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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA Registration No. 8340-17
Triphenyltin Hydroxide: CORE Classification of the
Cannon Laboratories Mouse Oncogenicity Study

TOX Chem. No. 896E
TOX Project No. 1255
Record No. 164328

FROM: John Doherty 4/10/86
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Background:

In previous reviews from Toxicology Branch (TB), it was indicated that the mouse oncogenicity study with the test chemical triphenyltin hydroxide (TPTH) demonstrated lesions in the uterus which may or may not be neoplastic. The registrants were requested to provide additional information related to this study and to clarify the classification of the lesions in the uterus. Refer to J. Doherty memorandum dated August 11, 1983 (PP#3F2823/FAP#3H5384) and the Registration Standard (TB Chapter) dated March 27, 1984.

In response to TB's inquiries concerning this study, the American Hoechst Corporation has provided a letter of explanation prepared by Mr. Donald J. Lawatsch (dated November 21, 1985) and a report prepared by W. Ray Brown, Ph.D., D.V.M., a consultant in veterinary pathology (dated August 13, 1985).

Discussion of the information provided by the registrants

The registrants explained that the laboratory which conducted the mouse oncogenicity study (Cannon Laboratories), is no longer in business and critical information related to this study could not be retrieved and provided to the Agency. The registrants were, however, able to locate and obtain 125 of the 250 slides of the uterine tissue. These slides were reevaluated by Dr. W. Ray Brown.

In his report, Dr. Brown included the criteria for diagnosis of the lesions noted in the uterus. According to Dr. Brown there were 13 incidences of uteri with neoplastic findings as indicated in the following table:

| Group | Incidences | Types (number) |
|---|---|---|
| Control | 5/40* | Endometrial polyp**(3)<br>Hemangioma (2) |
| Low | 3/22* | Hemangioma (1)<br>Endometrial polyp (1)<br>Leiomyosarcoma (1) |
| Mid | 2/21* | Endometrial sarcoma (1)<br>Hemangioma (1) |
| High | 3/32* | Endometrial polyp (3) |

*Number of mice examined. **Dr. Brown defined polyp as neoplastic.

Based on the above diagnosis, there are no increased incidences of neoplasms with an increase in the presence of TPTH in the diet.

The following table compares the results of analysis of the uterine tissue from the original report with the results obtained by Dr. Brown with respect to incidences of "endometrial hyperplasia" and "endometrial hyperplasia with cysts."

| Dose | Original Incidences | Dr. Brown's Analysis |
|---|---|---|
| Control | 0/60* | 27/40** |
| Low (7 ppm) | 5/60 | 19/22 |
| Mid (28 ppm) | 23/60 | 19/20 |
| High (52 ppm) | 32/60 | 31/32 |

*Mice available for examination.
**Slides examined.

Based on the table as provided above, there is no test chemical related increase in lesions in the uterus according to Dr. Brown's analysis.

TB notes however, that when the frequency of incidences is expressed as percentage and when the average degree of severity is determined for each dose group (using minimal = 1, slight = 2, moderate = 3, and marked = 4) there are indications of a test chemical effect as shown in the following table.

| Dose Group | Percent Mice with Uterine Lesions | Average Degree of Severity for the Group |
|---|---|---|
| Control | 67.5 | 1.81 |
| Low | 86.4 | 2.28 |
| Mid | 95.0 | 2.58 |
| High | 96.9 | 2.65 |

The above table indicates a possible test chemical effect of TPTH in the uterus. More specifically, the dosed groups have both higher percentages of incidences and higher degrees of severity. Thus, Dr. Brown's diagnosis as presented does not eliminate the uterus as a possible nonneopleastic target organ for TPTH. It should be noted that at least in one published study the uterus has been implicated as a target organ for TPTH toxicity (I.Iwamoto J. Tokyo Med. Coll. 18:1351 (1960)).

Conclusions

This study is assigned CORE classification INVALID. The registrants were unable to provide critical (the) information requested by TB to allow this study to be upgraded to MINIMUM.

According to Mr. Lawatsch's letter of November 21, 1986, another mouse oncogenicity study is currently underway and the registrants will eventually submit this study in attempts to satisfy the mouse oncogenicity testing requirement.

TB requests that since there is still a question that the uterus may be a target organ for TPTH in the mouse, special attention to this organ should be given when the mice on the replacement study are necropsied and examined microscopically. Such special procedures should include:

1. At necropsy, the entire uterus should be examined.

2. At least three slides taken from identical sites from each uterus should be taken and examined microscopically.