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

CONFIDENTIAL

MAR 29 1990

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Quizalofop P-ethyl [D(+) isomer]/Assure® II: DuPont registration proposal (I.D. Nos. 352-LUE and 352-LUR; Record Nos. 250157 and 250158; MRID Nos. 41224001 and 41206101 thru -03; DEB Nos. 5852 and 5853)

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THRU: Andrew R. Rathman, Chief
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PRODUCT INGREDIENT SOURCE INFORMATION IS NOT INCLUDED

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Introduction

E.I. duPont de Nemours & Co. proposes to register a 95% technical grade (TGAI; 352-LUE) of the resolved, herbicidally-active D(+) enantiomer of quizalofop-ethyl (ethyl(R)-2-[4-[(6-chloro-2-quinoxalin-2-yl)oxy]phenoxy]propanoate). DuPont also proposes to register a 9.4% (0.8 lb ai/gal) D(+)-quizalofop-ethyl emulsifiable concentrate (EC), Assure® II Herbicide (352-LUR). Currently, the racemic mixture is registered (EPA Reg. Nos. 352-441 and 352-526). The TGAI producer is [redacted] Tolerances have been established (40 CFR 180.441, 185.5250, and 186.5250) for combined residues of quizalofop-ethyl and its metabolite quizalofop acid in/on soybeans (0.05 ppm), soybean flour (0.5 ppm), hulls (0.02 ppm), meal (0.5 ppm), and soapstock (1.0 ppm). Tolerances have been established for combined residues of quizalofop-ethyl, quizalofop-methyl, and quizalofop acid in eggs (0.02 ppm), milk (0.01 ppm), milk fat (0.05 ppm), and the fat (0.05 ppm), meat (0.02 ppm), and meat by-products (0.05 ppm) of cattle, goats, hogs, horses, poultry, and sheep. The registrant feels that the existing tolerance levels should be maintained.

Detailed Considerations

Conclusions/Deficiencies

1a. Under 62-1, the registrant must explain the differences, if any, between impurities [redacted] (current process for racemic mixture) and impurities [redacted] (pending process for D(+) enantiomer).

1b. Under 63-13, stability to light must be determined (translatable environmental fate data may be available).

1c. Under 63-17, stability of the TGAI stored in the commercial container for 1 year under expected conditions must be studied (rather than 3 mo. at 50 C in a glass jar) including any effects of the TGAI on the container.

2. Spray volume and equipment (aerial vs. ground) used in the subject field residue trials must be specified.

3. Conditions of storage/shipping between field trial sample collection and receipt by the analytical lab (including any fluctuations/thawing events) must be reported.

4. All future residue data should be generated using DuPont AMR-153-83 Rev. 3 or a similarly validated method that includes an enzymatic hydrolysis step to release quizalofop acid conjugates.

Recommendations

DEB cannot recommend in favor of registration of the subject pending D(+)-quizalofop-ethyl products nor concomitantly reassess the existing tolerances until Deficiencies 1a, 2, and 3 have been resolved. Although Deficiencies 1b and 1c must be resolved, conditional registration would be appropriate until such time as the relevant data are submitted and deemed adequate.

Notes to PM:

1. 40 CFR 186.5250 incorrectly lists the feed additive tolerance for quizalofop-ethyl residues in/on soybean hulls as 0.02 ppm (the RAC tolerance is 0.05 ppm). The correct soybean hull value is 0.2 ppm.

✓2. It is possible that all or most of the information in the Confidential Appendix [redacted] that is to be protected, even from the registrant, DuPont.

3. It is DEB's understanding that the TGAI, produced [redacted] under some EPA registration. RD is

advised to verify that the DuPont TGAI label will be affixed to containers of the TGAI during all stages of shipping.

Product Chemistry

61-1. Product Identity and Disclosure of Ingredients

DuPont states that the CAS No. is 100646-51-3 (unverified), common name is quizalofop P-ethyl, and company code is DPX-79376-16. [redacted] The DuPont code for the racemic mixture is DPX-Y6202. Refer to the Confidential Appendix for the Confidential Statement of Formula (CSF).

The submitted data are adequate to satisfy this requirement.

61-2. Description of Beginning Materials and Manufacturing Process

Refer to the Confidential Appendix for a summary of the manufacturing process.

The submitted process used to produce D(+)-quizalofop-ethyl has been adequately detailed. Although specifics of the process currently used to produce the racemic mixture are limited, the two syntheses appear to be largely similar [redacted] racemic mixture.

