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

OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Date: September 5, 2008

SUBJECT: Trinexapac-Ethyl: Revised Human Health Assessment Scoping Document in Support of Registration Review.

PC Code: 112602
Decision No.: 392037
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
MRID No.: NA

DP Barcode: D356118
Registration No.: NA
Regulatory Action: Registration Review Scoping Document
Case No.: 7228
CAS No.: 95266-40-3
40 CFR: NA

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HED completed a human health scoping document for registration review of trinexapac-ethyl, a plant growth regulator. During the development of the Agency's preliminary work plan for registration review, clarification of the data supporting the residential and occupational exposure assessments was requested. This revised document addresses the data supporting these assessments, and supersedes the 7/18/2008 scoping document (D351407).

Executive Summary

Attached is the Health Effects Division's (HED) human health risk assessment scoping document for trinexapac-ethyl to support Registration Review. Trinexapac-ethyl is a cyclohexadione plant growth regulator registered for non-food uses by homeowners and professional applicators on turf grasses and on grasses grown for seed production by growers and professional applicators. HED has considered recent updates to the toxicology, exposure, and usage databases and the latest Agency science policy and risk assessment methodologies and has identified numerous deficiencies in the trinexapac-ethyl risk assessment. The toxicology database is complete, with the exception of an immunotoxicity study (870.7800) and acute and subchronic neurotoxicity studies (870.6200) that are newly required by the Part 158 guidelines. The most recent point of departure determinations are consistent with current policy, based on the available data.

Although the use on grasses grown for seed has, in the past, been considered a non-food use, the Agency now believes that once the seed is harvested, the regrowth of the grass can be grazed or cut and used as feed for cattle. Consequently, this is now considered to be a feed use. Available data suggest that quantifiable residues of trinexapac-ethyl may be found in animal commodities; however, no U.S. tolerances have been established and dietary and aggregate exposure assessments have not been conducted. Assuming that the registrant wants to support the use on grass grown for seed, tolerances may need to be established on plant and animal commodities. The following residue chemistry data deficiencies must be addressed prior to determining the need/establishing tolerances: 1) the cattle feeding study (860.1480; required to support food uses that were later withdrawn, based on measurable residues in the goat metabolism study) should be reviewed, 2) the plant analytical method (860.1340) should be revised to measure conjugates, since conjugated residues are residues of concern for both tolerance setting and risk assessment purposes, 3) an animal analytical method (860.1340) should be proposed and validated, since residues are expected in animal commodities, 4) the field rotational crop study (860.1900) should be reviewed, and 5) additional grass field trial studies (860.1500) are required. Dietary exposure from food (if tolerances are established) and drinking water, as well as aggregate exposure, should be assessed.

During registration review, short- and intermediate-term residential post-application exposure, which was not previously considered, should be assessed for 1) high contact activities of adult and toddler, 2) mowing by adults and youth, 3) golfing by adults and youth, 4) hand-to-mouth exposure to toddlers, 5) object-to-mouth exposure to toddlers, and 5) incidental ingestion by toddlers. Short-term residential handler exposure should be assessed for homeowner lawn treatment using 1) drop/spreaders and 2) shakers. Intermediate-term occupational handler and short-term occupational post-application exposures, which were not previously considered, should be assessed.

Unit exposure values are not available for many of the residential and occupational scenarios. Given the substantial revisions prescribed by this scoping document, preliminary estimates for the residential and occupational exposure scenarios expected to pose the highest risk were calculated using surrogate data from the Pesticide Handlers Exposure Database (PHED) and the draft SOPs for Residential Exposure Assessment. These risk estimates do not indicate that the existing use patterns exceed HED's level of concern.

Introduction

HED has evaluated the status of the human health assessments for trinexapac-ethyl to determine whether sufficient data are available and whether a new human health risk assessment is needed to support Registration Review. Trinexapac-ethyl was first registered in 1992 and, as a result, was not subject to the reregistration process recently completed on August 3, 2006 for chemicals registered prior to 1984. Additionally, no tolerances have been established for any use of trinexapac-ethyl. Consequently, neither a Reregistration Eligibility Decision (RED) nor a Tolerance Reregistration Eligibility Decision (TRED) was issued. A comprehensive human health risk assessment does not exist, but an FQPA hazard characterization was drafted in 2007 to support proposed uses that were later rescinded. This hazard characterization considers all available trinexapac-ethyl toxicology studies received to date, including new studies. Existing toxicology studies were re-evaluated (D328850). For scoping purposes, HED also considered HED and OPPIN databases. The structure, chemical name, and other identifiers may be found in Table 1 attached to this document; physicochemical properties may be found in Table 2.

Trinexapac-ethyl is a cyclohexadione plant growth regulator registered for non-food uses by homeowners and professional applicators on turf grasses and on grasses grown for seed production by growers and professional applicators. The registered formulations of trinexapac-ethyl are provided in Table 3 and include emulsifiable concentrates (ECs), wettable powder packed in water-soluble bags (WP/WSB), and granules. Application rates are provided in Table 4. The maximum application rate (0.88 lb ai/A) is for use on the edges of residential and ornamental turf areas. The reentry interval (REI) for all formulations is zero days, but there is a livestock pre-grazing interval (PGI) of 60 days for use on grasses grown for seed.

Hazard Identification/Toxicology

Trinexapac-ethyl is a cyclohexadione plant growth regulator that inhibits the biosynthesis of gibberellin (GA_1), which is a phytohormone that promotes growth of various plant organs. In mammals, the compound is rapidly and extensively absorbed (> 95% of the administered dose) and rapidly eliminated (> 85% of the administered dose eliminated within 12 h), with no significant bioaccumulation. Significant residues identified in the rat metabolism study were the acid metabolite of trinexapac-ethyl (approximately 80 – 90% of radioactivity) and the parent compound (<1%). These results indicate that toxicity of both the parent and the acid metabolite has been accounted for in the submitted toxicity studies. The acute toxicity of the technical material (Table 5) is low via the oral, dermal, or inhalation routes of exposure (Categories III-IV), and it is not a dermal sensitizer. The toxicity profile of trinexapac-ethyl is attached (Table 6). With the exception of immunotoxicity and neurotoxicity studies required by the new Part 158 guidelines, the toxicology database is complete and adequate to support non-food and food uses.

Evidence of increased qualitative and quantitative susceptibility of the offspring was seen in the developmental, but not the reproduction, studies. Developmental toxicity was observed in the rat (increased incidence of asymmetrical sternebrae) and rabbit (decreased number of live fetuses/litter and increased post-implantation loss), with no evidence of maternal toxicity observed at the highest dose tested in either species. However, in the multi-generation reproduction study in rats, the first indications of parental systemic toxicity were observed at a lower dose level than offspring toxicity. No reproductive toxicity was observed up to the limit dose.

