7-25-80

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

001492

JUL 25 1980

DATE:

SUBJECT: EPA Registration Nos. 148-689 and 148-1195 and PP# OF 2282 and FAP# OH 5242. Conditional registrations for the use of DU-TER to control fungal diseases on soybeans and petitions for tolerances of triphenyltin hydroxide on soybeans, soybean products and animal products.

Tox. Chem. No. 896E

FROM: John Doherty, Toxicology Branch, HED (TS-769) 6/23/80

TO: Henry Jacoby, PM #21, RD (TS-767)

ACTION REQUESTED:

The Thompson-Hayward Company is requesting to establish permanent tolerances for triphenyltin hydroxide as follows:

0.05 ppm in/on soybean seeds
0.05 ppm in eggs, milk, meat, fat and meat byproducts of cattle, goats, hogs, horses, poultry and sheep.
0.15 ppm in soybean process fraction soapstock.

Conditional registrations are sought to use the following products containing triphenyltin hydroxide on soybeans.

1. DU-TER FUNGICIDE (EPA Registration No. 148-1195)

2. DU-TER FUNGICIDE wettable powder in water soluble bags (EPA Registration No. 148-689)

CONCLUSIONS:

Following a comprehensive review of available data, TOXICOLOGY BRANCH has determined that the proposed tolerances are not toxicologically supported. The following observed toxic properties of triphenyltin hydroxide are not understood sufficiently to recommend in favor of exposure of this chemical to agricultural workers or exposure by the dietary route. See remarks below.

REMARKS:

1. Triphenyltin hydroxide caused lowering of the white blood cells in both rats and guinea pigs and this is an indication of interference with the lymphopoietic system. Moreover, substituted tin derivatives as a chemical class are known to adversely affect the lymphopoietic system. The registrant is requested to conduct three of the following four tests in order to appraise the potential for triphenyltin hydroxide to affect the immune system.

i. the $^{125}I$ isotopic footpad assay for measuring the delayed type hypersensitivity response.

ii. Cunningham's plaque-forming cell procedure for cells producing IgM antibodies

iii. the microculture lymphocyte proliferation assay

iv. tumor susceptibility assays

Appropriate positive controls should be included in each test. The registrant is referred to the following article: J.H. Dean et al. "Assessment of Immunobiological Effects Induced by Chemicals, Drugs, or Food Additives. Studies with Cyclophosphamide" In: Drug and Chemical Toxicology 2:(1&2), 133-135 (1979).

If the registrant wishes to use methods that are not listed above, it is requested that the protocols be reviewed by TOXICOLOGY BRANCH prior to initiation of the study.

2. There is no adequate teratology study which shows a clear NOEL for teratogenic/fetotoxic effects. The single available teratology study using rats showed dose related increases in hydrocephalus and hydronephrosis. Additional teratology studies in two species (with clear NOEL) are requested.

3. The three generation reproduction study was assigned a CORE INVALID rating because the raw data were not submitted and the summary of data indicated lesions in testicular and spleen development. INVALID studies cannot be used to support tolerances and/or registrations. Thus, the registrant will have to submit the raw data or conduct an additional study.

4. An inhalation $LC_{50}$ study with the product as formulated is required. The submitted study was assigned CORE SUPPLEMENTARY classification and cannot be used to support labeling. Moreover, the data suggested that toxicity by inhalation route may be a hazard as judged by the persistence of effects beyond the 14 day observation period.

Because the product will be used as a spray mist and the acute inhalation data indicate that the inhalation route may be a serious hazard, a 21 day subacute inhalation study is required.

5. A dermal irritation study with the product as formulated is required in order to assure proper labeling precautionary statements.

6. The two studies submitted to determine the acute oral $LD_{50}$ in rats (for the technical material and the formulated product) revealed that triphenyltin hydroxide causes a thickening of the cardiac tissue. TOXICOLOGY BRANCH requests the necropsy reports in order to appraise the extent and significance of this lesion.

