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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: 23-July-2009

SUBJECT: **Tebuthiuron.** Revised**:** Registration Review Scoping Document for Human Health Assessments.

PC Code: 105501
MRID No.: NA
Petition No.: NA
Assessment Type: Single Chemical/Aggregate
T**XR No.:** NA

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1. EXECUTIVE SUMMARY

The Health Effects Division (HED) Tebuthiuron Registration Review Team has evaluated the status of the human health assessments for the broad-spectrum herbicide tebuthiuron to determine the scope of work necessary to support Registration Review. Tebuthiuron is primarily used as a broad-spectrum herbicide that provides long-term control of annual and perennial grasses, herbaceous plants and woody brush. Tebuthiuron was first registered as a pesticide in the U.S.A. in 1974. A reregistration eligibility decision (RED) for Tebuthiuron, was completed June 15, 1994, prior to FQPA enactment. Reassessment of the tolerances under the FQPA standard was completed in July 05, 2002. EPA issued a Registration Standard for tebuthiuron in July 1987 (NTIS #PB87-231866), which identified the Agency's concern for the potential of groundwater contamination (through leaching) and surface water contamination (through run-off) since tebuthiuron is persistent and mobile.

The acute toxicity studies indicate that tebuthiuron, is more toxic via the oral (Toxicity Category II) route than via either inhalation (Toxicity Category III) or dermal (Toxicity Category IV) routes. Tebuthiuron is not an eye or skin irritant and not a skin sensitizer. Following subchronic dietary exposures to rats, toxicity was limited to decreased body weight and histopathological changes of the pancreas. Following subchronic exposures to dogs, toxicity manifested as anorexia, with resulting weight loss, and alterations in clinical chemistry parameters. No dermal or systemic toxicity was seen following repeated dermal applications to rabbits.

Following chronic exposures to dogs, tebuthiuron-induced toxicity included clinical signs, decreased body weight, changes in liver enzymes and increases in organ weights. In the combined chronic toxicity/carcinogenicity study in rats and in the carcinogenicity study with mice, there was no systemic toxicity or evidence for carcinogenicity. Tebuthiuron is classified as a Group D Carcinogen – not classifiable as to human carcinogenicity. There are no mutagenic concerns with tebuthiuron.

There was no evidence of increased susceptibility following *in utero* exposures to rats and rabbits following pre and post natal exposures to rats for two generations. In accordance with the revised 40 CFR Part 158 data requirements, a neurotoxicity battery (i.e., acute and subchronic neurotoxicity) and an immunotoxicity study is required for all food and non-food use chemicals. Once these studies are received and reviewed; HED will reevaluate the points of departure and uncertainty factors for the dietary assessments.

The only source of dietary (food) exposure is the consumption of secondary residues in meat and milk from livestock fed tebuthiuron-treated grass forage, hay, pasture and range land. The current tolerances were established using adequate feeding study data relative to the maximum theoretical dietary burden of tebuthiuron for beef cattle and dairy cattle (OPPTS Guideline Test Series 860, Table 1, August 1996). New calculations using the maximum reasonable balanced dietary burden for beef cattle and dairy cattle are recommended according current HED policy (Table 1, June 2008). The only source of dietary (food) exposure is the consumption of secondary residues in meat and milk from livestock fed tebuthiuron-treated grass forage, hay, pasture and range land. The dietary risk both (acute and chronic) is below HED's level of concern <1% of the chronic or acute population adjusted dose for both (surface and ground

water). A new dietary assessment may be needed if warranted by any change in the toxicological endpoints selected, or by any other new data submitted to the Agency.

There are currently no residential uses for tebuthiuron; hence a residential risk assessment is not required. The major uses also include railroad rights of way, electric utility rights of way, and industrial facilities and pipelines. Postapplication worker or bystander exposures are not thought to occur because it is applied to sites where reentry is unlikely. In addition, occupational handler exposures have not been considered quantitatively in any existing risk assessment. Given the use patterns occupational handler exposures can occur and an occupational handler risk assessment is recommended using the current tebuthiuron use patterns.