The dog appears to be the most sensitive species. In adult animals, no adverse effects were seen in rats, rabbits, or mice below the limit dose (1000 mg/kg/day) following subchronic or chronic oral exposure. In the dogs, however, decreased body weight gain and food consumption, diffuse thymic atrophy, and changes in the epithelial cells of the renal tubules were seen in the 90-day study at 516/582 mg/kg/day (males/females). Following chronic exposure, evidence of neurotoxicity was seen at 366/356 mg/kg/day in male and female dogs, respectively, including minimal, focal bilateral vacuolation of the dorsal medial hippocampus and/or lateral midbrain**,** which was associated with the astrocytes and oligodendrocytes. The lesions remained confined to the supporting cells in the central nervous system and did not progress to more advanced or more extensive damage of the nervous tissue. They were not associated with other neuropathological findings or overt neurological signs, so their biological significance is unknown. Similar lesions were not observed in the rat (including neonates) or mouse following subchronic or chronic dietary exposure, and there was no other evidence in any other species tested to indicate a neurotoxicity potential. There are no neurotoxicity studies available; therefore, both acute and subchronic neurotoxicity studies will be required, according to the new Part 158 guidelines. A developmental neurotoxicity study may be required, based on the results observed in the required acute and subchronic neurotoxicity studies.

The combined chronic toxicity/carcinogenicity study in the rat did not demonstrate an increase in any tumor type that would be relevant to humans. The observation of squamous cell carcinomas in the non-glandular portion of the stomach of two males at 806 mg/kg/day does not provide reasonable evidence of a possible deleterious effect of trinexapac-ethyl on the pharynx and/or esophagus (non-glandular areas) of the human because trinexapac-ethyl would not be in contact with the human tissues for a significant period of time compared with how it would have been in contact with the rat stomach. In the mouse, there was no evidence of carcinogenicity. The mutagenicity database is complete, with no evidence of mutagenicity. The cancer classification for trinexapac-ethyl is “Not likely to be carcinogenic to humans.”

Clear No Observed Adverse Effect Levels (NOAELs) have been established for both the developmental toxicity and the neurotoxicity seen in dogs. The acute reference dose (aRfD) is based on the most sensitive acute endpoint observed in the database, which is from the developmental rabbit study. It is, therefore, considered protective of all of the developmental/offspring effects observed. Similarly, the chronic reference dose (cRfD) is based on the most sensitive effect in the database, which is from the chronic dog toxicity study. The NOAEL for this study is more than 10-fold lower than the LOAEL at which neurotoxicity is observed. Since the point of departure for the chronic assessment is also approximately 10-fold

lower than the dose levels where developmental toxicity was seen in the developmental rabbit study, it is considered protective for developmental and offspring toxicity. Once the newly required data have been received and reviewed, the appropriate FQPA safety factor will be determined.

With the exception of an ***immunotoxicity study (870.7800)*** and ***acute and subchronic neurotoxicity studies (870.6200)*** that are newly required by the Part 158 guidelines, the toxicology database for trinexapac-ethyl is complete. The endpoint selections and safety factors are provided in Table 7. While the current short-term dermal and inhalation endpoints are based on a developmental endpoint that is appropriate for adults (NOAEL = 60 mg/kg/day), the registration review team may wish to consider age-specific short-term dermal and inhalation endpoints for toddlers based on the same effects (pup body weight changes) as the short-term incidental oral endpoint (NOAEL = 594 mg/kg/day). Note that the current endpoints are highly protective for all types of toxicity expected in toddlers with dermal or inhalation exposure.

Dietary Exposure

The EPA typically establishes tolerances for residues on food and feed commodities derived from use of pesticides on grass grown for seed. Although trinexapac-ethyl is registered for this type of feed use and available data suggest that quantifiable residues may be found in animal commodities, ***no US tolerances*** have been set, and a dietary exposure assessment has not been conducted. At the time that trinexapac-ethyl was registered, the Agency considered grass grown for seed to be a non-food use and did not require tolerances. Since that time, due to the fact that grazing and/or cutting of the regrowth of the grass once the seed is harvested may occur, this use is no longer considered to be non-food and tolerances may be required. However, for trinexapac-ethyl, a number of deficiencies preclude establishment of permanent tolerances.

The nature of trinexapac-ethyl residues in grass commodities and ruminants is understood, based on available grass, rice, and goat metabolism studies. The available wheat metabolism study, which is not required for use on grass, supports the findings of the grass and rice metabolism studies. When residues measured in the goat metabolism study are extrapolated down to a 10x feeding level, the maximum expected residues are 0.212 ppm in liver, 2.01 ppm in kidney, 0.106 ppm in muscle, 0.036 ppm in fat, and 0.026 ppm in milk (pm sample). Based on these results, a ***cattle feeding study (860.1480)*** was required to support proposed food uses that were later withdrawn. Although this study was received, it has not yet been reviewed by the Agency. Because there are no regulated poultry or swine feed items associated with grasses, a poultry metabolism study is not required to set tolerances.

The residues of concern in plants and animals for both tolerance establishment and risk assessment purposes include free and conjugated residues of both parent and its acid metabolite, trinexapac. The data collection method (HPLC/MS, Method 110-10) is the same as the proposed tolerance enforcement method. The method does not determine conjugated residues. In the grass and rice metabolism studies, significant fractions of the trinexapac-ethyl residues in the various fractions were conjugated. As a result, the existing ***plant analytical method (860.1340)*** is inadequate and should be revised to include an enzymatic and/or mild acid hydrolysis step to release conjugated residues of trinexapac. Additionally, a confirmatory analysis must be proposed and the method must undergo a successful independent laboratory validation (ILV).

An ***animal analytical method (860.1340)***, with the ability to hydrolyze conjugates, must also be proposed and validated. A ***field rotational crop study (860.1900)*** has been received by the Agency but not reviewed. There are also deficiencies in the number and geographic distribution of the ***grass field trial studies (860.1500)***.

A ***dietary exposure assessment*** that includes ***drinking water levels*** should be conducted during registration review, if the registrant decides to support the grass grown for seed use.

Residential Exposure

Two granular formulations of trinexapac-ethyl are labeled for application by homeowners to residential lawns, the use of which results in exposure to residential handlers, as well as residential post-application exposures to adults and children. Several other formulations are registered for use on residential and recreational turf areas, including golf courses, residential lawns, sport fields, cemeteries, and edges of sidewalks, curbs, parking lots, driveways, posts, storage buildings, pet pens, fences, trees, shrubs, flower beds, border plants, ornamental beds, steeply sloped areas, driveways, and fence posts. These applications are made by commercial applicators but result in residential post-application exposures to adults and children. When trinexapac-ethyl was first registered for residential use, the Agency relied mainly on exposure estimates prepared by the registrant, rather than conducting exposure assessments in-house. However, during registration review, residential handler and post-application exposures will be assessed as discussed below, using current policies and procedures.

Residential Handlers

Residential handler exposure scenarios include loading/applying of granules by homeowners using a (i) broadcast/spreader, (ii) drop/spreader, or (iii) shaker. For the purposes of this scoping document, preliminary risk estimates were calculated for short-term exposures resulting from the broadcast/spreader scenario, using the maximum single application rate of 0.88 lb ai/A, where a margin of exposure (MOE) of 100 or more is considered adequate to protect handlers from residential exposures to trinexapac-ethyl (Table 8). The risk estimate for short-term exposure to residential handlers who apply granules to home lawns using a broadcast/spreader **(MOE = 18,000)** does not exceed HED's level of concern (LOC). ***Short-term residential handler exposure*** from homeowner lawn treatment using drop/spreaders and shakers were not examined here, due to the ***absence of surrogate unit exposures***, but should be assessed during registration review.

Residential Post-Application

There are emulsifiable concentrates (ECs), wettable powder packed in water-soluble bags (WP/WSB), and granular formulations of trinexapac-ethyl registered for use on residential turf. The use of these products results in post-application exposures to adults and children.

