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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

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OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

Subject: Metam Sodium
Identifying Number 2390
Tox Chem No. 780
HED Project No. 0-0499

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Registrant: ICI Agricultural Products
Wilmington, Delaware 19897

on behalf of the Metam Sodium
Task Force

Action Requested: Review of the position document submitted for the proposed toxicology testing program.

Reviewer's Comments: Toxicology Branch II acknowledges receipt of the position document prepared by the Metam Sodium Task Force (12/20/89). This document is based upon the summarized conclusions of a joint meeting

between the representatives of Metam Sodium Task Force and the OPP staff scientists dated November 29, 1989. The major points of discussion in this meeting were focused on the proposed toxicology testing program for Metam Sodium to demonstrate the feasibility of bridging the existing subchronic and chronic toxicology data on MITC to Metam Sodium, as follows:

1. The Registrant's request for bridging is to satisfy the current California CDFA SB950 data requirements for chronic studies should EPA decide they are necessary.

2. The Metam Sodium can decompose quickly to form MITC (Methylisothiocyanate). Soil sterilant activity is due to the presence of MITC vapor in soil. MITC is itself regulated as an active ingredient by the EPA. Although Metam Sodium is not in itself a volatile compound, the active moiety MITC may volatilise into the local atmosphere following application of Metam Sodium and thus MITC may present an inhalation risk. Because operators working with the concentrate and spray dilutions have the potential for dermal exposure to Metam Sodium, an assessment of dermal absorption and metabolism of Metam Sodium is, therefore, of prime importance in determining the validity of the bridging concept.

3. Based on the results from the kinetic/metabolism study of 14C-Metam Sodium in the rat (Toxicology Branch II MEMO 9/30/88 S. Stolzenberg), it is clear that despite some points of difference, Metam Sodium and MITC display a similar profile after a single oral administration in the rat with regard to absorption, distribution, and excretion.

4. Proposed Testing Program

A. Worker Exposure Study: A protocol for this study is not submitted at the present time;

B. Outline Protocol for Dermal and Metabolism Study in the Rat: Appendix 1 attached.

Recommendation:

1. Toxicology Branch II has no objection to the bridging concept if some conclusive evidence can be found from the plant metabolism study, field residue study, or dermal absorption and metabolism study in the rat to support this concept that no necessary concern of dietary exposure should be considered for either the Metam Sodium or the MITC.

2. The submitted protocol for dermal absorption and metabolism study with Metam Sodium in the rat is just an outline of the described protocol. No specific details of the test design were given. A detailed evaluation will be conducted when the complete protocol of such study has been submitted to the Agency.

3. Based on the toxicological data submitted in support of the Registrant's request for food use, the following data gaps are noted (Toxicology Branch II MEMO 4/24/89 John Chen):

82-1 Subchronic Oral Toxicity in Two Species
82-3 Subchronic Dermal Toxicity (90-day)
82-4 Subchronic Inhalation Toxicity
83-1 Chronic Toxicity in Two Species
83-2 Oncogenicity in Two Species
83-3 Teratology in Two Species
83-4 Reproduction Study

APPENDIX 1

METAM SODIUM: OUTLINE PROTOCOL FOR DERMAL ABSORPTION AND METABOLISM STUDY

Dermal absorption of a pesticide is usually determined by measuring the radioactivity in urine, faeces and carcass at various times after dermal application of a radiolabelled pesticide. In the case of metam sodium excretion studies following oral administration have shown that a significant proportion of the dose is eliminated as metabolites (carbon disulphide and methyl isothiocyanate) in exhaled air, and consequently an assessment of dermal absorption requires collection of exhaled metabolites. Unfortunately metam sodium is unstable under acid conditions and the degradation products are known to be identical to the exhaled metabolites. If metam sodium is unstable on skin any collection of exhaled metabolites will therefore, under normal animal housing conditions, include collection of the degradation products. As a result dermal absorption of metam sodium could be overestimated.

The rate of degradation of metam sodium on skin has been investigated in an in vitro study. Metam sodium was applied fresh, to full thickness skin held at 37°C in an apparatus normally used to assess percutaneous absorption. The apparatus was modified so that the degradation products of metam sodium, viz carbon disulphide and methyl isothiocyanate, could be quantified by headspace analysis. Three application rates were used and headspace was analysed 4h after application, this being considered the maximum period during which the skin tissue remained viable.

The results are shown below:

Concentration of Metam Sodium	% Degradation to Carbon disulphide	% Degradation to Methyl isothiocyanate
30%	0.04	1.51
3%	0.36	3.94
0.3%	1.59	4.80

The in vivo dermal absorption study recommended by EPA requires application of a pesticide to skin for up to 24h. If the above data obtained after 4h are linearly extrapolated to 24h it would indicate that between 9% and 38% of the applied material would be degraded to volatile products during that period, and therefore collection of carbon disulphide and methyl isothiocyanate in an in vivo dermal absorption study could lead to an overestimate of the absorbed dose.

It may be possible to trap the degradation products by siting an activated charcoal filter over the application site. This technique has been used in a published study of the dermal absorption of volatile solvents (Susten et al. J.Applied Tox., 43, 6, 1986). The efficiency with which carbon disulphide and methyl isothiocyanate are trapped by such a filter will be determined in a preliminary experiment. If an acceptable efficiency is obtained the filter will be used to trap volatile degradation products during the periods that [^{14}C] metam sodium is applied to rat skin in vivo.

The dermal absorption study will be conducted to a recommended EPA protocol. Four application rates will be used, 10, 1, 0.1 and 0.01mg/rat. The [^{14}C] metam sodium will be applied using 20, 2, 0.2 and 0.02% aqueous solutions buffered to pH7. The highest concentration used will therefore be similar to that for metam sodium concentrate.

Each concentration of [^{14}C] metam sodium will be applied to a minimum of 24 rats. Only female animals will be used. Urine, faeces and exhaled volatiles will be collected from groups of 4 rats for 0.5, 1, 2, 4, 10 and 24h after the dermal application of metam sodium. At the end of the collection period the animals will be anaesthetised and the skin washed. The rats will then be sacrificed and a sample of blood and the skin application site will be removed. All the above samples, the residual carcass and the charcoal filter will be analysed for radioactivity content and the amount of metam sodium absorbed will be calculated from these results.

A separate kinetics study will also be done following dermal application of metam-sodium. Blood concentrations of metam sodium, carbon disulphide and methyl isothiocyanate will be determined by radiochromatography using rats to which [^{14}C] metam sodium has been applied dermally using the same four doses as in the absorption study. Blood sampling times will be determined using the results of radiochemical analysis of the blood samples taken during the absorption study. Blood will be taken from four rats at each time point. Whether these should be serial or terminal samples will be decided during discussion with the laboratory performing the study.

The blood kinetics study will only start after the dermal absorption study has been completed and will not be done if no radioactivity has been found in blood during the absorption study.