61-3. Discussion of the Formation of Impurities

Refer to the Confidential Appendix for this discussion.

The submitted data are adequate to satisfy this requirement.

62-1. Preliminary Analysis of Product Samples

Refer to the Confidential Appendix for the analysis of 10 batches of the TGAI. With minor (possible) exceptions, the impurities in D(+)-quizalofop-ethyl TGAI and the racemic TGAI are similar.

The submitted data are largely adequate to satisfy this requirement. However, the registrant must explain any differences between impurities [redacted] (racemic process) and impurities [redacted] (D(+) enantiomer process).

62-2. Certification of Ingredient Limits

Refer to the CSF (61-1) in the Confidential Appendix.

The submitted data are adequate to satisfy this requirement.

PRODUCT INGREDIENT SOURCE INFORMATION IS NOT INCLUDED
IMPURITY INFORMATION NOT INCLUDED

62-3. Analytical Methods to Verify Certified Limits

[redacted]

The submitted methods are adequate to enforce the limits of both enantiomers of quizalofop-ethyl and claimed impurities in the TGAI.

Physical and Chemical Properties

63-2. Color. Light brown.

63-3. Physical state. Crystalline solid.

63-4. Odor. Faint to none.

63-5. Melting point. 76.0-77.0 C (pure form).

63-6. Boiling point. 220 C at 0.2 mmHg (pure form).

63-7. Density/specific gravity. 1.35 g/cm^3 at 20 C (pure form).

63-8. Solubility. In g/l (ppm for water) at 20 C:

methanol	22	ethanol	22
acetone	650	cyclohexanone	440
chloroform	1350	dichloromethane	1970
benzene	680	toluene	430
xylene	360	carbon disulfide	660
DMSO	200	n-hexane	5
THF	1160	water	0.4 ppm

63-9. Vapor pressure. 8.3×10^{-10} mmHg at 20 C.

63-10. Dissociation constant. N/A.

63-11. Octanol/water partition coefficient. log P_{ow} 4.66.

63-12. pH. 6.6 (1% aqueous slurry).

✓63-13. Stability. No loss of pure D(+)-quizalofop-ethyl at 50 C stored in a glass bottle for 3 months. In buffered aqueous solutions at 0.2 ppm in a brown bottle at 21±2 C, pure D(+) enantiomer is stable at pH 4 for 50 days, undergoes a 35% loss at pH 7 within 50 days, and an 82% loss within 48 hours at pH 9. Stable in acetone, benzene, chlorobenzene, cyclohexanone, 1,4-dioxane, DMF, ethanol, and methylnaphthalene at 50 C for 30 days in brown sealed tubes. No racemization had occurred in any solution (aqueous or organic solvent).

63-14. Oxidizing or reducing action. TGAI does not contain oxidizing or reducing agents.

63-15. Flammability. Nonflammable solid [does not contain flammable liquids].

63-16. Explodability. D(+)-quizalofop-ethyl is not explosive.

✓63-17. Storage stability. No data provided (DuPont refers to 63-13).

63-18. Viscosity. N/A (solid).

63-19. Miscibility. N/A (solid).

63-20. Corrosion characteristics. At 50 C for 30 days, small pieces of iron, aluminum, and polyethylene showed no appearance changes (except slight rust of iron) and no changes in weight.

The test methods used were adequate.

Although the bulk of the physical and chemical property data are adequate, the following deficiencies exist: (i) under 63-13, the stability to light must be determined (environmental fate data may be translatable) and (ii) under 63-17, stability of the TGAI stored under expected conditions for 1 year in the commercial container must be determined (this must include any effects of the TGAI on the container).

Residue Chemistry

Proposed use. Assure® II Herbicide, a 9.4% (0.8 lb ai/gal) emulsifiable concentrate (EC), is proposed for use on soybeans to control grasses. The only apparent change in label directions from the existing Assure® label is the 50% reduction in application rate expected as a result of an approximate 2x concentration of the biologically active D(+) enantiomer. Use is proposed at 5-12 fl oz product/A (0.031-0.075 lb ai/A or 0.5-1.2 oz ai/A) for the initial application. If retreatment of perennial grasses is required, 0.7-0.8 oz ai/A is to be applied. If tank-mixed with Basagran or Classic, the Assure® II rate must be increased by 0.2 oz ai/A. No more than 2 oz ai/A/season may be applied. Aerial (≥3 gal/A) or ground (10-40 gal/A) equipment may be used. A spray adjuvant (petroleum oil concentrate or nonionic surfactant) must be used. Treatment is not to be made after pod set. An 80-day PHI is in effect. Rotation with crops other than soybeans is not permitted prior to 120 days posttreatment. Treated fields may not be grazed or harvested for forage or hay.

