1-31-92

MEMORANDUM

SUBJECT: ID # 111901-43813. Imazalil. Response to Phase IV Review. MRID # 420120-05 through -09. CBRS # 8933. DP Barcode: D171401.

FROM: Leung Cheng, Chemist
Special Review Section II
Chemistry Branch II - Reregistration Support
Health Effects Division (H7509C)

THROUGH: Francis B. Suhre, Section Head
Chemistry Branch II - Reregistration Support
Health Effects Division (H7509C)

TO: Kathryn Davis, Review Manager
Generic Chemical Support Branch
Special Review/Reregistration Division (H7508C)

Janssen Pharmaceutical N. V. has submitted several metabolism study summaries and full reports in support of reregistration of imazalil. Product chemistry reports to fulfill data requirement §63-20 for end use products Imazalil 500 EC and 800 EC were also submitted. However, review of end use products data is not under the purview of CBRS. Imazalil is the common name for 1-[2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl]-1H-imidazole.

The following studies were submitted:

a) The Metabolic Fate of Imazalil on Banana Plants Report No. R23979/21, Rec # 379: summary MRID # 420120-07, full report MRID # 420120-09.

b) The Metabolic Fate of Imazalil on Oranges Report No. R23979/18, Rec # 393: summary MRID # 420120-06, full report MRID # 420120-08.

c) Excretion, Metabolism and Tissue Depletion of ^{14}C-Enilconazole (R23979) After Repeated Oral Dosing in Broiler Chickens Report No. R23979/47, (V5388): summary MRID # 420120-05 [only].

Imazalil is on List B for reregistration and the Phase IV review was completed 10/19/90 (S. Funk). The review did not discuss any Phase III plant metabolism summary data and instead concluded that the registrant must provide data to prove the stability of the tritium labeled imazalil used in the various plant metabolism studies. The

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review also concluded that the submitted goat metabolism study was inadequate and cited as data gap that the registrant must provide a goat metabolism study and a poultry metabolism study. CBRS's position on the use of tritium labeled compound and the requirement of goat and poultry metabolism studies was reiterated in a subsequent evaluation of Janssen's response to the Phase IV DCI (S. Funk, 12/3/91).

The registrant has submitted a stability study (as Appendix 1, Serial number R 23 979/27) "Stability of the tritium label of imazalil-^{3}H in acidic, alkaline, neutral and biological medium" to support the validity of their metabolism studies in which tritium was used as the radioactive marker.

Tritium labeled T824 (R 14 821, 1-(2,4-dichlorophenyl)-2-(1H-imidazole-1-yl)-1-ethanol) was made by tritiated sodium borohydride reduction on the ketone precursor. This was followed by alkylation with allyl chloride and subsequent sulfuric acid addition to yield imazalil sulfate. Radio-HPLC analysis showed a radiochemical purity of 99.5%.

Aliquots of imazalil sulfate were sealed in 5-mL ampoules in the presence of various media (see Table below) at 40 °C (one experiment conducted at 100 °C) for 11 days. At the end of this period, the ampoules were cooled to room temperature and opened. Six 100-μL aliquots were removed into scintillation vials; 3 were used for total activity counting and 3 were lyophilized before they were counted for non-volatile activity. The profile of these mixtures were also analyzed by HPLC on a RP8 column coupled to a UV detector set at 230 nm. Activity counting was averaged from 3 determinations. Results are tabulated below.

