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

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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

Subject: HWG 1608 (Tebuconazole) technical. Upgrade of metabolism study.
Tox Chem No. 463P
HED Project No. 2-1282
MRID Nos. 421762-01, 421762-02
DP Barcode: D174266
Submission No.: S411275
Action: 115

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and

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Health Effects Division (H7509C)

ACTION: Review of the following study on the chemical HWG 1608 (Tebuconazole) Technical submitted by Miles Inc.:

Addendum I. FOLICUR®: Metabolism Part of the General Metabolism Study in the Rat. Additional Information requested by the EPA. [Report 97438-1; MRID 421762-02].

CONCLUSIONS:

A rat metabolism study of tebuconazole by Mobay was initially reviewed in a DER dated 12/19/90 (Microfiche 008241). The metabolism study was submitted in the following two volumes:

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1. Study of Biokinetic Behavior in the Rat (Mobay Report No. 97439, MRID 409959-11)
2. FOLICUR®: Metabolism Part of the General Metabolism Study in the Rat. (Mobay Report No. 97439, MRID 409959-12).

As stated in the DER, the metabolism study was classified as core supplementary, and was considered upgradeable if the following additional information was provided and it was found to be acceptable:

1. A rationale for dose selection is required. The change in metabolite ratios observed at the high-dose suggests a possible trend towards changes in detoxication patterns at the high-dose.

2. Additional work of metabolite identification at a dose higher than 20 mg/kg would be required to elucidate the apparent trend in metabolite patterns observed at the current high dose.

3. A discussion of the origin of the isopropyl derivative (HWG 2251) is required. HWG 2251 is not depicted in the author's scheme for the biotransformation pathways of HWG 1608 and its origin is not discussed in the text.

4. A rationale as to why GLP requirements of 40 CFR Part 160 do not apply to this study should be submitted.

5. A statement indicating whether the rats were acclimated prior to dosing should be included.

The Registrant has now responded with additional information (MRID 421782-02), which is presented below:

Item 1.

A rationale for dose selection is required. The change in metabolite ratios observed at the high-dose suggests a possible trend towards changes in detoxication patterns at the high-dose.

Registrant's Response:

The low dose (2 mg/kg) chosen lies below the NOEL of the chronic or subchronic rat study (5 mg/kg for males, 20 mg/kg for females). The high dose (20 mg/kg) was selected at or above the NOEL. The high dose showed some but no severe pharmacokinetic signs (delay in time to achieve peak plasma level and lower plasma level per unit dose, suggesting saturation of absorption).

Agency's Response:

The Registrant meets the minimum guideline requirements for the high dose.

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Item 2.

Additional work of metabolite identification at a dose higher than 20 mg/kg would be required to elucidate the apparent trend in metabolite patterns observed at the current high dose.

Registrant's Response:

The dosing in the metabolism study is in compliance with the requirements of the guidelines, if the rationale for the high dose group is accepted. It is Mobay's contention that additional work of metabolite identification at a higher dose than 20 mg/kg would be redundant and therefore request that this work not be required.

Agency's Response:

The Registrant meets the minimum guideline requirement of at least 2 dose levels.

Item 3.

A discussion of the origin of the isopropyl derivative (HWG 2251) is required. HWG 2251 is not depicted in the author's scheme for the biotransformation pathways of HWG 1608 and its origin is not discussed in the text.

Registrant's Response:

Metabolite HWG 2551 was identified in extracts of feces by cochromatography with the authentic, independently synthesized reference compound. The origin of metabolite HWG 2251 is explainable as decarboxylation (maybe by the gut flora) of the anion of HWG 2443 ("acid"). Metabolite HWG 2251 is not an impurity. Metabolite HWG 2251 has now been included in the Revised Figure labeled "The biotransformation pathway of HWG 1608 in rat", Scheme 2, p. 84 of MRID MRID 421762-02.

Agency's Response:

The revised figure with the biotransformation pathway of HWG 1608 [tebuconazole] is attached to this memorandum. Metabolite HWG 2251 has been highlighted by the reviewer by means of an asterisk.

Item 4.

A rationale as to why GLP requirements of 40 CFR Part 160 do not apply to this study should be submitted.

Registrant's Response:

"This was an error on Mobay's part when we submitted the report which we

had received from our parent company, BAYER. The study was conducted under GLP standards; the appropriate certificate had already been included as paga 116 in the report reviewed. The wrong Good Laboratory Practice Certification statement was included as page 3 of the report. The statement will be corrected to indicate that the GLP requirements do apply to the rat study."

Revised text: page 3, paragraph 1, line 1.

"Good laboratory practice requirements of 40 CFR part 160 do apply to the study described in this document."

Agency's Response:

The above remarks by the Registrant address in an acceptable fashion the issue of GLP compliance for the portion of the study contained in document No. 97438.

However, without an explicit statement by the Registrant it is not possible to determine if the above remarks also pertain to the portion of the study contained in document No. 97439 (MRID 409959-12; [Phenyl-U-^{14}C] HWG 1608: Study of Biokinetic Behavior in the Rat). Document No. 97439 contains a statement indicating that "Good laboratory practice requirements of 40 CFR part 160 do not apply to the study described in this document." and there is no signed and dated statement of GLP compliance. Without a clarification by the Registrant the subject metabolism study cannot be upgraded from supplementary to minimum.

