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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

PRIORITY

NOV 21 1986

MEMORANDUM

SUBJECT: Proposed one-year dog feeding study with linuron; Caswell 528; EPA I.D. # 035506; Project 7-0151; Record No. 184984

TO: Michael McDavit, Review Manager
Special Review Branch (TS-767C)
and
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Registration Division (TS-767C)

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James N. Rowe 11/18/86

THRU: Laurence D. Chitlik, D.A.B.T.
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and
Theodore M. Farber, Ph.D.
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LDC 11/18/86

11/21/86

ACTION: Review of proposed one-year dog feeding study with linuron; Caswell 528; EPA I.D. # 035506; Project 7-0151; Record No. 184984

RECOMMENDATIONS:

It is not the policy of the Toxicology Branch to review general chronic study protocols. For general requirements, the registrant is referred to § 82-3, pages 107-117 of the FIFRA Pesticide Assessment Guidelines, Subdivision F. However, two issues, dose level requirements and the method of blood pigment analysis, require some comment since they have been raised as issues in regard to data gaps and to previously submitted data (rat blood pigment study).

The registrant has proposed dose levels of 0, 25, 125 and 625 ppm. It should be noted that in the dog study performed by Hodge et al.(1968) an effect level (LEL) at 25 ppm for abnormal blood pigments was demonstrated. Therefore, in order to be assured of establishing a no-observed effect level (NOEL) in the proposed study, the low dose level should probably be below the LEL previously observed.

The method for the analysis of blood pigments has been recently reviewed by the EPA in a separate discussion on industry rebuttal comments (see review of linuron rebuttal comments on met- and sulfhemoglobin; EPA I.D. # 035506). EPA

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See - D-6502

D-06503 / LINURON

considers the proposed method for the measurement of methemoglobin (p. 9 of protocol) to be appropriate. Since sulfhemoglobin was the blood pigment of concern in the original study, it is logical for it to be examined in the new dog study. It is recognized, from the difficulties encountered in the rat study in measuring small percent conversions (1-2%) of total hemoglobin to sulfhemoglobin, that the sensitivity of the method may not allow small changes in blood pigments to be evaluated. On the other hand, there may be qualitative or quantitative differences between the rat and dog blood pigment picture which will enable some reasonable analysis to be made.

Other suggestions are given below for the registrant's consideration:

1. GLP considerations

As per the EPA Good Laboratory Practices, the protocol should make provision for the determination of the stability of the stock test substance, i.e., in addition to its stability and concentration in the feed mixture [see § 160.105(e)]. In addition, for studies of more than 4 weeks' duration, reserve samples from each batch of test and control subtances must be retained for the period of time provided by §160.195 [see § 160.105 (d)].

2. Other comments (as per the 1982 FIFRA Pesticide Assessment Guidelines)

- clinical chemistry: magnesium and phosphorus should be evaluated
- urine analysis: specific gravity should be included
- organ weights: include the measurement of ovary weights (absolute, relative)
- pathological examination: include optic nerve of the eye
- food should be administered ad libitum so that any compound-related effects upon food consumption can be determined