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

006402

OCT 29 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Reg. No.: 8340-17 - Triphenyltin hydroxide. Review of second immunotoxicity study testing host resistance in rats to Trichinella spiralis.

TOX CHEM No.: 896E
TOX PROJECT No.: 7-0998
Record No.: 201957

FROM: John Doherty 10/14/87
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THRU: Edwin Budd
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Toxicology Branch
Hazard Evaluation Division (TS-769) 10/20/87 10/21/87

Background

The American Hoechst Corp. previously submitted an immunotoxicity study in which the host resistance to Trichinella spiralis infection in rats treated with triphenyltin hydroxide (TPTH) was assessed. This study was determined to be unacceptable by the Agency and the question was raised as to the possibility that TPTH was toxic to the larvae which would have obscured a potential positive response.

1

The registrant has submitted a second study of this type which has included an assessment of the potential for TPTH to be toxic to the larvae used for infecting the host rats. The study has been reviewed and determined to be SUPPLEMENTARY information. Although no evidence of potential immunotoxicity of TPTH was evident in this study, additional immunotoxicity studies with TPTH are still required. The results of this study will, however, be taken into consideration when reassessing the overall potential of the immunotoxicity of TPTH.

STUDIES REVIEWED

Study Type	Results	Classification
Immunotoxicity-rats (Host resistance to Trichinella spiralis) Authors: K.-H. Diehl and K.-H. Leist, Hoechst Aktiengesellschaft No. 87.0955, May 12, 1987.	No indications of immuno-suppression at 2.5 mg/kg/day (10 doses, only dose level tested). No pharmacological/ toxicological responses to TPTH were evident at this dose level. Positive controls demonstrated a positive response.	SUPPLEMEMTARY

Reviewed by: J.D. Doherty* J.D. Doherty 10/14/87
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006402

*With the assistance of Dr. R. Sjoblad, Toxicology Branch, HED.

DATA EVALUATION REPORT

STUDY TYPE: Immunotoxicity (Special) TOX CHEM NO.: 896E

ACCESSION No: 403037-01 MRID NO.:

TEST MATERIAL: Triphenyltin hydroxide (97.2% a.i.)

SYNONYMS: TPTH

STUDY NUMBER(S): 87.0955

SPONSOR: American Hoechst Corporation

TESTING FACILITY: Pharma Research Toxicology and Pathology (Frankfurt, Germany)

TITLE OF REPORT: Testing of host resistance in the female Wistar rat (Immunotoxicological screening with Trichinella spiralis).

Note: Second study with the same title.

AUTHOR(S): Dr. K.-H. Diehl and Dr. K.-H. Leist

REPORT ISSUED: May 12, 1987

CONCLUSIONS:

No evidence of immunosuppression after dosing with 2.5 mg/kg/day (10 successive doses, only dose level tested). No pharmacological effects of TPTH noted. Positive controls gave expected positive response.

Study type does not has an established protocol.

Classification: SUPPLEMENTARY

Specical Review Criteria (40 CFR 154.7) - N/A

REVIEW

Procedure.

The study to assess for possible immunotoxic potential of TPTH consisted of four groups of 8 female Wistar rats each.

-Group A: Dosed with 50 mg/kg bw cyclophosphamide (in a vehicle described as aqua pro injectione) intraperitonealy 3 days before and 2 days after infection. This group was a positive control.

-Group B: Dosed with 25 mg/kg bw dexmethasone (in a vehicle described as aqua pro injectione) subcutaneously 2 days before and 3 days after infection. This group was also a positive control.

-Group C: Dosed with 2.5 mg/kg bw of TPTH (97.2% pure in sesame oil) by gavage daily over a 10 day period "from 2 d(ays) before to 7d(ays) after infection".

-Group D: Negative control. No treatment.

