Caswell

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

AUG 25 1987

006230

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: N-521 PAC - Fungicide/Bactericide - Response to the Registrant - EPA Registration No. 476-2228

TOX Chem No.: 840

FROM: Yiannakis M. Ioannou, Ph.D.
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C) Y.M. Ioannou 8-21-87

TO: Lois A. Rossi, PM 21
Fungicide-Herbicide Branch
Registration Division (TS-767C) LWSW for ABK 8-21-87

THRU: Albin B. Kocialski, Ph.D., Supervisory Pharmacologist
Section VII, Toxicology Branch
Hazard Evaluation Division (TS-769C) Mfor WBF 8/25/87

and

Theodore Farber, Ph.D., Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Registrant: Stauffer Chemical Company

Stauffer Chemical Company has submitted comments to the Agency pertaining to the review and classification by Toxicology Branch of a variety of acute and mutagenicity studies submitted earlier by Stauffer Chemical Company in support of N-521 PAC (dazomet 24% ai) registration. The major comments by the registrant are listed below followed by our comments.

1. Registrant's Comments:

This letter [by Henry Jacoby] requested that Stauffer repeat an acute oral LD_{50} study conducted on the registered formulation (dazomet 24% ai, approved in 1984). Since no such study was ever conducted, we

are not sure which data the reviewer refers to as being Supplementary. In addition, because this formulation has a pH of 13.2 and contains [redacted] we requested a waiver from the requirements of conducting an acute oral LD_{50}. This waiver request was not addressed in this correspondence.

Reviewer's Comments

The acute oral LD_{50} study mentioned above referred to the 5% suspension of N-521 PAC and not to dazomet 24% ai.

We agree with the registrant that an acute oral LD_{50} study with dazomet 24% ai is not required for this product and is therefore waived.

2. Registrant's Comments

Mr. Jacoby's letter also states that an acute dermal LD_{50} study must be conducted on this formulation. We do not agree with this requirement. The Pesticide Assessment Guidelines-Subdivision-F-81-2 states that an acute dermal LD_{50} is not required if the manufacturing- or end-use product is "corrosive or a gas or highly volatile." Since N-521 PAC has a pH of 13.2 and the corrosivity hazard is clearly identified on the EPA-approved label, no dermal LD_{50} study should be required.

Reviewer's Comments

We agree with the registrant's comments that this study (acute dermal LD_{50}) is not required and therefore is waived.

3. Registrant's Comments

Ames Salmonella Assay T-6081 was classified as unacceptable (Ref. No. 251207) based on ". . . The concentrations of the test material used were not high enough to determine the mutagenic potential of this compound (5000 ug/plate should have been tested for conclusive evidence of positive or negative mutagenicity)."

Chemical dose selection is usually guided by three parameters: the solubility of the substance, its toxicity, or, for freely soluble nontoxic compounds, a reasonable upper limit such as 5 mg/plate. The

Agency recognizes this in its TSCA guidelines [FEDERAL REGISTER 50 (188), p. 39440, September 27, 1985]. Section 789.5265 (d)(6) ii notes that "among the criteria to be taken into consideration for determining the upper limits of test chemical concentrations are cytotoxicity and solubility. Toxicity may be evidenced by a reduction in the number of spontaneous revertants, a clearing of the background lawn or by a decrease of survival of treated cultures." The guidelines go on to note that 5 mg/plate is generally acceptable as a maximum concentration for freely soluble, nontoxic chemicals.

FIFRA guidelines do not provide explicit details of the test procedure; they rely on good scientific judgment.

The tests for N-521 were conducted to determine its genotoxic potential and to comply with FIFRA and TSCA guidelines. The reason that 500 ug/plate was chosen as an upper dose limit was based on toxicity. Toxicity was demonstrated by a reduction in the number of colonies per plate to below spontaneous levels for all tester strains.

In fact, on some plate counts were reduced to 0; the use of 5000 ug/plate would not have reduced the revertant count anymore and could not have increased it significantly. Since the doses were chosen on an experimental basis using prescribed scientifically acceptable criteria, the reviewer should reclassify the reports as acceptable.

Reviewer's Comments

This study remains classified as unacceptable due to the following deficiencies:

a. The registrant did not provide the Agency with data to support the statement that "evidence of toxicity" was achieved at the high dose tested.

b. This assay was not tested to limit dose.

c. Only one plate per experimental point was used with no repeats to confirm the negative results of this study.

4. Registrant's Comments

Ames Salmonella Assay T-10044 was considered unacceptable for the same reason and the same response applies.

In addition, for this study the reviewer also concluded that "inappropriate positive controls were used in most assays."

The FIFRA guidelines 40 CFR 15 84-1 and 84-2 require only that appropriate positive controls be used. The TSCA guidelines cited earlier provide some specific guidance (798-5265 (d)(5) ii A, B, and C and iii).

These guidelines note "Strain specific positive controls should be included in the assay. Examples of strain specific positive controls are as follows:

[A] Strain TA 1535, TA 100, sodium azide
[B] TA 98, 2 nitrofluorene
[C] TA 1537, 2 nitrofluorene."

2-aminoanthracene is cited as an acceptable example of a positive control to be used with activation.

Since the positive controls used in study T-10044 are exactly the same as the ones recommended in the FEDERAL REGISTER, we would need further clarification from the reviewer to understand why they were "inappropriate."

Reviewer's Comments

We agree with the registrant that for this assay appropriate positive controls were used and that toxicity was evident at dose levels greater than 300 ug/plate. Thus, this study is reclassified as acceptable.

5. Registrant's Comments

Balb/3T3, morphological transformation assays (reports T-6412 and T-10137) were classified as unacceptable by the EPA reviewer based on the "failure of the authors to carry out a metabolic activation assay."

Please note that the transformation assay comes under the FIFRA guidelines 84-2 (3) iii, i.e., tests for other genotoxic effects. Since the sister chromatid exchange data satisfy this category, the transformation assay is not absolutely necessary but supports the other endpoints.

In response to the reviewer, FIFRA guidelines do recommend that an exogenous activation system be incorporated with the test system where appropriate because it is recognized that chemicals may be metabolized to active components. It is currently not possible to routinely conduct the transformation assay with activation because S-9 is toxic to the cells when using the standard protocol. Balb/3T3 cells have also been shown to possess transforming activity for several classes of compounds normally requiring an exogenous liver activation system.

Reviewer's Comments

a. The transformation assay T-6412 remains classified as unacceptable due mainly to the fact that it was not tested at toxicity levels, i.e., the concentrations used for testing were derived from "a predetermined set of concentrations" and not from preliminary cytotoxicity testing.

b. We agree with the registrant that for the transformation assay T-10137 no metabolic activation is needed and that appropriate positive controls were used. Thus, this study is reclassified as acceptable.

Based on our reevaluation of the four aforementioned mutagenicity studies (assay nos. T-6081; T-10044; T-6412, and T-10137) and the reclassification of two of these studies (T-10044 and T-10137) as acceptable, the requirement for mutagenicity studies is fulfilled and no further testing is required by the registrant.