7. The current labeling of the formulated product is not consistent with a corrosive eye irritant (TOXICITY category I). The label must be changed.

8. The ingredient statement for the formulation does not total to 100%. The remaining 7.5% must be accounted for.

9. The chronic feeding study in dogs was CORE SUPPLEMENTARY, thus an additional long term feeding study is required using a non-rodent species. This requirement is being revised since the Guidelines were published in 1978. Should tolerances for triphenyltin hydroxide be otherwise allowable, the registrant will have to agree to initiate a long term feeding study in a non-rodent species when the conditions of the new requirement are established.

10. The NCI studies to determine the carcinogenesis potential of triphenyltin hydroxide were judged to be CORE SUPPLEMENTARY. Thus, in order to secure tolerances, oncogenesis studies in two species must be submitted and found to be acceptable to TOXICOLOGY BRANCH.

    Either the information noted in the review must be provided and the study found to be acceptable or new studies will have to be initiated.

11. This chemical has three potential RPAR triggers under the category of "other biological effects:"

    i. impairment of the immune reponse system

    ii. adverse effects on the male reproductive system

    iii. teratogenic/fetotoxic effects

    Thus, adequate responses to the above remarks are essential before these tolerances or others can be toxicologically supported.

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MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

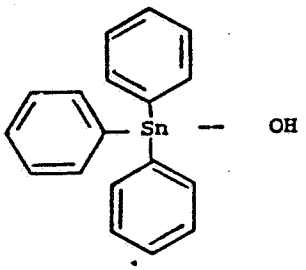
A. Substance Identification:

1. Chemical name: triphenyltin hydroxide

2. Other names: DU-TER, TPTH

3. The technical material is said to be 97% pure. Possible impurities include: [redacted]

4. Structure:




B. Other Physical/Chemical Data:

1. Density/specific gravity: not given

2. Color/physical state: white or off white solid, fine powder

3. Shaughnessey number: not known

4. Vapor pressure: not volatile

5. Solubility: insoluble in water, soluble in polarorganic solvents

6. Chemical class: trialkyltin derivative

C. Referenced Petitions:

8F0700, 0F0900, 9F0841, 3H5031, 3G1393, 3F1315, 6F0496.

D. Established Tolerances:

See 40 CFR 180.236.

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INERT INGREDIENT INFORMATION IS NOT INCLUDED CONFIDENTIAL

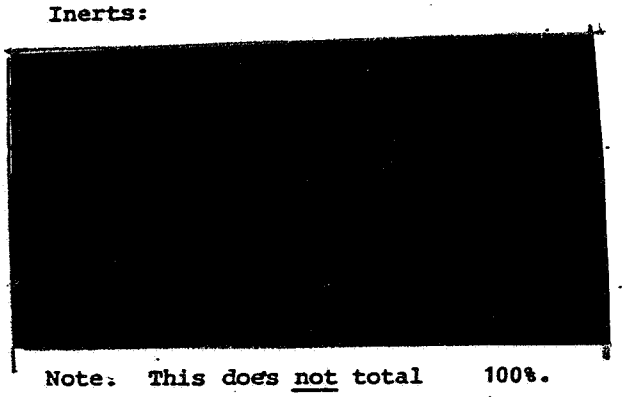
E. Formulations:

1. DU-TER Fungicide (EPA Registration No. 148-1195)

Active:

Triphenyltin hydroxide 50.0%

Inerts:



CONFIDENTIAL

Note: This does not total 100%.

