 MKH 3586 Subject file

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

OCT 15 1996

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: **ID#286039:** *Comments on Minutes from July 17, 1996 Conference with Bayer Corporation on MKH 3586.*
Chemical #Unknown; **CBTS** #17539
DP Barcode #D229528; **No MRID #**

FROM: María Isabel Rodríguez, Chemist María I. Rodríguez 10-10-1996
TPT I/CBTS/HED (7509C)

THROUGH: Elizabeth Haeberer, Acting Chief Elizabeth T. Haeberer
CBTS/HED (7509C)

TO: Deborah L. McCall, Acting Section Head
RS/RCAB/HED (7509C)

The registrant, Bayer Corporation, in letter dated August 13, 1996 from Dr. John S. Thornton, is requesting that CBTS review, for comments and concurrence, the minutes of the July 17, 1996 meeting on the experimental triazolone herbicide coded MKH 3586. Personnel present at the July 17, 1996 meeting included Dr. Richard A. Loranger and María I. Rodríguez from CBTS, Eugene Wilson from RD, and Dr. Michael E. Krolski, Dr. John Murphy, and Mr. Brian Dehart from Bayer Corporation. The purpose of the meeting was to discuss Residue Chemistry aspects of MKH 3586.

CBTS has examined the subject minutes and concludes that for the most part they accurately reflect the discussions held at the meeting. Data/information provided at the meeting and in this submission have been incorporated into our files.

The metabolism of MKH 3586 in corn, soil, confined rotational crops, ruminants and poultry was discussed. The possibility of waiving poultry and cattle feeding studies was discussed. Analytical methodology for plants and animals based on derivatization with subsequent chromatography/mass spectroscopy analysis was also discussed. Chromatograms and structures of the chemical and its metabolites were presented. The chemical is being developed for preemergence use in/on corn.

However, the possibility of postemergence use in/on corn and subsequently wheat was also discussed.

As indicated by the registrant, the proposed crop analytical method for MKH 3586 would employ either GC/MS or LC/MS. At the time of the meeting, Dr. Loranger was uncertain as to the acceptability of LC/MS methods for enforcement. At this time, the petitioner is requesting a decision of acceptability (by September 30, 1997).

The status of LC/MS methods at the present time has been discussed with the EPA Laboratory in Beltsville, MD (personal communication between Harvey Hundley and Dr. Loranger). Mr. Hundley stated that the laboratory has tested several LC/MS methods using conventional HPLC with electrospray interface. Such procedures should be acceptable for enforcement if they meet the basic requirements as outlined in the Residue Chemistry Guidelines (Refer to OPPTS Guideline 860.1340). At this time LC/MS/MS procedures would probably be considered too exotic for enforcement.

The petitioner is reminded that the method must be supplemented by a confirmatory method which is significantly different from the primary enforcement method. Alternatively, the GC/MS or LC/MS method can also serve as the confirmatory method if a sufficient number of unique ions is monitored.

The proposed common moiety procedure will only account for 50% of the total residue in milk. This is probably acceptable as CBTS could adjust the measured residues by a factor of two for dietary risk assessment.

CBTS has one clarification on the last paragraph under livestock metabolism in the minutes. The waiver of the cattle feeding study is not dependent on "field residues" being in the low ppb range. Residues in edible tissues and milk based on extrapolation from the goat metabolism study would need to be about 1 ppb or less from the anticipated dietary burden (1X) for consideration of a feeding study waiver. Based on available ^{14}C data, this appears unlikely for liver and kidney.

Once again, Bayer representatives are advised to submit the available data for formal consideration in CBTS.

Attachment: Meeting Minutes
cc (with attachment): MIRodríguez and MKH 3586 Subject File.
cc (without attachment): JMiller/EWilson (7505C), RALoranger (7509C), Reading File, and Circulation.
RDI: RALoranger (10-8-96); EHaeberer (10-10-96)
MIRodríguez: Draft (9-20-1996), Edited (10-10-1996).
Mail Code 7509C; Tel (703)-305-6710; CM #2, Rm 804-T.

