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

JUN 11 1990

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

Subject: Prodiamine: ID Number 55947-WR
Tox Chem No. 727A
HED Project No. 0-0687

From: John H.S. Chen, D.V.M. 6/8/90
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Health Effects Division (H7509C)

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Thru: Yiannakis M. Ioannou, Ph.D., Section Head J. M. Ioannou 6/8/90
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and

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Toxicology Branch II
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Registrant: Sandoz Crop Protection Co.
Des Plaines, Illinois 60018

Action Requested: Review of the Registrant's Response to the Previous Toxicology Branch II Comments concerning the Acute Rat Inhalation Study with Prodiamine 65 WDG, the L5178Y Mouse Lymphoma Mutation Assay with Technical Prodiamine, the Rat Production Study with Technical Prodiamine, and the Acute Toxicity Study with Technical Prodiamine.

Reviewer's Comments:

1. Acute Rat Inhalation Toxicity Study with Prodiamine 65 WDG. Huntingdon Research Center Study No. VCL 111/86831, November 7, 1986 (81-3).

Registrant's Response: "This study was done according to the guidelines in place during 1986 and technically is a sound study. It was submitted nearly two years before the SEP's latest amendment in April, 1989 and was put into

review February 1989, two months before the amendment. The latest previous SEP, August, 1988, discusses the two rejection criteria for this study (particle size and maximum concentration) but no difinitive changes are made, unlike the April, 1989 amendments. Under the 1988 guidelines, we are confident the Agency will find this study acceptable. In retrospect, the need for this study is in question. Prodiamine 65 WG is an end-use product formulation. Acute inhalation toxicity on the technical product (Accession No. 257489), and the 75 WP formulation (Accession No. 257490) do not indicate any toxicological concerns based on inhalation. Both were classified as core guideline data and both have a toxicity III, caution rating. At a minimum, 95% granules are in the 420 to 2000 micron range."

Reviewer's Comments: The Registrant's explanations for the deficiencies of this study are considered to be reasonable. Because both the acute inhalation toxicity studies in rats previously accepted by the Agency (Acute inhalation toxicity with the technical prodiamine in rats, Huntingdon Res. Center #VCL 49/84839, LC50 > 0.256g/m3, Toxicity Category III, Core Guideline 005267; Acute inhalation toxicity with the Prodiamine 75 WP formulation in rats Huntingdon Res. Center #VCL 54/8385, LC50 > 3.8 g/m3, Toxicity Category III, Core Guideline 005267) do not indicate any toxicological concerns based on inhalation, it is unlikely that the results of this study with the Prodiamine 65 WDG formulation will fall outside the range of the Toxicity Category III if repeated.

Recommendation: Since the clarification of the particle size from 5.5 um to less than 1 um and the application of maximum attainable concentration higher than 1.81 mg/L have no determinable effects to altering the outcome of the study results, The study is upgraded to Core Minimum.

LC50 > 1.81 mg/L (both sexes)

Toxicity Category: III

2. Mouse Lymphoma Assay with Technical Prodiamine. Microbiological Associates Study No. T2840.701 (84-2)

Registrant's Response: "The mouse lymphoma assay was conducted as part of a battery of five mutagenicity tests.

Four of these tests, covering the three mutagenicity categories, have been accepted by the Agency and all tested negative. As the mouse lymphoma assay is known to cause false positives and an acceptable study is on file for the guideline, we propose to conduct a CHO/HGPRT Forward Mutation Assay rather than to repeat the mouse lymphoma assay. The CHO/HGPRT Forward Mutation Assay is less likely to cause a false positive while measuring the same endpoint. We request the Agency's review and approval of this replacement study as outlined in the attached protocol."

Reviewer's Comments: The Registrant's request for conducting a CHO/HGPRT Forward Mutation Assay to replace the mouse lymphoma assay is considered reasonable. The test protocol for performing the CHO/HGPRT Forward Mutation Assay should be based on the method described by Hsie et al. (Hsie et al., A Report of U.S. EPA's Gene-Tox Program for CHO/HGPRT Assay, Mutation Res. 86: 193-214, 1981).

Recommendation: Toxicology Branch II has no objection to the Registrant's request. However, the mouse lymphoma assay with technical prodiamine remains unacceptable.

3. Effect of Prodiamine on Reproductive Function of Two Generations in the Rat. Huntingdon Research Center Study No. VCL 73/871075 (83-4)

Registrant's Response: "The purity of the test material was 94.3% Prodiamine."

Reviewer's Recommendation: The study is upgraded to Core Guideline. Parental Toxicity NOEL = 200 ppm; Reroductive Toxicity NOEL = 200 ppm.

4. Acute Dermal Toxicity Study with Technical Prodiamine (81-2)

Registarnt's Response: "An acute dermal study was previously submitted on technical prodiamine January 22, 1985 to EUP File 876-EUP-44 (Endurance 65 WDG Herbicide) and assigned Accession #256459. Results indicate an LD50 of >2000 mg/kg. We were under the impression that this study was accepted. Please advise."

Reviewer's Comments: The acute rat dermal study with an LD50 of >2000 mg/kg was tested on the 65 WDG formulation (Core Minimum 005656; Accession No. 263738). There is no acute dermal study with technical prodiamine in our toxicology data file.