For the initial registration of trinexapac-ethyl, children's exposure to trinexapac-ethyl from treated turf was estimated using two dislodgeable foliar residue (DFR) studies and assumptions about the duration of exposure, children's body weight, etc. (C. Lewis, D180718, December 28, 1992 and D. Hanke, D183213, January 22, 1993). These DFR studies may be used in conjunction with the Draft SOPs for Residential Exposure, along with the existing use patterns,

to determine potential post-application exposure and risk to children and adults associated with use of trinexapac-ethyl formulations on turf.

Short- and intermediate-term residential post-application exposure should be assessed for 1) high contact activities of adult and toddler, 2) mowing by adults and youth, 3) golfing by adults and youth, 4) hand-to-mouth exposure to toddlers, 5) object-to-mouth exposure to toddlers, and 5) incidental ingestion by toddlers. For this scoping document, a preliminary assessment of the scenarios expected to pose the highest risk was conducted according to current policy, using surrogate data, rather than data from the human study in children. The preliminary estimates based on surrogate data from PHED show that the short-term post-application risks to adults, youths, and toddlers **(MOEs = 230 – 180,000)** are not of concern to HED (for MOEs, LOC ≥ 100) at the maximum single application rate of 0.88 lb ai/A (Table 9).

Aggregate Risk Assessment

An ***aggregate exposure assessment*** has not been conducted; however, in accordance with the FQPA, when there are potential residential exposures to a pesticide, aggregate risk assessment must consider exposures from three major routes: oral, dermal, and inhalation. There are three sources for these types of exposures: food, drinking water, and residential uses. Short- and intermediate-term aggregate risk assessment is required for trinexapac-ethyl due to potential dietary exposure resulting from drinking water and, if tolerances are established, from use on grasses grown for seed and potential residential and/or recreational exposures to residues on turfgrass. The short-term dermal and inhalation endpoints are based on decreased fetuses/litter and increased post-implantation loss seen in a prenatal developmental toxicity study in rabbits; the short-term incidental oral endpoint is based on decreased F1 survival, body weights, and body weight gains in the reproduction study.

During registration review, adult short- and intermediate-term exposure via the dermal, inhalation, and dietary routes should be aggregated and compared to the short- and intermediate-term endpoints from the developmental rabbit and chronic dog studies, respectively.

For toddlers, short-term exposure via the dermal, inhalation, incidental oral, and dietary routes should be aggregated and compared to the short-term incidental oral endpoint from the reproduction study. It is not appropriate to examine aggregate risk to a toddler based on a developmental endpoint, because this form of toxicity would not occur in a child. As previously discussed, the team may wish to select new age-specific short-term dermal and inhalation endpoints for toddlers based on the pup body weight changes observed in the reproduction study. This type of toxicity could occur in toddlers via the oral, dermal, or inhalation route. Again, note that the existing short-term dermal and inhalation endpoints are highly conservative and protective for all types of toxicity expected with exposure to toddlers.

Occupational Exposure

ECs, WP/WSB, and granular formulations of trinexapac-ethyl are applied by commercial operators and/or growers on turf areas and grasses grown for seeds using a variety of ground sprayers and granule spreaders (Table 10).

Occupational Handlers

During the registration of trinexapac-ethyl, the registrant provided a short-term dislodgeable foliar residue (DFR) study for an EC formulation. Based on that data, a short-term handler assessment was performed, which indicated that the risks to mixer/loaders and applicators applying the EC with a ground boom sprayer did not exceed HED's level of concern if the handlers wore long-sleeved shirts, long pants, and shoes with socks and gloves (C. Lewis, D180718, December 28, 1992 and D. Hanke, D183213, January 22, 1993).

For this registration review scoping document, an occupational exposure assessment was performed using the current standards, including surrogate values from the pesticide handlers exposure database (PHED) and the maximum single application rate of trinexapac-ethyl on turf at 0.88 lb ai/A (Table 11). The preliminary short-term risk estimate to loader/applicators of granules with a push-type spreader (**MOE = 420**) does not exceed HEDs level of concern (**LOC ≤ 100**). Other short-term occupational handler scenarios were not examined here, due to the ***absence of surrogate unit exposures***. ***Intermediate-term exposure*** to occupational handlers should be assessed during registration review.

Occupational Post-Application

Post-application risk to workers who may enter the treated field has not been assessed at this time, but should be examined during registration review.

Public Health and Pesticide Epidemiology Data

A summary report listing incidents reported to EPA for trinexapac-ethyl will be provided for the docket. The reported incidents will be screened in more detail during the development of the Final Work Plan for trinexapac-ethyl.

Tolerances and International Harmonization

No US tolerances have been established for trinexapac-ethyl, although the use on grasses grown for seed production is considered a feed use, and available data suggest that quantifiable residues of trinexapac-ethyl may be found in plant and animal commodities. Maximum residue limits (MRLs) have not been established by Codex, Canada, or Mexico (Table 12); however, permanent or provisional/temporary MRLs have been established for a variety of commodities in Japan (Table 13), Australia, New Zealand, and European countries (Table 14), as summarized in the attached tolerance status tables.

Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in the 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/nepa/tools/guidance/Volume1/2-6-EO_12898envjustice.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 highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

Cumulative Risk Assessments
The Agency has not determined whether trinexapac-ethyl shares a common mechanism of toxicity with other chemical substances; therefore, at this time, a cumulative assessment to support registration review is not required.

Human Studies
The screening-level risks presented in this scoping document rely in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These studies, which comprise the Pesticide Handlers Exposure Database (PHED), have been reviewed by the Agency and found to have been conducted ethically.

Data Requirements
During registration review, the following outstanding data requirements should be fulfilled. See Table 9 in the Attachment of this document for more details.

Outstanding Data Requirements for Trinexapac-ethyl (PC Code 112602)	
860.1340	Plant Analytical Method
860.1340	Animal Analytical Method
860.1500	Crop Field Trials
870.6200a	Acute Neurotoxicity Study
870.6200b	Subchronic Neurotoxicity Study
870.7800	Immunotoxicity Study

References

Author	Barcode	Date	Title
Taylor, L.	D328850	1/18/2007	Trinexapac-ethyl (P. C. Code 112602): DP Barcode D328850. Transmittal of Amended Data Evaluation Records (DERs) [Executive Summaries] to upgrade the original DERs and Two New DERs on Trinexapac-ethyl.
Dotson, D.	D339864	5/17/2007	Trinexapac-ethyl. Response to Registrant Proposal dated May 4, 2007 Regarding Data Deficiencies Associated with Tolerance Petitions 3F6571 (Grass Grown for Seed) and 7F7203 (Wheat, Barley, and Sugarcane).
Dotson, D.	D328850, 328853, 328898	DRAFT	Trinexapac-ethyl. Petitions for Registration of Use on Grasses Grown for Seed. Summary of Analytical Chemistry and Residue Data. Petition Number 3F6571.

