protection of infants and children) was reduced to 1X.

Residue Chemistry Considerations

There are no outstanding residue chemistry data requirements for tebuthiuron. The nature and magnitude of the residue are well understood and adequate analytical methods exist to support the existing tolerances. No changes to existing tolerances are required. There are no harmonization issues associated with tebuthiuron.

Exposure/Risk Assessment and Risk Characterization

Dietary Risk Assessment

Since there are no direct applications to agricultural crops, the only source of food exposure is the potential consumption of secondary residues in meat and milk from livestock fed tebuthiuron-treated grass forage and hay. Additionally, the potential exists for dietary exposure via the consumption of drinking water. Acute and chronic dietary risk assessments were conducted for tebuthiuron which included tolerance level residues in animal commodities, and modelled estimates of drinking water concentrations, (EDWC) provided by the Environmental Fate and Effects Division, (EFED). However, since water was the risk driver, a time series water distribution was used. Percent crop treated information were not relevant to these assessments.

The partially refined acute estimated dietary risk for females 13-49 years old is not of concern; the dietary risk is 93% of the aPAD at the 95th percentile. The chronic estimated dietary risks are not of concern; the dietary risk for the general U.S. population is 30% of the cPAD and for the highest exposed population subgroup (all infants) is 72% of the cPAD. HED is concerned when the estimated dietary risk exceeds 100% of the PAD.

Residential Exposure and Risk Assessment

Residential exposure was not assessed as there are no residential uses for tebuthiuron.

Spray Drift Assessment

A non-occupational spray drift assessment has been conducted for tebuthiuron based on the highest rate currently registered for aerial application on pastureland/rangeland and general non-cropland (6 lbs. ai/acre). Spray drift occurs from the movement of tebuthiuron away from rangeland/pastureland application sites. The dermal and incidental oral risk estimates calculated for adults and children ages 1 to <2 years old were combined since the toxicological effects for these exposure routes were similar. The total applicable LOC is 100, so MOEs less than 100 represent risk estimates of concern. Adult dermal risk estimates and children's combined dermal and incidental oral risk estimates from indirect exposure to tebuthiuron related to spray drift indicate that exposure above the LOC could occur at distances from 0 feet to greater than 150

feet depending on the nozzle type, droplet size, and application equipment.

Occupational Handler and Post Application Exposure and Risk Assessments
Occupational handler risks were assessed for the dermal and inhalation routes of exposure. Since toxic effects are similar from the dermal and inhalation routes of exposure, but the LOC values for dermal exposure (100) and inhalation exposure (1000) are different, a total aggregated risk index (ARI) was used to estimate combined estimated handler risks. The LOC ARI is 1; therefore, ARIs of less than 1 are potentially of concern to the Agency. Several of the occupational handler scenarios resulted in ARIs < 1 with the personal protective equipment (PPE) currently required on the label and remain a concern despite consideration of possible mitigation methods such as requiring doubler layer dermal PPE, respirators, and engineering controls.

Based on the Agency's current practices, a quantitative occupational post-application inhalation exposure assessment was not performed for tebuthiuron at this time.

Use of Human Studies

This risk assessment relies, in part, on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemicals. These data, which include the Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1) and the Agricultural Handler Exposure Task Force (AHETF) database, are subject to ethics review pursuant to 40 CFR 26, have received that review, and are compliant with applicable ethics requirements. Certain studies within this assessment may have included reviews by the Human Studies Review Board. Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment.

2.0 HED Recommendations

2.1 Data Deficiencies

HED's Hazard and Science Policy Council (HASPOC) determined that a guideline 90-day inhalation study is required. (J. Leshin, TXR 0056925, May 27, 2014). No other toxicology studies are required to support the registration review of tebuthiuron.

There are no residue chemistry or occupational/residential exposure data gaps for tebuthiuron.

2.2 Tolerance Considerations

2.2.1 Enforcement Analytical Method

An adequate analytical method is available for the enforcement of plant and animal commodity tolerances established for tebuthiuron. A gas-liquid chromatography **(**GLC) method with flame photometric detection is designated as Method II in PAM Vol. II. Tebuthiuron and regulated metabolites 104 and 109 are thermally degraded on the GLC column and are determined as 5-(1, 1-dimethylethyl)-N-methyl-1,3,4-thiadiazol-2-amine; metabolite 103 (OH) is determined as 5-(2-

hydroxy-1,1-dimethylethyl)-N-methyl-1,3,4-thiadiazol-2-amine. The stated detection limits are 0.1 ppm for tebuthiuron and metabolites 104 and 109, and 0.2 ppm for metabolite 103(OH). The structures of these metabolites are shown in Appendix B Table B.4: Figure A.

2.2.2 Established Tolerances

Tolerances are established for the herbicide tebuthiuron under 40 CFR: §180.390; for Grass, (forage and hay) –10 ppm; Cattle, (fat and meat) –1.0 ppm; Goat (fat and meat) –1.0 ppm; Horse, (fat and meat) – 1.0 ppm; Sheep (fat and meat) –1.0 ppm; Cattle, Goat, Horse and Sheep, meat (byproducts) – 5.0 ppm and milk at 0.8 ppm. These tolerances are adequate to support the currently established uses of tebuthiuron.

2.2.3 International Harmonization

There are no Codex, Canadian, or Mexican Maximum Residue Limits (MRLs) established for tebuthiuron; therefore issues of harmonization are not relevant to this risk assessment The International Residue Limit (IRL) Status sheet is attached as Appendix C .

2.3 Label Recommendations

2.3.1 Recommendations from Occupational Assessment

HED recommends PRD ensure that that worker protection standard (WPS) language appears on all registered labels. Also if pastureland is intended for haying harvest, a re-entry interval (REI) of 12 hours based on the acute toxicity must be on the labels to protect workers from post-application exposures.

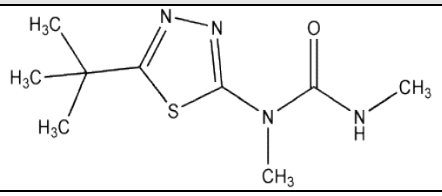
HED notes that the occupational assessment resulted in dermal and inhalation risk estimates of concern for several exposures scenarios (presented in section 9.1) with the current PPE on labels.

3.0 Introduction

Tebuthiuron is a relatively nonselective substituted urea herbicide that acts by inhibiting photosynthesis. It is used to control broadleaf, grassy weeds, and woody plants. Use sites include pastureland, rangeland, and a variety of non-food sites and uncultivated areas/soils. Tebuthiuron is not registered for agricultural crops or for residential use. The only source of dietary (food) exposure is the consumption of secondary residues in meat and milk from livestock fed tebuthiuron-treated grass forage and hay. Tebuthiuron primary environmental properties affect drinking water sources. The chemical is resistant to biological and chemical degradation, and its principle route of dissipation in the environment appears to be off-site transport. Because of tebuthiuron's environmental persistence and low adsorption to soil it can be transported to ground water through leaching and to surface water through run-off and off-target spray drift.

3.1 Chemical Identity and Physical/Chemical Characteristics

Tebuthiuron is a solid at room temperature. Any losses due to volatilization/sublimation are expected to be minimal due to the vapor pressure (2 x 10^{-6} mm Hg at 25 °C). Tebuthiuron is stable to anaerobic soil metabolism and is likely to persist in an anaerobic soil environment. See Table 3.1 and Appendix B for a summary of tebuthiuron nomenclature and physical/chemical properties.

Table 3.1- Tebuthiuron Nomenclature	
Chemical structure	
Common Name	Tebuthiuron
Empirical Formula	$C_9H_{16}N_4OS$
IUPAC Name	1-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-1,3-dimethylurea
CAS Name	Urea, N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethyl
CAS Registry Number	34014-18-1

3.2 Pesticide Use Pattern

Pastureland and rangeland appear to be the dominate use site in the western part of the United States (US). The final biological assessment prepared by the Bureau of Land Management in 2007 estimated the number of public land acres treated with tebuthiuron at an average of 48,000 from the years 1997 to 2005. In addition, registrant provided information estimating a significant amount of tebuthiuron is applied aerially to pastureland/rangeland in western US states. While tebuthiuron retreatment intervals (RTI) are once every 2 to 3 years and twice every 6 years, large agribusiness and/or commercial applicators could apply tebuthiuron over a period of weeks for multiple clients within a region. In addition to pastureland/rangeland, tebuthiuron can be applied aerially, by ground, and with handheld equipment on general non-crop land, wildlife clearings and rights-of-way. Tebuthiuron end-use formulations include dry flowable, water dispersible granular, pelleted/tablets, and granules. A summary of the existing use patterns for tebuthiuron are shown in Tables 3.2.1 below.

Table 3.2.1 Summary of Directions for Use of Tebuthiuron

Company	Formulation Name EPA Reg. No.	% a.i	Application Equipment and Rate (lb ai/A)		Max. No. Application per Season	Max. Seasonal Application Rate (lb ai/A)	Use sites	Use Directions and Limitations
Dry Flowable								
Dow AgroSciences LLC	Spike 80DF 62719-107	80	Broadcast Aerial and Ground Handheld for Spot Treatment	4 lb ai/A aerial pastureland, and 6 lb ai/A ground broadcast or 1.6 lb ai/gallon (spot treatment)	1 application every year with up to 6 lb ai/acre in a 6 year period. .	4 lb ai/acre per year for haying and no more than two treatments totaling 6 lb ai/A every 6 years	Non-cropland, including rangeland, permanent grass pastures, fencerows, and wildlife clearings	PPE includes eye protection, long-sleeved shirt, long pants, shoe and socks, and chemical resistant gloves. Not registered in Florida or Nassau and Suffolk NY. Not for use in California. Not for residential use. Do not apply on field crops. Aerial by helicopter and wing fixed for herbicidal firebreaks on rangeland. Aerial application limited to helicopter for rights-of-way.
Alligare LLC	Tebuthiuron 80WG 81927-37							
Pellet								
Dow AgroSciences LLC	Spike 20P 62719-121	20	Aerial, Ground, and Handheld for Spot Treatment	4 lb ai/A aerial pastureland, and 6 lb ai/A for ground broadcast and spot treatment	1 application /3 years	4 lb ai/acre per year for haying and no more than two treatments totaling 6 lb ai/A every 6 years	Rights-of Way, pastureland, rangeland, non-cropland, fence rows, firebreaks, industrial sites, wildlife clearings.	No PPE listed. Dormant season application. Do not feed to livestock for 1 year after treatment. Do not apply to soil that is frozen. Not used in Nassau and Suffolk Counties in NY and restrictions in Florida.
	Spike 40P 62719-122	40						PPE includes long sleeved shirt and long pants, shoes plus socks, waterproof gloves, protective eyewear. Dormant season application. Do not feed to livestock for1 year after treatment. Do not apply to soil that is frozen. Not used in Nassau and Suffolk Counties in NY and restrictions in Florida.
Alligare, LLC	Tebuthiuron 20P 81927-41	20						No PPE listed. Dormant season application. Do not feed to livestock for 1 year after treatment. Do not apply to frozen soil. Not used in Nassau and Suffolk Counties in NY restrictions in Florida.
Granular								
Rainbow Technology Corporation	Rainbow Weed Killer 4037 13283-18	2	Ground and handheld spot treatment	6 lb ai/A broadcast and spot treatment	2 applications per year with retreatment	6 lb ai/A every 6 years	Buried cable closures, telephone booths, cross-connect boxes, transformer	PPE includes NIOSH filter respirator for tractor drawn spreaders, and all loaders**.** All handlers must wear long sleeved shirt, long pants shoes plus socks, and chemical

Table 3.2.1 Summary of Directions for Use of Tebuthiuron

Company	Formulation Name EPA Reg. No.	% a.i	Application Equipment and Rate (lb ai/A)		Max. No. Application per Season	Max. Seasonal Application Rate (lb ai/A)	Use sites	Use Directions and Limitations
	Rainbow Weed Killer 4049 13283-21	1		(0.00015 lb ai/ft$^{2)}$	interval of 90 days 6 lb ai/Ain a 6 year period		pads, fire plugs, rights-of-way and industrial areas.	resistant gloves. Do not uses in any recreational areas or in homes. Do not apply by air. Do not enter until dust settles. Spoon or pump -feed spreader is prohibited. Applied anytime except when ground is frozen.
SSI Maxim Co. Inc.	Sprakil Sk-13 34913-15	1						
	Sprakil SK-26 34913-16	2						
	Sprakil SK-13 34913-15	1						
	Sprakil S-5 34913-10	5						PPE includes long sleeved shirt, long pants shoes plus socks, and chemical resistant gloves. Do not use on areas such as walks, driveways, streets. Not apply on or near field crops.
Technical								
Dow AgroSciences LLC	Spike Technical Herbicide 62719-109	99 %						
Makhteshim Agan of North America, Inc.	Tebuthiuron Technical 83558-33							

3.3 Anticipated Exposure Pathways

Exposure to tebuthiuron can be expected through food and drinking water. There are no direct applications to agricultural crops. The only source of food exposure is the potential for consumption of secondary residues in meat and milk from livestock fed tebuthiuron-treated grass forage and hay. Dietary exposure can also occur from consumption of drinking water. There are no residential uses of tebuthiuron, so exposure in residential or non-occupational settings is not likely, however as mentioned previously, a spray drift assessment was conducted to assess for possible exposure from contact to deposits on off target sites. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. Occupational post-application dermal exposure from workers re-entering tebuthiuron treated areas is not anticipated because the chemical is a non-selective herbicide used in non-agricultural areas.