2. INTRODUCTION

Tebuthiuron is a relatively nonselective, soil activated herbicide that acts by inhibiting photosynthesis. It is used to control broadleaf and woody weeds, grasses and brush on feed crop sites (pasture and 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. There is no agricultural crop use of tebuthiuron. HED has evaluated the most recent human health exposure and risk assessments for tebuthiuron to determine if sufficient data are available and if updates are needed to support registration review. HED has considered the most recent exposure and risk assessments for this chemical, updates to its toxicity, exposure and usage databases, and the latest Agency science policy and risk assessment methodologies.

3. CHEMICAL IDENTITY

Tolerances for residues of tebuthiuron have been established for grasses and animal commodities *[40 CFR §180.390]*. These tolerances are expressed in terms of the combined residues of N-[5-(1, 1diemethylethyl)-1,3,4-thiadiazol-2-yl]-N,N'-dimethylurea and its metabolites containing the dimethylethyl thiadiazole moiety. The chemical structure and nomenclature of tebuthiuron (technical grade) and its dimethyl thiadiazole-containing degradate (Compound 104), and the physicochemical properties of tebuthiuron are presented in Tables 19.1a and 19.1b.

4. HAZARD IDENTIFICATION/TOXICOLOGY

The acute toxicity studies indicate that tebuthiuron, technical, is more toxic for oral (Toxicity Category II) exposure than for either dermal (Toxicity Category IV) or inhalation (Toxicity Category III). Tebuthiuron is not an eye or skin irritant and not a skin sensitizer. In the 21-day dermal toxicity study in rabbits, no dermal or systemic toxicity was observed at 1000 mg/kg/day (limit dose).

In the preliminary human health risk assessment for the Tolerance Reassessment Eligibility Decision (HED, DP274580) document, a number of toxicology data gaps were identified. The toxicology data gaps include a developmental toxicity study in rabbit, as well as the chronic feeding/carcinogenicity study in the rat and oncogenicity study in the mouse; all of these studies

were found to be unacceptable. An *in vivo* bone marrow cytogenetic assay was needed to evaluate the mutagenic potential of tebuthiuron. A 28-day inhalation study in the rat was required to characterize the effects of tebuthiuron via the inhalation route. Furthermore, the requirement for a developmental neurotoxicity study is being held in reserve, pending submission of the rabbit developmental toxicity study.

Although the most consistent toxicological effect was decreased body weight, histopathological changes in the pancreas were observed in both the subchronic and chronic toxicity studies in the rat. Pancreatic acinar cells of both sexes showed vacuolation, which was described as generally slight or affecting only a few cells; males also had increased relative spleen and prostate gland weights. In a rat developmental study, however, pancreatic tissue appeared normal. Subchronic and chronic toxicity studies were available for the dog. In a subchronic study, anorexia, with resulting body weight loss, and clinical chemistry effects (increased blood urea nitrogen and alkaline phosphatase) were observed at 50 mg/kg/day. In a chronic (1-year) dog study, clinical signs of toxicity (emesis anorexia, and diarrhea), decreased body weight, increased alanine aminotransferase (ALT) and alkaline phosphatase (ALP) (males only), increased absolute and relative liver weights, and increased relative kidney (females only) and thyroid (males only) weights.

There was no evidence of increased susceptibility following *in utero* exposures to rats and rabbits following pre and post natal exposures to rats. At the doses tested, neither the rat nor mouse showed any treatment-related increase in the incidence of neoplasms. However, the HIARC (TXR No. 0050672, April 16, 2002) concluded that the dose levels were too low to assess the carcinogenic potential of tebuthiuron. Tebuthiuron is classified as a Group D Carcinogen – not classifiable as to human carcinogenicity based on the lack of evidence for carcinogenic potential in mice and rats.

Tebuthiuron was not mutagenic in bacteria, but was weakly positive for gene mutations in cultured mouse lymphoma cells. The effect in mammalian cells was, however, confined to non-activated test conditions. There was also some evidence of a clastogenic response at cytotoxic doses both with and without S9-activation. Since an acceptable *in vivo* bone marrow cytogenetic assay was not available, final conclusions regarding the mutagenic potential of tebuthiuron can not be made at this time. An *in vivo* bone marrow cytogenetic assay was requested to evaluate the mutagenic potential of tebuthiuron. Since the 2002 TRED, the Agency have received the requested Mammalian erythrocyte micronucleus test study, once the study is reviewed, HED will evaluate the mutagenic potential of tebuthiuron.

