Spatz ✓

Shaughnessy No.: 128201

Date out of EAB: DEC 18 1987

To: R. Taylor
Product Manager 25
Registration Division (TS-767)

From: Emil Regelman, Supervisory Chemist
Environmental Chemistry Review Section #3
Exposure Assessment Branch/HED (TS-769C)

Thru: Paul F. Schuda, Chief
Exposure Assessment Branch/HED (TS-769C) Paul F. Schuda

Attached, please find the EAB review of...

Reg./File # : 352-UUR

Chemical Name: DPX-Y6202 (Quizalofop ethyl)

Type Product : Herbicide

Product Name : ASSURE

Company Name : E.I. duPont de Nemours and Co.

Purpose : Review of a Confined Accumulation on Rotational Crops study and an EAB response concerning the Anaerobic Aquatic Soil Metabolism requirement.

Action Code: 111 EAB # (s): 70978

Date Received: 9/24/87 Total Reviewing Time: 5 days

Date Completed: 12/17/87

Monitoring Study Requested: ____

Monitoring Study Volunteered: __

Deferrals to: ____ Ecological Effects Branch

____ Residue Chemistry Branch

_X_ Toxicology Branch

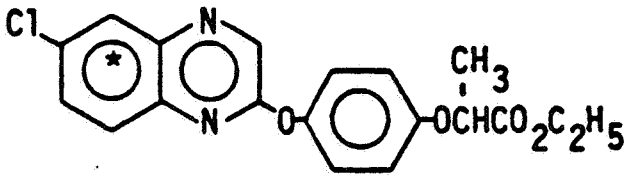
1. CHEMICAL:

chemical name: Ethyl 2-[4-(6-chloroquinoxalin-2-yloxy) phenoxy] propanoate

common name: Quizalofop Ethyl, DPX- Y6202

trade name: ASSURE

structure:



physical/chemical properties:

molecular formula: $C_{19}H_{17}ClN_2O_4$
molecular weight: 372.5
physical state: white, crystalline solid
melting point: 91.7 - 92.1°C
vapor pressure: 3×10^{-7} mm Hg at 20°C

2. TEST MATERIAL:

Radiolabeled [quinoxaline-phenyl(U)-^{14}C]DPX-Y6202, (ethyl-2-[4-(6-chloroquinoxalin-2-yloxy)phenoxy] propanoate with a specific activity of 19.3 uCi/mg and radiochemical purity of more than 99%.

3. STUDY/ACTION TYPE:

Review of an Accumulation Study of DPX-Y6202 on Rotational Crops. Also, a response from EAB concerning the Anaerobic Aquatic Soil Metabolism of DPX-Y6202 Study.

4. STUDY IDENTIFICATION:

A. Cadwgan, G.E. "Accumulation Study of [Quinoxaline-Phenyl(U)-^{14}C]DPX-Y6202 on Rotational Crops". E.I. du Pont de Nemours and Company, Inc., Wilmington, Delaware. Study completed on 9-25-86, accession number 402423-02.

2

B. Anderson, Jeffrey. "Response to Reviewer's Comments, Anaerobic Aquatic Soil Metabolism of [Quinoxaline-^{14}C]-DPX-Y6202 and Phenyl-^{14}C(U)-DPX-Y6202." E.I. du Pont de Nemours and Company, Inc., Wilmington, Delaware. Study completed on 4-9-87, accession number 402423-01.

5. REVIEWED BY:

Dana Spatz
Chemist, Review Section 3
EAB/HED/OPP

Date: DEC 18 1987

6. APPROVED BY:

Emil Regelman
Supervisory Chemist, Review Section 3
EAB/HED/OPP

Date: DEC 18 1987

7. CONCLUSIONS:

A. The accumulation in rotational crops study requirement is partially fulfilled by this submission. The question that still must be answered is what happens to the other end of the ether upon cleavage; 2-[(4-hydroxyphenyl)oxy] propanoic acid, for example. Since only the quinoxaline ring was labeled, one cannot determine the fate of the other end of the molecule upon cleavage of the ether linkage.

Having recently been assigned to review DPX-Y6202 studies, this reviewer has done a thorough evaluation of all previously submitted studies and has come across an inconsistency in the way the radiolabeling has been done. Because the quinoxaline moiety and phenyl moiety are separated upon cleavage of the ether linkage, both moieties must be labeled in all studies employing radiolabeling techniques. Therefore, since the aerobic soil metabolism study was done with only the phenyl group labeled, this study must also be performed with the radiolabel on the quinoxaline ring in order to satisfy the requirements for registration.