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MKH 3586 Meeting Minutes;

Meeting on The Residue Chemistry of MKH 3586

Those in Attendance

EPA	Bayer
Dr. Eugene Wilson	Dr. Mike Krolski
Dr. Richard Loranger	Dr. John Murphy
Dr. Maria Rodriguez	Mr. Brian Dehart

MKH 3586 is a new corn broadleaf herbicide being developed by the Bayer Corporation. A meeting was held on July 17, 1996 to discuss with EPA some residue chemistry questions on MKH 3586. A presentation was made by Dr. Krolski (overhead transparencies attached) which concisely summarized the issues on which Bayer was seeking the Agency's guidance.

Corn Metabolism

After an overview of MKH 3586 which included comments about its proposed use, the soil metabolism of MKH 3586 was described. Dr. Krolski then presented the data available to date from the corn metabolism study. The test compound was applied preemergence at 1.6X (0.72 lbs) the proposed label rate. Samples of forage, fodder and kernels were taken. Residue levels in these RACs ranged from 0.05 ppm (kernel) to 0.99 ppm (forage). A comparison of the plant and soil metabolites indicated that, although the few soil metabolites were also seen in the plant, most of the MKH 3586 metabolites were produced in corn. With this in mind Dr. Krolski proposed that no additional crop metabolism data would be needed to support a postemergent, as well as preemergent registration on corn. Dr. Krolski reasoned that little metabolism occurs in the soil but much occurs in the crop so applying MKH 3586 post emergence to plants will not make a difference in the outcome of the study. Dr. Loranger agreed that this was reasonable.

Confined Rotational Crops

The results of the confined rotational crop study were presented next. In this study, which was initiated on October 4, 1995, problems were encountered with the thirty day rotational crop. The crops planted were kale, turnips and wheat. Severe phytotoxicity was noted on both kale and turnips. After 47 days, all three crops were planted again and less phytotoxicity was noted. The second set of rotational crops was planted on February 19, 1996. Because residue levels of MKH 3586 were significant in the crops from the 2nd rotation, a field rotational crop study has been scheduled. This study will begin in the spring of 1997. Based on this information Bayer asked the Agency if another confined rotational crop study would be required since the 30 day rotational crop was lost due to herbicide injury. Dr. Loranger said it appeared that an additional

study with a thirty day plant back interval was not possible because of the efficacious amounts of MKH 3586 residues present in the soil. Similar data will be provided from the field rotational crop study. Dr. Loranger said the field data would serve as a substitute for the missing confined study data.

Dr. Krolski then presented the following facts which led to the question below.

1.) Wheat metabolism data are available from the confined rotational crop study.

2.) The metabolism of MKH 3586 in corn and wheat is similar.

3.) Wheat and corn are in the same crop group (cereal grains) and a corn metabolism study is underway.

4.) Soil metabolism of MKH 3586 is negligible and the preemergent metabolism studies reflect the metabolism of MKH 3586 regardless of the application method.

Therefore, would additional metabolism data be required to support a postemergent registration on wheat? Dr. Loranger's response was that based on the data presented, additional metabolism data on wheat would not be needed. Dr. Loranger cautioned Bayer that this was his initial decision based on the information he has to date about MKH 3586.

Crop Residue Analytical Method

The next topic discussed was the development of a crop analytical method for MKH 3586. The method Bayer proposed would convert all the MKH 3586 residues to the iPr-2-OH DA, a crop metabolite. The compounds that would be converted are the parent MKH 3586, the DA MKH 3586 metabolite and MKH 3586 glucoside conjugates. Dr Loranger said that the decision on the acceptability of the total residue method would most likely be deferred to the Agency's Toxicology Branch. If they had concerns about the toxicity of either MKH 3586 or the DA MKH 3586 then the method would be insufficient because it would not indicate at what levels these compounds were occurring in RACs. However, if there were no toxicological concerns, a total method as proposed would be acceptable.