3.4 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. 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.

3.5 Incident Reports

HED completed a review of tebuthiuron incidents in the OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases. Based on the low frequency and severity of incident cases reported for tebuthiuron in both IDS and NIOSH SENSOR Pesticides, there does not appear to be a concern

at this time that would warrant further investigation (M. Hawkins, Updated Review of Tebuthiuron Incident Reports, May 7, 2009). The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be conducted. The Agricultural Health Study (AHS) is also a potential source of information associated with human health effects associated with certain pesticides. Tebuthiuron is not included in the AHS.

4.0 Hazard Characterization and Dose-Response Assessment

4.1 Toxicology Studies Available for Analysis

The toxicology database for tebuthiuron is not complete but provides sufficient information to adequately identify hazards for risk assessment purposes. The database includes the following studies:

- 90-Day oral toxicity studies in the rat and dog,
- 28-Day dermal toxicity in the rabbit,
- Developmental toxicity in the rat and rabbit,
- 2-Generation reproductive toxicity in the rat,
- Chronic toxicity in the dog,
- Genetic toxicity battery,
- Metabolism study in the rat, and
- Immunotoxicity study in the rat.

The Hazard and Science Policy Council (HASPOC, TXR 0056925 05/27/2014) determined that the acute neurotoxicity study and sub-chronic neurotoxicity, chronic/carcinogenicity study in the rat, and the carcinogenicity study in the mouse may be waived. A sub-chronic inhalation study was required and a route-specific 10x database uncertainty factor has been retained.

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

Tebuthiuron is highly absorbed (84-95%) and rapidly excreted (within 24 hours) following oral administration in rats. Following administration of ^{14}C-tebuthiuron, metabolites in the urine accounted for up to 97.1% of the dose, and metabolites in the feces accounted for an average of 3.5% of the administered dose. Biliary excretion studies in rats indicated most of the radioactivity eliminated in the feces was absorbed from the gastrointestinal tract and eliminated through the bile. The major metabolite in 0-24 hour urine of male (58.3%) and female (62.1%) rats was identified as hydroxylated tebuthiuron metabolites (109-OH and /or 104-OH). The second most abundant metabolite was identified as metabolite 106 of tebuthiuron. This comprised between 9-15% of the administered dose in 0-24 hour urine of low dose rats, and between 1-10% of the administered dose in high dose rats. Two other metabolites identified, 104/109 and 103-OH, comprised between 2-10% of the administered dose in male and female 0-24 hour urine. No evidence of bioaccumulation was identified.

4.3 Toxicological Effects

The most consistent toxicological effect across the mammalian database is decreased body weight, occurring in rats, rabbits and dogs. No effects were observed in mice following long-term exposure up to the highest dose tested (240 mg/kg/day). At higher doses in rats, slight vacuolization of the pancreatic cells were observed, and in dogs, signs of liver toxicity were observed (including increased liver weights and enzyme activity). Toxicity in the 90-day and long-term rat and dog studies occurred at similar doses indicating no progression of toxicity over time. In a dermal toxicity study, no effects were observed up to the limit dose. Based on the available data, no evidence of reproductive, neurological, genotoxic, or immunotoxic effects were identified in the database.

No evidence of qualitative/quantitative susceptibility was observed in the database. In rabbits significantly decreased fetal body weights were observed at 25 mg/kg/day. An increase in the number of litters with early resorptions was also observed at this dose level. However, as limited data are available, and the etiology of the increased resorptions is unknown, this effect is considered to reflect toxicity in both the dams and pups. No developmental toxicity was observed in rats. In a 2-generation reproductive toxicity study decreases in pup body weights were observed on PND 21 in the F1 and F2 generation pups at 26 mg/kg/day. These effects occurred in the presence of maternal toxicity (decreases in F1 female adult bodyweights). In rats, decreases in pup body weights were observed PND 21 in the first and second (F1 and F2) generation pups at 26 mg/kg/day. These effects occurred in the presence of maternal toxicity (decreases in F1 female adult bodyweights).

The acute toxicity studies indicate that tebuthiuron is more toxic following oral (Toxicity Category II) exposure than either dermal (Toxicity Category IV) or inhalation (Toxicity Category III) exposure. This is supported by ADME data, indicating complete and rapid absorption of tebuthiuron following oral administration. Tebuthiuron is not an eye or skin irritant and not a skin sensitizer.

In the 2002 Preliminary Human Health Risk Assessment, tebuthiuron was classified as a Group D compound “not classifiable as to human carcinogenicity.” For more detail on cancer classification see Section 4.5.3.

4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

HED recommends that the 10X FQPA Safety Factor (for the protection of infants and children) be reduced to 1X. No evidence of increased quantitative/qualitative susceptibility was observed. The effects observed in the rabbit developmental and rat 2-generation reproduction studies occur in the presence of maternal toxicity. Nevertheless, these studies have clearly defined NOAEL/LOAELs and the selected points of departure (PODs) are protective of all observed adverse effects. No clinical signs indicative of neurotoxicity were identified throughout the database for tebuthiuron. The dietary and residential bystander assessments are based on reliable data and will not underestimate exposure.

4.4.1 Completeness of the Toxicology Database

The toxicology database for tebuthiuron is not complete, but provides sufficient information to adequately identify hazards for risk assessment purposes. HASPOC (TXR 0056925) decided based on a weight of evidence determination, that the acute neurotoxicity study and subchronic neurotoxicity, chronic/carcinogenicity study in the rat, and the carcinogenicity study in the mouse may be waived. The required sub-chronic inhalation study was not waived as the oral endpoint results in unacceptable MOEs for workers. Therefore, an additional 10X uncertainty factor was retained for the occupational inhalation assessment.

4.4.2 Evidence of Neurotoxicity

No evidence of neurotoxicity was observed in any of the submitted studies for tebuthiuron. The HASPOC determined that the acute and subchronic neurotoxicity studies are not required at this time based on the following rationale: 1) the lack of neurotoxicity signs in the available toxicology database for tebuthiuron; 2) the primary toxic effect throughout the database is decreased bodyweights; and 3) using an oral POD, the acute and chronic dietary exposures (food and water) for tebuthiuron result in risk estimates of less than 100% and therefore not of concern.

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

The available data do not provide evidence of any increased susceptibility in the offspring in either of the rat or rabbit developmental toxicity studies for tebuthiuron, nor in the rat two-generation reproduction study.

Decreased fetal body weights and early resorptions were observed in the rabbit developmental toxicity study, and decreased post-natal body weights were observed in the rat 2-generation toxicity study. Both of these effects occurred in the presence of maternal toxicity. No developmental effects were observed occurred in the rat developmental study.

4.4.4 Residual Uncertainty in the Exposure Database

There are no residual uncertainties in the exposure database. Since the dietary estimates were based on conservative assumptions, HED is confident that the assessments do not underestimate dietary (food and water) exposure.

4.5 Toxicity Endpoint and Point of Departure Selections

4.5.1 Dose-Response Assessment

A detailed description of the toxicity studies used for selecting toxicity endpoints and PODs for various exposure scenarios is presented in Appendix A and summarized in Table 4.5.4.

For acute dietary assessment of females 13 – 49 years old, the developmental toxicity study in rabbits was selected with a NOAEL of 10 mg/kg/day for dams and pups. The LOAEL is 25 mg/kg/day for dams and pups based on early resorptions and decreased fetal body weights. Early resorptions could be from a single exposure during pregnancy and are therefore considered a potential acute effect, and therefore, appropriate for the acute dietary endpoint scenario for

females of child-bearing age. No appropriate toxicological endpoints attributable to a single exposure were identified for the general population.

For chronic dietary exposure and risk assessment, the 2-generation reproductive toxicity study in rats was selected with a NOAEL of 14 mg/kg/day. The LOAEL is 26 mg/kg/day based on decreased body weights in F1 parental females (13%) and decreased pup body weights (17%) on PND 21 in the F1 and F2 generation (5-8%). The 2-generation reproductive toxicity study was selected for the chronic dietary exposure because the endpoint is applicable to the population of concern (general population) and the duration of exposure. As the NOAEL/LOAEL values are similar between the developmental and 2-generation toxicity studies (10/14 mg/kg and 25/26 mg/kg, respectively), the 14 mg/kg/day NOAEL represents a smaller dose spread between the NOAEL/LOAEL of both studies and the agency is confident that the NOAEL of 14 mg/kg/day is protective of both the developmental effects observed in the rabbit and the parental and offspring effects in rats.

For short-term incidental oral exposure (1-30 days), the 2-generation reproductive toxicity study in rats was selected with a NOAEL of 14 mg/kg/day. The LOAEL is 26 mg/kg/day based on decreased body weights in F1 adult females (13%) and decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%). The endpoint of concern in this study (bodyweight) is appropriate for the age of the population (infant and children) and the duration of concern. Intermediate and long-term incidental oral exposure assessment are not required because these exposure lengths are not expected based on current use patterns.

For short and intermediate-term dermal exposure, a 28-day rabbit dermal toxicity is available. However, the dermal study does not evaluate the endpoint of concern, resorptions. Therefore, the 2-generation reproductive toxicity study in rats was selected with a NOAEL of 14 mg/kg/day. The LOAEL is 26 mg/kg/day based on decreased body weights in F1 females (13%) and decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%). A dermal risk assessment is being conducted for the following reasons: the dermal toxicity study conducted is not protective of the adverse outcome (resorptions) of concern for pregnant females; no dermal absorption data are available, and the physical properties of the chemical support the potential for dermal absorption (log K_{ow} of 1.8 and a molecular weight of < 500). As discussed above, the 2-generation reproductive toxicity study with a NOAEL of 14 mg/kg was selected as it is protective of both developmental effects in rabbits and offspring effects observed in the rats. There is no proposed long-term use; therefore, risk assessment for long-term dermal exposure is not required.

For short and intermediate-term inhalation exposure, no route-specific inhalation study is available for tebuthiuron. Consequently, the 2-generation reproductive toxicity study with a NOAEL of 14 mg/kg was selected for risk assessment, because it is protective of both developmental effects in rabbits and offspring effects observed in the rats. There is no proposed long-term use; therefore, risk assessment for long-term inhalation exposure is not required.

For acute and chronic dietary, incidental oral and dermal exposures a 100X uncertainty factor is applied (interspecies factor of 10X and intraspecies factor of 10X). An additional 10x database

uncertainty factor has been applied for inhalation exposure due to the lack of a subchronic inhalation study.

4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

When there are potential occupational and residential exposures to a pesticide, the risk assessment must address exposures from three major sources: incidental oral, dermal, and inhalation. Oral, dermal, and inhalation routes can be combined as the points of departure are based on the same study and toxicological effects of decreased body weight.

4.5.3 Cancer Classification and Risk Assessment Recommendation

In the 2002 Preliminary Human Health Risk Assessment, Tebuthiuron was classified as a Group D compound "not classifiable as to human carcinogenicity." There is no concern for mutagenicity. In the rat carcinogenicity study, there was no evidence of carcinogenicity. The mouse carcinogenicity study was inadequate to determine carcinogenic activity due to the lack of adverse effects at the highest dose tested. In 2004, HED's Dosage Adequacy Review Team (DART) determined that the mouse carcinogenicity needs to be repeated due to the lack of effects at the highest dose tested. On March 13, 2014, however, HASPOC, based on a weight of evidence approach considering all of the available hazard and exposure information for tebuthiuron concluded that a repeat mouse study is not required. Despite the inadequacy of the mouse carcinogenicity study, EPA has determined that an additional mouse carcinogenicity study is not needed and that the rat chronic/carcinogenicity study will be adequate for assessing chronic risk, including cancer. This finding is based upon the following conclusions: (1) the rat is more sensitive than the mouse for the chronic assessment; (2) the effect seen in the most sensitive species (rats) and most sensitive sub population (i.e., F1 offspring) in the two-generation rat reproduction study has been used as the point of departure for the chronic assessment; (3) a new mouse study would only use doses well above the current POD for the chronic assessment; and (4) even if a new mouse study identified positive carcinogenicity effects, that finding would not result in the adoption of a quantitative linear assessment of cancer risk due to the negative carcinogenicity finding in the rat study and the lack of a positive finding for genotoxicity.