B. It does not appear that an effort was made to identify all the residues greater than 0.01 ppm in the Anaerobic Aquatic Soil Metabolism study. The analytical technique used (TLC) was not of sufficient sensitivity to identify metabolites 1, 2, and 3. These unknown metabolites were present at levels >0.01 ppm. Other, more highly sensitive, techniques should have been employed in an attempt to identify these degradates.

3

8. RECOMMENDATIONS:

A. The registrant should submit a duplicate confined accumulation study with a radiolabel on the phenyl ring at the other end of the DPX-Y6202 molecule. The two studies together will then allow EAB to assess the accumulation of DPX-Y6202 and its metabolites on rotational crops. Also, an aerobic soil metabolism study, as discussed above in the conclusions, should be submitted to EAB for review.

The registrant stated that the level of residues found in the rotational crops was insignificant. EAB, however, requests that the Toxicology Branch determine the significance of these residues. If the residues are found to be insignificant, then EAB can concur with the 128 day rotational interval, pending the results of the required phenyl-labeled rotational crop study. However, if the Toxicology Branch determines these residues to be of significance, then EAB cannot concur with the 128 day rotational interval, and a new accumulation study must be performed at a sufficiently longer rotational interval.

B. The anaerobic aquatic soil metabolism study should be repeated at the maximum application rate and all residues occuring in quantities greater than 0.01 ppm should be identified.

9. BACKGROUND:

This Confined Accumulation Study on Rotational Crops was submitted in support of full registration of terrestrial food/ non-food uses.

DPX-Y6202 is a herbicide to be used for the postemergent control of annual and perennial grass weeds in soybeans, cotton, peanuts, sugar beets, flax, rape seed, alfalfa, vegetables, and other broadleaved crops. The 9.5% EC (Assure, 0.8 lb ai/gal) is to be applied at 0.075 - 0.250 lb ai/acre depending on regional rainfall (proposed label dated August, 1985). In arid regions, a second application applied 2-3 weeks following the initial application is recommended; however, the total amount applied should equal the recommended rate.

10. DISCUSSION OF INDIVIDUAL TESTS OR STUDIES:

A. STUDY IDENTIFICATION

Cadwgan, G.E. "Accumulation Study of [Quinoxaline-Phenyl(U)-^{14}C]DPX-Y6202 on Rotational Crops". E.I. du Pont de Nemours and Company, Inc., Wilmington, Delaware. Study completed on 9-25-86, accession number 402423-02.

4

B. Materials and Methods

The test material was radiolabeled [quinoxaline-phenyl(U)-^{14}C]DPX-Y6202, (ethyl-2-[4-(6-chloroquinoxalin-2-yloxy) phenoxy] propanoate, with a specific activity of 19.3 uCi/mg and radiochemical purity of more than 99%. Non-radiolabeled standards included: DPX-Y6202, DPX-Y6202 acid, hydroxylated 6-chloroquinoxalin-2-ol, 4-(6-chloroquinoxalin-2-yloxy)phenol, and 6-chloroquinoxalin-2-ol.

Treatment of Soil (November 14, 1984)---

Six new, clay pots (16'' top diameter, 18'' deep) were filled within 2'' of the top with Sassafras sandy loam soil:

sand	73%	CEC	4.5 meq/100 g
silt	20%	OM	2.3%
clay	7%	pH	6.4

50 ml of solution containing 6.5 mg of radiolabeled compound was pipetted evenly over the surface of the soil in each of 4 pots to achieve an application rate of 8 oz/acre. The soil in each treated pot was sampled to its full depth. The compound was watered into the soil and the soil aged for 128 days, the expected crop rotation interval for this compound.

Planting of Crops (March 22, 1985)---

After 128 days aging, soil samples were taken and the soil was lightly raked. One pot was planted with barley (Custer), one with beets (Detroit Dark), one with cotton (Stoneville 213), and one with peanuts (Valencia). One control pot was planted half with barley and half with beets. The second control pot was planted half with cotton and half with peanuts. The crops were grown to maturity under greenhouse conditions.

Harvest of Beets and Barley (May 29, 1985)---

68 days after planting, the barley and beets matured and were harvested. Crop fractions and soil were sampled as well as the control plants and soil.

Harvest of Cotton and Peanuts (August 28, 1985)---

159 days after planting, the cotton and peanuts matured and were harvested. Crop fractions and soils were sampled as well as the control plants and soils.

To determine total ^{14}C-residues in crop fractions, six or more

samples (100-300 mg each) of freeze-dried crop fractions were combusted. Evolved $^{14}CO_2$ was trapped, mixed with liquid scintillation cocktail and counted by LSC.

A flow chart for extraction of radioactive residue from soil is shown in Figure 1.