2. The above formulation is also specially packed in water soluble plastic bags (EPA Registration No. 148-689)

3. The inerts are cleared under 40 CFR 180.1001 (c or d).

F. Use proposed as a spray (aerial) to control various spot diseases of soybeans prior to harvest.

SUMMARY OF TOXICITY DATA (on Technical TPTH)

| Test | Results | CORE Classification |
|---|---|---|
| Acute Oral $LD_{50}$ - rats | 313 mg/kg, males<br>345 mg/kg, females | MINIMUM |
| Acute Dermal $LD_{50}$ - rabbits | 3.0 gm/kg | Guidelines |
| Eye Irritation - rabbits | CORROSIVE | Guidelines |
| Dermal Irritation - rabbits | No study | |
| Acute Inhalation $LC_{50}$ - rats | 0.21 mg/l | SUPPLEMENTARY |

| Test | Results | CORE Classification |
|---|---|---|
| 90-Day Subchronic Feeding - rats (0, 5, 10 and 25 ppm) N.I.P.H. - Utrecht, Nov. 19, 1962 | NOEL < 5 ppm depression of leukocytes at this level in females | SUPPLEMENTARY |
| 90-Day Subchronic Feeding - guinea pigs 0, 2.5, 5, 10, 20 and 50 ppm N.I.P.H., Utrecht May 30, 1960 | NOEL < 2.5 ppm (decreased WBC at all levels) | MINIMUM |
| 90-Day Subchronic Feeding - rats (0, 1.0, 3.1, 10.0, 31.0 and 5.0 ppm) IBT, Dec. 29, 1966 | NOEL = 31 ppm(?) | INVALID |
| 90-Day Subchronic Feeding - rats (supplement to 3-generation reproduction study) Centraal Instituut Voor Voedingsonderzoek (0, 0.5, 1.0, 2.0 and 5.0 ppm) | NOEL = 1.0 ppm(?) | INVALID (insufficient determinations) no raw data. |
| 3-Generation rat reproduction (0, 0.5, 1.0, 2.0, 5.0 ppm) Centraal Instituut Voor Voedingsonderzoek, August, 1967) | NOEL = 0.5 ppm(?) (spleen and and testicular effects). | INVALID (provisionally) |
| Teratology - rat (0, 1.25, 5.0, 8.75, and 12.5 mg/kg/day. Cannon Laboratories, October 12, 1976) | NOEL for hydrocephalus and hydronephrosus not established. | CORE MINIMUM and demonstrates teratogenic effects. |
| 2-year Dog Feeding Study, (0, 0.5, 2.5, 5 and 10 ppm) Centraal Instituut Voor Voedingsonderzoek, July, 1968. | NOEL = 2.5 ppm | CORE SUPPLEMENTARY |
| 2-year Chronic Feeding/ Oncogenesis in rats (0, 0.5, 1.0, 2.0, 5.0 and 10.0 ppm) Centraal Instituut Voor Voedingsonderzoek, August, 1970 | NOEL = 2.0 ppm (WBC decreases at higher levels) Not oncogenic | CORE MINIMUM As a chronic feeding study. SUPPLEMENTARY as an oncogenesis study. |

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| Test | Results | CORE Classification |
|---|---|---|
| NCI Oncogenic Studies: | | |
| A. rat<br>0, 37.5 and 75.0 ppm | Not oncogenic | CORE SUPPLEMENTARY<br>(for oncogenesis) |
| B. mouse<br>0, 37.5 and 75.0 ppm | Not oncogenic | CORE SUPPLEMENTARY<br>(for oncogenesis) |

The NCI studies were conducted by Litton Bionetics, and the report is dated June 15, 1978 (dated as camera ready).

mmary of Toxicity Data on Formulation (DU-TER Wettable Powder, EPA Reg. 148-1195).

| Test | Results | Tox. Cat. | CORE Classfication |
|---|---|---|---|
| Acute Oral $LD_{50}$ - rats | 375 mg/kg | II | MINIMUM |
| Acute Dermal $LD_{50}$ - rabbits | 11.0 gm/kg | III | GUIDELINES |
| Eye Irritation - rabbits | CORROSIVE | I | GUIDELINES |
| Acute Inhalation $LC_{50}$ - rats | 0.243 mg/l | II | SUPPLEMENTARY |

ote: There is no dermal irritation study with this product.

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REVIEW OF STUDIES SUBMITTED

(These studies are in EPA Acc. No. 099046, 099049, -50, -51, and -52.