ATTACHMENTS

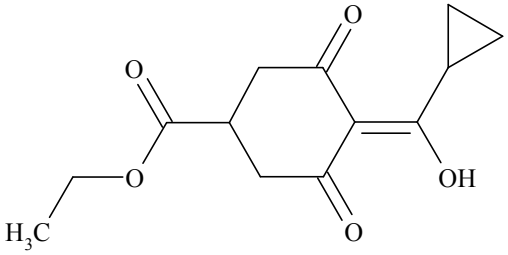
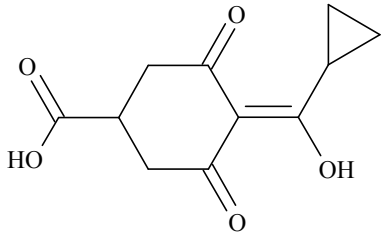
Table 1. Chemical Identity of Trinexapac-ethyl.	
Compound	
Common name	Trinexapac-ethyl
Company experimental name	CGA-163935
IUPAC name	ethyl (*RS*)-4-cyclopropyl(hydroxy)methylene-3,5-dioxocyclohexanecarboxylate
CAS name	ethyl 4-(cyclopropylhydroxymethylene)-3,5-dioxocyclohexanecarboxylate
CAS registry number	95266-40-3
PC Code	112602
Registration review case no.	7228
Regulated metabolite	
Common name	Trinexapac
Company experimental name	CGA-179500
IUPAC name	(*RS*)-4-cyclopropyl(hydroxy)methylene-3,5-dioxocyclohexanecarboxylic acid
CAS name	4-(cyclopropylhydroxymethylene)-3,5-dioxocyclohexanecarboxylic acid
CAS registry number	104273-73-6

Table 2. Physicochemical Properties of Trinexapac-ethyl.		
Parameter	Value	Reference
Melting point/range	36.1-36.6°C	Provided in MRID 46809305
pH	3.3	
Density (20ºC)	1.215 g/cm^3	
Water solubility (g/L at 25°C)	2.8 at pH 4.9 10.2 at pH 5.5 21.1 at pH 8.2	
Solvent solubility	Acetone 100% Ethanol 100% Toluene 100% n-octanol 100% n-hexane 5%	
Vapor pressure (25ºC)	1.62 x 10^{-5} mm Hg	
Dissociation constant, pK_a	4.57	
Octanol/water partition coefficient, Log(K_{OW}) at 25ºC	2.44 at pH 5.3	
UV/visible absorption spectrum	Neutral: 9335 L/mol·cm @ 240.2 nm 13976 L/mol·cm @ 277.4 nm Acidic: 11712 L/mol·cm @ 240.0 nm 12368 L/mol·cm @380.4 nm Basic: 21320 L/mol·cm @ 270.8 nm	

Table 3. Trinexapac-ethyl: Registered Formulations.								
EPA Reg. Nos.	AI %	Formul. Type	Sites	Handler	Application Equipment	Spray vol gal/A	Signal word	Label PPE
1. 100-727	97.0	tech/MP	--	--	--	--	Caution	--
2. 100-729	12.0	EC	turf	grower/comm. applicator	BP, BS, HS, SG	22-175	Warning	B, G, E
3. 100-752	25.0	WP/WSB	turf	" " "	BP, BS, HS, SG	22-175	Caution	B, G
4. 100-930	0.01-1.0	granule	turf	home owner/comm. appl	shaker, fertilizer spreader *	--	Caution	none
5. 100-931	0.01-1.0	granule	turf	" " "	shaker, fertilizer spreader *	--	Caution	none
6. 100-937	11.3	EC	turf	grower/comm. applicator	BP, BS, HS, SG	22-175	Caution	B, G
7. 100-949	12.0	EC	g. g. seed	" " "	broadcast sprayer	10-20	Warning	B, G, E
8. 100-1241	25.5	EC	g. g. seed	" " "	broadcast sprayer	10-20	Caution	B, G, E
9. 34704-1005	11.3	EC	turf	" " "	BP, BS, HS, SG	22-175	Caution	B, G
10. 72112-11	11.3	EC	turf	" " "	BP, BS, HS, SG	22-175	Caution	B, G
11. 72167-54	97.0	tech/MP	--	--	--	--	Caution	--
12. 73220-12	11.3	EC	turf	" " "	BP, BS, HS, SG	22-175	Caution	B, G
13. 79676-24	11.3	EC	turf	" " "	BP, BS, HS, SG	22-175	Caution	B, G
14. 79676-37	12.0	EC	turf	" " "	BP, BS, HS, SG	22-175	Warning	B, G
15. 81943-12	11.3	EC	turf	" " "	BP, BS, HS, SG	22-175	Caution	B, G
16. 81959-27	98.0	tech/MP	--	--	--	--	Caution	--
17. 83070-4	11.3	EC	turf	" " "	BP, BS, HS, SG	22-175	Caution	B, G
18. MN020010	12.0	EC	seed rye grass	" " "	broadcast sprayer	10-20	Warning	B, G, E
19. OR000007	12.0	EC	seed fescue	" " "	broadcast sprayer	10-20	Warning	B, G, E
20. WA030007	12.0	EC	seed fescue	" " "	broadcast sprayer	10-20	Warning	B, G, E

EC= emulsifiable concentrate, MP = manufacturing-use product, NA = not applicable, WP/WSB= wettable powder packed in water-soluble bags,
PPE - B (baseline consisting of long sleeved shirt, long pants, and shoes with socks), C (gloves), and E (eye wear)
Application equipment: BP = back-pack sprayer, BS = boom sprayer, HS = hand sprayer, and SG = spray gun
* = fertilizer spreaders can be either broadcast or drop spreaders

Table 4. Trinexapac-ethyl - Application Rates on Turf and Grasses Grown for Seeds.									
EPA Reg. No.	AI %	Formul. Type	Home lawns max single lb ai/A	Golf course max single lb ai/A	Res/Commerc. max single lb ai/A	Edging max single lb ai/A	Grass gr seeds max single lb ai/A	# Appl./yr	Max/yr lb ai/A
1. 100-727	97.0	tech/MP	--	--	--	--	--	--	--
2. 100-729	12.0	EC	--	0.17	0.34	0.69	--	multiple	2.4
3. 100-752	25.0	WP/WSB	--	0.17	0.34	0.68	--	multiple	2.7
4. 100-930	0.01-1.0	granule	0.44	--	--	0.88	--	multiple	2.5
5. 100-931	0.01-1.0	granule	0.44	--	--	0.88	--	multiple	2.5
6. 100-937	11.3	EC	--	0.16	0.32	0.65	--	multiple	2.25
7. 100-949	12.0	EC	--	--	--	--	0.5	multiple	0.5
8. 100-1241	25.5	EC	--	--	--	--	0.45	multiple	0.5
9. 34704-1005	11.3	EC	--	0.16	0.32	0.65	--	multiple	2.25
10. 72112-11	11.3	EC	--	0.16	0.32	0.65	--	multiple	2.25
11. 72167-54	97.0	tech/MP	--	--	--	--	--	--	--
12. 73220-12	11.3	EC	--	0.16	0.32	0.65	--	multiple	2.25
13. 79676-24	11.3	EC	--	0.16	0.32	0.65	--	multiple	2.25
14. 79676-37	12.0	EC	--	0.17	0.34	0.68	--	multiple	2.4
15. 81943-12	11.3	EC	--	0.16	0.32	0.65	--	multiple	2.25
16. 81959-27	98.0	tech/MP	--	--	--	--	--	--	--
17. 83070-4	11.3	EC	--	0.16	0.32	0.65	--	multiple	2.25
18. MN020010	12.0	EC	--	--	--	--	0.5	multiple	0.5
19. OR000007	12.0	EC	--	--	--	--	0.5	multiple	0.5
20. WA030007	12.0	EC	----	--	--	--	0.5	multiple	0.5

EC= emulsifiable concentrate, NA= not applicable, P/WSB= wettable powder packed in water-soluble bags.

