CASWELL FILE

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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCE

MEMORANDUM

SUBJECT: DEET (N, N-dimethyl-m-toluamide): Proposed 90-day dermal toxicity study protocol

Caswell No.: 346

TO: Joseph Tavano, PM (17)
Registration Division (767C)

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and
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Background:

On Aug. 8, 1986, a meeting was held among EPA personnel and members of the DEET Steering Committee of Chemical Specialties Manufacturers Association (CSMA). The toxicologists of CSMA presented summary data on a 90-day oral range finding study with rats, a 90-day oral range finding study with mice, and a 90-day dermal toxicity study with rats.

In both 90-day oral and dermal toxicity studies with rats, enlarged kidney and microscopic changes in kidneys of all treated male rats were observed. The microscopic changes were characterized by granular casts, inflammation, and regeneration. Because of these changes in the low dose male rats there is no no-effect level for either oral or dermal toxicity in rats. This situation will affect the planned chronic toxicity/oncogenicity study on DEET in rats.

The toxicologists of the DEET Steering Committee feel that the kidney lesions observed in male rats are sex and species specific, and they wish to explore if the rats are the appropriate test animals for testing DEET. They have proposed the following studies:

1). Repeating the 90-day dermal toxicity study using miniature swine as the test animal.
2). Another 90-day dermal toxicity study using castrated rat.
3). 90-day oral feeding study using hamsters and subsequently using hamsters for chronic/oncogenicity study.

Discussion:

We have carefully considered the summary data on the 90-day subchronic dermal toxicity study with rats, 90-day feeding study with rats, and 90-day feeding study with mice. In additional, this reviewer has found a 13-week dermal toxicity study on DEET with rabbits (Woodward Research, 1959; MRID No. 00001029). In this study groups of 6 rabbits/dose (3/sex/dose) were dermally administered Meta Delphene which contained 85% m-DEET at dose levels of 0, 0.75, 1.5, and 3.0 ml/kg/day. However, the density of Meta-Delphene was not reported. Rabbits which received 3.0 ml/kg/day died within 6 days of dosing. All rabbits which received 1.5 ml/kg/day developed enlarged kidneys, and histopathologically the kidneys of these animals showed "many granular structures throughout the cortex in which the capillaries are congested". The findings in rabbits and male rats in both recent 90-day studies appear similar, and they may indicate that the effects of DEET on kidneys are not species and sex specific.

In view of the available data, it would be appropriate to repeat the 90-day dermal toxicity studies using both rats and rabbits with doses lower than 100 mg/kg/day. At present, the proposed 90-day studies on miniature swines and castrated rats should be postponed. Toxicology Branch requests the completed 90-day dermal toxicity study with rats and 90-day feedies studies with rats and mice be submitted for review prior to repeating any studies. The reason is that previously the proposed NOEL was 100 mg/kg/day which was indicated to be derived from a gavage study and which was also used for exposure analysis, but the current data of both 90-day dermal and feeding toxicity studies with rats indicate the NOEL should be lower than 100 mg/kg/day (CSMA submitted summary data; attachment)

At present, CSMA are concerned about the proposed dates for submission of data for registration standard. Under the present conditions, it would be appropriate to reconsider the proposed submission dates and to provide additional time for Toxicology Branch to review the 90-day dermal and oral toxicity studies with rat.

Conclusion:

The DEET Steering Committee should be requested to submit complete reports of the 90-day dermal and 90-day oral toxicity studies in rats, including the kidney slides for our consideration. Additional time should also be provided for evaluating these studies.