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

Table 4.5.4. Summary of Toxicological Doses and Endpoints for Tebuthiuron for Use in Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/ FQPA Safety Factors	RfD/PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (General Population)	No appropriate endpoint attributable to a single dose was identified. An acute RfD was not established.			
Acute Dietary (Females 13 to 49 years of age)	NOAEL = 10 mg/kg/day	UF_A 10x UF_H 10x FQPA SF = 1X	aRfD = 0.1 mg/kg/day aPAD = 0.1 mg/kg/day	Developmental Toxicity (rabbit) MRIDs: 00020644, 40776301 LOAEL = 25 mg/kg/day, based on significantly decreased fetal weights and increased resorptions.
Chronic Dietary (All populations)	Parental NOAEL=14 mg/kg/day	UF_A 10x UF_H 10x FQPA SF = 1X	cRfD =cPAD 0.14 mg/kg/day	2-Generation Reproductive Toxicity MRIDs: 00090108 Parental LOAEL = 26 mg/kg/day, based on decreased body weights in F1 females (13%)
Incidental Oral Short-Term (1-30 days)	Offspring NOAEL = 14 mg/kg/day	UF_A 10x UF_H 10x FQPA SF = 1X	LOC = 100x	2-Generation Reproductive Toxicity MRIDs: 00090108 Offspring LOAEL = 26 mg/kg/day, based on decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%).
Dermal Short-Term (1 – 30 days) and Intermediate-Term (1 – 6 months)	NOAEL = 14 mg/kg/day	UF_A 10x UF_H 10x	LOC = 100x	2-Generation Reproductive Toxicity MRIDs: 00090108 Parental LOAEL = 26 mg/kg/day, based on decreased body weights in F1 females (13%) Offspring LOAEL = 26 mg/kg/day, based on decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%).
Inhalation Short-Term (1-30 days) and Intermediate-Term (1 – 6 months)	NOAEL = 14 mg/kg/day	UF_A 10x UF_H 10x FQPA UF_{DB} = 10X	LOC = 1000x	2-Generation Reproductive Toxicity MRIDs: 00090108 Parental LOAEL = 26 mg/kg/day, based on decreased body weights in F1 females (13%) Offspring LOAEL = 26 mg/kg/day, based on decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%).
Cancer (oral)	Classification: "Not classifiable as to human carcinogenicity".			

Point of Departure (POD) = A data point or an estimated point derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animals to humans (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_{DB}= Data base Uncertainty Factor. FQPA SF = FQPA Safety Factor. aPAD = acute population adjusted dose. cPAD = chronic population adjusted dose. RfD = reference dose.

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. As part of its most recent registration decision for tebuthiuron, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), tebuthiuron is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

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

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. A second list of chemicals identified for EDSP screening was published on June 14, 2013[1] and includes some pesticides scheduled for registration review and chemicals found in water. Neither of these lists should be construed as a list of known or likely endocrine disruptors.

For further information on the status of the EDSP, the policies and procedures, the lists of chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website.[2]

5.0 Dietary Exposure and Risk Assessment

5.1 Summary of Plant and Animal Metabolism Studies

<u>Plant</u>

[1] See http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPPT-2009-0477-0074 for the final second list of chemicals.

[2] 2 http://www.epa.gov/endo/

Tebuthiuron metabolism in grass is adequately understood. All data requirements for the magnitude of the residue in plants have been evaluated and deemed acceptable. A metabolism study (MRID 00020756) was submitted in which a [^{14}C] tebuthiuron solution (labeled in the 5-position of the thiadiazole ring; specific activity of 16.9 µCi/mg) was applied to the surface of the soil in which 10-week old tall fescue (0.374 lb ai/A), little bluestem and Indian grass (0.75 lb ai/A.) were grown. The residues of concern are the parent compound and its metabolites 103 (OH), 104, and 109 (Dodd, N., 12/10/87). See Appendix B for structures. Two major metabolic pathways are involved: N-demethylation of tebuthiuron to form 104 and alkyl hydroxylation of the dimethylethyl side chain to form 103(OH).

Livestock

The regulatory requirements for data depicting the magnitude of the residue in milk, and livestock tissues are fulfilled. The livestock feeding study (MRID 43703201) depicting the magnitude of the residue in milk, and livestock tissues (fat, meat, liver, and kidney), demonstrate a transfer of tebuthiuron residues. The residues of concern in milk are tebuthiuron and metabolites 104, 104(OH), 106, 109; the residues of concern in livestock commodities are tebuthiuron and its metabolites 104, 106, 108, and 109. No poultry or swine feed items are associated with the registered uses on grass; there is no reasonable expectation of detectable residues of tebuthiuron and its metabolites in poultry and swine commodities resulting from the uses and no tolerances are needed.

Current tolerances are adequate to cover secondary transfer of residues.

Rotational Crops

Tebuthiuron is only used for the restoration of grasses in natural rangelands, permanent pasturelands and in non-cropland areas such as energy and transportation rights-of-ways; rotational crops are not concomitant to these uses.

5.1.1 Summary of Environmental Degradation

Tebuthiuron is persistent, mobile and can potentially leach to ground water. Tebuthiuron is not lipophilic. It is resistant to biological and chemical degradation, and its principle route of dissipation in the environment appears to be off-site transport. Transport to ground water through leaching and to surface water through run-off and off-target spray drift are likely as a result of the chemical's environmental persistence and low adsorption to soil. Based on the available data, the parent and degradate 104 (residues of concern) are persistent and mobile.

5.1.2 Residues of Concern Summary and Rationale

For dietary risk assessment, HED previously concluded that the residue of concern in plants are the parent compound and its metabolites 103, 103(OH), 104, and 109. As stated previously, the residues of concern in livestock commodities (fat, meat, kidney, and liver) are tebuthiuron and its metabolites 104, 106, 108, and 109; the terminal residues of concern in milk are tebuthiuron and metabolites 104, 104(OH), 106, 109, and 109(OH).

For the drinking water assessment, HED previously concluded that the parent compound and degradate 104 should be included in the drinking water risk assessment. Additionally, the metabolism assessment review committee (MARC) committee did not recommend including the other degradates in a drinking water risk assessment because they were not likely to be present. Metabolites 103(OH), 104(OH) and 109 (OH) were not detected in the environmental fate studies although identified as residues of concern. The drinking water risk assessment included metabolites 106, 108 and 109 based on aerobic soil metabolism and soil photolysis assumptions and on similarity in structure and that they have comparable chemical properties as the parent compound. The structures are shown in Appendix B, Figure B.1.

5.2 Food Residue Profile

Tebuthiuron is not registered for agricultural uses. Its use is limited to application to grasses. No residues in raw agricultural commodities are expected. However, residues are seen in livestock feedstuff, and those residues do appear to transfer to livestock fed tebuthiuron-treated feedstuffs. The highest residues are found in meat by products (kidney/liver), with residues also found in fat, meat, and milk.

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) in the following memorandum: "Tier II Estimated Surface Drinking Water Concentrations and Estimated Ground Water Concentration (EDWCs) for Tebuthiuron for Use in Human Health Risk Assessment," (D414241, I. Abdel-Saheb,01/16/2014). Water residues were incorporated in the dietary exposure evaluation modeling (DEEM-FCID) into the food categories "water, direct, all sources" and "water, indirect, all sources."

Only the parent compound and degradates 104, 106, 108, and 109 were included in the drinking water exposure estimates (i.e., Appendix B, Table B3 and Figure A) for the details. The values entered into the dietary exposure assessment model to assess the contribution from drinking water were specified by the results of the Pesticide Root Zone Model for Groundwater, (PRZM-GW) modeling program. No percent crop area (PCA) adjustment is applied to estimated ground drinking water concentrations (EDWCs).

EFED has developed six standard drinking water modelling scenarios that represent vulnerable watersheds in specific areas in the country. "Crop-specific" modelling scenarios are not available for all crops, however each groundwater scenario represents a different region known to be vulnerable to groundwater contamination. For chemicals which have a very limited number of labeled crops, as long as those limited crops are grown all over the country, the maximum registered application rate is used in each of the six modelling scenarios. For tebuthiuron, which is registered on grasses only, the water number derived from using the grass rate in the Wisconsin corn scenario. The scenario that results in the highest estimated environmental concentration, is used in the dietary assessment as an estimate of the drinking water concentrations that would arise in that vulnerable watershed from the specific registered

uses. This scenario does not imply that the pesticide is actually registered for use on corn. Since the WI corn scenario produced the highest EDWCs and it was used in the dietary assessment. See Appendix B, Table B4 for summary of EDWCs residues.

5.4 Dietary Risk Assessment

5.4.1 Description of Residue Data Used in Dietary Assessment

The unrefined chronic dietary exposure and risk analysis is based on tolerance-level residues, direct incorporation of drinking water residues (chronic) and the DEEM default processing factor for dried beef. The partially refined acute dietary exposure and risk analysis is based on tolerance-level residues, time series distribution of drinking water residues and the DEEM default processing factor for dried beef.

5.4.2 Percent Crop Treated Used in Dietary Assessment

Percent crop treated refinements were not applicable to these assessments, tolerance-level residues are established on animal and non-food grass (forage and hay) commodities.

5.4.3 Acute Dietary Risk Assessment

The acute dietary food (tolerance level residues) and water (time series water distribution) risk estimates reported in the tables are for females 13-49 years old. An acute assessment was performed only for females 13-49 years old since an acute endpoint for the general population was not selected. The resulting dietary (food and water) risk estimates are not of concern (less than 100%); acute dietary risk for females 13 – 49 years old is 93% of the aPAD at the 95th percentile.

5.4.4 Chronic Dietary Risk Assessment

The chronic dietary risk estimates reported in the tables below are for the general U.S. Population, all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, females 13-49, adults 20-49, and adults 50-99 years. The resulting dietary risk estimates are not of concern; (less than 100%); the most highly exposed population subgroup is all infants at 72% of the cPAD, while the general U.S. population utilized 30% of the cPAD.

5.4.5 Summary Table

Table 5.4.5 Summary of Dietary (Food and Drinking Water) Exposure and Risk for Tebuthiuron
***The subpopulation(s) with the highest risk estimates bolded**

Population Subgroup	Acute Dietary (95 th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD	Dietary Exposure (mg/kg/day)	% cPAD
General U.S. Population			0.042379	30
All Infants (<1 year old)			**0.100488**	**72**
Children 1-2 years old			0.088184	63

Table 5.4.5 Summary of Dietary (Food and Drinking Water) Exposure and Risk for Tebuthiuron *The subpopulation(s) with the highest risk estimates bolded				
Population Subgroup	**Acute Dietary (95 th Percentile)**		**Chronic Dietary**	
	Dietary Exposure (mg/kg/day)	**% aPAD**	**Dietary Exposure (mg/kg/day)**	**% cPAD**
Children 3-5 years old			0.064471	46
Children 6-12 years old			0.043157	31
Youth 13-19 years old			0.031694	23
Adults 20-49 years old			0.039849	29
Adults 50-99 years old			0.039135	28
Females 13-49 years old	0.093157	93	0.039754	28

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no registered residential uses for tebuthiuron. Residential handler and post-application exposure assessments are not included in this document.

6.1 Residential Bystander Post-application Inhalation Exposure

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for tebuthiuron at this time. However, 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[3]. The Agency is in the process of evaluating the SAP report and may, as appropriate, develop policies and procedures to identify the need for and, subsequently, the way to incorporate post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are developed, the Agency may revisit the need for a quantitative post-application inhalation exposure assessment for tebuthiuron.

6.2 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 onto 50 feet wide lawns coupled with methods employed for residential risk assessments for turf products.

[3] Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html

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.[4] 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.

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

A screening approach was developed based on the use of the AgDRIFT model in situations where specific label guidance that defines application parameters is not available.[5,6] AgDRIFT is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDRIFT was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed). Section 6.2.1 and Appendix D provide the screening level drift related risk estimates.

In many cases, risks are of concern when the screening level estimates for spray drift are used as the basis for the analysis. In order to account for this issue and to provide additional risk management options additional spray drift deposition fractions were also considered. These drift estimates represent plausible options for pesticide labels

[4] This approach is consistent with the requirements of the EPA's Worker Protection Standard.
[5] http://www.agdrift.com/
[6] Note that for many cases the scenarios outlined in the screening approach represent actual use practice so risk assessors should be aware and characterize these appropriately.

6.2.1 Combined Risk Estimates from Lawn Deposition Adjacent to Applications

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. Tebuthiuron can be applied via groundboom, and aerial equipment at a maximum rate of 6 lb ai/acre to large acreages of pastureland/rangeland as well as for total vegetative control in non-cropland areas. The recommended drift scenario screening level options are listed below:

- *Groundboom applications*; are based on the AgDRIFT option for high boom height and using very fine to fine spray type using the 90th percentile results.

- *Aerial applications:* are based on the use of AgDRIFT Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).[7]

In addition to the screening level spray drift scenarios described above, additional results are provided which represent viable drift reduction technologies (DRTs) that represent potential risk management options. In particular, different spray qualities have been considered as well as the impact of other application conditions (e.g., boom height, use of a helicopter instead of fixed wing aircraft, crop canopy conditions).

Dermal risk estimates based on 100% absorption were calculated for adults. Dermal and incidental oral risk estimates for children 1 to <2 years old were combined because the toxicity endpoint for each route of exposure is the same. The total applicable level of concern is 100 so MOEs < 100 represent risk estimates of concern. Adult dermal and children's (1 to <2 year old) dermal and incidental oral risk estimates from indirect exposure to tebuthiuron related to spray drift result in buffers that range from 0 feet to greater than 150 feet depending on the nozzle type, droplet size, and application equipment. Aerial application has more risk estimates of concern. Dermal absorption data could lead to refinement in the spray drift analysis.

Spray drift analysis results are presented in Appendix D Tables D.1 and D.2. Appropriate drift reduction technologies such as changing the spray type/nozzle configuration to coarser spray applications may in less drift and reduced risk concerns (i.e., higher MOEs) from aerial applications. Similarly, using coarser sprays and lowering boom height for groundboom sprayers reduces risk concerns.

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

7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate tebuthiuron 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. There are no residential uses of tebuthiuron; therefore, the aggregate risk includes only exposure from food and drinking water. The acute and chronic dietary risk estimates are not of concern (less than 100%) of the aPAD and cPAD, respectively (see Section 5.0 for specific information on the dietary exposure estimates).

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 tebuthiuron and any other substances and tebuthiuron does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has not assumed that tebuthiuron 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/Risk Characterization

9.1 Short-/Intermediate Handler Risk

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

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the registered and proposed uses of tebuthiuron. The quantitative exposure/risk assessment developed for occupational handlers is based on the following scenarios:

- Mixing/loading DF/WDG for aerial application;
- Mixing/loading DF/WDG for groundboom application;

- Loading P/G for aerial application;
- Loading P/G for tractor drawn spreader application;
- Applying DF/WDG by aerial application;
- Applying DF/WDG by groundboom application;
- Applying P/G for aerial application;
- Applying P/G for tractor drawn spreader application;
- Loading/applying P/G for application with belly grinder;
- Loading/applying P/G for application with a rotary push-type spreader;
- Mixing/loading/applying DF/WDG for mechanically pressurized handgun application;
- Mixing/loading/applying DF/WDG for manually pressurized handwand application;
- Mixing/loading/applying DF/WDG for backpack application;
- Applying P/G by cup;
- Applying P/G by spoon;
- Applying P/G by shaker can;
- Applying P/G by hand; and
- Flaggers from aerial application of spray and granules.

Chemigation applications are prohibited on the product labels.

Exposure is most likely to be short (1 to 30 days) and intermediate-term (1 to 6 months) given the use pattern and limitations. There are no agricultural crop use sites and the recommended timing of application is prior to the resumption of active seasonal growth in the spring when the ground is not frozen or before expected seasonal rainfall. Applications are limited to once every two to three years and to twice every six years. However it is possible that a commercial applicator could apply the product over a period of weeks within a region. Therefore, based on the use pattern short-term and intermediate-term exposures are expected for tebuthiuron.

Estimates of dermal and inhalation exposure were calculated for various levels of personal protective equipment. 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 the addition of various levels of PPE as necessary (e.g., gloves, respirator, engineering control, etc). Worker protection standard (WPS) language should appear on all registered labels. Currently two out of the three pelleted tebuthiuron formulations do not have any WPS listed on the labels. The DF and WDG formulations list PPE as baseline dermal attire plus gloves. The granular formulations direct tractor drawn spreaders and loaders to use a respirator with NIOSH approved filter with the addition of baseline dermal plus chemical resistant gloves

Based on the assessment of registered uses, there are risk estimates of concern (*i.e.,* dermal MOEs <100 and inhalation MOEs < 1000) for the short/intermediate dermal and inhalation exposure. In evaluating handler exposure scenarios, the dermal MOE values range from 0.18 to 7,100 at baseline dermal *(i.e.,* no gloves), 1.8 to 71,000 with gloves, and 2.4 to 71,000 with double layer protection consisting of baseline dermal with the addition of a coverall. In evaluating handler exposure scenarios, the inhalation MOE values range from 26 to 64,000 at

baseline inhalation (*i.e.*, no respirator), 130 to 320,000 with PF5 respirator, 260 to 640,000 with a PF10 respirator, and 970 to 480,000 with engineering controls. See Appendix E, tables E.1.1 through E.1.3 for occupational risk estimate summary.

A total aggregated risk index (ARI) was used since the LOC values for dermal exposure (100) and inhalation exposure (1000) are different. The target ARI is 1; therefore, ARIs of less than 1 are risk estimates of concern. Several of the occupational handler scenarios remain a risk of concern even with the addition of doubler layer dermal PPE consisting of double layer dermal wear, respirators, and engineering controls. These scenarios are as follows:

- Mixing/loading of DF/WDG and P/G for aerial applications on pastureland/rangeland (4 and 6 lb ai/acre) has a baseline PPE combined 0.1 ARI value. ARI values ranges from 0.02-0.25 with various PPE additions including engineering control such as a closed mixing/loading system;

- Mixing/loading P/G for aerial applications on non-crop land (6 lb ai/acre) has a baseline PPE combined 0.06 ARI value. ARI values ranges from 0.07-0.16 with various PPE additions including engineering control such as a closed mixing/loading system;

- Aerial application of P/G on pastureland, which resulted in a combined 0.16 ARI value with the use of engineering controls and on non-crop land a combined ARI value of 0.11.

- Flagger exposure to aerial spray of tebuthiuron on pastureland resulted in an ARI of 0.74 with double layer dermal PPE and PF10 respirator;

- Mixing/Loading/Applying DF/WDG with backpack, manually pressurized handgun, mechanically pressurized handwand resulted in an ARIs <1 even with double layer dermal PPE and PF10 respirator;

- Mixing/Loading/Applying P/G with a belly grinder, and hand dispersal, resulted in ARIs <1 even with double layer dermal PPE and PF10 respirator.

9.2 Short-/Intermediate-term Post-Application Risk

9.2.1 Dermal Post-application Risk

Occupational post-application dermal exposure from workers re-entering tebuthiuron treated areas is not anticipated because the chemical is a non-selective herbicide used in non-agricultural areas such as pastureland/rangeland, industrial, and rights-of-way sites. Occupational post-application exposures are not thought to occur because reentry is unlikely. Labels currently instruct workers to not enter fields until dusts have settled and delay grazing until one year after application. However, some of the labels use the term haying. If pastureland is intended for haying harvest the REI specified on labels should be based on the acute toxicity of tebuthiuron. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 12 hours is adequate to protect agricultural workers from post-application exposures to tebuthiuron from harvesting hay.

9.2.2 Inhalation Post-application Risk

Based on the Agency's current practices, a quantitative post-application inhalation exposure assessment was not performed for tebuthiuron at this time primarily because of the low acute inhalation toxicity (Toxicity Category III) and low vapor pressure (2×10^{-6} mm hg at 25 degrees Celsius). However there are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The Agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010[8]. The Agency is in the process of evaluating the SAP report as well as available post-application inhalation exposure data generated by the ARTF and may, as appropriate, develop policies and procedures, to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the Agency's risk assessments. If new policies or procedures are put into place, the Agency may revisit the need for a quantitative occupational post-application inhalation exposure assessment for tebuthiuron.

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.

[8] Available: http://www.epa.gov/scipoly/SAP/meetings/2009/120109meeting.html

10.0 References

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Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for [Type of Use (e.g., food vs. non-food)] for Tebuthiuron are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A1: Summary of Tebuthiuron toxicology data requirements.

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	yes
870.2500 Primary Dermal Irritation	yes	yes
870.2600 Dermal Sensitization	yes	yes
870.3100 Oral Subchronic (rodent)	yes	yes
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	yes
870.3250 90-Day Dermal	no	no
870.3465 90-Day Inhalation	yes	no
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	yes
870.4100a Chronic Toxicity (rodent)	yes	waived[1]
870.4100b Chronic Toxicity (nonrodent)	no	yes
870.4200a Oncogenicity (rat)	yes	waived[1]
870.4200b Oncogenicity (mouse)	yes	waived[1]
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5395 Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a Acute Delayed Neurotox. (hen)	no	no
870.6100b 90-Day Neurotoxicity (hen)	no	no
870.6200a Acute Neurotox. Screening Battery (rat)	yes	waived[1]
870.6200b 90-Day Neuro. Screening Battery (rat)	yes	waived[1]
870.6300 Developmental Neurotoxicity	CR	no
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	no
870.7800 Immunotoxicity	yes	yes
Special Studies for Ocular Effects	no	no

1) Acute and subchronic neurotoxicity studies, chronic/carcinogenicity study in the rat, and a carcinogenicity study in the mouse are not required for Tebuthiuron (HASPOC TXR0056927

A.2 Toxicity Profiles

Table A2: Tebuthiuron Toxicity Profile

Guideline No.	Study Type	MRID No. (year)/ Classification /Doses	Results
870.3100	90-Day oral toxicity (Haerlan Rat)	00020662 (1972) **Acceptable/Guideline** 0, 20, 50, and 125 mg/kg/day	**NOAEL =** 50 mg/kg/day **LOAEL** = 125 mg/kg/day based on decreased body weight (25-28%) and an increase in slight vacuolization of the pancreatic acinar cells.
870.3100	90-Day oral toxicity (Beagle Dog)	00020663 (1972) **Acceptable/Guideline** 0, 12.5, 25, and 50 mg/kg/day	**NOAEL** = 25 mg/kg/day **LOAEL** = 50 mg/kg/day based on significant decreases in body weight and increased ALP activity.
870.3200	21/28-Day dermal toxicity	00149733 (1985) 00160796 (1986) **Acceptable/Guideline** 0, 1000 mg/kg/day	**NOAEL** = 1000 mg/kg/day No treatment related effects were observed.
870.3700a	Prenatal developmental (Harlan Rats)	00020803 (1972) 40485801 (1972) **Acceptable/Guideline** 0, 37, 72, and 110 mg/kg/day GD 6-14	**Maternal NOAEL** = 110 mg/kg/day D**evelopmental NOAEL** = 110 mg/kg/day No treatment related effects were observed.
870.3700b	Prenatal developmental (Dutch rabbits)	00020644 (1975) 40776301 (1988) **Acceptable/Guideline** 0, 10, and 25 mg/kg/day	**Maternal NOAEL** = 10 mg/kg/day **LOAEL** = 25 mg/kg/day based on increased resorptions at the high-dose. **Developmental NOAEL** = 10 mg/kg/day **LOAEL** = 25 mg/kg/day based on significantly decreased fetal weights.
870.3800	2-Generation Reproduction and fertility effects (Wistar rat)	00090108 (1981) **Acceptable/Guideline** 0, 14, and 30 mg/kg in males and 0, 14, and 26 mg/kg in females.	**Parental NOAEL** = 14 mg/kg/day **LOAEL** = 26 mg/kg/day based on decreased body weights in F1 females (13%). **Reproductive NOAEL** = 26 mg/kg/day. No effects were observed on reproductive parameters as measured by sperm morphology, fertility index for females, and the number of litters produced. **Offspring NOAEL** = 14 mg/kg/day **LOAEL** = 26 mg/kg/day based on decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%).
870.4100b	Chronic toxicity (Beagle dog, capsule)	00146801 (1985) **Acceptable/Guideline** 0, 12.5, 25, and 50 mg/kg/day	**NOAEL** = 25 mg/kg/day **LOAEL** = 50 mg/kg/day based on decreased body weight (-12.5%), increased ALT (4-5 fold), AP (3-fold), and significantly increased absolute and relative liver weights.
870.4200	Carcinogenicity (Harlan ICR mice)	00020717 (1986) **Unacceptable/Guideline** 0, 60, 120, and 240 mg/kg/day	**NOAEL** = 240 mg/kg/day No significant treatment-related effects were identified.

Table A2: Tebuthiuron Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4300	Combined chronic toxicity/carcinogenicity (Sprague-Dawley rat)	00020714 (1976) 00098190 (1981) 40870101 (1988) **Unacceptable/Guideline** 0, 20, 40, and 80 mg/kg/day	No NOAEL may be established for this study as several major deficiencies were identified. 25% or fewer animals were living at study termination in all groups. Additionally, respiratory infections were prevalent among the controls and treated groups confounding the study results.
870.5100	Bacterial reverse gene mutation assay	MRID 00141691 (1984) **Acceptable/Guideline**	There was no increase in mutant colonies in tested bacterial strains exposed up to the limit dose (5000 µg/plate) with or without S9 activation.
870.5100	Bacterial reverse gene mutation assay	MRID 00141690 (1984) **Acceptable/Non-Guideline**	There was no increase in mutant colonies in any S. typhimurium or E. coli tested strain exposed to tebuthiuron (98.0 %) with or without metabolic activation. There was no evidence of induced mutant colonies over background in tested *S. typhimurium strains* and E. coli strains with or without S9 activation.
870.5300	*In vitro* mammalian cell gene mutation	MRID 00145041 (1984) **Acceptable/Guideline**	In a mammalian cell gene mutation assay in vitro, cultures of mouse lymphoma were exposed to Tebuthiuron (98.0%) technical at concentrations limited by cytotoxicity. Mutations were not induced at any concentration with S9- activation. Tebuthiuron was considered weakly mutagenic but only in the absence of metabolic activation. No evidence of an increased mutant frequency was observed in the presence of metabolic activation.
870.5550	Unscheduled DNA synthesis in mammalian cell culture	MRID 40750901 (1988) **Acceptable/Guideline**	In an unscheduled DNA synthesis (UDS) assay, primary rat hepatocyte cultures were exposed to Tebuthiuron (99.1 %) to the limit of cytotoxicity (≥900 µg/mL). UDS activity was evaluated at concentrations up to 800 µg/mL and there was no evidence of induction of UDS. There was no evidence that UDS, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.
870.5375	*In vitro* mammalian cell chromosome aberration	MRID 41134101 (1989) **Acceptable/Guideline**	In a mammalian chromosome aberration assay, Chinese Hamster Ovary (CHO) cell cultures were exposed to Tebuthiuron (99.08%) at concentrations limited by cytotoxicity. A significant increase in the percent of cells with aberrations was noted in nonactivated and activated cultures at cytotoxic doses. The predominant types of aberrations were chromosome and chromatid breaks. No significant increases were observed at lower concentrations; however, rare complex aberrations, such as triradials, quadriradials and complex rearrangements were noted, providing further support for clastogenicity. Positive control values were acceptable. There was evidence of an increase in structural chromosomal aberrations over background in the presence and absence of metabolic activation at cytotoxic doses.

Table A2: Tebuthiuron Toxicity Profile			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5915	In vivo sister chromatid exchange	MRID 40750902 (1988) **Acceptable/Guideline**	In an in vivo cytogenetic assay measuring sister chromatid exchange (SCE) frequency in Chinese hamster bone marrow cells female Chinese hamsters (3/group) were administered single oral doses of tebuthiuron (99.1%, Lot No. 729AS7) in 10% aqueous acacia at 3000, 4000, or 5000 mg/kg. Tebuthiuron was tested up to cytotoxic concentrations. Hypo-activity was noted in all treatment groups and bone marrow cytotoxicity (as evidenced by an increase in the percent division metaphases) was observed at 5000 mg/kg. There was no increase in the number of cells containing SCEs compared to controls at any concentration of tebuthiuron tested. Cyclophosphamide (50 mg/kg) and vehicle control values were acceptable. There was no evidence of an increase in SCEs over background.

A.3 Hazard Identification and Endpoint Selection

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

Study Selected: Developmental Toxicity in rabbits
MRIDs: 00020644 and 40776301
Dose and Endpoint for Risk Assessment: NOAEL= 10 mg/kg/day increased resorptions at LOAEL of 25 mg/kg/day.
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability, 1x FQPA Safety Factor)
Comments on Study/Endpoint/Uncertainty Factors: This study is considered to be the most appropriate for acute dietary dose and endpoint selection. Unlike the increased resorptions, the fetal body weight reductions at 25 mg/kg/day, were no considered to be an acute effect. Thus, the basis for the acute dietary risk assessment for females of reproductive age is the resorptions. Note: No endpoint was selected for the general population. The endpoint from the developmental rabbit study for females 13-49 would be protective of any clinical signs seen at much higher doses in the acute oral toxicity study in rats.

$$\textbf{Acute RfD} = \frac{10\text{mg/kg/day}}{100\,(UF)} = \textbf{0.1 mg/kg/day}$$

A.3.2 Chronic Reference Dose (cRfD)

Study Selected: 2-Generation Reproduction Study in Rats
MRIDs: 00090108
Dose and Endpoint for Risk Assessment: Parental NOAEL= 14 mg/kg/day. Parental LOAEL = 26 mg/kg/day, based on decreased body weights in F1 females (13%).

Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability, 1x FQPA Safety Factor)
Comments on Study/Endpoint/Uncertainty Factors: The 2-generation reproduction study in rats is appropriate for both the population of concern (adults) and the duration of exposure.

$$\textbf{Chronic RfD} = \frac{14\text{mg/kg/day}}{100\,(UF)} = \textbf{0.14 mg/kg/day}$$

A.3.3 Incidental Oral Exposure (Short-term, 1-30 days)

Study Selected: 2-Generation Reproduction Toxicity Study in Rats
MRIDs: 00090108
Dose and Endpoint for Risk Assessment: Offspring NOAEL= 14 mg/kg/day based on decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%) at the LOAEL of 26 mg/kg/day.
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability, 1x FQPA Safety Factor)

Comments on Study/Endpoint/Uncertainty Factors: The endpoint of concern in this study is appropriate for the population (infant and children) and the duration of concern.

A.3.4. Dermal Exposure (Short-, Intermediate-Term) (Based on e-review post-ToxSAC meeting)

Study Selected: 2-Generation Reproduction Toxicity Study in Rats
MRIDs: 00090108
Dose and Endpoint for Risk Assessment: Offspring NOAEL= 14 mg/kg/day based on decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%) at the LOAEL of 26 mg/kg/day.
Uncertainty Factor: 100x (10x interspecies extrapolation, 10x intraspecies variability, 1x FQPA Safety Factor)

Comments on Study/Endpoint/Uncertainty Factors: A dermal risk assessment is being conducted for the following reasons 1) physical properties of the chemical support the potential for dermal absorption and 2) resorptions observed in the developmental toxicity study occurred in the absence of other maternal effects, and therefore, use of the dermal toxicity study which does not test pregnant animals may be under-protective as resorptions are not measured. The 2-generation reproductive toxicity study with a NOAEL of 14 mg/kg was selected as the NOAELs and LOAELs are similar (10/14 mg/kg and 25/26 mg/kg), the 14 mg/kg/day NOAEL represents a smaller dose spread between the NOAEL/LOAEL of both studies, and is protective of both the developmental effects observed in the rabbit and offspring effects in pups. There is no proposed long-term use; therefore, risk assessment for long-term dermal exposure is not required.

A.3.5 Inhalation Exposure (Short-, and Intermediate-Term) (Based on e-review post ToxSAC meeting)

Study Selected: 2-Generation Reproduction Toxicity Study in Rats
MRIDs: 00090108
Dose and Endpoint for Risk Assessment: Offspring NOAEL= 14 mg/kg/day based on decreased pup body weights on PND 21 in the F1 and F2 generation (5-8%) at the LOAEL of 26 mg/kg/day.
Uncertainty Factor: 1000x (10x interspecies extrapolation, 10x intraspecies variability, 10x database uncertainty (inhalation study required by HASPOC), 1x FQPA Safety Factor).

Comments on Study/Endpoint/Uncertainty Factors: No route-specific inhalation study is available for tebuthiuron. The 2-generation reproductive toxicity study with a NOAEL of 14 mg/kg was selected as it is protective of both developmental effects in rabbits and offspring effects observed in the rats. There is no proposed long-term use; therefore, risk assessment for long-term inhalation exposure is not required.

A.4 Executive Summaries

A.4.1 Subchronic Toxicity

870.3100 90-Day Oral Toxicity- Rat

The NOEL is 1000 ppm (50 mg/kg) in the diet based on increased relative liver, kidney, prostate, spleen and gonad weights in high-dose males and females. There was also slight vacuolization of the pancreatic acinar cells in the high-dose group of both sexes.

Classification: CORE- Minimum data.

870.3150 90-Day Oral Toxicity – Dog

Anorexia was noted especially in the high-dose animals, leading to weight loss. No mortality was observed. Behavior and appearance were unremarkable. No abnormalities were observed in hematological or urinalysis studies.

Clinical chemistry findings indicated increased BUN in the 2000 ppm females; in addition, this group exhibited increasing levels of ALP, up to 4-fold over the control group. Females at 1000 ppm demonstrated increased relative thyroid and spleen weights.

The LOAEL is 50 mg/kg/day based on significant decreases in body weight and increased ALP activity. The NOAEL is 25 mg/kg/day.

870.3200 21/28-Day Dermal Toxicity – Rat

No effects were observed up to the limit dose.

A.4.2 Prenatal Developmental Toxicity

870.3700a Prenatal Developmental Toxicity Study – Rat

In a developmental toxicity study (MRID 00020803, 40485801), 25 presumed pregnant Harlan rats per group were administered tebuthiuron (purity not given; Lot No. 1093-316A-259) at dietary concentrations of 0, 600, 1200, or 1800 ppm on gestation days (GD) 6-15, inclusive. Doses to the animals were 0, 37, 72, or 110 mg/kg/day, respectively. Individual data for maternal body weights and food consumption, cesarean parameters, and fetal examinations were given in MRID 40485801. On GD 20, dams were sacrificed and subjected to gross necropsy; pancreatic tissue was saved from 10 females/group for histopathological examination. Fetal sex, weight, and viability were determined and each fetus was examined for external abnormalities. Approximately one-third of all fetuses were fixed in Bouin's solution for subsequent visceral examination and the remainders were cleared for skeletal examination.

All dams survived to terminal sacrifice. No treatment-related clinical signs of toxicity, changes in body weight, body weight gain, or food consumption were observed in any group. No treatment-related lesions were observed in any dam at necropsy. Pancreatic tissue, as evaluated by both gross and microscopic examination, appeared normal.

The maternal NOAEL is 110 mg/kg bw/day.

No differences were observed between the treated and control groups for pregnancy rate, number of corpora lutea/dam, number of implantation sites/dam, pre- or post-implantation losses, number of fetuses/litter, fetal body weights, or fetal sex ratios. No dead fetuses were observed. No treatment-related abnormalities were found in any fetus.

The developmental NOAEL is 110 mg/kg bw/day.

This study is classified as **Acceptable/Guideline** and satisfies the requirements for a developmental toxicity study [870.3700 (§83-3a)] in rats. It should be noted that test article concentrations in the diets were not measured; therefore, it may be possible that the doses to the animals were different from nominal.

870.3700b Prenatal Developmental Toxicity Study – Rabbit

In a developmental toxicity study (MRID 00020644, 40776301, 41122401), 15 presumed pregnant Dutch belted rabbits per group were administered tebuthiuron (96.5% a.i.; Lot No.: B30-23-149) by gavage at doses of 0, 10, or 25 mg/kg/day on gestation days (GD) 6-18, inclusive.

No clinical signs of toxicity were observed in any animal. No effects on body weights, body weight changes, or food consumption were noted for the treated groups as compared with the controls. No treatment-related lesions were found at gross necropsy. An increase in total early resorptions and the percentage of litters with early resorptions was observed in the high-dose group.

The maternal toxicity LOAEL is 25 mg/kg/day based on increased resorptions at the high-dose. The NOAEL is 10 mg/kg/day.

No differences between the treated and control groups were noted for pregnancy rate or numbers of corpora lutea, implantations, or fetuses/litter. A decrease in the mean fetal body weight was observed at 25 mg/kg/day (17.3%). An increase in total early resorptions and the percentage of litters with early resorptions was observed in the high-dose group. Additionally, an increase in early resorptions was indicated in the range-finding study at doses of 25 mg/kg/day and above.

The developmental toxicity LOAEL is 25 mg/kg/day based on decreased fetal body weights and increased early resorptions. The developmental toxicity NOAEL is 10 mg/kg/day.

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

A.4.3 Reproductive Toxicity

870.3800 Reproduction and Fertility Effects – Rat

In a two-generation reproduction study (MRID 90108), tebuthiuron (Lot No. 00880-1L-1, X-35920, 98.0% a.i.) was fed to groups of 25 male and 25 female Wistar rats per dose at dietary concentrations of 0, 100, 200, and 400 ppm. The dietary levels corresponded to doses of 6-7, 13-14, and 26-28 mg/kg/day, respectively, for F_0 and F_1 males and 7-8, 14-15, and 30-31 mg/kg/day, respectively, for F_0 and F_1 females averaged over the premating period only. Adult rats of both generation were fed the treated or control diets during the premating period (98 days for F_0 and 124 days for F_1 rats) and during mating, gestation, and lactation of two litters per generation. Pups from the F_{1a} litters were selected to parent the F_2 generation.

No treatment-related deaths, clinical signs of toxicity, gross lesions, or microscopic lesions were observed in adult rats of either generation. No treatment-related effects were observed on body weight, body weight gain, food consumption, or food efficiency in F_0 male rats, F_1 male rats, or F_0 female rats fed any dose at any time during the study including the premating, mating, gestation, and lactation periods. F_1 females in the 200 and 400 ppm groups had mean weekly body weights 7-9% (not biologically significant) and 8-13% ($p<0.01$ or <0.05), respectively, less than the control group throughout the premating period starting with day 21 for the 200 ppm group and day 7 for the 400 ppm group. Weight gain over the entire premating period was 7% (N.S.) less than controls for 200 ppm group F_1 females and 14% ($p<0.05$) less for the 400 ppm group. Cumulative food consumption was not significantly affected, but food efficiency was reduced by 13% ($p<0.01$) for 400 ppm group F_1 females. It is important to note that the body weight decreases of F1 parents occurred only at the high-dose where F1 pups had impaired body weight gain. Throughout the database, adult rat body weight impairment does not begin until doses 3 to 4 fold higher than administered in this study.

The parental systemic LOAEL was established at 400 ppm (26 mg/kg/day) based on decreases in body weight and weight gain in F1 female rats. The parental systemic NOAEL was established at 200 ppm (14 mg/kg/day).

No effects were observed on reproductive parameters as measured by sperm morphology, fertility index for females, and the number of litters produced.

The reproductive LOAEL was not established; the NOAEL was established at 400 ppm (26 mg/kg/day).

Biologically significant decreases in pup body weights (5-8%) were observed on PND 7-21 in the F1 and F2 litters.

The offspring LOAEL was established at 400 ppm (26 mg/kg/day) based on decrease pup body weights on PND 7-21. The offspring NOAEL was established at 200 ppm (14 mg/kg/day).

This study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a two-generation reproductive study (OPPTS 870.3800, §83-4) in the rat. This study was conducted years before the test guidelines were established; therefore, some of the elements of a two-generation reproduction study were not included in this study. Nevertheless, this study had a sufficient number of required elements to be used for the evaluation of reproductive and offspring toxicity. The reviewer notes that the rats could have tolerated a higher dose, which may have allowed for better characterization of tebuthiuron toxicity to developing rats.

