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

DEC 6 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of DEET Protocols

EPA No. CSMADEET
Record No. 161165

Tox. Chem. No. 346
Project No. 762

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12-5-85

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12/5/85

The Chemical Specialties Manufacturers Association (CSMA) has submitted, for Toxicology Branch comment, the following protocols for the toxicologic evaluation of DEET (N,N-diethyltoluamide):

1. Protocol for the Evaluation of DEET in a 90-Day Subchronic Dermal Toxicity Study in Rats.

2. Protocol for the Evaluation of DEET in a 90-Day (Oral) Dose Range-Finding Study in Rats. [preliminary to protocols 3 and 4]

3. Protocol for the Evaluation of DEET in an (Oral) Two Generation Rat Reproduction Study.

4. Protocol for the Evaluation of DEET in an (Oral) Chronic Toxicity and Oncogenicity Study in Rats.

5. Protocol for the Evaluation of DEET in a 90-Day (Oral) Dose Range-Finding Study in Mice. [preliminary to protocol 6]

6. Protocol for the Evaluation of DEET in an (Oral) Oncogenicity Study in Mice.

The December 1980 EPA Registration Standard listed eight toxicology studies required to fulfill data requirements for the technical product. The submitted protocols are in answer to some of these requirements. Most of these studies, including the chronic, reproduction, and oncogenicity studies, were to be performed using the dermal route. The route was changed to oral via the feed

for these studies (ref. D. Campt memorandum, 4-3-84) because:

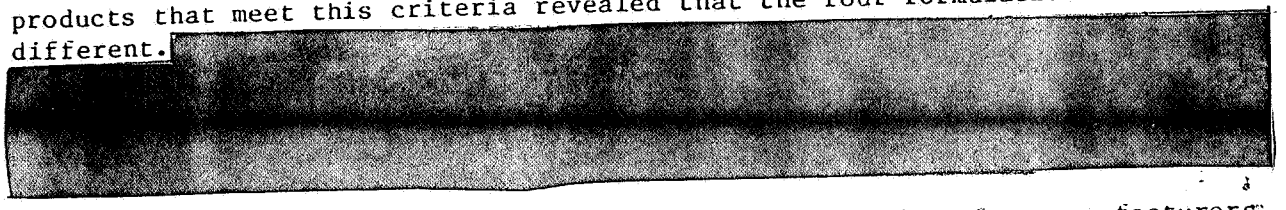
1. systemic toxicity will be more readily apparent in oral dosing, and
2. the additional stress of handling the animals and providing measures to prevent oral contamination could result in toxic manifestations not related to DEET.

Thus, all of the submitted protocols except the 90-Day Subchronic Dermal Toxicity Study in Rats use the oral route.

There are few deficiencies in these protocols. They generally meet and exceed the requirements of the EPA Guidelines and have built-in redundancy to allow for potential complications in the performance of these studies. There are, however, several concerns which affect all six rodent protocols.

Each rodent protocol stated that the undiluted commercial grade DEET will be used as the test article. Ralph Engel, President, further elaborated in his cover-letter that, "The technical chemical N,N-diethyl-toluamide, to be used in all toxicological studies, will be a blend of the four technical chemical sources currently available (MGK, Virginia Chemical, Morflex Chemical and Miles Laboratories). The use of this blend will therefore be representative of all technical DEET currently available in the market place." This test article information was conspicuously absent from all six protocols.

Technical grade DEET, as defined in the December 1980 EPA Registration Standard, must contain a minimum of 95% of the meta isomer. File copies of the Confidential Statements of Formulation (dated 1971-1977) for the four technical products that meet this criteria revealed that the four formulations were different.



Based on the available data, mixing technical products from four manufacturers is inappropriate. The Registrant must submit current Confidential Statements of Formulation (including inerts) and market poundage for the four manufacturers. A battery of mutagenicity studies must be submitted for any impurities (other than the ortho- and para-DEET isomers). The Toxicology Branch will assess this information and select one technical product to be the test article in the six protocol studies. Preference will be given to the technical product with the least impurities and the greatest market poundage.

Five of the six protocols describe the dosing of animals on a mg/kg/day basis, adjusted regularly to compensate for changes in body weight. Only in the Two Generation Rat Reproduction Study is the dose to be administered as a constant concentration in the diet (i.e. on a ppm basis). It would be advisable to dose all animals on a similar basis; using a constant diet concentration would probably be the best approach. The Environmental Protection Agency will not assume responsibility for selection of proper dosage levels in these protocols.

Critiques on the six rodent protocols are presented on the following pages.

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1. Protocol for the Evaluation of DEET in a 90-Day Subchronic Dermal Toxicity Study in Rats.

