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

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MEMORANDUM

Caswell No. 755 D

OFFICE OF
PESTICIDES AND TOXIC SUBSTANC

DATE: DEC 2 1981

SUBJECT: Addendum to TB Review of PP#1F2482 (A Reevaluation of the Blazer Two year Rat Feeding Study).

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TO: Mr. Richard Mountford, PM #23
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THRU: Bruce Jaeger, Section Head
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12/2/81

The rat, 2-year chronic feeding/oncogenicity study for Blazer was reevaluated with respect to biochemistry, hematology, bone marrow differentials, urinalysis, food and body weight measurements, neoplastic and non-neoplastic lesions, relative and absolute organ weight data, mortality and survival. All parameters examined indicated that this two year rat study is valid both as an oncogenic study and a feeding study. However, because of the experimental design employing multiple shifts in dose levels and duration within each of the four basic dosage levels (copy attached), it is difficult to establish at what point in time and at what dose level changes in biological perameters if any, would occur. While this is not a conventional protocol and one which is generally recommended by TB, it does provide some useful information.

No obvious toxicity was shown which could be related to test compound at any of the doses tested. TB has chosen the high-mid dose level as the no observable effect level, using the initial dose given the animals in this group - 90 ppm. The rat at 90 ppm or 4.5 mg/kg, is not as sensitive as the dog with the no observed effect level at 1.25 mg/kg for chronic toxicity. The dog therefore will continue to be used as the animal of choice to establish the ADI.

Classification:

This study is considered core minimum. NOEL for chronic toxicity = 90 ppm.

Attachment

Three and Twenty-Four Month Oral Safety Evaluation
Study of RH-6201 In Rats

DRC 5800

Procedure (Con't)

Dosing

The test compound* was incorporated into fresh feed weekly, and the mixture was available ad libitum. The controls received a basal diet. The males and females of each group received the same treatment. Feed - test compound samples were collected weekly from each dosage group and forwarded to the sponsor for analysis.

The group diets were prepared at a concentration of parts per million (ppm) of active ingredient (A.I.) according to the following chart:

	Dietary Level (ppm) of RH-6201**		
Treatment Group	Day +1 to +13	Day +14 to +27	Day +28 to (designated)
Low Dose*** Low→High Dose	2.5	3.54	5.0 (to Day +225) 1080 (Day +226 to termination)
Low-Mid Dose	15.0	21.20	30.0 to termination
High-Mid Dose	90.0	127.30	180.0 to termination
High Dose	540.0	736.60[f]	1080.0 (to termination at +3 month)

The compound concentration was adjusted after the second and fourth week of treatment to maintain a more constant compound intake as food consumption on a g/kg/day basis decreases with growth of rats. The dosage was increased from 5 to 1080 ppm in the low dose group at Day +226 because no definite effect had been seen in any of the groups.

* See Addendum II
** Lot PL 76/8017 (39.8% A.I.), days +1 to +364
Lot PL 76/8077 (39.4% A.I.), days +365 to termination.
*** This group is referred to as the Low→ High Group (from Day +226).
f Due to a transposition error, the dosage was 736.60 ppm rather than the intended 763.6 ppm.