At the time of infection, the rats were administered approximately 550 Trichinella larvae by a special stomach tube. In order to minimalize random fluctuations in distribution, the larvae were distributed to one rat from each group in turn. Three rats from each group were sacrificed 7 days after infection and the remaining five were sacrificed 53 days after infection. For the rats that were sacrificed 7 days after infection, the adult Trichinella worms in the intestine were counted, thymus weights were determined, and percentages of lymphocytes in the differential blood count were calculated. For the remaining rats which were sacrificed 53 days after infection, the tongues were removed and the Trichinella larvae count determined. In addition to the specific parameters above, body weight gain and general appearance were monitored.

Results.

1. Determination of adult Trichinella worms in the intestine.

The purpose of this investigation was to determine if the test agent actually poisoned the larvae after infection while in the intestine. The assay procedure involved removing the small

intestine, cutting it into small (2 cm) sections and washing out the adult worms with physiological saline. The adult worms were sedemented out and eventually determined (counted) by microscopic examination.

It was stated in the results section of the report that the rats dosed with TPTH had an average of 93 adult worms and the control rats had an average of 91 adult worms. No actual data were presented and apparently the rats dosed with cyclophosphamide and dexamethasone were not assessed. It was also stated that it is expected that 10% or more larvae administered to rats develop into adult worms. Since in this study about 15% developed into adult worms for both the control and TPTH treated rats, it was concluded that TPTH was not toxic to the larvae in the intestine.

2. Trichinella larvae in the tongue (after 53 days).

The excised tongues were digested with a pepsin solution and the Trichinella larvae separated by filtration. The larvae were collected in a beaker allowed to sediment and eventually counted under a microscope.

Graph 1 (attached, zeroxed from the study report) demonstrates that there were many more larvae for the positive controls cyclophosphamide (28.3) and for dexamethasone (40.7) than for TPTH (8.9) or the negative control (12.9). The units are count per gm of tongue. These data did not indicate that TPTH under the experimental conditions impaired the immunesystem to lower the resistance to Trichinella infection as did the two positive controls.

3. Thymus weights (after 7 days)

The mean thymus weights for the TPTH treated rats was 0.396 g which compared favorably with the mean weight of the control rats of 0.380 g. Both the thymus weights of the cyclophosphamide (0.186 g) and dexamethasone (0.017 g) were markedly decreased relative to the control.

4. Percentage of lymphocytes in the white blood count (after 7 days)

The mean percentage of lymphocytes for the TPTH (86.5%) and cyclophosphamide (86.0%) and the control (85.9%) were comparable but that for dexamethasone (60.6%) was reduced.

5. Body weight gain.

The body weight gains for TPTH and the control groups were comparable. Both of the positive control groups (cyclophosphamide and dexamethasone) showed decreases in body weight gain which the test report attributed to the decreased resistance to the infectious agent.