Page 7 (III, G):

The Study Design section (page 1; II) mentions the use of a "treated" control group. The Dosage Levels section (page 7; III, F) mentions the use of an "untreated" control. The Preparation or Application Sites and Test Article Application section (page 7; III, G) describes the procedure for dosing the control with tap water. Although a vehicle is not used in this study, the application of tap water is appropriate in order to subject the control rats to the same handling as the treated rats.

The rats should be fitted with elizabethan collars or other appropriate means of preventing oral ingestion of the dermal doses.

Page 13 (IV, F, 1):

The list of tissues to be examined grossly and microscopically should include untreated skin.

Page 16 (VI, B):

The Quality Assurance Statement in the final report should list the critical study phases examined, including the dates of examination and report to management.

Page 17 (IX):

All protocol amendments must include reasons for the changes.

The protocol lacks signature blocks for the Principal Investigator, Study Monitor, Quality Assurance Officer, and any other key personnel responsible for the conduct of this study.

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2. Protocol for the Evaluation of DEET in a 90-Day [Oral] Dose Range-Finding Study in Rats. [preliminary to protocols 3 and 4]

It is not necessary for a range-finding study to be in compliance with the Good Laboratory Practice regulations, nor is it necessary for a range-finding study to be submitted to the EPA for evaluation. Therefore, it is possible to perform a simpler, less costly study if so desired.

If, however, this study is intended to be submitted to the EPA and be in compliance with the EPA Guidelines, then the following would be required:

Page 5 (III, D) and Page 8 (IV):

An ophthalmic examination, using an ophthalmoscope or equivalent suitable equipment, should be made prior to the administration of the test substance and at the termination of the study. The high-dose and control animals of each sex should be examined. If changes in the eyes are detected, then all animals should be examined.

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Page 12 (IV, E, 1):

The list of organs/tissues to be examined grossly and microscopically should be expanded to comply with the EPA Guidelines.

Page 15 (VI, B):

The Quality Assurance Statement in the final report should list the critical study phases examined, including the dates of examination and report to management.

Page 16 (IX):

All protocol amendments must include reasons for the changes.

The protocol lacks signature blocks for the Principal Investigator, Study Monitor, Quality Assurance Officer, and any other key personnel responsible for the conduct of this study.

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3. Protocol for the Evaluation of DEET in a Two Generation Rat Reproduction Study.

Page 15 (IV, C, 2):

All organs demonstrating pathology in the high-dose and control groups should be examined microscopically in all groups.

Page 15 (V):

The Quality Assurance Statement in the final report should list the critical study phases examined, including the dates of examination and report to management.

Page 17 (VIII):

All protocol amendments must include reasons for the changes.

The protocol lacks signature blocks for the Principal Investigator, Study Monitor, Quality Assurance Officer, and any other key personnel responsible for the conduct of this study.

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4. Protocol for the Evaluation of DEET in a Chronic Toxicity and Oncogenicity Study in Rats.

Page 17 (VI, B):

The Quality Assurance Statement in the final report should list the critical study phases examined, including the dates of examination and report to management.

Page 19 (IX):

All protocol amendments must include reasons for the changes.

The protocol lacks signature blocks for the Principal Investigator, Study Monitor, Quality Assurance Officer, and any other key personnel responsible for the conduct of this study.

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5. Protocol for the Evaluation of DEET in a 90-Day Dose Range-Finding Study in Mice. [preliminary to protocol 6]

It is not necessary for a range-finding study to be in compliance with the Good Laboratory Practice regulations, nor is it necessary for a range-finding study to be submitted to the EPA for evaluation. Therefore, it is possible to perform a simpler, less costly study if so desired.

If, however, this study is intended to be submitted to the EPA and be in compliance with the EPA Guidelines, then the following would be required:

Page 4 (III, D) and Page 7 (IV):

An ophthalmic examination, using an ophthalmoscope or equivalent suitable equipment, should be made prior to the administration of the test substance and at the termination of the study. The high-dose and control animals of each sex should be examined. If changes in the eyes are detected, then all animals should be examined.

Page 10 (IV, D):

The list of organs/tissues to be weighed, and examined grossly and microscopically should be expanded to comply with the EPA Guidelines.

Page 13 (VI, B):

The Quality Assurance Statement in the final report should list the critical study phases examined, including the dates of examination and report to management.

Page 15 (IX):

All protocol amendments must include reasons for the changes.

The protocol lacks signature blocks for the Principal Investigator, Study Monitor, Quality Assurance Officer, and any other key personnel responsible for the conduct of this study.

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6. Protocol for the Evaluation of DEET in an Oncogenicity Study in Mice.

Page 16 (VI, B):

The Quality Assurance Statement in the final report should list the critical study phases examined, including the dates of examination and report to management.

Page 18 (IX):

All protocol amendments must include reasons for the changes.

The protocol lacks signature blocks for the Principal Investigator, Study Monitor, Quality Assurance Officer, and any other key personnel responsible for the conduct of this study.

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