Field trials. Field residue trials were conducted on soybeans grown in KS, MS, NC, NE, and WI (one site/state) to compare residues resulting from the registered use of Assure® (EPA Reg. No. 352-441; racemic mixture) with residues resulting from the proposed use of Assure® II (I.D. No. 352-LUR; D(+)-resolved). At each site, Assure® was applied once at 4 or 8 oz ai/A (1x or 2x the registered seasonal rate) and Assure® II was applied at 2 or 4 oz ai/A (1x or 2x the proposed seasonal rate). The spray volume and equipment (aerial vs. ground) were not specified. Mature soybeans were harvested 57 days (NE site), 74 days (MS site), or 80 days (KS, NC, and WI sites) posttreatment. The existing and proposed PHI is 80 days. Untreated controls were collected from each site.

Samples were received frozen by the analytical laboratory and stored at -15 to -30 C for ≤40 days. Samples had been collected ca. 7-8 mo earlier but conditions of storage (including fluctuations/thawing events) prior to receipt of samples by the analytical laboratory were not provided. Storage stability of the parent compound and quizalofop acid in soybeans is good for ≥3 years at -20 C.

Samples (one/treatment) were analyzed using DuPont AMR-153-83 Rev. 4 with minor revisions. This method is similar to AMR-153-83 Rev. 3, which has undergone a successful method trial (6/27/88, G.F. Otakie). Both methods are HPLC procedures involving spectrophotometric detection at 335 nm. A major difference is that conjugates of quizalofop acid, released via enzymatic hydrolysis using Rev. 3, are not determined using Rev. 4. Also, quizalofop acid is not methylated prior to

chromatography using Rev. 4. Recoveries of the parent compound from soybeans were 80-122% and of quizalofop acid were 58-126%. Residues of the parent compound were nondetectable (<0.05 ppm) in all treated and control samples. Quizalofop acid was nondetectable (<0.05 ppm) in all samples collected 74 or 80 days posttreatment (PHI is 80 days) but was detected at 0.09 ppm or 0.17 ppm 57 days after respective 1x or 2x applications of Assure® (2x or 4x the proposed maximum Assure® II rate).

Discussion/conclusions regarding field trials. DEB feels that, for bridging purposes, the use of a residue analytical method incapable of determining conjugates of quizalofop acid is acceptable for the following reasons: (i) Assure® and Assure® II treatments (1x and 2x) were juxtaposed; (ii) proposed Assure® II rates are 0.5x those registered for Assure® ; (iii) metabolism studies show that foliage residues of the acid conjugate account for ≤14% of the total radioactive residues (PP#5F3252; M.P. Firestone; 9/25/85); (iv) residues of parent and quizalofop acid (free and conjugated) were ND (0.05 ppm) 72-80 days after treatment at 6.4 oz ai/A (3.2x the proposed seasonal rate) at seven sites (PP#5F3252; G. Otakie; 12/18/87); and (v) the 1x rates in the subject residue trials are actually exaggerated rates since they represent the 1x seasonal rate, rather than split applications of ≤0.6x and ≤4x, the latter of which is to be made only in the event regrowth of perennial grasses occurs.

The submitted residue data appear to provide the bridging information necessary to determine the adequacy of the existing tolerances in light of the subject proposal to effectively reduce the single and seasonal application rates by 50% by resolving the D(+) enantiomer of quizalofop-ethyl from the racemic mixture. The test sites represent several major soybean growing areas and are adequate for bridging purposes. However, before a final determination can be made, the following information must be provided: (i) spray volume and equipment (aerial vs. ground) used in the field residue trials and (ii) conditions of storage between sample collection and receipt by the analytical laboratory (including any fluctuations/thawing events).

cc (with CBI): PP#5F3252, SF, RF, C. Furlow (PIB/FOD), TOX, W. Hazel

cc (without CBI): Circ.

RDI:A.R.Rathman:3/28/90:E.Zager:3/28/90

H7509C:CM#2:Rm812D:DEB:W.Hazel:557-7677:wh:3/26/90

CONFIDENTIAL APPENDIX

D(+)-QUIZALOFOP-ETHYL

DUPONT; 352-LUE AND 352-LUR

DEB NOS. 5852 AND 5853

W.J. HAZEL

3 PAGES

ASSURE

Page_____ is not included in this copy.

Pages 9 through 10 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

X Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.