5-3-94

MEMORANDUM

SUBJECT: Imazalil. Case No. 2325. Phase IV Review of Orange and Banana Metabolism Studies. MRID No. 42012008 & 42012009. DP Barcode:D198235. CBRS No. 13072.

FROM: Leung Cheng, Chemist
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THROUGH: Andrew R. Rathman, Section Head
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TO: Kathleen Depukat, CRM No. 52
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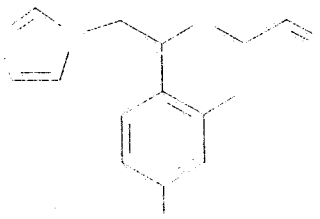
The Phase IV review for imazalil (S. Funk, 10/18/90) states that all plant metabolism studies, except the apple metabolism study, used tritium labeled at the C-2 ethyl position of imazalil. The reviewer concluded that the registrant must provide detailed data on the stability of the tritium-labeled imazalil for the banana, orange, and barley metabolism studies. Imazalil is 1-[2-(2,4-dichlorophenyl)-2-(2-propenyloxy)ethyl]-1H-imidazole.



IMAZALIL.013

Chemical Number: 111901
Chemical Name: Imazalil

Studies relating to the stability of tritium labeled imazalil were reviewed in CBRS No. 10342 (L. Cheng, 9/25/92). It was concluded that the data submitted were equivocal and recommended to proceed with the review of the tritium labeled plant metabolism studies. These plant studies must account for a substantial portion of the radioactivity recovered and demonstrate that all significant activity is unrelated to loss of tritium from imazalil. Any additional plant metabolism studies must use radioactive imazalil labeled with carbon-14 at a stable position.

CBRS recently completed a review of a wheat metabolism study in which carbon-14 labeled imazalil was used. Since both wheat and barley share the same use pattern and have identical established tolerances, the barley study may be substituted with the wheat study as a data requirement for reregistration. The wheat metabolism study was concluded to be adequate (CBRS No. 11295, L. Cheng, 1/10/94).

CONCLUSIONS AND RECOMMENDATION

1. For the citrus metabolism study, the registrant must provide the area counts for the peaks corresponding to parent, R14821, and unknown MX in those HPLC chromatograms submitted, and calculations supporting the percents TRR reported for imazalil, the despropenyl compound and MX in the orange peel. The citrus metabolism study following postharvest treatment of imazalil may be upgraded upon submission of the requested information.

2. The submitted banana metabolism study is not adequate. The metabolism study was not properly conducted in that developing bananas must be exposed to imazalil during treatment. In addition, soil must not be covered to prevent any uptake by the root system. Chemical analyses should be emphasized on the peel and the pulp. A new banana metabolism study conducted according to the use pattern must be submitted.

Nature of Residues - Oranges (MRID No. 42012008)

The metabolic fate of imazalil on oranges, report number R 23979/18, was described in a Phase 3 submission with an assigned MRID No. 92072037. Janssen carried out the study at their research facilities at Beerse, Belgium.

Forty Spanish navel oranges were dipped for one minute in an aqueous solution of tritium labeled imazalil (at the 2-ethyl carbon or benzylic carbon) sulfate, equivalent to 500 ppm of imazalil. By radioscanning and high-performance liquid chromatography,

the radiochemical purity was determined to be greater than 97%. Its final specific activity after dilution with unlabeled imazalil sulfate was 14.6 μCi/mg. Following treatment, the oranges were grouped into 5 lots. One lot was processed 2 hours after dipping and drying, while the rest was processed after 1, 3, 6 and 12 weeks of storage in a dark room maintained at temperature of 12 C and relative humidity of about 90%. The oranges were peeled by hand with a knife. Care was taken to protect the fruit (pulp) from cross-contamination during peeling by changing plastic gloves between peeling and handling of the pulp. The peel and pulp were separately homogenized in water. The samples were determined for radioactivity and the homogenates were frozen and stored frozen for a period of up to six months before analyses. One lot of five oranges served as control.

The mean levels of the total radioactivity residues (TRR) by combustion ranged from 1.90 to 2.60 ppm in whole oranges, from 5.8 to 7.2 ppm in the peel (presumably on the peel weight basis), and from 0.04 to 0.11 ppm in the pulp. Radioactivity was analyzed by HPLC (uv detector set at 230 mμ) and GC (detector ?). The characterization or identification of metabolites in citrus peel is presented in Table 1. R14821 is despropenyl imazalil.

Table 1. Distribution and fractionation of TRR by HPLC in peel from oranges treated with imazalil at 1x rate (week 12).