A.4.4 Chronic Toxicity

870.4100b Chronic Toxicity – Dog

All animals survived to scheduled termination. Clinical signs of toxicity in high-dose animals included anorexia, emesis, and diarrhea. Absolute body weights for females and food consumption for males and females were not affected by treatment. Body weights of the high-dose males were less than those of the controls throughout most of the study with statistical significance attained occasionally. Overall weight gains by the high-dose males and females were 67% and 82%, respectively, of the control levels. No treatment-related ophthalmological lesions, changes in urinalysis parameters, or microscopic lesions were noted and gross necropsy was unremarkable.

Thrombocyte counts were significantly ($p \leq 0.05$) increased in high-dose males at 6 and 12 months as compared with the controls. Alanine aminotransferase (ALT) levels were increased in males after 1 month and in females after 3 months to 186-529% and 228-407%, respectively, of the control group levels. In addition, alkaline phosphatase (AP) levels in males were increased to 283-408% of the control levels at 6 and 12 months. Statistical significance was not attained at all-time points for the increases in enzyme levels due to large variability between individual animals.

Absolute liver weights were significantly ($p \leq 0.05$) increased in the high-dose males and females. No other differences in absolute organ weights were found. Also for the high-dose groups, significant ($p \leq 0.05$) differences in organ weights relative to final body weight included increased relative liver weights in males and females, increased relative kidney weights in females, and increased relative thyroid weights in males.

The LOAEL was established at 50 mg/kg/day based on clinical signs (anorexia, emesis, and diarrhea), decreased body weight gains, increased alanine aminotransferase and alkaline phosphatase (males only) levels, increased absolute and relative liver weights, increased relative kidney weights (females only), and increased relative thyroid weights (males only). The NOAEL was established at 25 mg/kg/day.

This study is classified as **Acceptable/Guideline** and satisfies the guideline requirements for a chronic toxicity study [OPPTS 870.4100 (83-1b)] in dogs.

A.4.5 Carcinogenicity

870.4300a Combined Chronic Toxicity/Carcinogenicity – Rat

In a chronic toxicity/carcinogenicity study (MRID 0020714), tebuthiuron (>97% a.i., lot number, 6SG43 and B30-23-149) was administered to male and female Wistar rats (40/group/sex) at dietary concentrations of 400, 800, or 1600 ppm (20, 40, and 80 mg/kg/day, based on the default food factor of 0.05). Two control groups of 60 male and 60 female Wistar rats administered untreated basal diet. No interim sacrifice was conducted for this study. Two replicate studies were carried out.

No treatment-related effects were reported for clinical signs, mortality, or clinical pathology in male or female rats receiving any dose of the test material. The mortality rate for all groups was high. During the first year of treatment, 10-19% of males died while at the end on the study, only 26% of all rats remained alive. Pneumonia affected the majority of animals in all groups at various times during the study; antibiotic treatment was required during one episode. Absolute body weights presented graphically indicated that high-dose males and females weighed less than controls throughout most of the study. The magnitude of the reduction in absolute body weight could not be determined for assessment of statistical or toxicological significance. A 15% reduction in body weight in high-dose females was observed at study termination. Food consumption was measured but not reported.

Relative kidney weights were depressed in high-dose male rats, but no histopathological correlates were observed. Each animal was necropsied, but gross findings were not tabulated. Vacuolization of pancreatic acinar cells (generally slight or affecting only a few cells) was observed in 11 males and 13 females receiving the high-dose and in none of the controls of either sex. Only selected histopathological data were presented in the summary tables of the study report; therefore, a complete assessment of histopathological findings could not be conducted. No treatment-related neoplasms were reported; common neoplasms included pituitary adenomas and mammary fibro adenomas in female rats. The microscopic findings in the pancreatic acinar

cells were generally slight, affected only a few cells, and caused no physiological effect on glucose levels.

Based on the results of this study (decreased terminal body weight in females), the LOAEL for systemic toxicity was established at 80 mg/kg/day; a LOAEL was not established in males. The NOAEL was established at 40 mg/kg/day in females at 80 mg/k/day in females.

This chronic toxicity/carcinogenicity study in the rat is **Unacceptable/Guideline** and does not satisfy the guideline requirement for a chronic toxicity/carcinogenicity oral study [OPPTS 870.4300 (§83-5)] in the rat. There were numerous deficiencies in this study. The major deficiencies are listed as follows:

- The mortality rate for all groups was high, leaving only 25% or fewer animals in some groups out of an initial number of at least 80 per group.
- Respiratory infections were very prevalent in all groups and may have affected the outcome of the study.
- Summary tables were not available for clinical signs, body weights, body weight gains, food consumption, urinalysis data, and gross findings.
- Summary tables for microscopic findings were not complete, contained errors, and did not include the number of animals examined at each anatomical site.
- The data were not analyzed statistically.
- The evidence suggests that this study does not comply with GLP procedures.

870.4200b Carcinogenicity (feeding) – Mouse

In a carcinogenicity study (MRID 00020717) Tebuthiuron (>97% a.i., lot # B30-23-149) was administered to groups of 80 Harlan ICR mice/sex/dose in pelleted diet at dose levels of 400, 800, or 1600 ppm (equivalent to 60, 120, or 240 mg/kg/day based on the default food factor of 0.15) for 2 years. The control group, consisting of 120 males and 120 females was fed untreated pelleted diet. Animals were equally subdivided by dose and sex into two sub-studies; the second sub-study was started 1 week after the first. It should be noted that animals were not assigned by body weight.

Although there was a statistically significant decrease (32.4 g, 12%) in the terminal body weights of high-dose females in one of the sub-studies (M9153), this is likely due to the higher body weight (36.7 g) of the control females in this sub-study. The terminal body weight of the control females in the other sub-study was 34.1 g.

There were no compound related effects on mortality, clinical signs, hematology or clinical chemistry, organ weights, or gross or microscopic pathology.

The LOAEL for systemic toxicity was not established. The NOAEL was established at 1600 ppm (240 mg/kg/day).

At the doses tested, there was no treatment related increase in tumor incidence when compared to that of controls. Dosing was not considered adequate based on the absence of systemic effects.

This carcinogenicity study in the mouse is **Unacceptable/Guideline** and does not satisfy guideline requirements for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

A.4.6 Mutagenicity

Table A.4.6: Tebuthiuron Mutagenicity Studies

Study	Results
870.5100 Bacterial reverse gene mutation assay	There was no increase in mutant frequency in tested bacterial strains exposed up to the limit dose (5000 µg/plate) with or without S9 activation.
870.5100 Bacterial reverse gene mutation assay	There was no increase in mutant frequency in any S. typhimurium or E. coli tested strain exposed to tebuthiuron (98.0%) with or without metabolic activation. There was no evidence of induced mutant colonies over background in tested *S. typhimurium strains* and E. coli strains with or without S9 activation.
870.5300 *In vitro* mammalian cell gene mutation	In a mammalian cell gene mutation assay in vitro, cultures of mouse lymphoma were exposed to Tebuthiuron (98.0%) technical at concentrations limited by cytotoxicity. Mutations were not induced at any concentration with activation. Tebuthiuron was considered weakly mutagenic but only in the absence of metabolic activation. No evidence of an increased mutant frequency was observed in the presence of metabolic activation.
870.5550 Unscheduled DNA synthesis in mammalian cell culture	In an unscheduled DNA synthesis assay, primary rat hepatocyte cultures were exposed to Tebuthiuron (99.1%) to the limit of cytotoxicity (≥900 µg/mL). UDS activity was evaluated at concentrations up to 800 µg/mL and there was no evidence of induction of UDS. There was no evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.
870.5375 *In vitro* mammalian cell chromosome aberration	In a mammalian chromosome aberration assay, Chinese Hamster Ovary (CHO) cell cultures were exposed to Tebuthiuron (99.08%) at concentrations limited by cytotoxicity. A significant increase in the percent of cells with aberrations was noted in nonactivated and activated cultures at cytotoxic doses. The predominant types of aberrations were chromosome and chromatid breaks. No significant increases were observed at lower concentrations; however, rare complex aberrations, such as triradials, quadriradials and complex rearrangements were noted, providing further support for clastogenicity. Positive control values were acceptable. There was evidence of an increase in structural chromosomal aberrations over background in the presence and absence of metabolic activation at cytotoxic doses.

870.5915 In vivo sister chromatid exchange	In an in vivo cytogenetic assay measuring sister chromatid exchange (SCE) frequency in Chinese hamster bone marrow cells female Chinese hamsters (3/group) were administered single oral doses of tebuthiuron (99.1%, Lot No. 729AS7) in 10% aqueous acacia at 3000, 4000, or 5000 mg/kg. Tebuthiuron was tested up to cytotoxic concentrations. Hypo-activity was noted in all treatment groups and bone marrow cytotoxicity (as evidenced by an increase in the percent division metaphases) was observed at 5000 mg/kg. There was no increase in the number of cells containing SCEs compared to controls at any concentration of tebuthiuron tested. Cyclophosphamide (50 mg/kg) and vehicle control values were acceptable. There was no evidence of an increase in SCEs over background.

A.4.7 Neurotoxicity

870.6200 Acute Neurotoxicity Screening Battery- Rat

Waived by HASPOC.

870.6200 Subchronic Neurotoxicity Screening Battery -Rat

Waived by HASPOC.

A.4.8 Metabolism

870.7485 Metabolism – Rat

Terminal distribution data showed no significant amounts of residual radioactivity in any tissue examined, but the skin showed the highest amounts relative to other tissues. Excretion was rapid at both the low and high dose levels in both sexes, but was delayed during the first 12 hours post-dose, indicating saturation of biotransformation or excretion. Six metabolites of tebuthiuron were identified. The major metabolite in 0-24 hour urine of male (58.3%) and female (62.1%) rats was identified as hydroxylated tebuthiuron metabolites (109-OH and /or 104-OH). The second most abundant metabolite was identified as metabolite 106 of tebuthiuron. This comprised between 9-15% of the administered dose in 0-24 hour urine of low dose rats, and between 1-10% of the administered dose in high dose rats. Two other metabolites identified, 104/109 and 103-OH, comprised between 2-10% of the administered dose in male and female 0-24 hour urine. Feces contained minor amounts of 104-OH and 109-OH, accounting for an average of 3.5% of the administered dose.

A.4.9 Immunotoxicity

870.7800 Immunotoxicity- Rat

In an immunotoxicity study (MRID #48722705), Tebuthiuron (99.8 % a.i., Lot no. EQ 4821, TSN 100583) was administered to female Crl: WI (Han) (10/dose) in the diet at dose levels of 0, 400, 1000, or 2000 ppm (equivalent to 0, 33.8, 84.9, and 148 mg/kg/day, respectively) for 29 days. The positive control group (10 females) was administered 20 mg/kg bw/day of cyclophosphamide (10 mL/kg at a concentration of 5 mg/mL) by intraperitoneal injection from study Days 24-28. During the study, clinical condition, bodyweight, food and water consumption, organ weight, and macroscopic pathology were evaluated. On the study Day 24, all animals in all groups received a single intravenous dose of sheep red blood cells (SRBC) (4 x 10^8 SRBC/mL, 0.5 mL/animal). At sacrifice, selected organs were removed and weighed (kidney, liver, spleen and thymus). The anti-SRBC IgM response was measured with Enzyme Linked Immunosorbent Assay (ELISA).

There were no premature deaths and no treatment-related effects on clinical signs. Animals in 2000 or 1000 ppm groups had treatment-related decreases in body weight, body weight gain and food consumption throughout the study. Animals in 2000 ppm group also had treatment related consistently higher reticulocyte counts than the control. There were statistically significant decreased in absolute and relative thymus weights; statistically significant increased relative liver weights; and statistically significant decreased in absolute kidney and spleen weights in this group. Positive control group treated with cyclophosphamide had statistically significant decreased in absolute and relative spleen and thymus weights. There was lower body weight gain from study Day 22-29, when compared to the vehicle control group; however, it was not statistically significant.

The systemic LOAEL was 1000 ppm (equivalent to 84.9 mg/kg/day) based on decreased body weight and body weight gain. The systemic NOAEL was 400 ppm (equivalent to 33.8 mg/kg/day).

There were no statistically significant differences observed in anti-SRBC IgM levels in treated groups when compare to the vehicle control group. High inter-individual variability was noted in all the treatment groups as well as in the control group. Evaluation of the individual animal data of this study did not show any trend or distribution that would demonstrate significant suppression of anti-SRBC antibody response. Positive control group had statistically significant decrease in the anti SRBC IgM levels. This confirmed the ability of the test system to detect immuno-suppressive effects and confirmed the validity of the study design.

The Natural Killer (NK) cells activity was not evaluated in this study. The toxicology database for tebuthiuron does not reveal any evidence of immunotoxicity. The overall weight of evidence suggests that the chemical does not directly target the immune system. Under HED guidance a NK cell activity assay is not required at this time.

The NOAEL for immunotoxicity was 2000 ppm (equivalent to 148 mg/kg/day), the highest dose tested. The immunotoxicity LOAEL was not established.

This immunotoxicity study is classified **acceptable/guideline** and satisfy the guideline requirement for an immunotoxicity study (OPPTS 870.7800) in rats.