Table 5. Acute Toxicity Profile of Trinexapac-ethyl (97%).				
Guideline No.	**Study Type**	**MRID**	**Results**	**Toxicity Category**
870.1100	Acute oral [rat]	41563901	♂ LD_{50} = 4613 mg/kg ♀ LD_{50} = 4212 mg/kg Combined LD_{50} = 4458 mg/kg	III
870.1200	Acute dermal [rabbit]	41563910	LD_{50} > 4000 mg/kg	III
870.1300	Acute inhalation [rat]	41563912	$LC_{50} \geq 5.3$ mg/L	IV
870.2400	Acute eye irritation [rabbit]	41563914	Minimal irritant; cleared by 72 hours	III
870.2500	Acute dermal irritation [rabbit]	41563916	Slightly irritating; cleared by day 7	IV
870.2600	Skin sensitization [guinea pig]	41869522	Not a dermal sensitizer	N/A

Table 6. Subchronic, Chronic and Other Toxicity Profile of Trinexapac-ethyl.		
Guideline No./ Study Type	**MRID No. (year) Classification /Doses**	**Results**
870.3100 90-Day oral toxicity [rat]	MRID 41563921 (1989) 0, 5, 50, 500, 5000, 20000 ppm [males 0, 3, 34, 346, 1350 mg/kg/day] [females 0, 4, 38, 395, 1551 mg/kg/day] acceptable/guideline	NOAEL = 20000 ppm [males 1350/females 1551 mg/kg/day HDT
870.3150 13-week oral toxicity in nonrodent (dog) 7-week pilot study	MRID 41563920 (1989) 0, 50, 100, 15000, 30000 ppm [males 0, 2.0, 34.9, 515.9, 927.1 mg/kg/day] [females 0, 1.9, 38.8, 582.4, 890.8 mg/kg/day] acceptable/guideline MRID 41869523 0, 500, 5000, 15000-50000 ppm [males 0, 22, 219, (686, 956, 734)* mg/kg/day] [females 0, 23, 214, (680, 1373, 965)* mg/kg/day] *15000 ppm (days 1-3); 30000 ppm (days 4-28); 50000 ppm (weeks 4-7)	NOAEL = 15000 ppm [males 515.9/females 582.4 mg/kg/day LOAEL = 30000 ppm [males 927.1/females 890.8 mg/kg/day, based on clinical signs (few feces and emaciation) decreased BWG/FC/FE in both sexes (related to lack of palatability) and diffuse thymic atrophy Negative BWG in males HDT from week 5 on; HDT females from week 6 on; BW of HDT males 81% of control/females 74% control at week 7; severe decrease in food consumption HDT; tubular dilatation and degeneration/regeneration of epithelial cells of renal tubules at HDT; diffuse thymic atrophy at mid- and high-dose females and high-dose males
870.3200 21/28-Day dermal toxicity (rabbit)	MRID 41563922 (1989) [46809310 (2006)] 0, 10, 100, or 1000 mg/kg/day, acceptable/guideline	**Systemic toxicity** NOAEL: 1000 mg/kg/day LOAEL: Not determined **Local dermal irritation** NOAEL: 10 mg/kg/d LOAEL: 100 mg/kg/d based on hyperkeratosis and subacute lymphocytic infiltrates in the skin
870.3250 90-Day dermal toxicity	no study located/not required	

Table 6. Subchronic, Chronic and Other Toxicity Profile of Trinexapac-ethyl.		
Guideline No./ Study Type	**MRID No. (year) Classification /Doses**	**Results**
870.3465 90-day inhalation toxicity	no study located on technical	
870.3700a Prenatal developmental in rodent [rat]	MRID 41563923 (1988) 0, 20, 200, 1000 mg/kg/day gestation days 6-15 acceptable/guideline	**Maternal** NOAEL = 1000 mg/kg/day, highest dose tested **Developmental** NOAEL = 200 mg/kg/day **Developmental** LOAEL = 1000 mg/kg/day, based on increased incidence of asymmetrically-shaped sternebrae
870.3700b Prenatal developmental in nonrodent (rabbit)	MRID 41869524 (1990) 0, 10, 60, or 360 mg/kg/day gestation days 7-19 acceptable/guideline	**Maternal toxicity NOAEL** = 360 mg/kg/day, highest dose tested **Developmental toxicity NOAEL** = 60 mg/kg/day **Developmental toxicity LOAEL** = 360 mg//kg/day, based on a decrease in the mean number of fetuses/litter and an increase in post-implantation loss
870.3800 Reproduction and fertility effects (rats)	MRID 43128604 (1991) 0, 10, 1000, 10000, 20000 ppm [P0 males: 0, 0.59, 59.97, 595.26, 1169.16 mg/kg/day] [P0 females: 0, 0.75, 74.84, 736.89, 1410.08 mg/kg/day] F1 males: 0, 0.59, 59.10, 591.76, 1254.96 mg/kg/day] F1 females 0, 0.77, 77.17, 765.20, 1559.65 mg/kg/day] acceptable/guideline	**Parental toxicity NOAEL** = 10000 ppm [males 593.5/females 751.1 mg/kg/day] **Parental toxicity LOAEL** 20000 ppm [males 1212.1/females 1484.9 mg/kg/day], based on reduced premating and gestation body weight/body-weight gain and food consumption **Reproductive NOAEL** = 20000 ppm [males 1212/females 1484 mg/kg/day]. No adverse treatment-related effect on reproductive parameters up to and including 20000 ppm (HDT) **Offspring NOAEL** = 10000 ppm [males 593.5/females 751.1 mg/kg/day] **Offspring LOAEL** = 20000 ppm [males 1212.1/females 1484.9 mg/kg/day], based on decreased F1 postnatal survival and reduced pup body weights in both generations [both sexes].
870.4100a Chronic toxicity rodents (rat)	MRID 42238104 (1992) 0, 10, 100, 3000, 10000, 20000 ppm M 0, 0.38, 3.87, 115.6, 392.7, 805.7 mg/kg/day F 0, 0.49, 4.88, 147.4, 494.0, 1054 mg/kg/day acceptable/guideline	**Systemic toxicity NOAEL =** 20000 ppm [males 806/females 1054 mg/kg/day, highest dose tested.
870.4100b Chronic toxicity nonrodent (dogs)	MRID 42779402/42779401 (1991-92) 0, 40, 1000, 10000, or 20000 ppm [males 0, 1.56, 31.62, 356.72, or 726.65 mg/kg/day] [females 0, 1.37, 39.54, 357.13, 783.83 mg/kg/day] acceptable/guideline	**Systemic toxicity NOAEL** = 1000 ppm [males 31.62/females 39.54 mg/kg/day **Systemic toxicity LOAEL** = 10000 ppm [males 365.72/females 357.13 mg/kg/day], based on elevated serum cholesterol values in females, mucoid feces in females and bloody feces in both sexes, and minimal, focal vacuolation of the dorsal medial hippocampus and/or lateral midbrain in both sexes.