The method would employ either GC/MS or LC/MS. Since the method would ultimately be used by USDA and or FDA for monitoring, Dr. Loranger was uncertain of the acceptability of a method which used LC/MS. He felt that a GC/MS method would be acceptable. **Bayer requests that the Agency determine the acceptability of LC/MS methods by September 30, 1997.**

Livestock Metabolism

Two livestock metabolism studies were discussed; poultry and ruminant (goat). In the poultry metabolism study ten chickens were dosed at 0.82 mg/kg body weight (12.5 ppm in feed) with

MKH 3586. This dose level is approximately 320 times the anticipated level in poultry feed when MKH 3586 is used at label rates. Analyses for MKH 3586 residues was performed on liver, muscle, fat and eggs (days 1, 2, and 3). To date, the parent MKH 3586 and six metabolites have been identified. When the residue levels were adjusted to approximate 1X levels in these matrices they were below that which could be detected with a reasonable analytical method. Bayer proposed to the Agency that a poultry feeding study waiver would be reasonable based on the low levels of MKH 3586 residues detected in tissue and eggs. Dr. Loranger responded that issuing a poultry feeding study waiver would probably be dependent on the results of field residue trials. Field residue trials would provide a realistic estimate of the dietary burden. If the poultry dietary burden from MKH 3586 residues was low enough, a waiver would be issued.

The ruminant (goat) metabolism study was performed at a dose of 1.90 mg/kg body weight (32 ppm in feed). This level corresponds to 30 times the expected level in livestock feed when MKH 3586 is used on the target crop at label rates. Muscle, fat, liver, kidney, and milk samples were collected and analyzed. When corrected for the 30X dose, residues of MKH 3586 ranged from 0.024 to 0.163 ppm in tissues and from 0.006 to 0.007 ppm in milk. The major compounds identified in goat tissues and milk were MKH 3586, DA MKH 3586, and iPr-2-OH DA MKH 3586. These are also the major metabolites seen in the corn metabolism study. Six other minor metabolites have also been identified in goat tissues and milk.

Bayer asked the Agency if they would consider waiving the requirement for a cattle feeding study if calculations indicate that tissue and milk residues arising from a 1X dietary burden, based on data from crop field trials, would be <0.01 ppm? Dr Loranger responded that this is not very likely unless field residues of MKH 3586 are in the low ppb range. A waiver of this data requirement is not likely primarily due to the relatively high residues in liver.

Animal Tissue Residue Method

Bayer's approach to developing the animal tissue residue method is similar to that presented for crop analyses. The proposed animal tissue residue method for MKH 3586 will convert the parent compound and DA MKH 3586 to iPr-2-OH DA MKH 3586. Quantitation will utilize GC/MS or LC/MS. While the proposed method would cover the majority of residues in tissues, only 50% of the residues in milk would be detected. However because of the low total residues anticipated in milk (0.01 ppm) Dr. Loranger indicated that milk should not pose a problem to the acceptability of a total residue method.

General Metabolism-Rat

The rat metabolism study is being performed as per the Agency's proposed Tier 1 Guidelines. As mentioned in Bayer's letter to the Agency on July 9, 1996 it was recently suggested by the Agency that Bayer perform a rat metabolism study under the proposed Tier 1 Guidelines for another Bayer compound. The protocol for the General Metabolism-Rat study is under review in the Agency's Toxicology Branch (Dr. Mike Ioannou).

In the rat metabolism study for MKH 3586, Fischer rats were administered a single oral dose of the test compound at 5 mg/kg body weight. Samples of urine, feces, respired gases, blood, fat, kidney, liver, spleen, and carcass were collected and analyzed. The total amount of radioactivity recovered ranged from 91 to 97.4 percent. All of the metabolites seen in the plant were also identified in samples from rats.