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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: VITAVAX (Carboxin) RS - Company Response, dated May 1, 1984.
Registration #400-81 Chemical #090201-5
CASWELL #165A

TO: Henry Jacoby, PM#21
Registration Division (TS-767C)

FROM: Irving Mauer, Ph.D.
Section V, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: William L. Burnam, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

7/9/84

07-02-84

Registrant: Uniroyal

Action Requested: Appraise company response to the following mutagenicity assay judged UNACCEPTABLE (see original review, memo: Irving Mauer to H. Jacoby, dated February 8, 1984):

In vivo Bone Marrow Chromosome Study in Rats (Acc. #251658), performed by Hazleton Laboratories America, Report #HLA298-199, July 29, 1983.

TB Recommendation: The Agency maintains that this study is not acceptable as a comprehensive assay for the potential of the test substance to induce chromosome aberrations, mainly because of a lack of evidence of transport to target tissue (bone marrow). A point for-point appraisal of the response submitted follows.

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Point 1: "..... insufficient dosage to induce clinical toxicity in animals, or cytotoxicity in target cells."

Hazleton: It was felt that sufficient evidence for a clinical effect was demonstrated, as indicated by body weight data and clinical observation at 2,000 mg/kg (= HDT). The performing laboratory also offers statistical analysis on the body weight data from this study, citing a significant ($p < .05$) variance from concurrent controls in 24-hr post-treatment samples, for both males and females at the HDT, and for males at the mid-dose level. It was also suggested from the LD_{50} data supplied by Uniroyal ("... 17% of rats dosed at 2,000 mg/kg died within 4-7 days") that: (i) "..... it can be assumed that at least a small percentage of the animals used for cytogenetic analysis received a lethal dose of VITAVAX," although no deaths were seen in this 48-hr test; and (ii) "... testing at higher levels would be difficult due to severe toxicity and is not necessary for determining the clastogenic potential of VITAVAX."

Agency: The primary purpose in testing for in vivo cytogenetic effects (as indeed, of all testing for intrinsic mutagenicity) is ".... for the ability of a chemical to induce chromosomal aberrations in mammalian species," at dose levels such that the HDT ".... should produce some indication of toxicity as evidenced by animal morbidity (including death) or target cell toxicity." (See enclosed EPA guidance document, "in vivo Mammalian Bone Marrow Cytogenetic Tests: Chromosomal Analysis").

No material evidence of clinical or cytotoxicity that these criteria were observed was presented in Hazleton's original Final Report submitted to the Agency (Acc. #251658), and the statement regarding statistical analyses provided in the presently submitted company response does not modify our position, unaccompanied by data and appropriate analytical presentations. Body weight loss may have been due to unpalatability of the compound, and not an adverse effect of absorbed Vitavax.

Further, as noted in the Agency's original review of this study, selection of the HDT (2,000 mg/kg) was based upon a footnote regarding an "..... LD_{50}, reported by the sponsor in a separate study involving "albino rats" as 3820 mg/kg p.o., but no data presented here," which is also unacceptable.

Finally, in the absence of radioactive localization to bone marrow cells of test substance and/or metabolites, or cell survival data, the reported lack of compound-induced changes in mean mitotic indices gives no information on potential cytogenetic effect of Vitavax. This apparent lack of effect on cell cycle dynamics may be due to one or more of the following:

(i) Vitavax and/or its metabolites penetrated to bone marrow cells, but are inactive genetically at any concentration.

(ii) Vitavax is metabolized to inactive substances rapidly and effectively before transport to bone marrow.

(iii) Sufficient test substance is not absorbed by the oral route to transport to bone marrow.

Without adequate evidence of clinical toxicity or adverse effect on bone marrow cells, we cannot decide which, if any, of these possibilities apply.

Point 2: "..... lack of multiple dosage schedule to assay cumulative effects."

Hazleton: Correspondance from R. Julian Preston (Oak Ridge National Laboratory) is submitted, and "EPA Guidelines for bone marrow studies" cited, (presumably the document attached to this memo), to refute the necessity of repeat dose schedules in the absence of pharmacokinetic or toxicological information indicating activity (only) from cumulative effects.

Agency: As indicated above, the lack of perturbation on the cell cycle (indicated by no changes in mitotic indices) does not provide any information, or perhaps, indeed, Vitavax cannot adversely affect bone marrow cells (for reason of pharmacokinetics and/or inactivation). However, in the absence of clinical and/or cytological evidence to offset the potential for Vitavax to actually transport to the target cells and affect them adversely, even in the absence of cytogenetic damage (either structural or numerical chromosome aberrations), the rule-of-thumb for such short-term assays governs: Lethality or severe toxicity intervening before any aberrations are induced, supported by evidence for the presence of active chemical at the target.