Table 6. Subchronic, Chronic and Other Toxicity Profile of Trinexapac-ethyl.		
Guideline No./ Study Type	**MRID No. (year) Classification /Doses**	**Results**
870.4200 Carcinogenicity (rat) Sprague-Dawley	MRID 42238104 (1992) 0, 10, 100, 3000, 10000, 20000 ppm M 0, 0.38, 3.87, 115.6, 392.7, 805.7 mg/kg/day F 0, 0.49, 4.88, 147.4, 494.0, 1054 mg/kg/day acceptable/guideline	see above under 870.4100a There was a possible treatment related increased incidence of squamous cell carcinoma of the forestomach in M at 20000 ppm (HDT); however, this is not considered toxicologically relevant to humans. No treatment-related difference detected in total number of animals with tumors or in the total number of benign or malignant tumors at 52 or 104 weeks. No treatment-related effect on the time-dependent occurrence of tumor-bearing animals. **Not Likely to be Carcinogenic to Humans**
870.4300 Carcinogenicity (mouse) CD-1 [Crl:CD-1 (ICR)Br]	MRID 43128603 (1991) 0, 7, 70, 1000, 3500, 7000 ppm [males 0, 0.91, 9.01, 130.81, 450.72, 911.77 mg/kg/day] [females 0, 1.08, 10.66, 154.08, 538.73, 1073.42 mg/kg/day] acceptable/guideline	**Systemic toxicity NOAEL** = 7000 ppm [males 911/females 1073 mg/kg/day], the highest dose tested. There was no treatment-related increase in tumors of any type in either sex at dose levels up to an including 7000 ppm, the HDT **Not Likely to be Carcinogenic to Humans**
870.5100 Bacterial Reverse Gene Mutation Assay	46809308 (2001) *Salmonella typhimurium* strains TA98, TA100, TA102, TA1535 and TA1537 *Escherichia coli* strain WP2*uvr*A 0, 312.5, 625, 1250, 2500, or 5000 µg/plate ± S9 metabolic activation Acceptable/guideline	**Negative** acceptable/guideline
870.5300 Mouse Lymphoma Cells/Mammalian Activation Gene Forward Mutation Assay at $TK^{+/-}$ locus	43128605 (1993 Mouse lymphoma L5178Y cells (at the thymidine kinase locus) 0, 7.54, 30.16, 120.62, or 1930 µg/mL for 4 hours ± S9 metabolic activation	**Negative** acceptable/guideline

Table 6. Subchronic, Chronic and Other Toxicity Profile of Trinexapac-ethyl.		
Guideline No./ Study Type	**MRID No. (year) Classification /Doses**	**Results**
870.5395 Structural chromosomal aberration test - Micronucleus Test Mouse	41563926 (1989) 42081402 (1991) 41869527 (1991) M and F mouse bone marrow cells (erythrocytes) 0, 1000, 2000, or 4000 mg/kg bw (sacrifice at 16, 24, and 48 h) Initial assay: 0 or 3000 mg/kg bw (sacrifice at 16, 24, and 48 h) Confirmatory assay: 0, 750, 1500, or 3000 mg/kg bw (sacrifice at 48 h)	**Negative** acceptable/guideline Significant increased frequency of micronucleated polychromatic erythrocytes in M and sexes combined at 48 h in the initial assay; however, values were within historical control range and not observed in the confirmatory assay at 3000 mg/kg bw at 48 h . In this study possible weak clastogen, however, weight of evidence suggests CGA-163935 not likely clastogenic.
870.5550 Other Genotoxicity *In vitro* UDS in Primary Rat Hepatocytes	41604205 (1987) 41869528 (1991) Preliminary cytotoxicity assay: 0, 5, 10, 21, 41, 82, 164, 328, 656, 1313, 2625, or 5250 µg/mL Initial UDS assay: 0, 0.8, 4, 20, 100, 200, or 400 µg/mL; Confirmatory UDS assay: 0, 4, 20, 100, 150, 200, 300, 400, or 500 µg/mL	**Negative** acceptable/guideline
870.6200a Acute neurotoxicity screening battery	No study available	
870.6200b Subchronic neurotoxicity screening battery	No study available	
870.6300 Developmental neurotoxicity	No study available	
870.7485 Metabolism and pharmacokinetics (rat)	MRID 41563927 (1990) i. v. 0.91 mg/kg [^{14}C- CGA-163935] oral 0.97 or 166 mg/kg [^{14}C- CGA-163935] oral 0.97 mg/kg/day [CGA-163935] for 14 days followed by 0.97 mg/kg [^{14}C-CGA-163935] acceptable/guideline	Rapidly, extensively absorbed (both sexes) w/ >95% of administered dose being absorbed; little potential for accumulation; >85% eliminated w/in 12 hours via urine; 2% via feces w/in 24 hours; very little or no biliary excretion; no sex difference; free acid derivative resulting from hydrolysis of the ester bond of parent compound is major component in urine and feces; only other component was parent, found only in feces.
870.7600 Dermal penetration (rat)	MRID 42238105 (1990) 0, 0.01, 0.1, or 1.0 mg/cm^2 [^{14}C- CGA-163935] single dermal dose acceptable/guideline	Recovery of applied dose 97%-117%; most recovered in skin washes and urine; <1% in blood and feces; excreted in urine within 2 hours of dose 56.5% absorbed, with 21% associated with application site dermal absorption factor 77.5%

Table 7. Toxicological Doses and Endpoints for Trinexapac-ethyl 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, including Infants and Children)	No appropriate endpoint found for the general population (infants and children)			
Acute Dietary (Females 13-49 years of age)	NOAEL = 60 mg/kg	UF_A= 10x UF_H = 10x FQPA SF (UF_{DB})= 1x	Acute RfD = 0.6 mg/kg aPAD = 0.6 mg/kg	*Developmental rabbit study* LOAEL = 360 mg/kg, based on a decrease in mean number of fetuses/litter and an increase in post-implantation loss
Chronic Dietary (All Populations)	NOAEL= 31.6 mg/kg/day	UF_A= 10x UF_H = 10x FQPA SF (UF_{DB})= 1x	Chronic RfD = 0.32 mg/kg/day cPAD = 0.32 mg/kg/day	*Chronic oral toxicity study - dog* LOAEL = 357 mg/kg/day, based on elevated serum cholesterol values in females, mucoid feces in females and bloody feces in both sexes, and minimal, focal vacuolation of the dorsal medial hippocampus and/or lateral midbrain in both sexes
Incidental Oral (All Durations)	NOAEL= 594 mg/kg/day	UF_A= 10x UF_H = 10x FQPA SF (UF_{DB})= 1x	Residential LOC for MOE = 100	*Multi-generation reproduction study* LOAEL = 1212 mg/kg/day, based on decreased F1 postnatal survival and reduced pup body weight/body-weight gain in both generations (both sexes)
Short-Term Dermal & Inhalation (1-30 days)	NOAEL= 60 mg/kg/day Dermal absorption rate = 77.5% Inhalation absorption rate = 100%	UF_A= 10x UF_H = 10x FQPA SF (UF_{DB})= 1x	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	*Developmental rabbit study* LOAEL = 360 mg/kg, based on a decrease in mean number of fetuses/litter and an increase in post-implantation loss
Intermediate-Term Dermal & Inhalation (1-6 months)	NOAEL= 31.6 mg/kg/day Dermal absorption rate = 77.5% Inhalation absorption rate = 100%	UF_A= 10x UF_H = 10x FQPA SF (UF_{DB})= 1x	Residential LOC for MOE = 100 Occupational LOC for MOE = 100	*Chronic oral toxicity study - dog* LOAEL = 357 mg/kg/day, based on elevated serum cholesterol values in females, mucoid feces in females and bloody feces in both sexes, and minimal, focal vacuolation of the dorsal medial hippocampus and/or lateral midbrain in both sexes
Cancer (oral, dermal, inhalation)	Classification: "Not likely to be Carcinogenic to Humans"			

