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

MEMORANDUM

12/10/82

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TO: Marilyn Mautz (16)
Registration Division (TS-767)

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

THRU: Orville E. Paynter, Ph.D.
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Re-evaluation of Validated IBT Study of Curacron; Acute Delayed Neurotoxicity in Chickens, Study#8580-10426
CASWELL#266AA

Registrant: Ciba-Geigy Corp.
Agricultural Division
Greensboro, North Carolina 27409

Background Information:

This study has been validated by HPB Canada and classified as "Valid with reservations". The Canadian validation has necessitated a reevaluation of the study.

Recommendation:

It is recommended that as a result of our evaluation, this study be classified as Core Minimum Data. As per the review of 11/2/78 from D. Ritter, no delayed neurotoxicity was noted in birds treated with this chemical at dose levels up to an including 52 mg/kg. The requirement noted in the memo of May 13, 1982 that Ciba-Geigy "provide an acceptable (neurotoxicity) study by 6/1/83" has now been satisfied.

Review of Data:

Acute Delayed Neurotoxicity, Chickens. IBT No. 8580-10426. June 6, 1977. Submitted by Ciba-Geigy.

(This study was validated by Dr. Davies of HPB Canada on August 4, 1981 and classified as "Valid with reservations" on the basis of the following deficiencies:

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1) The preliminary acute toxicity study was poorly contrived.

2) The age of the test birds could not be confirmed by the raw data.

3) Some question exists concerning the form of the test material actually used in the present study i.e. technical vs. emulsifiable concentrate.

4) Lack of atropine or 2-PAM pretreatment.)

See review of July 16, 1980 from Dr. Woodrow for a discussion of study protocol. Dose levels, corrected for percent of active ingredient, were 13, 26 and 52 mg/kg.

Results:

Clinical observations or microscopic findings of acute delayed neurotoxicity were not observed in animals receiving Curacron or corn oil. Perivascular lymphoid infiltrates of the spinal cord and peripheral (sciatic) nerve of minimal to mild severity were observed in most animals, probably due to background viral disease. All positive control birds exhibited delayed clinical symptoms and showed microscopic findings of acute delayed neurotoxicity. Based on the results of this study it appears that dose levels of Curacron up to and including 52 mg/kg do not induce delayed neurotoxicity.

Discussion:

Based on correspondence in the raw data, on the Final Report and on the mortality pattern, it is clear that a formulation rather than the technical material was bioassayed in this study. Per a telephone conversation of November 19, 1982 with Richard L. Fuelner of Ciba-Geigy (to be confirmed in a letter from Ciba-Geigy to the EPA Product Manager), the composition of the formulation tested was as follows:

Confidential Business Information

[redacted]

Given this composition of the formulation tested it appears that this study can be used both qualitatively and quantitatively to evaluate the acute delayed neurotoxicity of Curacron. Qualitatively, none of the inert ingredients are considered by this reviewer to be likely to interfere with the interpretation of the clinical or histological correlates of acute delayed neurotoxicity; quantitatively [redacted] However, based on the mortality pattern of the birds (the initial dose eliciting approximately 30% mortality) enhanced absorption of test material is not suggested.

Other reservations expressed in the Canadian validation are also not considered by this reviewer to significantly compromise the usefulness of this assay in detecting acute delayed neurotoxicity. The three remaining validation issues are, respectively; the conduct of preliminary acute study, the age of the test birds and the lack of pretreatment with atropine or 2-PAM.

The conduct of the preliminary acute study is admittedly deficient. However, appropriate dose levels in the primary study appear to have been used based on the pattern of mortality. As is noted in the validation, the age of the test birds cannot be confirmed. However, as is also noted in the validation, "Juvenile hens (up to 70 days of age) are recognized to be generally resistant to chemical induction of delayed neurotoxicity. However, on the basis of body weight data (average weight of birds at initiation was 1.5 kg, which translates into an age of at least 3 months), one cannot refute the claim that mature hens were employed in the present study. Further, positive control birds (similar in weight to treated animals) showed clinical and histopathological evidence of delayed neurotoxicity, thereby possibly demonstrating test animal sensitivity". Finally, lack of pretreatment of test groups (other than the high dose group which, despite pretreatment, had 100% mortality) with atropine or 2-PAM for the initial dosing is not considered by this reviewer to be a serious deficiency witn this compound as atropine and 2-PAM are expected to have no protective effects for the anticholinesterase effects of Curacron (memo of July 16, 1980 from W. Woodrow reviewed an antagonism study in the rat of Curacron which found neither atropine or toxigonin, a 2-PAM analog, to have an antagonistic effect on

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Curacron toxicity (Acc. No. 097797). The lack of protection by atropine is further indicated by the observation that, although atropine was administered to the hens for the second (21 days) dosing, the percent mortality (66%) was greater than the percent mortality after the first dose (30%). Furthermore, the number of animals surviving the initial acute effects of cholinesterase inhibition (18) is sufficient to satisfy U.S. regulatory requirements.

Gary J Burin 12/10/82

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12/13/82

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