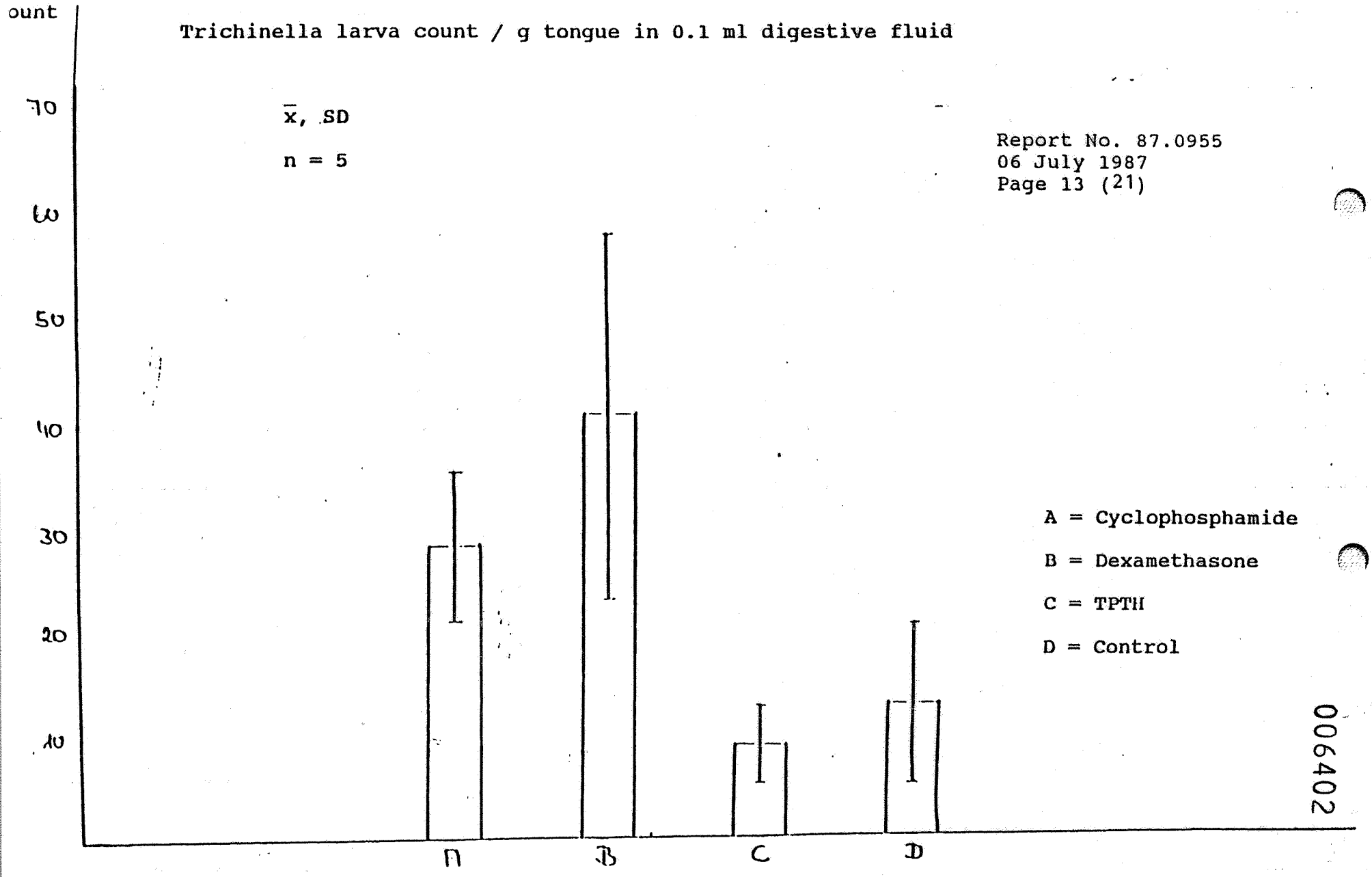
CONCLUSION

The study does provide a limited amount of useful information with regard to assessing the potential immunotoxicity of TPTH. Since the positive control groups were demonstrated to produce their expected immunosuppressive effects and because it could not be demonstrated that TPTH was toxic to the larvae at the time of and locus of infection, the study demonstrates that TPTH is not immunosuppressive at 2.5 mg/kg/day (for 10 successive days) under the conditions used in this assay. The study, however, does not establish that TPTH at higher doses or for other conditions of dosing is not immunosuppressive to Trichinella infection.

The study is considered SUPPLEMENTARY information. The study utilized only a single dose level of TPTH which did not produce any evidence of pharmacological signs. It is customary for the highest test dose level to demonstrate generalized pharmacological responses in studies designed to assess specific endpoints such as were investigated here.

The use of sesame oil as the vehicle for TPTH is this study is also questionable. The registrant is requested to justify the use of this substance as the vehicle for this study when a different vehicle was used for the positive control.

Graph 1



Report No. 87.0955
06 July 1987
Page 13 (21)

A = Cyclophosphamide

B = Dexamethasone

C = TPTH

D = Control

006402