Appendix B. Physical/Chemical Properties

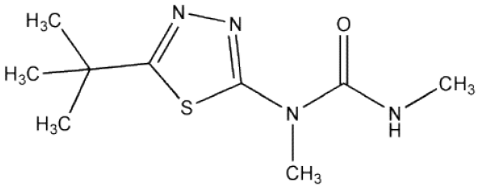
Table B1: Chemical Identity of Tebuthiuron	
Common Name	Tebuthiuron
Chemical Name	N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-y1] N,N ’dimethyl urea
IUPAC	1-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-1,3-dimethylurea
PC Code	105501
Chemical Abstracts Number	34014-18-1
Registration Review Case Number	0054
Chemical Structure	

Table B2: Physico-Chemical Properties for Tebuthiuron			
Parameter	**Value**		**Reference**
Molecular Weight	228.3		PubChem
Melting point/range	161 ºC at 760 mm Hg		D256269, A. Smith, 06/29/1999 WSSA Herbicide Handbook Committee. Herbicide Handbook of the Weed Science Society of America, 6th Ed. WSSA, Champaign, IL. 1989.
pH	NA: Solid at 25 ºC		
Water solubility	2.5 mg/mL		
Solvent solubility (g/100mL)	25.0 in chloroform	0.37 in benzene	
	17.0 in methanol	7.0 in acetone	
	0.61 in hexane	6.0 in acetonitrile	
Vapor pressure	2 x 10^{-6} mm Hg at 25 degrees Celsius		
Chemical class/use	Herbicide Urea carbamate		
Soil Half-life	12 to 15 months w/40 in rainfall		1996 EXTOXNET
Partition-coefficient in n-octanol / water	K_{ow} = log P 1.8 ; pH=7 at 25 C		MSDS

Table B3: Summary of Metabolites and Degradates to be Included in the Risk Assessment and Tolerance Expression Followed by Chemical Structures in Figure A.		
Matrix		
Plants	Primary Crop	Combined residues of the herbicide tebuthiuron (**103):** (N-(5- (1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N,N'-dimethylurea) and its metabolites, **103(OH):** N-(5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N,N'-dimethylurea, **104:** N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N-methylurea, and **109:** N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N'-hydroxymethyl-N-methylurea.
Livestock	Ruminant	Combined residues of the herbicide tebuthiuron **(103):** (N-(5-(1,1-dimethylethyl) -1,3,4-thiadiazol-2-yl)-N,N'-dimethylurea) and its metabolites **104:**N-(5-(1,1-dimethyl ethyl)-1,3,4-thiadiazol-2-yl)-N-methyl-urea, **106:** N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)urea, **108:** 2-dimethylethyl-5-amino-1,3,4-thiadiazole, and **109:**N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N'-hydroxymethyl-N-methylurea.
Milk		Combined residues of the herbicide tebuthiuron **(103):** (N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N,N'-dimethylurea) and its metabolites **104:** N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N-methyl-urea, **104 (OH):** N-(5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N-methylurea, **106:** N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)urea, **109:** N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N'-hydroxymethyl-N-methylurea, and **109 (OH):** N-(5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N'-hydroxymethyl-N-methylurea
Drinking Water		Combined residues of the herbicide tebuthiuron **(103):** (N-(5- (1, 1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N,N'-dimethylurea) and its metabolites **104**: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]- N-methy-lurea.

Table B.4:

Figure A. The chemical structures of the metabolites of concern of tebuthiuron

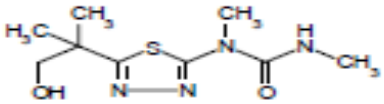
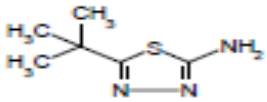
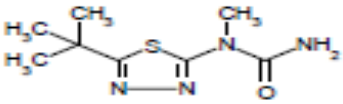
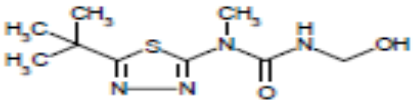
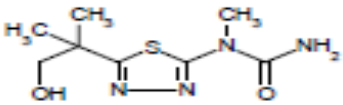
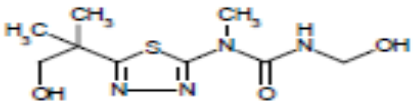
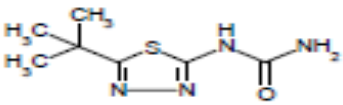
Structure **Metabolite**: Chemical name	Structure **Metabolite**: Chemical name
 **103 (OH)**: N-[5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea	 **108**: 2-dimethylethyl-5-amino-1,3,4-thiadiazole
 **104**: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N-methylurea	 **109**: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N'-hydroxymethyl-N-methylurea
 **104 (OH)**: N-[5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N-methylurea	 **A [109 (OH)]**: N-[5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]-N'-hydroxymethyl-N-methylurea
 **106**: N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]urea	

Table B5: Tebuthiuron EDWCs for the Wisconsin Corn Scenario in Groundwater			
Drinking Water Source (Model)	**Highest Daily Value Acute**	**Post Breakthrough average Chronic**	**Average simulation Breakthrough Time**
	(µg/L)	**(µg/L)**	**(days)**
Groundwater (PRZM-GW)	2020*	1740	2230
*A time series water residue distribution was used in the acute dietary assessment.			

The drinking water models and their descriptions are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

Appendix C. Residue Summary Table

Table C.1: International Residue Limits for Tebuthiuron (105501; 05-NOV-2013)				
Summary of US and International Tolerances and Maximum Residue Limits				
Residue Definition:				
US		Canada	Mexico[1]	Codex
40 CFR 180.390 (a) General (1) combined residues of the herbicide tebuthiuron (N-(5- (1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N,N'-dimethylurea) and its metabolites N-(5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N,N'-dimethylurea, N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N-methylurea, and N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N'-hydroxymethyl-N-methylurea		None		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Grass, forage	10.0			
Grass, hay	10.0			
(2) combined residues of the herbicide tebuthiuron (N-(5-(1,1-dimethylethyl) -1,3,4-thiadiazol-2-yl)-N,N'-dimethylurea) and its metabolites N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N-methylurea, N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)urea, 2-dimethylethyl-5-amino-1,3,4-thiadiazole, and N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N'-hydroxymethyl-N-methylurea		None		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Cattle, fat	1.0			
Cattle, meat	1.0			
Cattle, meat byproducts	5.0			
Goat, fat	1.0			
Goat, meat	1.0			
Goat, meat byproducts	5.0			
Horse, fat	1.0			
Horse, meat	1.0			
Horse, meat byproducts	5.0			
Sheep, fat	1.0			
Sheep, meat	1.0			
Sheep, meat byproducts	5.0			
US		Canada	Mexico[1]	Codex
(3) combined residues of the herbicide tebuthiuron (N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N,N'-dimethylurea) and its metabolites N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N-methylurea, N-(5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N-methylurea, N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)urea, N-(5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N'-hydroxymethyl-N-methylurea, and N-(5-(2-hydroxy-1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl)-N'-hydroxymethyl-N-methylurea		None		None
Commodity	*Tolerance (ppm) /Maximum Residue Limit (mg/kg)*			
	US	Canada	Mexico[1]	Codex
Milk	0.8			
Completed: M. Negussie; 11/05/2013				

Appendix D. Spray Drift

Table D.1: Adult Risk Estimates (MOEs) Related to Indirect Exposure to Spray Drift for Tebuthiuron for the Dermal Route of Exposure

Crop/Rate Group	Spray Type/ Nozzle Configuration	Application Rate (lb ai/A)	Estimated or Adjusted TTR (ug/cm2)	At Edge	10 Feet	25 Feet	50 Feet	75 Feet	100 Feet	125 Feet	150 Feet	200 Feet	250 Feet	300 Feet
				Dermal MOE	Dermal MOE	Dermal MOE	Dermal MOE	Dermal MOE	Dermal MOE	Dermal MOE	Dermal MOE	Dermal MOE	Dermal MOE	Dermal MOE
Pastureland														
Aerial	***Fine to Medium***	4	0.4446	**36**	**45**	**55**	**72**	**95**	120	150	170	230	270	330
	Medium to Coarse			**44**	**60**	**81**	110	160	210	270	320	440	580	720
	Coarse to Very Coarse			**51**	**75**	110	180	250	330	420	520	720	930	1,200
	AT401, M, 10 mph, 37% SD			**40**	**51**	**66**	**89**	120	60	190	220	290	360	440
	WASP, M, 10 mph, 37% SD			**43**	**55**	**72**	110	150	190	230	270	360	440	520
	AT401, C, 10 mph, 25% SD			**47**	**66**	**94**	140	200	260	320	390	550	720	850
	WASP, C, 10 mph, 25% SD			**55**	**77**	110	180	250	330	410	520	720	930	1,000
	AT401, VC, 10 mph, 20% SD			**53**	**81**	130	210	300	410	520	670	930	1,200	1,600
	WASP, VC, 10 mph, 20% SD			**68**	110	160	260	370	490	670	780	1,200	1,300	1,600
Groundboom	High Boom Fine to Medium/Coarse			190	490	720	1,000	1,300	1,600	1,900	1,900	2,300	3,100	3,100
	Low Boom Fine to Medium/Coarse			280	780	1,200	1,600	1,900	2,300	3,100	3,100	4,700	4,700	4,700
	High Boom Fine to Medium/Coarse	6	0.6669	130	330	480	690	890	1,000	1,200	1,200	1,600	2,100	2,100
	Low Boom Fine to Medium/Coarse			190	520	780	1,000	1,200	1,600	2,100	2,100	3,100	3,100	3,100

1. The AT401 is the representative fixed wing aircraft and the WASP is the representative helicopter.

Table D.2: Children (1<2 years old) Risk Estimates (MOEs) Related to Indirect Exposure to Spray Drift for Tebuthiuron for the Combined Dermal and Oral Routes of Exposure

Crop/Rate Group	Spray Type/ Nozzle Configuration	Application Rate (lb ai/A)	Estimated or Adjusted TTR_t (ug/cm2)	At Edge	10 Feet	25 Feet	50 Feet	75 Feet	100 Feet	125 Feet	150 Feet	200 Feet	250 Feet	300 Feet
				Combined MOE	Combined MOE	Combined MOE	Combined MOE	Combined MOE	Combined MOE	Combined MOE	Combined MOE	Combined MOE	Combined MOE	Combined MOE
Pastureland														
Aerial	***Fine to Medium***	4	0.4446	**18**	**22**	**27**	**36**	**47**	**61**	**73**	**86**	110	140	160
	Medium to Coarse			**22**	**30**	**40**	**56**	**80**	100	130	160	220	290	360
	Coarse to Very Coarse			**25**	**37**	**56**	**87**	120	160	210	260	360	460	580
	AT401, M, 10 mph, 37% SD			**20**	**25**	**33**	**44**	**59**	**77**	**94**	110	140	180	220
	WASP, M, 10 mph, 37% SD			**21**	**27**	**36**	**54**	**73**	**94**	120	140	180	220	260
	AT401, C, 10 mph, 25% SD			**23**	**33**	**47**	**69**	**98**	130	160	190	270	360	420
	WASP, C, 10 mph, 25% SD			**27**	**38**	**55**	**87**	120	160	200	260	360	460	510
	AT401, VC, 10 mph, 20% SD			**26**	**40**	**64**	100	150	200	260	330	460	580	770
	WASP, VC, 10 mph, 20% SD			**33**	**52**	**81**	130	180	240	330	380	580	660	770
Groundboom	High Boom Fine to Medium/Coarse			**94**	240	360	510	660	770	920	920	1,200	1,500	1,500
	Low Boom Fine to Medium/Coarse			140	380	580	770	920	1,200	1,500	1,500	2,300	2,300	2,300
	High Boom Fine to Medium/Coarse	6	0.6669	**63**	160	240	340	440	510	620	620	770	1,000	1,000
	Low Boom Fine to Medium/Coarse			93	260	380	510	620	770	1,000	1,000	1,500	1,500	1,500

1. The AT401 is the representative fixed wing aircraft and the WASP is the representative helicopter.

Appendix E. Occupational Exposure Scenarios and Risk Estimates

Table E.1: Occupational Dermal Handler Non-Cancer Exposure and Risk Estimates for Tebuthiuron