Since the 2002 TRED (DP274580), The Agency received waiver requests from the registrant to reconsider the need to repeat the rat and mouse cancer studies. In response, the HED Dose Adequacy Review Team (DART) reevaluated the need for additional rat and mouse cancer data on 12/09/2004 (TXR#0050751). Based on this review, it was concluded that there was adequate evidence that tebuthiuron was tested at high enough doses in the rat chronic/cancer study and that no additional data were needed to satisfy this requirement (OPPTS 870.4300). The Agency has also determined that very little value would be added to the knowledge of the toxicity of tebuthiuron by repeating the mouse cancer/ chronic study especially considering the very low human exposure expected from registered uses. Therefore, the Agency has determined that the rat and mouse cancer/ chronic studies are not required. In addition, the Agency has noted due to certain science policy changes, the Developmental Toxicity study in a nonrodent, 28 -Day

Inhalation study and Developmental Neurotoxicity study are not required (SRRD, Feb, 2005; TXR#0054232, 01/31/2005).

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) *"may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate."* Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there were scientific bases for including, as part of the program, androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. When the appropriate screening and/or testing protocols being considered under the Agency's Endocrine Disrupter Screening Program (EDSP) have been developed and vetted, tebuthiuron may be subjected to additional screening and/or testing to better characterize effects related to endocrine disruption.

In accordance with the revised 40 CFR Part 158 data requirements, a neurotoxicity battery (i.e., acute and subchronic neurotoxicity) and an immunotoxicity study is required for all food and non-food use chemicals. Although the available studies showed no neurotoxicity, these studies do not use optimal methods to evaluate the nervous tissue structure and function. Consequently, the neurotoxicity studies are required to detect and more fully characterize these potential neurotoxic effects of tebuthiuron. Once these studies are made available to the Agency, they will be reviewed and HED will reevaluate the points of departure and uncertainty factors for the dietary assessments. The Toxicity Profile (Table 18a) and Hazard Endpoints (Table 18b) are presented in the attachments.

5. RESIDUE CHEMISTRY

In support of the reevaluation of tolerances on grasses and animal commodities, the registrant submitted an animal feeding study to reassess the adequacy of established tebuthiuron tolerances on animal commodities. The tolerances for grass and hay were reevaluated and lowered from 20 ppm to 10 ppm. Data pertaining to magnitude of the residue in animal commodities were considered confirmatory. The regulatory requirements for data depicting magnitude of the residue in milk, eggs, and livestock tissues are fulfilled. Enforcement methods for milk and animal tissues have been proposed; while an independent laboratory validation is required. The registrant submitted MRIDs 43983701 and 43983702 which are under review.

The animal feeding data relative to the maximum theoretical dietary burden (OPPTS Test Guidelines Series 860, Table 1, 1996) of tebuthiuron to beef cattle and dairy cattle were used to establish the current tolerances. The only source of dietary (food) exposure is the consumption of secondary residues in meat and milk from livestock fed tebuthiuron-treated grass forage, hay, pasture and rangelands. 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). The feeding study has demonstrated a transfer of tebuthiuron to livestock tissue (meat, meat byproducts…etc.). A new maximum reasonable balanced dietary burden calculation for beef

cattle and dairy cattle is recommended in accordance with current HED policy using OPPTS Test Guidelines Series 860, Table 1 circa June 2008.

6. DIETARY EXPOSURE AND RISKS

Tebuthiuron acute and chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model (DEEM™) software Version 7.74, which incorporates consumption data from USDA's Continuing Surveys of Food Intake by Individuals (CSFII), 1989-1992. The 1989-92 data are based on the reported consumption of more than 10,000 individuals over three consecutive days, and therefore represent more than 30,000 unique "person days" of data. A refined acute and chronic dietary exposure risk assessment was conducted for tebuthiuron registered for foliar application to pastures and rangeland (secondary transfer to livestock commodities). [S. Piper, D281821, 04/02/2002]. 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.