1. The Acute Oral Toxicity of Technical TPTH in rats

Cannon Laboratories, Inc., January 31, 1978

Five groups of ten rats (5 male and 5 female) were dosed with 0, 100, 200, 300, 400 and 500 mg/kg of "Technical TPTH" in corn oil.

Results: Animals dosed with the test chemical displayed piloerection, decreased locomotor activity, oily or wet ventral surfaces, nasal hemorrhaging, ptosis, alopecia, diarrhea, decreased food consumption, and body weight gain.

Acute oral $LD_{50}$ of -

for males 313 (422 - 232) mg/kg

for females 345 (862 - 138) mg/kg

Autopsy of all test animals revealed irregular thickening of the tissue separating the pylorus and cardia and thickening of the cardiac muscosa.

This test is CORE MINIMUM. No autopsy report is presented, the pathological findings are statements only. The autopsy report should be presented in order to appraise the extent of lesions described as irregular thickening of various tissues. Toxicity Category II.

2. The Acute Dermal $LD_{50}$ of Technical TPTH on New Zealand albino rabbits

Cannon Laboratories, February 15, 1978

Four groups of four rabbits (2 of each sex) were prepared and dosed dermally with 3, 4, 5 or 6 gm/kg body weight of Technical TPTH.

These rabbits exhibited edema, erythema, decreased locomotor activity, loss of righting reflex and mortality. All dose levels exhibited a decrease in body weight and food consumption. Necropsy revealed "injected blood vessels" in the intestines.

The dermal $LD_{50}$ was 3.00 (1.82 to 4.95) gm/kg.

This test is CORE GUIDELINES. Toxicity Category III. Following the dermal route of exposure, a persistent lesion develops.

3. Acute $LC_{50}$ Inhalation Study of Technical TPTH

Cannon Laboratories, Inc., February 22, 1978.

Groups of 10 (5 male and 5 female) rats were exposed to atmospheric concentrations of 0.18 t 0.32 mg/l for single four hour periods. The exposure chamber was a 40 liter glass housing. The atmosphere was generated as a dust using a 3-neck, roundbottom, 250 ml Pyrex flask. The dust was introduced into the chamber by blowing across the surface of the test material. The atmospheric concentration was monitored by glass fiber filters. The particle sizes were monitored by a cascade impactor.

Results: The mean particle size was determined to be 1.25 to 2.67 μ. During exposure the rats exhibited marked inactivity, reddened ears, decreased respiration, lacrimation and gasping inactivity and death. A variety of symptoms were noted during the 14 day post exposure period.

The $LC_{50}$ was determined to be 0.21 mg/li (0.25 - 0.18) for males; for females: 0.24 (mg/li) (0.26 - 0.22). This is Toxicity category II criteria.

This test is CORE SUPPLEMENTARY. The large std. errors obtained in determining the mean concentrations indicate that this chemical may be more toxic than this test determines and belong in Toxicity category I. This test indicates that this chemical may be more hazardous by the inhalation route than by the dermal or oral exposure. Even at the lower doses, some of the toxic signs persist after 14 days in the survivors. These included red ears, puffy eyes, loss of hair and moribund appearance.

4. The Effects of Technical TPTH (Lot No. pp. 523A, - 94.8%) on the eye mucosa of New Zealand albino rabbits.

Cannon Laboratories Inc., October 19, 1977

Nine New Zealand albino rabbits were dosed with 50 mg of technical TPTH by instillation into the right eye. Three of these rabbits were further treated by rinsing the eye 30 seconds after instillation.

Corneal opacity that did not reverse within 7 days developed in all 9 rabbits. Washing reduced the severity but the opacity persisted to 7 days in these rabbits.

This test is CORE GUIDELINES. Toxicity category I. The Technical TPTH is CORROSIVE.

5. The Acute Oral Toxicity of DU-TER Fungicide Wettable Powder 47.8 Active Ingredients in Rats.

Cannon Laboratories, Inc., February 23, 1978

Five groups of 10 rats (Sprague-Dawley, 5 male and 5 female) were dosed at 100, 300, 400, 500 or 600 mg/kg of DU-TER formulation and observed for signs of toxicity.