Exposure Scenario		Crop / Target Category	Application Rate[2]		Amount Handled / Area Treated[3]		Dermal Unit Exposures (ug/lb ai)[1]				Dermal Dose (mg/kg/day)[4]				Dermal MOE[5]			
Formulation	**Application Equipment**		**Value**	**Units**	**Value**	**Units**	**SL/NoG**	**SL/G**	**DL/G**	**EC**	**SL/NoG**	**SL/G**	**DL/G**	**EC**	**SL/NoG**	**SL/G**	**DL/G**	**EC**
Mixer/Loader																		
DF/WDG	Aerial	Pastureland Rangeland	4	lb ai/A	1200	acres	227	51.6	41.2	9.8	13.6	3.1	2.48	0.59	**1**	**4.5**	**5.6**	**24**
	Groundboom				200		227	51.6	41.2	9.8	2.28	0.52	0.41	0.1	**6.1**	**27**	**34**	140
	Groundboom	Non-crop land	6		200		227	51.6	41.2	9.8	3.4	0.77	0.62	0.15	4.1	18	23	95
P/G	Aerial	Pastureland Rangeland	4		1200		8.4	6.9	3.4	8.6	0.50	0.41	0.20	0.52	**28**	**34**	**69**	**27**
		Non-crop land	6				8.4	6.9	3.4	8.6	0.76	0.62	0.31	0.77	**19**	**23**	**46**	**18**
	Tractor-drawn spreader	Pastureland Rangeland	4		200		8.4	6.9	3.4	8.6	0.08	0.07	0.03	0.09	170	200	410	160
		Non-cropland	6				8.4	6.9	3.4	8.6	0.13	0.10	0.05	0.13	110	130	270	110
Applicator																		
Spray	Aerial	Pastureland Rangeland	4	lb ai/A	1200	acres				2.08				0.13				110
	Groundboom				200		78.6	16.1	12.6	5.1	0.79	0.161	0.126	0.05	**18**	87	110	270
	Groundboom	Non-crop land	6		200		78.6	16.1	12.6	5.1	1.18	0.24	0.19	0.08	**12**	**58**	**74**	180
P/G	Aerial	Pastureland Rangeland	4		1200					1.7				0.10				140
		Non-crop land	6											0.15				**92**
	Tractor-drawn Spreader	Pastureland Rangeland	4		200		9.9	7.2	4.2	2	0.1	0.072	0.04	0.02	140	190	330	700
		Non-crop land	6				9.9	7.2	4.2	2	0.15	0.11	0.06	0.03	**94**	130	220	470
	Hand dispersal	Non-crop land and Rights-of-way	0.00014	lb ai/ft2	10,000	ft2	104000	71000	40280		1.83	1.24	0.71		**7.7**	**11**	**20**	
	Shaker can						112	11.2	11.2		0.002	0.0002	0.0002		7100	71000	71000	
Flagger																		
Spray	Aerial	Pastureland Rangeland	4	lb ai/A	350	acres	11	12	10.6		0.19	0.21	0.185		**73**	**67**	**76**	
P/G							2.75	2.73	1.59		0.05	0.05	0.03		290	290	500	
		Non-crop land	6	lb ai/A			2.75	2.73	1.59		0.072	0.07	0.04		190	200	330	

Mixer/Loader/Applicator																		
DF/WDG	Backpack	Non-crop land and Rights-of-way	1.6	lb ai/gallon	40	gallons	8260	8260	4120		6.61	6.61	3.3		**2.1**	**2.1**	**4.2**	
	Manually-pressurized Handwand						100000	430	365		80	0.34	0.293		**0.18**	**41**	**48**	
	Mechanically-pressurized Handgun				1000	gallons	1300	390	290		26	7.8	5.8		**0.54**	**1.8**	**2.4**	
P/G	Belly grinder		6	lb ai/A	1	acres	10000	9300	5700		0.75	0.7	0.43		**19**	**20**	**33**	
	Rotary spreader				5		440	240	130		0.17	0.09	0.05		**85**	160	290	
	Cup		0.00014	lb ai/ft2	10,000	ft2	112	11.2	11.2		0.002	0.0002	0.0002		7100	71000	71000	
	Spoon						4170	3030	1580		0.07	0.05	0.03		190	260	510	

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (May 2013); Level of mitigation: Dermal baseline PPE includes no gloves, long sleeved shirt, long pants, socks plus shoes. The addition of gloves and double layer protection is included in the far right column for comparison. Eng. Controls (EC) assumes enclosed cockpits for the aerial and ground application of tebuthiuron for all formulations. Shaded out cells are not applicable to scenario or there is no dermal unit exposure data.
2 Based on registered labels (Table 3.2.1).
3 Exposure Science Advisory Council Policy #9.1.
4 Dermal Dose = Dermal Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ **80** (kg).
5 Dermal MOE = Dermal NOAEL (mg/kg/day) ÷ Dermal Dose (mg/kg/day).

Table E.2: Occupational Inhalation Handler Non-Cancer Exposure and Risk Estimates for Tebuthiuron

Exposure Scenario		Crop / Target Category	Application Rate[2]		Amount Handled / Area Treated[3]		Inhalation Unit Exposures (ug/lb ai)[1]				Inhalation Dose (mg/kg-day)[4]				Inhalation MOE[5]			
Formulation	**Application Equipment**		**Value**	**Units**	**Value**	**Units**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**	**No-R**	**PF5 R**	**PF10 R**	**EC**
Mixer/Loader																		
DF/WDG	Aerial	Pastureland Rangeland	4	lb ai/A	1200	acres	8.96	1.79	0.9	0.24	0.54	0.11	0.05	0.014	**26**	**130**	**260**	**970**
	Groundboom				200		8.96	1.79	0.9	0.24	0.09	0.018	0.009	0.002	**160**	**780**	1600	5800
	Groundboom	Non-crop land	6		200		8.96	1.79	0.9	0.24	0.14	0.03	0.01	0.004	100	520	1000	3900
P/G	Aerial	Pastureland Rangeland	4		1200		1.7	0.34	0.17	0.08	0.10	0.02	0.010	0.005	**140**	**690**	1400	2800
		Non-crop land	6				1.7	0.34	0.17	0.08	0.15	0.03	0.02	0.01	**92**	**460**	**920**	1900
	Tractor-drawn Spreader	Pastureland Rangeland	4		200		1.7	0.34	0.17	0.08	0.02	0.003	0.002	0.0008	**820**	4100	8200	17000
		Non-crop land	6				1.7	0.34	0.17	0.08	0.03	0.01	0.002	0.001	**550**	2700	5500	11000
Applicator																		
Spray	Aerial	Pastureland Rangeland	4	lb ai/A	1200	acres				0.005				0.0003				48000
	Groundboom				200		0.34	0.07	0.03	0.04	0.003	0.0007	0.0003	0.0004	4100	21000	41000	33000
	Groundboom	Non-crop land	6		200		0.34	0.07	0.03	0.04	0.005	0.001	0.0005	0.0006	2700	14000	27000	22000
P/G	Aerial	Pastureland Rangeland	4		1200					1.3				0.08				**180**
		Non-crop land	6							1.3				0.12				**120**
	Tractor-drawn Spreader	Pastureland Rangeland	4		200		1.2	0.24	0.12	0.22	0.01	0.002	0.001	0.002	1200	5800	12000	6400
		Non-crop land	6				1.2	0.24	0.12	0.22	0.02	0.004	0.002	0.003	**780**	3900	7800	4200
	Hand dispersal	Non crop land and Rights-of-way	0.00014	lb ai/ft2	10,000	ft2	470	94	47		0.008	0.002	0.0008		1700	8500	17000	
	Shaker can						12.5	2.5	1.25		0.0002	0.00004	0.00002		64000	320000	640000	
Flagger																		
Spray	Aerial	Pastureland Rangeland	4	lb ai/A	350	acres	0.35	0.07	0.04		0.006	0.001	0.0006		2300	11000	23000	
P/G		Pastureland Rangeland	4				0.15	0.03	0.02		0.004	0.001	0.0004		5300	27000	53000	
		Non-crop land	6				0.15	0.03	0.02		0.004	0.001	0.0004		3600	18000	36000	
Mixer/Loader/Applicator																		
DF/WDG	Backpack		1.6		40	gallons	2.58	0.52	0.26		0.002	0.0004	0.0002		6800	34000	68000	

	Manually-pressurized Handwand	Non-crop land and Rights-of-way		lb ai/gallon			30	6	3		0.02	0.005	0.002		**580**	2900	5800	
	Mechanically-pressurized Handgun				1000	gallons	3.9	0.78	0.39		0.08	0.02	0.01		**180**	**900**	1800	
P/G	Belly grinder		6	lb ai/A	1	acres	62	12.4	6.2		0.005	0.001	0.0005		3000	15000	30000	
	Rotary spreader				5		10	2	1		0.004	0.0008	0.0004		3700	19000	37000	
	Cup		0.00014	lb ai/ft2	10000	ft2	12.5	2.5	1.25		0.0002	0.00004	0.00002		64000	320000	640000	
	Spoon						121	24.2	12.1		0.002	0.0004	0.0002		6600	33000	66000	

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (May 2013); Level of mitigation: Inhalation baseline PPE includes no respirator. The addition of PF5, PF10 respirators on handlers is included in the far right column for comparison. Eng. Controls included enclosed cockpits for the aerial application of tebuthiuron for all formulations. Shaded out cells are not applicable to scenario or there is no inhalation unit exposure data.
2 Based on registered labels (Table 3.2.1).
3 Exposure Science Advisory Council Policy #9.1.
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled Daily (A or gal/day) ÷ **80** (kg).
5 Inhalation MOE = Inhalation NOAEL (mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

Table E.3: Occupational Dermal and Inhalation Handler ARI Risk Estimates for Tebuthiuron[1]

Exposure Scenario		Crop / Target Category	Application Rate[2]	Amount Handled [3]		ARI[4]						
Formulation application equipment				**Value**	**Units**	**SL/No G + No-R**	**SL/G + No-R**	**SL/G + PF5 R**	**DL/G + PF5 R**	**SL/G + PF10 R**	**DL/G + PF10 R**	**EC**
Mixer/Loader												
DF/WDG	Aerial	Pastureland/Rangeland	4 lb ai/A	1,200	acres	**0.01**	**0.02**	**0.03**	**0.04**	**0.04**	**0.05**	**0.19**
	Groundboom			200		**0.04**	**0.1**	**0.2**	**0.24**	**0.23**	**0.28**	1.1
	Groundboom	Non-crop land	6 lb ai/A	200		**0.03**	**0.06**	**0.13**	**0.16**	**0.15**	**0.19**	**0.76**
P/G	Aerial	Pastureland/Rangeland	4 lb ai/A	1,200		**0.09**	**0.1**	**0.2**	**0.35**	**0.27**	**0.46**	**0.25**
		Non-crop land	6 lb ai/A			**0.06**	**0.07**	**0.15**	**0.23**	**0.18**	**0.31**	**0.16**
	Tractor-drawn Spreader	Pastureland/Rangeland	4 lb ai/A	200		**0.55**	**0.58**	1.3	2.1	1.6	2.7	1.5
		Non-crop land	6 lb ai/A			**0.37**	**0.39**	**0.88**	1.4	1.1	1.8	1
Applicator												
Spray	Aerial	Pastureland/Rangeland	4 lb ai/A	1,200	acres							1.1
	Groundboom			200		**0.17**	**0.72**	**0.84**	1	**0.85**	1.1	2.5
	Groundboom	No-crop land	6 lb ai/A	200		**0.11**	**0.48**	**0.56**	**0.7**	**0.57**	**0.72**	1.7
P/G	Aerial	Pastureland/Rangeland	4 lb ai/A	1,200								**0.16**
		Non-crop land	6 lb ai/A									**0.11**
	Tractor-drawn Spreader	Pastureland/Rangeland	4 lb ai/A	200		**0.65**	**0.74**	1.4	2.1	1.6	2.6	3.3
		Non-crop land	6 lb ai/A			**0.43**	**0.49**	**0.98**	1.4	1.1	1.7	2.2
	Hand dispersal	Rights-of-Way	0.00014 lb ai/ft2	10,000	ft2	**0.07**	**0.1**	**0.11**	**0.2**	**0.11**	**0.2**	
	Shaker can					34	59	220	220	340	340	
Flagger												
Spray	Aerial	Pastureland/Rangeland	4 lb ai/A	350	acres	**0.55**	**0.52**	**0.63**	**0.71**	**0.65**	**0.74**	
P/G		Pastureland/Rangeland				1.9	1.9	2.6	4.2	2.7	4.6	
		Non-crop land	6 lb ai/A			1.2	1.3	1.8	2.8	1.9	3	
Mixer/Loader/Applicator												
DF/WDG	Backpack	Non-crop land, and Rights-of-way (e.g., utilities, railroad, roadways)	1.6 lb ai/gallon	40	gallons	**0.02**	**0.02**	**0.02**	**0.04**	**0.02**	**0.04**	
	Manually-pressurized Handwand					**0.002**	**0.24**	**0.36**	**0.41**	**0.38**	**0.44**	
	Mechanically-pressurized Handgun			1,000		**0.005**	**0.02**	**0.02**	**0.02**	**0.02**	**0.02**	
P/G	Belly grinder		6 lb ai/A	1	acres	**0.18**	**0.19**	**0.2**	**0.32**	**0.2**	**0.33**	
	Rotary spreader			5		**0.69**	1.1	1.5	2.5	1.5	2.7	
	Cup		0.00014 lb ai/ft2	10,000	ft2	34	59	220	220	340	340	
	Spoon					1.5	1.9	2.4	4.4	2.5	4.7	

1 Refer back to previous table 9.1.1. and 9.1.2 for "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" ([May 2013]); Level of mitigation: Dermal baseline (long sleeve shirt, pants, shoes plus socks), dermal baseline plus gloves, and dermal double layer plus gloves, Inhalation baseline (no respirator), PF5 respirator, and PF10 respirator. Eng. Controls (EC) included enclosed cockpits for the aerial application of tebuthiuron for all formulations. Shaded out cells are not applicable or no unit exposure data

2 Based on registered labels (Table 3.2.1).

3 Exposure Science Advisory Council Policy #9.1.

4 ARI = Aggregate Risk Index = 1÷ [(Dermal LOC (**100**) ÷ Dermal MOE) + (Inhalation LOC (**1000**) ÷ Inhalation MOE)]