Item 5.

A statement indicating whether the rats were acclimated prior to dosing should be included.

Registrant's P sponse:

The rats were acclimated for 7 days prior to the start of the individual tests; this has been documented with the raw data.

Agency's Response:

The requirement specified under item 5 has been met by the Registrant.

Agency's Conclusions:

- The additional information submitted by the Registrant has adequate responses to above items 1,2,3 and 5.
- The response to item 4 (CLP compliance) appears to be incomplete. Although the matter of GLP compliance has been clarified for document

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No. 97438 (metabolite identification), the matter of GLP compliance is not clear for document No. 97439 (biokinetics/pharmacokinetics). As noted above, document No. 97439 contains a statement indicating that "Good laboratory practice requirements of 40 CFR part 160 do not apply to the study described in this document." and there is no signed and dated statement of GLP compliance with the report.

Thus, the subject metabolism study may be upgraded from supplementary to minimum if the following information is submitted and is deemed acceptable:

a. A clarification as to why it is stated (in Report 97439) that GLP requirements do not apply to the portion of the study in Mobay Report No. 97439 (Pharmacokinetics) [MRID 409959-12].
b. A signed and dated GLP compliance statement for the portion of the study in Mobay Report No. 97439 (MRID 409959-12).

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Attachment 1

Revised Biotransformation Pathway of HWG 1608 in the Rat
(From p. 84 of MRID 421762-01)

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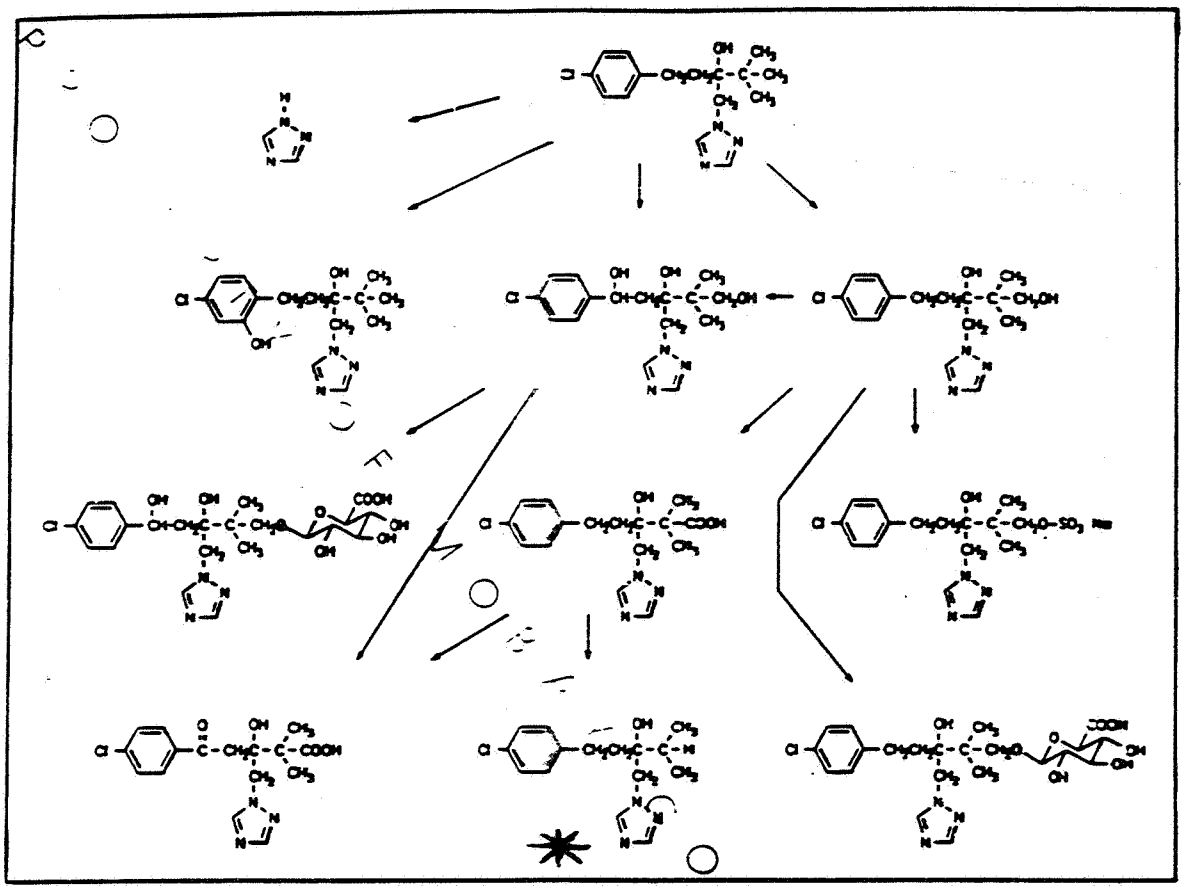
Scheme 2: Biotransformation pathway of HWG 1608 in the rat.



Compound HWG 2551 is indicated by an asterisk