Animals displayed pilcerection, decreased motor activity, oily or wet ventral surfaces, nasal hemorrhaging, ptosis, alopecia, exophtholmas, diarrhea and dried blood around the eyes. Food consumption and body weight were decreased. The following $LD_{50}$'s were calculated:

Males = 375 mg/kg (280-502, lower and upper limits)
Females = 380 mg/kg (288-502, lower and upper limits)

It is stated that autopsy revealed irregular thickening of the border tissue separating the pylori and cardia and a thickening of the cardiac mucosa.

This test is CORE MINIMUM. The $LD_{50}$ range data exceed 10% of $LD_{50}$ value, but sufficient data to assign the classification of Toxicity Category II are obtained. The autopsy report is summary statement only and should be submitted in order to fully appraise the extent of thickening of these tissues as mentioned above.

6. The acute dermal $LD_{50}$ of DU-TER Fungicide Wettable Powder 47.5% active on New Zealand Albino Rabbits

Cannon Laboratories, Inc., February 15, 1980

Four groups of rabbits (2 per sex per dose) were prepared and dosed with 5, 8 15 or 20 gm/kg of DU-TER formulation and observed for signs of toxicity.

These rabbits showed edema, erythema, decreased locomotor activity, salivation, loss of righting reflex and mortality.

An $LD_{50}$ of 11.0 gm/kg (15.95 and 7.58 upper and lower limit) was calculated.

Necropsy revealed injected blood vessels in the intestines and trachea.

This test is CORE GUIDELINES. The product is Toxicity Category III based on dermal $LD_{50}$ data.

7. Acute Inhalation $LC_{50}$ Study of DU-TER Fungicide Wettable Powder 47.5% Active

Cannon Laboratories, Inc., February 22, 1978

Five groups of 10 Sprague-Dawley rats (5 of each sex) were exposed to atmospheric concentrations of 0.21, 0.56, 1.26, 0.34 or 0.41 mg/l) of DU-TER formulation. All exposures were in a 40-liter (36 X 36 X 31 cm glass exposure chamber.) The test substance was generated as a dust using a 3-neck, round-bottom Pyrex flask. Atmospheric concentrations were determined by using a preweighted glass fiber filter. Particle size determinations were made using a Cascade Impactor.

The rats were exposed to the test material for a single 4 hour exposure and observed for 14 days.

Results: This method of application gave standard errors ranging from 38 to 93% of the desired dose. Thus it is difficult to precisely know the atmospheric concentrations. The particle size was stated as being 1.84 to 3.41 μ.

An $LD_{50}$ of 0.243 mg/li for males and 0.275 mg/li for females was determined. Toxicity symptoms included inactivity, reddened ears, respiratory problems, eye and nasal discharges. In the surviving rats, some of these symptoms persisted to 14 days. All but one of the rats exposed to concentrations greater than 0.34 mg/l died as a result of exposure.

Necropsy revealed a variety of distension and congestion symptoms in the intestines and the lungs appeared affected in the rats that survived the 14 day recovery period. The rats that died as a result of the exposure had gelatinous material in their intestines.

This test in CORE SUPPLEMENTARY. It is apparent that this chemical is very toxic by the inhalation route of exposure. The $LC_{50}$ stated is brought into question due to the high standard errors in the determinations of the atmospheric concentrations of test material. All (except one) rats tested above the lowest dose died. The data, together with the lower limits of the $LD_{50}$, suggest an assignment to Toxicity Category I, rather than Toxicity Category II.

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8. The effects of DU-TER Fungicide Wettable Powder 47.5% active ingredients in the eye mucosa of New Zealand albino rabbits.

Cannon Laboratories, Inc., October 19, 1977

Nine New Zealand albino rabbits were divided into 2 groups: 6 in one group and 3 in the other. 50 mg of test material (DU-TER formulation) were instilled into the lower lid of the right eye. The left eye was used as a control. The 3 rabbits in the smaller group had each treated eye washed 30 seconds after instillation.