Fraction	% TRR	ppm	Characterization/identification
Whole orange (2.08 ppm)			
Orange peel (ppm on a whole orange weight basis not given)			
Orange pulp (0.06 ppm, 2% TRR)			
Orange peel			
Methanol	91.5		
Alkaline extract	76.3		parent as the major component with R14821 as the minor peak (percent for each component was not provided)
Aqueous layer	15.3		four separate extractions done at pH 11 (2.4%), 9 (3.9%), 5 (0.1%), & 2 (0.9%). Chromatograms showed parent being the major component with R14821 and unknown MX being the minor components (percent for each was not provided).
Water fraction B	8		Not analyzed
Residue	8.5		Further fractionated with methanol, warm DMSO, or alkaline extraction. Chemical characterization not provided.

The registrant concluded that after 12 weeks of storage imazalil accounted for the major part (80-90%) of the TRR in the peel of treated oranges. Metabolite R14821

increased with time upon storage and accounted for up to about 10% of the TRR. In the pulp, the registrant stated that parent accounted for 40-50%, and R14821 accounted for 10-20%, of the TRR.

The registrant ascribed the high recovery of radioactivity at time 0 to contamination and reported that imazalil was slowly metabolized to the alcohol R14821. The report summarized levels of imazalil and its despropenyl metabolite (determined by gc) in the peel and pulp at various intervals in several tables. The accountability in the peel ranged from 61% (week 12) to 80%. The registrant explained this difference (week 12 interval) was due to that gc only measured "unbound" imazalil. (GC analyses were not conducted on those fractions analyzed by HPLC as described in Table 1.) The registrant also stated that no tritium-hydrogen exchange took place but did not provide analytical data from this citrus study showing negative finding of tritiated water.

CBRS is not concerned with further characterization the radioactivity present in the pulp since it was less than 10% of the TRR. However, the registrant must provide the area counts for the peaks corresponding to parent, R14821, and unknown MX in those HPLC chromatograms submitted, and calculations supporting the percents TRR reported for imazalil, the despropenyl compound and MX in the orange peel. The citrus metabolism study following postharvest treatment of imazalil may be upgraded upon submission of the requested information.

Nature of Residues - Bananas (MRID No. 42012009)

The metabolic fate of imazalil on banana plants, report no. R 23979/21, was described in a Phase 3 submission with an assigned MRID No. 92072036. Janssen conducted the study at their research facilities at Beerse, Belgium.

Two batches of tritium labeled at the 2-ethyl carbon of imazalil were used with specific activity of 3.91 and 4.24 μCi/mg and purity of >97.2%. Imazalil was applied as the sulfate salt.

Banana plants were grown from rhizomes in individual plastic containers in a greenhouse. Greenhouse temperature ranged from 26 to 30 C and relative humidity ranged from 50 to 70%. Day length was maintained up to 14 hours per day by artificial lighting.

Banana plants were foliarly sprayed from above. The soil in the plastic containers was covered with a plastic sheet and the inflorescence/bunch of one plant was sleeved with a plastic bag. Plants received between one to nine treatments at 50 mg imazalil per treatment made at 14-day intervals. The plant with inflorescence was sprayed five times at 200 mg imazalil each time.

Samples were collected by hand. Plants were cut into various parts of leaves including new leaves, pseudostem, rhizome and roots, and the parts were weighed.

Bananas were sampled from the upper and lowest hand of the bunch.

The report stated that translocation to the rhizome, roots, and new leaves was minimal (<3% TRR). Radioactivity in banana homogenates (0.026 ppm and 0.030 ppm from upper and lower hand, respectively) from a sleeved bunch was considered not significantly above background (background levels not provided). Residues in the bananas were not characterized or identified. The report concluded that in leaves the parent compound accounted for 15-20%, R14821 accounted for 15-25%, of the TRR, with the remainder attributed to a large number of transformation products. However, the registrant did not provide data supporting their conclusion.

According to the submission, pre- and postharvest uses of imazalil on bananas are permitted. An earlier petition review (PP#8E2100, M. J. Nelson, 3/12/79) indicated that this fungicide may be used on bananas throughout the growth cycle and as late as 2 days before harvest. CBRS thus concludes that the metabolism study was not properly conducted in that developing bananas must be exposed to imazalil during treatment. In addition, soil must not be covered to prevent any uptake by the root system. Chemical analyses should be emphasized on the peel and the pulp. The submitted banana metabolism study is not adequate. A new banana metabolism study conducted according to the use pattern must be submitted.

cc:Circ, SF, RF, List B File, Cheng
RDI:ARathman:4/28/94:MMetzger:4/28/94:EZager:5/2/94
7509C:CBRS:LCheng:CM#2:RM804D:2/24/94:5/2/94:03:IMAZALIL\PLANTMET