6.1. Acute

A refined acute dietary risk assessment was conducted for all supported tebuthiuron uses. Dietary risk estimates are provided for females 13-50 years of age (acute). This assessment concludes that for all included commodities, the acute risk estimates are *below* the Agency's level of concern (<100% acute PAD) at the *95th* exposure percentile for females 13-50 years of age (<1% of the acute PAD).

6.2. Chronic

A refined chronic dietary risk assessment was conducted for all supported tebuthiuron food uses. This assessment also concludes that for all commodities, the chronic risk estimates are *below* the Agency's level of concern (<100% chronic PAD) for the general U.S. population (<1% of the chronic PAD) and all population subgroups.

7. DRINKING WATER

HED has not identified any acute or chronic risk concerns from exposure to tebuthiuron in drinking water. Tebuthiuron and its dimethyl thiadiazole-containing degradate (Compound 104) are resistant to biological and chemical degradation, Tebuthiuron's principle route of dissipation in the environment appears to be mobility.

Surface water concentrations of tebuthiuron were modeled using the PRZM/EXAMS (Tier II) programs for pasture/rangeland using EFED's standard scenario for alfalfa in Texas. The alfalfa scenario was chosen because its hydrologic and agronomic practices are expected to approximate those of pasture/rangeland. Groundwater concentrations were modeled using the SCI-GROW program.

The most recent dietary risk assessments relied on comparison of modeled surface and ground water estimated environmental concentrations (EECs) to back calculate DWLOCs (drinking

water levels of concern). Modeled acute EECs were two to three orders of magnitude lower than calculated acute DWLOCs for the general population and all population subgroups. Modeled chronic EECs were 50X – 100X lower than the calculated chronic DWLOCs for the general population and all subpopulations. HED concludes that the direct incorporation of modeled acute and chronic drinking water estimates are not likely to result in a dietary (food and water) risk of concern without the need to quantitatively repeat the assessments. However as HED now incorporates drinking water estimates directly into the dietary exposure assessment and not longer uses the DWLOC approach, a new assessment will usually be required in conjunction with registration review.

8. RESIDENTIAL EXPOSURE AND RISKS

There are currently no residential uses for tebuthiuron; therefore a residential risk assessment is not required.

9. AGGREGATE RISK ASSESSMENT

The aggregate risk assessment evaluates the combined risk from dietary exposure (food and water) and any non-occupational (residential) uses. Since there are currently no residential uses for tebuthiuron and the only dietary exposure is through secondary residues from livestock and drinking water, no aggregate risk assessment is needed. HED did not identify any aggregate risk concerns. The aggregate acute and aggregate chronic dietary risk estimates include exposure to residues of tebuthiuron in food and water. Acute dietary (food) exposure is <1% of the aPAD for females 13-50 years of age. Chronic dietary (food) exposure is <1% of the chronic PAD for the general U.S. population and all population subgroups.

10. SHORT- AND INTERMEDIATE-TERM RISK

There are no currently registered residential uses for tebuthiuron. Therefore, aggregate short- and intermediate-term risk assessments were not conducted.

11. OCCUPATIONAL EXPOSURE AND RISKS

Tebuthiuron is used to control broadleaf and woody weeds in pastureland/rangeland, non-crop industrial areas such as highways, fence rows, firebreaks, utility rights-of-ways, railroad rights-of-ways, and clearings for wildlife habitat. There are currently three registered formulations of tebuthiuron: (1) granular, (2) dry flowable (DF) and (3) pellets.

11.1. <u>Occupational Handlers</u>

Occupational exposures have not been considered quantitatively in any existing risk assessment to date for tebuthiuron but it is clear given the use patterns that occupational handler exposures can occur. The Agency has determined that occupational handlers could be exposed during the following activities:

- Loading granules for tractor drawn spreader application;
- Loading pellets for tractor drawn spreader application;
- Loading pellets for aerial application;
- Mixing/loading DF for aerial application;
- Mixing/loading DF for groundboom application;
- Mixing/loading DF for rights-of-way application;
- Mixing/loading/applying DF for handgun application;
- Mixing/loading/applying DF for low pressure handwand application;
- Loading/applying granular for application with belly grinder;
- Loading/applying granular for application with push-type spreader;
- Applying granular by shaker can;
- Applying granular by hand;
- Loading/applying pellets for application with belly grinder;
- Loading/applying pellets for application with push-type spreader;
- Applying pellets by shaker can; and
- Applying pellets by hand.

In the Registration Eligibility Document (RED) completed June 15, 1994 (http://www.epa.gov/oppsrrd1/REDs/old_reds/tebuthiuron.pdf) it is indicated that human health risks from exposure to tebuthiuron are considered to be minimal due to its low toxicity (acute toxicity category IV by dermal route and III by inhalation route, negative for developmental and reproductive adverse effects and its then current classification as non-carcinogenic to humans). Additionally, no occupational or residential exposure data were required. The Tolerance Reassessment Eligibility Document (TRED) was completed July 05, 2002, (DP Barcode #: D74580) and it does not include an occupational risk assessment. In summary, an occupational handler risk assessment would be required in registration review since a quantitative exposure and risk assessment has not been previously conducted, and occupational handler exposure can occur.

11.2. Occupational Postapplication Workers

Postapplication worker exposures are not thought to occur because tebuthiuron is applied to sites where reentry is unlikely. No such assessment for these types of tasks has been completed and would not be warranted unless use patterns change in the future.

Conclusion for Occupational Exposure

An occupational handler risk assessment would be required in registration review based on the current tebuthiuron use patterns.

12. HUMAN STUDIES

Since no occupational or residential risk assessments have been conducted, no data was used from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical.

13. PUBLIC HEALTH AND PESTICIDE EPIDEMIOLOGY DATA

The OPP Incident Data System was consulted for poisoning incident data on the active ingredient tebuthiuron. The purpose of the database search is to identify potential patterns on the extent and severity of the health effects attributed to tebuthiuron exposure. The IDS includes reports of incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6 (a)(2) reports from registrants, other federal and state health and environmental agencies and individual consumers. This report represents 3 incidents occurring in the United States from 2002 to the present for the single chemical only.

The evaluation of incident data for tebuthiuron chemicals has reported (relatively *low volume of incident, no moderate or severe health effects that are plausibly related to the pesticide in question, based on toxicological data, sporadic incidents of an undefined or non-specific nature such as that clear trends or patterns cannot be discerned)* only 3 incidents. Symptoms appear generic and not confirmed to be related to exposure. There is no clear evidence of a trend or exposure pattern. Therefore, at this time, there are no remarkable case reports which suggest a plausible association between a moderate or severe health outcome and exposure to the pesticide tebuthiuron. Nor can we discern any suggestion of a trend or pattern regarding the health effects due to the alleged exposure to pesticide tebuthiuron. The current review of the incident data does not warrant further investigations at this time.

14. TOLERANCE ASSESSMENT AND INTERNATIONAL HARMONIZATION

US permanent tolerances for tebuthiuron are listed in 40 CFR§180.390. The Codex Commission has established that there are no maximum residue limits (MRLs) for residues of tebuthiuron in/on various raw agricultural and processed commodities. Therefore, issues of compatibility with respect to U.S. tolerances and Codex MRLs do not exist.

15. 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.epa.gov/compliance/resources/policies/ej/exec_order_12898.pdf. The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S., and people who may be exposed when harvesting crops. Should these high exposures indicate potential risks of concern, OPP will further refine the risk assessments to ensure that the risk estimates are based on the best available information.

16. CUMULATIVE RISK ASSESSMENT

The Food Quality Protection Act (FQPA) requires the Agency to consider the cumulative risks of chemicals sharing a common mechanism of toxicity. The Agency has not determined if there are any other chemical substances that have a mechanism of toxicity common with that of Tebuthiuron. If HED identifies other substances that share a common mechanism of toxicity with tebuthiuron, HED will perform aggregate exposure assessments on each chemical, and will begin to conduct a cumulative risk assessment.

17. RECOMMENDATIONS

- Recalculate/evaluate total dietary burden for beef and dairy cattle using Feedstuffs outlined in OPPTS Guideline Test Series 860, Table 1 circa June 2008.
- An occupational handler risk assessment would be required in registration review based on the current tebuthiuron use patterns.

18. DATA REQUIREMENTS

HED does not anticipate that additional occupational/residential exposure data, or residue chemistry data with the exception of (1) below, or toxicology data with the exception of (2) and (3) will be required for the tebuthiuron registration review process:

(1) A confined field rotational crop studies will be conditionally required unless the registrant can provide information that the pastureland use area is either insignificant in acreage or is predominantly perennial grasses that are not rotated annually. (S. Piper, D277103, 09-Apr-02).

(2) OPPTS Test Guideline Number: 870.7800 Immunotoxicity on Tebuthiuron.

(3) OPPTS Test Guideline Number: 870.6200 Neurotoxicity Battery for Tebuthiuron.

Table 18.a OPPTS Test Guideline Number: 870.7800
Study Title: Immunotoxicity on Tebuthiuron

Rationale for Requiring the Data

This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses).

The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies not specifically conducted to assess immunotoxic endpoints are inadequate to characterize a pesticide's potential immunotoxicity. While data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential immunotoxic effects, these endpoints alone are insufficient to predict immunotoxicity.

Practical Utility of the Data

How will the data be used?
Immunotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the immune system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures on immune parameters are limited and are inadequate to characterize a pesticide's potential immunotoxicity in humans, animal studies are used as the most sensitive endpoint for risk assessment. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997).

How could the data impact the Agency's future decision-making?
If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data.

If the Agency does not have this data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

Table 18.b
OPPTS Test Guideline Number: 870.6200
Study Title: Neurotoxicity Battery for Tebuthiuron (Acute and Subchronic Studies)

Rationale for Requiring the Data

This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses).

The Neurotoxicity Screening Battery (OPPTS 870.6200) is designed to evaluate the potential adverse effects on the nervous system from exposure to pesticide chemicals. The Agency believes that the guideline studies are inadequate in their assessment of behavioral effects and do not use optimal methods to evaluate the potential toxicity to the nervous tissue structure and function. To detect and characterize these potential effects more fully, a battery of more sensitive testing is required. The objective of this neurotoxicity battery testing is to evaluate the incidence and severity of the functional and/or behavioral effects, the level of motor activity, and the histopathology of the nervous system. The acute neurotoxicity study is required to detect possible effects resulting from a single exposure. The subchronic neurotoxicity study is intended to detect possible effects resulting from repeated or long-term exposures.

Practical Utility of the Data

How will the data be used?
The acute and subchronic neurotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the nervous system from pesticide exposure. These studies can provide data on a wide range of functional tests for evaluating neurotoxicity including sensory effects, neuromuscular effects, learning and memory and histopathology of the nervous system For example, animal studies with organophosphorous chemicals have shown neurotoxicity to be the primary toxic endpoints (e.g., cholinesterase inhibition) of concern in rodents and non-rodents. These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. The Agency has established an oral reference dose (RfD) for assessing dietary risks for a number of chemicals (e.g., organophosphates and carbamates) where neurotoxicity was the most sensitive endpoint of concern.

How could the data impact the Agency's future decision-making?
If the acute or subchronic neurotoxicity studies show that the pesticide poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessment may need to be revised to reflect the magnitude of potential risk derived from the new data.

If the Agency does not have this data, a 10X database uncertainty factor may be applied when conducting a risk assessment using the currently available studies.

19. ATTACHMENTS

19.1. Chemical Properties

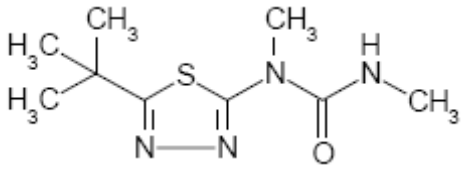
Table 19.1a	Chemical Identity of Tebuthiuron
Common Name	Tebuthiuron
Chemical Name	N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-y1] N,N ’dimethyl urea
IUPAC	1-(5-tert-butyl-1,3,4-thiadiazol-2-yl)-1,3-dimethylurea
PC Code	105501
Chemical Abstracts Number	34014-18-1
Registration Review Case Number	0054
Chemical Structure	

Table 19.1b	Physicochemical Properties of Tebuthiuron		
Parameter	**Value**		**Reference**
Melting point/range	161 ºC at 760 mm Hg		_____. 1984. Memorandum from Stuart Z. Cohen. List of potential groundwater contaminants. Office of Pesticides and Toxic Substances. Washington, D.C. Photocopy 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		

