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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

AUG 28 2002

MEMORANDUM

SUBJECT: Methylene Bis(Thiocyanate): review of a 90-day Inhalation Toxicity study in rats.

EPA Identification Numbers:

P.C. Code: 068102 MRID's: 45366301
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Action Requested: Review of a 90-day inhalation toxicity study with NOBS.

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Background

The registrant, Rodia Consumer Specialties Limited, has submitted a 90-day inhalation toxicity study conducted with technical methylene bis(thiocyanate) for review. The executive summary of this study is presented below:

CITATION: Jones, L.J., Blagden, S.M., Blackwell, M.P., and Brooks, P.N. (1999) Methylene bisthiocyanate (MBT): Ninety day repeated exposure inhalation toxicity study in the rat. Safepharm Laboratories Limited, P.O. Box No. 45, Derby DE1 2BT UK. Project No. 071/621. December 9, 1999. MRID 45366301. Unpublished.

EXECUTIVE SUMMARY: In a subchronic inhalation study (MRID 45366301), methylene (bis)thiocyanate (MBT; 99.7%, a.i, Batch No. X1125) was administered by nose-only exposure to groups of 10 male and 10 female Sprague-Dawley Crl:CD®BR rats at concentrations of 0, 0.04, 0.20, or 0.99 mg/m^3 for 6 hours per day, 7 days per week for 13 weeks. For exposure, the test material was formulated as a 2% w/w solution in anhydrous polyethylene glycol (PEG) 400. As part of a functional observational battery (FOB), rats were subjected to a detailed clinical observation before initiation of treatment and weekly thereafter; motor activity, fore- and hind-limb grip strength, and sensory reactivity were assessed during week 12. All observations were done following completion of the 6-hour exposure period. The animals were monitored continuously during exposure. Body weight was recorded on day 0, weekly, and prior to sacrifice. Blood was collected for hematology and clinical chemistry measurements on day 91 (the day after the final exposure).

All animals survived to scheduled termination. Noisy respiration was heard in 10/10 males and 10/10 females administered the high concentration. The first incidence of noisy respiration occurred on day 4 for males and day 6 for females and persisted throughout the study. On several days, decreased respiratory rates, frequent sneezing, labored respirations, hunched posture, or piloerection were observed from 1-3 high-concentration males and females. Blisters on the soles of the feet were observed on 4-7 males beginning on day 76 and on 1-3 females beginning on day 75. These clinical signs were not observed in animals in the control or other treated groups. No treatment-related clinical signs of toxicity were observed in the low- or mid-concentration groups.

No statistically significant differences on absolute body weights were noted between the treated and control groups of either sex. Body weight gains by the high-concentration males were significantly ($p \leq 0.05$ or 0.01) less than those of the vehicle controls for weeks 1-3, 6, 9, and 11. Overall weight gain by the high-concentration males was 68% of the control level resulting in a mean final absolute body weight for this treated group 82% of the control value. Weekly body

weight gains by the treated female groups were not affected by treatment.

Weekly mean food consumption by the high-concentration males was 77-84% of the control amounts throughout the study with the exception of week 9 (99% of controls). Weekly mean food consumption by the high-concentration females was 81-90% of the control amounts for weeks 2, 3, 7, and 9-13. Food consumption by the low- and mid-concentration groups was similar to the controls throughout the study. Weekly food efficiency values were similar between the treated and control groups throughout the study.

Abnormal findings during open field observations were similar to those described under clinical signs. No other treatment-related behavioral changes were observed during the FOB. No treatment-related differences were found between the treated and control groups of either sex for any sensory reactivity or startle response assessments, fore- and hind-limb grip strengths, or motor activity.

No ophthalmoscopic lesions were found on any animal. Hematology, clinical chemistry, and urinalysis parameters were not affected by treatment. Differences in absolute and relative organ weights of the high-concentration males corresponded with reduced final body weights of these animals.

Gross necropsy was unremarkable with the exception of blistered feet observed on 7/10 males and 2/10 females administered the highest concentration. Microscopically, subepithelial inflammatory cell infiltrates were observed in the feet of 4/10 and 2/10 males and females, respectively, in the high concentration groups compared with 1/10 and 0/10 control males and females, respectively. In addition at the highest concentration, epithelial ulceration was seen in the foot of one male and subepithelial fibrosis was found on the feet of one male and one female. All treated male groups had a decreased incidence of globular accumulations of eosinophilic material in the renal tubules compared with the controls. The incidence (severity) of globular eosinophilic accumulations in the control, low-, mid-, and high-concentration groups was 8/10 (1.875), 3/10 (1.333), 3/10 (1.667), and 1/10 (1.00), respectively. The relationship of the foot and kidney lesions to treatment is uncertain but can not be discounted.

The systemic toxicity LOAEL is 0.99 mg/m^3 based on noisy respiration, other clinical signs of respiratory abnormalities, and blisters on the feet from males and females and decreased body weight gains of males. The systemic toxicity NOAEL is 0.20 mg/m^3.

This study is considered **Acceptable/Guideline** and does satisfy the requirements for a subchronic inhalation toxicity study in rats (OPPTS 870.3465 [§82-4]).