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

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AUG 22 1996

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: MKH 3586: Review of a protocol for a Metabolism study.

EPA Identification Numbers:

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P.C. Code: N/A
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Submission: S508888

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Registration Division (7505C)

and

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FROM: Timothy F. McMahon, Ph.D. 8/20/96
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THRU: Jess C. Rowland, M.S. 8/21/96
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and

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Registrant: Bayer Corporation, Agricultural Division

Action Requested: Review and comment on a metabolism protocol submitted by the registrant for MKH 3586.

Recommendations/Conclusions: Toxicology Branch II has reviewed the metabolism protocol for MKH 3586 submitted by the registrant. This protocol has also been reviewed for conformance to the revised metabolism guideline (OPPTS 870.7485). Toxicology Branch II has determined that the protocol is acceptable as a Tier I study under the revised metabolism guideline, with the modifications as suggested below.

Data Summary:

The registrant (Bayer Corporation) submitted a metabolism protocol for MKH 3586 which was written using the revised metabolism guideline (OPPTS 870.7485). The registrant desired that Toxicology Branch II review the protocol for acceptability under this revised guideline. A short summary of the protocol is presented in the following paragraph.

The absorption, distribution, metabolism, and excretion of MKH 3586 will be examined in male Fischer rats. Four rats will be individually housed for an acclimation period of 3 days prior to dosing. After this period, each rat will be dosed orally with 5 mg/kg body weight of an aqueous solution of [Triazolinone-3-^{14}C] MKH 3586. This dose is specified as comprising 5% of the NOEL. After dosing, each rat will be housed individually in a plastic metabolism cage for collection of urine, feces, and expired volatiles. Food and water will be provided *ad libitum* throughout the study. Excreta will be collected for 7 days or until 90% of the applied dose is recovered, whichever occurs first. Volatiles collection can be discontinued if <1% of the dose is recovered over a 24 hour period. Collection times for urine may include 6, 12 (or 4, 8), 24, 48, 72, 96, 120, 144, and 168 hours post-dose. Collection times for feces and expired air may include 24, 48, 72, 96, 120, 144, and 168 hours post-dose. At sacrifice, the liver, composite fat, kidney, spleen, whole blood (plasma), and residual carcass will be collected. Collected samples will be assayed for radioactivity. For analysis, composite urine samples comprising 50% of the sample from each rat will be prepared. The composite sample will be filtered and the filtrate analyzed by HPLC. Feces samples containing >5% of the applied dose will be blended in methanol/water (1:1) The resulting slurry will be filtered and the filtrate analyzed by HPLC.

Preliminary results of the *in vivo* portion of the study indicated that, on average, approximately 65% of the administered radioactivity was excreted in urine by 72 hours post-dose. Fecal excretion accounted for approximately 28% by 72 hours post-dose. Total excretion (urine, feces, volatile traps, cage washes) accounted for an average recovery of 94%. Tissue levels accounted for less than 0.100 ppm for any given tissue.

Conclusions

The protocol for the metabolism study as presented by the registrant is considered acceptable, but the following modifications should be incorporated into this protocol if possible:

1) For tissue collection, the gastrointestinal tract should also be collected at study termination as specified in the revised guideline. If this was not done, then it should be possible to remove this from the residual carcass, if the frozen carcasses are still available.

2) It is stated in the protocol that an "aqueous" solution of the test chemical will be administered. It is presumed that this implies that water was used as the dosing vehicle. If not, then this should be specified in the final report.

3) In the revised metabolism protocol, urine collection times for the first 24 hours are specified as 6, 12, and 24 hours post-dose. The registrant is free to include additional collection intervals; however, these may not be necessary.

4) The revised OPPTS metabolism protocol does not contain a provision as stated on page 11 of the registrant's submitted document that "As a rule of thumb, a minimum of 70% of the administered dose should be identified." The revised guideline recommends that metabolites comprising 5% or greater of the administered dose be identified, and that 90% or greater of the administered dose be recovered.

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