19.2 Toxicology Tables

Table 19.2a Acute Toxicity Profile - Tebuthiuron Technical				
Guideline No.	**Study Type**	**MRID(s)**	**Results**	**Toxicity Category**
870.1100	Acute oral [Rat]	40583901	LD_{50}=477.5mg/kg (m) =387.5 mg/kg (f)	II
870.1200	Acute dermal [Rabbit]	40583902	LD_{50}= >5000 mg/kg	IV
870.1300	Acute inhalation [Rat]	00155730	LC_{50}= 3.696 mg/L	III
870.2400	Primary eye irritation	40583903	Slight irritation	IV
870.2500	Primary skin irritation	40583902	No irritation	IV
870.2600	Skin sensitization	40583904	Non - sensitizer	---

Table 19.2b Toxicological Doses and Endpoint for Tebuthiuron Human Health Risk Assessment				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/ FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Acute Dietary (Females 13-49 yrs) (General US Pop.)	NOAEL= 25 mg/kg/day	UF_A= 10X UF_H= 10X FQPA SF= 3X Total UF= 300X	aPAD= Acute RfD / FQPA SF aPAD= 0.083 mg/kg/day	Developmental Toxicity study in rabbits (MRID's 00020644; 41122401) LOAEL not established. Arrange finding study showed increased early resorptions at 50 mg/kg/day.
Acute Dietary	NA	NA	NA	No appropriate acute end-point identified for these groups. There were no toxic effects attributable to a single dose.
Chronic Dietary (all populations)	NOAEL= 14 mg/kg/day	UF_A= 10X UF_H= 10X FQPA SF= 1X Total UF= 100X	cPAD= Chronic RfD / FQPA SF cPAD= 0.14 mg/kg/day	Two- generation reproduction study in rats (MRID 00090108). LOAEL = 30 mg/kg/day, based on decreased body weight and feed consumption in F1 females.

Point of Departure (PoD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). PAD = population adjusted dose (a = acute, c = chronic) = the NOEL/all appropriate uncertainty and safety factors. RfD = reference dose. FQPA SF = FQPA safety factor.

20. REFERENCES

References: HED Memoranda Relevant to Registration Review			
Author	Barcode/ TXR #	Date	Title
P. Deschamp	D274580	22-Apr-02	Tebuthiuron. Preliminary Human Health Risk Assessment. HED Chapter for the Tolerance Reassessment Eligibility Decision (TRED).
M. Hawkins & J. Cordova	----------	07-May-09	Updated Review of Tebuthiuron Incident Reports
S. Piper	D277103	09-Apr-02	Tebuthiuron Residue Chemistry Chapter for the Tolerance Reassessment Eligibility Decision (TRED).
S. Piper	D281821	03-Apr -02	Tebuthiuron Acute and Chronic Dietary Exposure Assessments for the Tolerance Reassessment Eligibility Decision (TRED).
S. Smearman	EPA-HQ-2002-0146-0012 [1]	28-Feb-02	Quantitative Usage Analysis for Tebuthiuron.
S. Piper and M. Corbin	TXR# 0050409	25-Feb-02	Tebuthiuron. (List A, Case No. 0054) The Outcome of the HED Metabolism Assessment Review Committee Meeting Held on 01/22/2002.
M. Corbin	EPA-HQ-2002-0146-0004	20-Feb-02	Addendum to Drinking Water Assessment for the Tolerance Reassessment (TRED) for Tebuthiuron.
W. Burnam & W. Hazel	TXR# 0054232	31-Jan-05	Tebuthiuron waiver requests.
J. Kidwell	TXR# 0052580	09-Dec-04	Tebuthiuron: Report of the Dose Adequacy Review Team (DART).
W. Livingston	----------	23-Feb-05	Tebuthiuron Tolerance Reassessment Eligibility Decision (TRED) Revised Data Requirements.
S. Funk	D217379	05-Dec-95	Tebuthiuron (Case No. 0054, Chemical 105501). Ruminant Feeding Study (171-4(j)). CBRS No. 15883. MRID 43703201.