Table 8. Non-cancer Short-term Exposures and Risks to Residential Handlers from Trinexapac-ethyl Granules Applied to Turf.							
Exposure Scenario	Application Equipment	Appl. rate, max single, lb ai/A	Derm. unit exp mg/lb ai.[1]	Inhal. unit exp mg/lb ai.[2]	Short-term dermal [3]	Short-term Inhalation [4]	Total Short-term MOE [5]
loading/applying granules	broadcast spreader	0.88	0.68	0.00091	Exp. 0.0033 MOE 18,000	Exp. 0.000006 MOE 1.0E+07	18,000

1. & 2. Dermal value is for short pants and short sleeves (worst case scenario). Both unit exposures are geometric means from ORETF Study OMA 003 (G. Bangs, April 30, 2001).
3. Dermal exposure = [unit exp * appl. rate * area treated/day (0.5A) * derm. absorp. rate (77.5%)] / body wt. (70 kg). Short-term dermal MOE = short-term dermal NOAEL (60 mg/kg/day) / dermal exposure.
4. Inhal. exposure = [unit exp * appl. rate * area treated/day (0.5A) * inhal. absorp. rate (100.0%)] / body wt. (70 kg). Short-term inhalation MOE = short-term inhalation NOAEL (60 mg/kg/day) / inhal. exposure.
5. Total MOE + 1/[(1/dermal MOE) + (1/inhal. MOE)]. The corresponding LOC of MOE is 100.

Table 9. Post-application Short-term Risks to Adults, Youths, and Toddlers from Trinexapac-ethyl Applied to Residential Turf.				
Exposure Scenario [1]	Routes of Exposure	Transfer coefficient (cm^2/hr) [2]	Short-term Exposures (mg/kg/day) [3]	Short.-term MOE [4]
Adults , high contact	dermal	14,500	0.0182	330
Adults, mowing	dermal	3,400	0.0430	1,400
Adults, golfing	dermal	500	0.0126	4,700
Youth, mowing	dermal	3,400	0.0661	910
Youth, golfing	dermal	500	0.0194	3,100
Toddlers, high contact	dermal	5,200	0.2628	230
Toddlers, hand-to-mouth	incidental oral	NA	0.0130	46,000
Toddlers, object-to- mouth	incidental oral	NA	0.0033	180,000
Toddlers, soil ingestion	incidental oral	NA	0.0437	14,000

1. Applicable scenarios were selected from Residential SOP Apr. 5, 2000 (Draft).
2. Residential SOP 1997 (Draft).
3. Algorithms are from Lowe, K.M., D334752, March 01, 2007. The max. single appl. rate used was 0.88 lb ai/A (Table 2).
4. Short-term MOE = short-term dermal NOAEL (60 mg/kg/day) / dermal exposure or short-term incidental oral NOAEL (594 mg/kg/day) / incidental ingestion.

Table 10. Trinexapac-ethyl: Occupational and Residential Handler Exposure Scenarios.			
Scen . #	Exposure Scenarios	Max single appl rate lb ai/A	Comments
	GROWER/COMMERCIAL USES ON TURF AND GRASS GROWN FOR SEEDS		
--	**Mixing / Loading**		
1	open mixing/loading of EC for BP, BS, HS, SG	0.68	
2	open mixing/loading of WP/WSBs for BP, BS, HS, SG	"	
--	**Applying**	--	
3	applying ECs using back-pack sprayer	0.68	
4	applying ECs using boom sprayer	"	
5	applying ECs using hand gun	"	
6	applying ECs using spray gun	"	
7	applying WP spray using back-pack sprayer	"	
8	applying WP spray using boom sprayer	"	
9	applying WP spray using hand gun	"	
10	applying WP spray using spray gun	"	
--	**Mixing / Loading / Applying**	--	
11	open mixing/loading and applying ECs using back-pack sprayer	0.68	
12	open mixing/loading and applying ECs using boom sprayer	"	
13	open mixing/loading and applying ECs using hand gun	"	
14	open mixing/loading and applying ECs using spray gun	"	
15	open mixing/loading and applying WP using back-pack sprayer	"	
16	open mixing/loading and applying WP using boom sprayer	"	
17	open mixing/loading and applying WP using hand gun	"	
18	open mixing/loading and applying WP using spray gun	"	
--	**RESIDENTIAL - HOME-OWNER USES**	--	
19	loading/applying granules using shaker	0.88	residential handler
20	loading/applying granules using spreader/broadcast	"	"" ""
21	loading/applying granules using spreader/dropper	"	"" ""

Table 11. Non-cancer Short-term Exposures and Risks to Occupational Handlers from Trinexapac-ethyl Granules Applied to Turf.							
Exposure Scenario	Application Equipment	Max single appl. rate, lb ai/A	Derm. unit exp mg/lb ai.[1]	Inhal. unit exp µg/lb ai.[2]	Short-term dermal [3]	Short-term Inhalation [4]	Total short-term MOE [5]
Loader/applicator of granules	spreader, push type	0.88	2.9	6.3	Exp. 0.141 MOE 425	Exp. 0.000396 MOE 1.5E+05	420

1. & 2. Unit exposures are from PHED for single layer clothing and no gloves.
3. Dermal exposure = [unit exp * appl. rate * area treated/day (5A) * derm. absorp. rate (77.5%)] / body wt. (70 kg). Short-term dermal MOE = Short term dermal NOAEL (60 mg/kg/day) / dermal exposure.
4. Inhal. exposure = [(unit exp/1000) * appl. rate * area treated/day (5A) * inhal. absorp. rate (100.0%)] / body wt. (70 kg). Short-term inhalation MOE = Short-term inhalation NOAEL (60 mg/kg/day) / inhal. exposure.
5. Total short-term MOE + 1/[(1/dermal MOE) + (1/inhal. MOE)]. The corresponding LOC of MOE is 100.

Tolerance/MRL Tables

Table 12. Summary of US and International Tolerances and Maximum Residue Limits for Trinexapac-ethyl.

Commodity	Tolerances or MRLs				
	US	Codex	Canada	Australia	New Zealand
Sugar cane	None	None	None	0.05 mg/kg	None
Rye, straw and fodder, dry	None	None	None	3 mg/kg	None
Sugar cane, fodder	None	None	None	1 mg/kg	None
Sugar cane, forage	None	None	None	1 mg/kg	None
Cereal grain	None	None	None	None	0.05 mg/kg

Table 13. Summary of Japanese (Provisional) Maximum Residue Limits for Trinexapac-ethyl.
MRLs are established for the sum of residues of trinexapac-ethyl and trinexapac calculated as trinexapac-ethyl.

