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

APR 4 2000

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Silver sodium hydrogen zirconium phosphate (AlphaSan® RC5000): review of the registrant's response to deficiencies cited in the toxicology data base; request for non-dietary risk assessment.

EPA Identification Numbers:

P.C. Code:072560 MRID's: N/A (correspondence)
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and

Norm Cook, Chief 04.04.2000
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Action Requested: Review of the registrant's response to the deficiencies cited for acute toxicity data on AlphaSan RC 5000 (3.8% active ingredient) in RASSB memorandum dated April 29, 1999 (D253509/D253496). Request for non-dietary risk assessment.

Background

Toxicology data were submitted to the Risk Assessment and Science Support Branch (RASSB), Antimicrobials Division (AD) pertaining to registration of AlphaSan ® RC5000, a product containing 3.8% silver sodium hydrogen zirconium phosphate as the active ingredient. Milliken Chemical Company is the registrant. These data were reviewed by RASSB, and certain deficiencies were noted in the acute toxicity database for the acute oral toxicity study, acute dermal toxicity study, the acute inhalation toxicity study, and the dermal sensitization study (see attached memorandum D253509/D253496). Chem Reg International, as agent for the registrant, addressed the deficiencies from the initial review of the toxicology data in order that the studies be considered acceptable to the Agency. A summary of the deficiencies and the registrant's responses is shown below.

In addition to the above, a non-dietary risk assessment was requested, based on the proposed use of the product (AlphaSan RC 5000, containing 3.8% silver sodium hydrogen zirconium phosphate) as a chemical incorporated into plastics, films, fibers, polymeric materials and ceramics during the manufacturing process. The product is not to be used for food contact or drinking water contact uses at this time.

Response to Toxicology Data Deficiencies

Acute Toxicity Data

1) CITATION: Parcell, B. and L.A. McRea (1998) Acute Oral Toxicity, Rat. Huntingdon Research Centre, Ltd. (Huntingdon, Cambridgshire, England). TSI 78a/940765/AC, September 12, 1994. MRID 44582906. Unpublished.

This acute oral study was classified **unacceptable** but upgradable, based on the lack of individual animal data for verification of clinical observation and necropsy statements made in the report. The registrant responded that the requested data will be provided "as soon as it can be obtained from the contract laboratory."

2) CITATION: Parcell, B. and L. McRae (1994) Acute Dermal Toxicity, Rat. Huntingdon Research Centre, Ltd. (Huntingdon, Cambridgeshire, England). TSI 67-940212/AC, September 12, 1994. MRID 44582907. Unpublished.

This acute dermal study was classified as **unacceptable** but upgradable because the study report did not contain individual and test group data as required in the guidelines. The registrant responded by stating that the requested information would be provided "as soon as it can be obtained from the contract laboratory."

3) CITATION: Blagden, S.M. (1998) Acute Inhalation Toxicity, Rat. Safe Pharm Laboratories (Derby, UK). SPL Project No. 656/014, April 15, 1998. MRID 45582908. Unpublished.

This acute inhalation study was classified as **unacceptable** but upgradable, based on the lack of information provided regarding the exact chemical identity and purity of the test material used in this study. The registrant provided the following information on chemical identity: "Experimental Additive 9823-37 (AlphaSan RC 2000, Batch 7170706) was used for this study. A Certificate of Analysis is included herein that showed silver at 9.9%. "

This information is considered adequate. The inhalation toxicity study is upgraded to **acceptable.**

4) CITATION: Allan, S. (1994) Skin Sensitization, Guinea Pig. Huntingdon Research Center, Ltd. (Huntingdon, Cambridgeshire, England). TSI 70/940132/SS, September 20, 1994. MRID 44582911. Unpublished.

This study was classified as **unacceptable** but upgradable because of the lack of individual animal data for the induction phase of the study. The registrant responded by stating that "individual induction phase animal data were not collected by the contract laboratory; only group observation data were collected."

Based on the weight of the evidence that the test material produced no dermal reactions or sensitization in the study, this study is upgraded to **acceptable.** However, it is noted that the lack of collection of individual animal data for induction and challenge is a deficiency which must be avoided in future studies.

Mutagenicity Data Deficiencies

CITATION: Proudlock, R.J. and K. Taylor. (1994) Application for pesticide registration: AlphaSan RC5000. Volume 16: Mouse micronucleus test. Huntingdon Research Centre, Ltd. (Cambridgeshire, England). HRC Study No. TSI 74/941459, September 15, 1994. MRID 44582914. Unpublished.

This study was graded as **unacceptable**, based upon the determination that too few polychromatic erythrocytes had been scored in this study; current OPPTS Guidelines (870.5395) require the analysis of 2000 PCEs per animal (to determine the frequency of micronucleated cells), rather than the 1000 PCEs per animal evaluated in this study.

The registrant responded to this deficiency by stating that the study results were clearly negative, and there was no evidence to suggest that any different result would be obtained from evaluation of additional polychromatic erythrocytes. The condition of the original slides from the study was also uncertain, as these are now more than 5 years old.

Aside from the issue of storage stability of the slides, RASSB recognizes that the proposed revision to the 870.5395 guideline, as shown in the public draft, indicates that 1,000 polychromatic erythrocytes for evaluation is recommended for purposes of harmonization with the OECD guideline. In this light, the mouse micronucleus study, having shown a negative response and having evaluated the number of polychromatic erythrocytes as required by the OECD guideline, is upgraded to **acceptable**.

Non-Dietary Risk Assessment

RASSB was requested to perform a non-dietary risk assessment for the AlphaSan RC 5000 active ingredient (3.8% silver sodium hydrogen zirconium phosphate). In a previous memorandum (D253509 and D253496, dated April 29, 1999) it was noted that the current toxicology data support non-food uses of the 3.8% product. Thus, hazard data are adequate for this type of risk assessment.

The available toxicology data for the 3.8% silver sodium hydrogen zirconium phosphate active ingredient, including the developmental toxicity data on the 10% silver sodium hydrogen zirconium phosphate active ingredient, show no systemic toxicity at doses up to and including a limit dose (i.e. 1000 mg/kg/day) in both the 90-day toxicity study and the developmental toxicity study. Mutagenicity data show a negative response in the submitted studies, and acute toxicity categories are in the Toxicity Category III and IV range. In general, the Agency is not concerned

with setting endpoints for risk assessment when systemic effect levels in experimental studies are above the limit dose, as this is an indication of the relative non-toxicity of the chemical in question. As the active ingredient in this case (3.8% silver sodium hydrogen zirconium phosphate) displays such behavior, a non-dietary risk assessment is not necessary at this time for the proposed uses of the product.

Conclusions

RASSB has reviewed the registrant's response to deficiencies as cited in a previous memorandum (D253509/D253496). RASSB concludes that the studies submitted under MRID's 44582906 and 44582907 remain **unacceptable** until additional requested information is provided by the registrant and/or the contract laboratory. RASSB also concludes that the studies submitted under MRID's 44582908, 44582911, and 44582914 are upgraded to **acceptable.**

With respect to non-dietary risk assessment, RASSB concludes that such an assessment is not needed at this time for the proposed non-food use patterns for AlphaSan RC5000 (containing 3.8% silver sodium hydrogen zirconium phosphate).

cc: Chemical File
Circulation

Attachment