To determine total amount of unextractable radioactive soil residues, three 2 g samples of soil were combusted and evolved $^{14}CO_2$ was trapped and counted by LSC.

All soil extract concentrates were analyzed by TLC. Non-radiolabeled standards of DPX-Y6202 and suspected metabolites were streaked on these plates along with the radioactive concentrates.

All crop fractions which contained more than 0.01 ppm radioactive residue were extracted and the extracts analyzed by RP-HPLC. A flow chart for the extraction of radioactive residues from plant material is shown in Figure 2.

All plant extract concentrates were analyzed by reversed phase liquid chromatography.

Extracted plant material also underwent enzyme hydrolysis with cellulase enzyme.

To determine total amount of unextractable radioactive plant residues, six 200-300 mg samples of each extracted plant material were combusted. Evolved $^{14}CO_2$ was trapped, mixed with liquid scintillation cocktail and counted by LSC.

Plant extract concentrates also underwent enzyme hydrolysis with B-glucosidase. Samples were analyzed by RP-liquid chromatography.

C. Reported Results

Distribution of Radioactivity in Soil---

The distribution of radioactivity (calculated as % of recovered radioactivity) between the top and bottom 5 inches of soil in the pots is tabulated in Table 1. In general, more than 90% of the radioactivity was found in the top 5 inches of soil.

Composition of Radioactivity in Soil---

The composition of radioactive residues present in soil samples taken at Day 0 (time of treatment), Day 128 (time of planting), Day 196 (barley and beet harvest) and Day 324 (cotton and peanut harvest is shown in Table 2.

day	ppm
0	0.345
128	0.098
196	0.060
324	0.056

See Table 2 for major metabolites present in the soil and Figure 3 for structures.

Total Radioactive Residues in Mature Crop Fractions---

Total radioactive residues are shown in Table 3 for all harvested crop fractions. Only barley, beet and peanut foliage, peanut shell and peanut had radioactive residues exceeding 0.010 ppm. Their residue levels were 0.016, 0.021, 0.031, 0.040, and 0.013 ppm, respectively. All other crop fractions of the beet and barley, as well as all crop fractions from cotton, had radioactive residues below 0.010 ppm.

Distribution of Radioactivity in Analyzed Crop Fractions---

The distribution of radioactivity is shown in Table 4 for each analyzed crop fraction.

Composition of Radioactivity in Analyzed Crop Fractions---

The composition of radioactivity is shown in Table 5 for barley, beet and peanut foliage, and peanut shell.

Hydrolysis of plant extract concentrates with B-glucosidase did not significantly alter the composition of these extracts. The radiochromatograms of the enzyme-treated concentrates were essentially the same as the untreated concentrates.

Hydrolysis of extracted plant material with cellulase enzyme did not release any significant amounts of radioactivity from the barley, beet or peanut foliage or peanut shell. Cellulase enzyme hydrolysis did release most of the radioactivity remaining in the extracted peanut but, for an unknown reason, the same amount of radioactivity was released into the control peanut sample, presumably by simple dissolution.

D. Study Author's Conclusions

Rotational crops (barley, beets, cotton, and peanuts) which were planted 128 days after treating soil with DPX-Y6202 at 8 oz/acre and grown to maturity, contained insignificant residues of DPX-Y6202 or metabolites of DPX-Y6202. The highest total residue found was

in peanut shell (0.040 ppm), but residue in the edible (or usable) crop fractions (barley grain, beet root, cotton fiber, cotton seed, and peanut) were all $\leq$ 0.013 ppm. These low levels are due to the rapid microbial breakdown of DPX-Y6202 in soil (typical first half-life for DPX-Y6202 is $\leq$ 1 week and for DPX-Y6202 acid is 4-8 weeks), and a low bioaccumulation factor for plants grown in soil treated with DPX-Y6202.

E. Reviewer's Discussion and Interpretation of Study Results

It appears that the author made an excellent attempt to extract and identify all residues in the soil and rotated crops, and the experimental method seems to be scientifically valid. The application rate was verified by a day 0 posttreatment soil analysis and was found to be at the maximum rate as specified on the product label.

However, EAB is concerned about the fate of the rest of the molecule, ie; the right side of the ether, upon cleavage of the ether linkage. Since the phenyl substituent of the molecule was not radiolabled, another confined accumulation study, with the ring labeled, should be submitted.

11. COMPLETION OF ONE-LINER:

Not applicable.

12. CBI APPENDIX:

Not applicable.

Assure exposure assessment review

Page _____ is not included in this copy.

Pages 9 through 20 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product impurities

___ Description of the product manufacturing process

___ Description of product 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

X 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.