Medium (40 °C unless otherwise stated)	Total Radioactivity	Non-Volatile Radioactivity	Percent Non-Volatile Radioactivity
1 N HCl (100 °)	186,577	192,496	103.17
1 N HCl (40 °)	178,577	177,469	99.38
pH 3.0 citrate-phosphate buffer	188,419	185,520	98.32
pH 6.0 citrate-phosphate buffer	183,562	180,332	98.24
pH 9.0 borax-HCl	186,326	185,772	99.70
1 N NaOH	169,147	178,014	105.24
pH 7.2 (?) Eagle's MEM*	168,714	167,590	99.33
pH 6.0 Eagle's MEM	186,552	184,117	98.69
pH 8.0 Eagle's MEM	189,512	190,435	100.49
pH 7.4 human plasma	176,330	177,172	100.48
pH 6.0 human plasma	185,155	184,314	100.46
pH 8.0 human plasma	191,169	191,514	100.18
Distilled water	177,911	184,342	103.61
* Eagle's MEM - a medium that contains 12 amino acids, choline, nicotinic acid, pantothenic acid, pyridoxal, riboflavine, thiamine, inositol, folic acid, glucose, and several inorganic salts			

HPLC chromatograms were also provided and according to p 57 of the

submission, these represent radio-HPLC chromatograms. However, these chromatograms are not totally legible and legible ones need to be submitted.

From the above tabulated results, it appears that very good accounting of total activity was obtained. However, before we can conclude on the stability of tritiated imazalil, CBRS needs additional data or information such as:

1) activity counting just before incubation; 2) HPLC analysis just before incubation; 3) demonstration that tritiated water was volatilized under the lyophilization conditions; 4) legible HPLC chromatograms along with activity counts for all the individual components/peaks and the corresponding column recoveries

We will postpone the review of the banana and oranges metabolism studies [a) and b)] until the stability of tritiated imazalil is concluded.

c) Poultry metabolism (summary MRID # 420120-05)

A reformat summary or full report for a poultry metabolism study was not submitted at the Phase III stage. In the current package, a summary report titled "Excretion, Metabolism and Tissue Depletion of ^{14}C-Enilconazole (R23979) After Repeated Oral Dosing in Broiler Chickens", Report No. R23979/47, (V5388) was submitted. Briefly, carbon-14 labeled imazalil in the benzylic carbon position was fed to broilers (weight not given) in the form of gelatin capsules for 10 doses (2 doses a day) at 2.5 mg imazalil per dose. Two male and 2 female birds were sacrificed each at 6, 24, 72, 144 and 240 hours after the last dose and for activity counting. At the 24 hour post-dosing interval, the following activity levels were obtained: 0.03 ppm in plasma, 5.57 ppm in liver, 0.99 ppm in kidney, $\leq$0.1 ppm in muscle (both femoral and pectoral), and $\leq$0.1 ppm in fat. Extraction of radioactivity in tissues other than liver was not attempted. Liver samples (at 6 hours) were homogenized and purified on Amberlite XAD-2. The metabolic profile was analyzed by HPLC to consist of at least 10 fractions and at least 5 fractions contained 5-16 ppm parent equivalents.

CBRS can not accept the poultry metabolism study since, among other data gaps (feed consumption, animal weight, etc), activity in the kidney, muscle, fat, and eggs must also be characterized and/or identified. For guidance on when and how to conduct livestock metabolism studies, Janssen is advised to consult the Phase III Guidance Document, especially the July 25, 1989 memo.

CONCLUSIONS AND RECOMMENDATION

1. The stability study on the tritium-labeled imazalil does not contain sufficient information to allow CBRS to conclude that no exchange of tritium with water took place. Additional data such as, activity counting before incubation, HPLC analysis

before incubation, the extent of removal of tritiated water under the lyophilization conditions used, and chromatograms along with activity counts for all the individual components/peaks and the corresponding column recoveries, are necessary.

2. CBRS will postpone the review of the plant metabolism studies (oranges and banana) in which tritiated imazalil (labeled at the benzylic position) was used until the stability of ^{3}H-imazalil has been demonstrated.

3. The summary report for the poultry metabolism study does not reflect an adequate study since residues in poultry tissues including eggs were not characterized or identified. Janssen is advised to consult the Phase III Guidance Document for conducting livestock metabolism studies.

cc:Circ, RF, List B File, Cheng, PIB/FOD
RDI:FSuhre:1/31/92:EZager:2/3/92
H7509C:CBII-RS:LCheng:CM#2:RM810:1/14/92:1/30/92:02: