REVIEWER
4-19-88

WASHINGTON, D.C. 20460

APR 19 1988

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No.: 8340-17 - Triphenyltin Hydroxide: Review of protocol for a subchronic (90 day) inhalation toxicity study to be conducted at the Research and Consulting Company Ag (Switzerland) in the spring of 1988.

TOX CHEM No.: 896E
TOX PROJECT No.: 8-0588
Record No.: 214182

FROM: John Doherty 4/12/88
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: Lois Rossi
Product Manager #21
Registration Division (TS-767)

THROUGH: Edwin Budd 4/14/88
Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

4/19/88

The Hoechst Celanese Corporation (Sommerville, New Jersey) has submitted a protocol for a 90 day subchronic inhalation study with rats which they request that the Agency review and that they be advised of any comments which Toxicology Branch (TB) may have "in order to make it a valid, acceptable study".

The registrant has submitted on two earlier occasions subchronic inhalation studies which the Agency determined to be either unacceptable or INVALID with respect to meeting the data requirement for this study type. Refer to the memo from J. Doherty for EPA Reg. No.: 8340- 17 dated August 27, 1987 for discussion.

TB has reviewed the protocol and the following comments apply:

Sent 5/12/88

H. Jamerson Lois Rossi PM-21 sent their review to H. G.

Toxicology Branch Comments

1. A copy of the protocol is attached.

2. The study protocol as presented is deficient because the method by which TPTH will be generated into the atmosphere was not described.

Since the previous study was determined to be INVALID in part because of difficulties in generating uniform test atmospheres at lower atmospheric concentrations and of the appropriate particle size, it is very important that the method used to generate a uniform atmosphere at the concentrations to be studied be defined. The method should be tried in preliminary studies and if the registrant wishes, the results of the preliminary studies sent to the Agency for review.

3. Another deficiency in this study protocol is that the method to be used for analytical assessment of the atmosphere was not included. The method to be used should be selected and tested prior to initiation of the main study. The results of the trial runs with the method that is to be selected may also be reviewed by TB if the registrant requests such a review.

4. The blood should be assessed for TPTH and/or its tin content at each blood sampling time (at least for the controls and high dose exposure groups).

5. As per discussion with Dr. Roy Sjoblad (TB coordinator for immnotoxicity testing), this study should include a series of tests to screen for potential immunotoxicity. In this regard, the study protocol already includes provisions for assessing the thymus weights and the weights of certain other organs. The clinical biochemistry section of the protocol includes plans for investigating the immunoglobulins (IgG, IgG1, IgG2, IgG2b, IgG2c, IgA and IgM) by laser nephelometry. The registrant and study sponsor should present the sensitivity and limits of detection for the Ig classes as compared to other methods for quantitative analysis of immunoglobulins. There is no mention of other specific parameters to screen for potential immunotoxicity.

TB requests that the following be included in the revised protocol:

1. spleen weight determinations
2. total and viable splenocyte and thymocyte count
3. T- and B- lymphocyte enumeration
4. bone marrow total and differential cell count

5. quantitative assessment of immunoglobulins using a method demonstrated to give accurate quantitative data.

CONCLUSION

The protocol should be rewritten to include all of the above comments.

TB strongly recommends that the method to be used in generating the test atmosphere containing TPTH be tried in practice runs before starting the exposure of the test animals to assure that a uniform distribution of low concentrations of TPTH is attained.

Lastly, the registrant is reminded that it is their responsibility to provide a study that will meet the Agency's criteria for acceptability. This includes that the high dose group should show clear signs of toxicity and the study must also demonstrate a NOEL.

Item Reviewed

Subchronic (90-day) repeated dose inhalation toxicity study with TPTH-Technical Grade (Code: HOE029664 OF ZD97 004) in Rats.

Research and Consulting Company AG, Project 202353

Study Director: Dr. F. Duchose,

The protocol is unsigned and undated.