The rabbits developed severe corneal opacity that persisted to 7 days. Washing lessened the degree, but did not prevent the formation of corneal opacity.

This test is CORE GUIDELINES. Toxicity Category I. This product is CORROSIVE.

9. 90-Day Semi-chronic Investigation as to the Toxicity of Triphenyltin Hydroxide in Guinea Pigs

National Institute of Public Health - Utrecht, May 30, 1960

5 groups of guinea pigs were grouped as control (20 males and 20 females), or test groups that were dosed with 2.5, 5, 10, 20, or 50 ppm of triphenyltinhydroxide (10 males and 10 females). The test groups receiving 50 ppm were not reported in complete form in this report.

Results:

1. Depressions in weight gain were noted in both males and females in the 20 ppm test groups only.

2. Composition of the Blood

White blood cells were adversely affected.

| | Lymphocytes | | Leukocytes | |
|---|---|---|---|---|
| Dose (ppm) | M | F | M | F |
| | % less than control | | | |
| 0 | 0 | 0 | 0 | 0 |
| 2.5 | 11 | 25* | 9 | 24* |
| 5 | 2 | 29** | 6 | 25* |
| 10 | 23* | 44** | 16 | 32** |
| 20 | 32** | 49** | 25* | 44** |

Data are in % less than the corresponding control. * = p of $<$0.05; ** p of $<$.01; *** p of $<$.001.

This table indicates that there is an adverse effect at the lowest dose tested in females.

3. Organ weights and organ to body weight ratios: The following differences were noted.

| Organ | | 2.5 | 5.0 | 10.0 | 20.0 |
|---|---|---|---|---|---|
| Liver | M | - | - | 19** | 25** |
| | F | - | - | - | 16** |
| Kidneys | M | - | - | 10** | 32** |
| | F | - | - | 11* | 21** |
| Spleen | M | - | - | -12* | 16 |
| | F | - | - | -29** | -24 |
| Heart | M | - | - | - | 16* |
| | F | - | - | - | 13* |
| Brain | M | - | - | - | 36** |
| | F | - | - | 7 | 18** |
| Pancreas | M | 15* | 16* | 7 | 15 |
| | F | 8 | 11 | 19** | 19** |
| Uterus | F | - | - | -14 | -31* |
| Testis | M | - | - | - | -35* |

These data are expressed in % less than (-) or greater than the corresponding controls and are for relative weights. In summary, the NOEL for adverse effects on the weights of organs is 5 ppm.

When these data are recalculated and expressed in relative heart weight, the thymus at the highest dose level for both males and females shows an indication of a loss in weight (29% for males and 31% for females).

4. Water content of brain and spinal cord (stated as being determined as quickly as possible after death). No differences reported.

5. Protein content in the urine - none reported as being detected.

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6. Histopathology - There was noted an apparent dose dependent atrophy of lymphoid tissue (at 20 and 50 ppm) and a lesion described as mesenteric lymphnodes with mycotic inflammatory process (50 ppm).

Conclusion:

The most sensitive criterion for the evaluation of triphenyltin compounds appears to be inhibition of lymphopoiesis. (see Verschieuren et al. Fd. Cosmet Toxicol 4: 35-45 (1966).

This test is CORE MINIMUM. A NOEL for effects of TPTH on blood elements was not established. Only 10 animals of each sex per test dose were used. Not all criteria were determined to qualify this test for a 90 day feeding study.

This study gives very valuable information relating to the effects of triphenyltin hydroxide on the white blood cells.

The observation that several relative organ weights were adversely affected at 10 ppm indicates that the guinea pig is a more sensitive species than the rat. Compare, for example, the rat two year feeding study.

10. 90-Day Semi-chronic investigation as to the toxicity of triphenyltin hydroxide in rats.

National Institute of Public Health - Utrecht, November 19, 1962

4 groups of 20 rats (10 male and 10 female) were dosed with 0, 5, 10 and 25 ppm of triphenlytin hydroxide. (The 10 ppm group actually consisted of 9 females and 11 males and were fed for 12 weeks).