Commodity	MRLs (ppm)	Classification of MRL
Rice (brown rice)	0.5	
Numerous commodities, including grains	0.02	provisional

Table 14. Summary of European Union *Temporary* Maximum Residue Limits for Trinexapac-ethyl. (Annex III to European Commission N 396/2005)

Code number	Groups and examples of individual products to which the MRLs apply	Trinexapac
0100000	1. FRUIT FRESH OR FROZEN; NUTS	0.050
0211000	(a) Potatoes	0.050
0212000	(b) Tropical root and tuber vegetables	1.000
0213000	(c) Other root and tuber vegetables except sugar beet	1.000
0220000	(ii) Bulb vegetables	1.000
0230000	(iii) Fruiting vegetables	1.000
0240000	(iv) Brassica vegetables	1.000
0250000	(v) Leaf vegetables & fresh herbs	1.000
0260000	(vi) Legume vegetables (fresh)	1.000
0270000	(vii) Stem vegetables (fresh)	1.000
0280000	(viii) Fungi	1.000
0290000	(ix). Sea weeds	1.000
0300010	Beans	10.000
0300020	Lentils	0.050
0300030	Peas	0.050
0300040	Lupins	0.050
0300990	Others	0.050
0401010	Linseed	0.050
0401020	Peanuts	0.050
0401030	Poppy seed	0.050
0401040	Sesame seed	0.050
0401050	Sunflower seed	0.050
0401060	Rape seed	2.000
0401070	Soya bean	0.050
0401080	Mustard seed	0.050
0401090	Cotton seed	0.050

Table 14. Summary of European Union *Temporary* Maximum Residue Limits for Trinexapac-ethyl. (Annex III to European Commission N 396/2005)		
Code number	Groups and examples of individual products to which the MRLs apply	Trinexapac
0401100	Pumpkin seeds	0.050
0401110	Safflower	0.050
0401120	Borage	0.050
0401130	Gold of pleasure	0.050
0401140	Hempseed	0.050
0401150	Castor bean	0.050
0401990	Others	0.050
0402000	(ii) Oilfruits	0.050
0500000	5. CEREALS	0.500
0600000	6. TEA, COFFEE, HERBAL INFUSIONS AND COCOA	0.050
0700000	7. HOPS (dried) , including hop pellets and unconcentrated powder	0.050
0800000	8. SPICES	0.050
0900000	9. SUGAR PLANTS	0.050
1000000	10. PRODUCTS OF ANIMAL ORIGIN-TERRESTRIAL ANIMALS	0.050

DCI Tables

Guideline Number: 860.1340 **Study Title: Plant Analytical Method and Animal Analytical Method**
Rationale for Requiring the Data
Data Collection Residue analytical methods are used to validate the residue field trial studies in plant and animal commodities. Data collection methods are necessary for all pesticides used on edible crops/animals and resultant produce, and for products (e.g., meat, milk) from animals that may consume treated crops. The trinexapac-ethyl registrant submitted a plant analytical method (HPLC/MS, Method 110-10); however, this method does not determine conjugated residues. The residues of concern in plants and animals for both tolerance enforcement and risk assessment purposes include free and conjugated residues of both parent and its acid metabolite, trinexapac. This determination is based on the results of grass and rice metabolism studies in which significant fractions of the trinexapac-ethyl residues in the various fractions were conjugated. The Agency recommends that the registrant revise the existing method to include an enzymatic and/or mild acid hydrolysis step to release conjugated residues of trinexapac. Additionally, a confirmatory analysis must be proposed, and the method must undergo a successful independent laboratory validation (ILV). The Agency also recommends that the registrant develop and validate an animal analytical method that has the ability to hydrolyze conjugates. *Enforcement* Plant and animal analytical methods submitted by the registrant must be suitable for use by various Federal and State enforcement agencies. The Food and Drug Administration (FDA) collects these methods and then publishes them to be used for enforcement purposes.
Practical Utility of the Data
How will the data be used? *Data Collection* The methods will be used to validate the residue field trials, which can then be used to establish tolerances and assess dietary risk. *Enforcement* EPA will review the submitted plant and animal analytical methods and determine their suitability as enforcement methods. If suitable, EPA will forward the methods to FDA. The enforcement analytical methods are published by FDA and are available to all regulatory laboratories for use in monitoring the specific pesticide concentrations in foods and feeds. They are a necessary tool for tolerance enforcement and residue monitoring and, as such, are essential in the efforts to ensure a safe food supply for the consumer.

Guideline Number: 860.1500
Study Title: Crop Field Trials

Rationale for Requiring the Data

Trinexapac-ethyl was considered a non-food use when originally registered in 1992. Tolerances were not established because it was not expected that detectable residues would be present in agricultural commodities. However, recently submitted data show that residues are detected in plant and animal commodities when used on grasses grown for seed. Therefore, tolerances need to be established for this use.

Crop field trials are required for each commodity/commodity group according to guidelines that take into account where the crop is grown and how much of the crop is grown. In general, the OPPTS Series 860 Guidelines, Section 1500, provide the recommended distribution and numbers of field trials for the various crops. For grasses grown for seed, however, OPP has a separate guidance document that is currently in draft status. The document is entitled: Additional Guidance on the Crop – 'Grasses Grown for Seed' (dated 09/2000). As with the 860 Guidelines, the additional guidance document provides the recommended number of field trials and their geographic distribution. In the United States, a significant fraction of the grasses grown for seed are grown in the Pacific Northwest. As a result, the guidance document has separate recommendations depending on whether the registrant wishes to obtain a national registration or a regional Pacific Northwest registration. Regardless of which type of registration the registrant is requesting, the two RACs, forage and hay, need to be analyzed.

For a national registration, the draft guidance document recommends that a total of 8 field trials be performed on representative varieties (specifically, 3 trials in EPA Growing Zone 12, 2 trials in Zone 11, and 3 trials in Zone 5). For a regional Pacific Northwest registration, the draft guidance document recommends that a total of 5 field trials be performed on representative varieties (specifically, 3 trials in EPA Growing Zone 12 and 2 trials in Zone 11).

The registrant originally submitted the results of 9 field trials that were performed in Regions 5, 10, 11, and 12. If stored samples of both forage and hay from these trials are available, and if storage stability of the residues can be demonstrated over the storage interval, the samples may be re-analyzed using the updated analytical method. The registrant may submit the results of these trials, and HED will evaluate their adequacy.

Practical Utility of the Data

How will the data be used?
These data will allow EPA to set enforceable tolerance levels that farmers and producers will be able to rely upon for trade and commerce. The farmers and producers depend upon EPA to set appropriate tolerance levels in conjunction with label directions (which can include restrictions on use of additives) that would prevent legal uses from producing over-tolerance residues, and thereby resulting in crop seizure. Once the tolerance levels are determined, dietary risk will be assessed.

How could the data impact the Agency's future decision-making?
These data might help in granting future new use requests.

Guideline Number: 870.6200
Study Title: Acute & Subchronic Neurotoxicity

Rationale for Requiring the Data

The acute and subchronic neurotoxicity studies are 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 Test Guideline (OPPTS 870.6200) prescribes functional and structural neurotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects on the nervous system. Although some information on neurotoxicity may be obtained from standard guideline toxicity study data, studies not specifically conducted to assess neurotoxic endpoints may be inadequate to characterize a pesticide's potential neurotoxicity. While data on clinical signs of toxicity or histopathology in routine chronic or subchronic toxicity studies may offer useful information on potential neurotoxic effects, these endpoints alone may be insufficient to detect more subtle neurological effects.

Practical Utility of the Data

How will the data be used?
Neurotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the nervous system from pesticide exposure. Since epidemiologic data on the effects of chemical exposures of trinexapac-ethyl on neurologic parameters are limited and may be inadequate to characterize a pesticide's potential neurotoxicity 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.

How could the data impact the Agency's future decision-making?
If the neurotoxicity studies show 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 these data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

Guideline Number: 870.7800
Study Title: Immunotoxicity

Rationale for Requiring the Data

The immunotoxicity study 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 these data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.