Results:

1. Food intake; in the later weeks females were said to consume more.

2. The data on weight gain are impossible to interpret.

3. Composition of the blood - Females exhibited a lower number of leukocytes at all doses (27% to 36%).

4. Content of the spinal fluid - No dose dependent differences noted.

5. Organ weights - In females: the adrenals were higher at both 10 and 25 ppm. The thyroid and hypophysis were lower at 25 ppm.

   In males: the thyroid and prostate were lower (29% and 22%) at the highest dose level.

   [No summary of pathology and histopathology accompanies this report]

Conclusion:

SUPPLEMENTARY: Only 10 rats/sex/dose. May be upgraded if the pathology and histcpathology reports are submitted for review. No NOEL for depression of blood elements was established by this test.

11. 90-day subacute oral toxicity of triphenyltin hydroxide - albino rats.

Industrial Biotest (B4634), December 29, 1966

6 groups of 20 rats (10 males and 10 females) were dosed with triphenytinhydroxide at levels of 0, 1.0, 3.1 10.0, 31.0 and 5.0 ppm in their diet for 90 days.

Results:

1. Weight gain - No observable adverse effects, females were lower but not progressively lower with dose. Food consumption was also not affected.

2. No untoward reactions or compound related deaths occured.

3. Hematologic studies - No consistent statistically significant dose related adverse effects are noted on lymphocytes. However, there were statistically significant depressions in lymphocytes reported.

4. Urine analysis - No differences.

5. Pathologic studies - No gross pathologic changes noted (no raw data presented).

6. Organ weight and ratio data - Only random deviation were noted.

7. Histopathological findings - No significant differences noted - raw data not presented, control and 31 ppm group only examined.

Discussion:

The testing laboratory asserts a NOEL of 31 ppm

Conclusion:

INVALID: IBT data, no raw data, summaries only, only 10 rats of each sex per dose level were tested, not all determinations were made to qualify this study for a 90-day feeding study. It is unlikely the study will be upgraded higher than SUPPLEMENTARY, therefore auditing is probably not worthwhile.

12. 90-day subacute oral toxicity of triphenyltinhydroxide in rats

[Supplemental to the reproduction study]

Central Instituut Voor Voedingoenderzock, August 1967

Rats were prepared for a 3 generation reproduction study at diet levels at 0, 0.5, 1.0, 2.0 and 5.0 ppm of technical triphenyltinhydroxide. 10 males and 10 females were selected from the $F_1b$ and $F_2b$ generations and continued on the diets for 90 days.

Results:

1. (Data are in summary tables only.) There was no compound related mortality. There were no evident adverse effects on growth, food consumption or utilization.

2. No differences in white blood cells or other elements of the blood were reported. The rats were analyzed after 14 weeks on the diet.

3. Organ weights - The kidney was higher in $F_1b$ males only at all levels, but did not exhibit a dose dependent response. $F_2b$ males were equivalent to controls. Spleen weights were higher in males ($F_1b$, high dose) and females ($F_2b$, two highest doses). Testicle weights were lower in the $F_2b$ high dose group only.

4. Gross Pathology - There was reported increased incidences of proteinacceous droplets in the kidneys of the $f_1b$ generation males only. These rats were also higher in kidney weight than others.

This test is CORE INVALID. Not all tests were conducted, data are in summary tables only. No raw data is presented.

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13. Reproduction study with Triphenyltinhydroxide in three generations of rats.

Central Instituut Voor Voedingoenderzock, August 1967

5 groups of Wistar derived rats (10 males and 20 females in each group) were dosed with diets containing 0, 0.5, 1.0, 2.0 and 5.0 ppm. These rats were mated within their groups at 12 and 20 weeks after being started on the diet to produce $F_1a$ amd $F_2b$ generations. The $F_1b$ litters were culled to produce $F_2a$ and $F_2b$ generations. $F_2b$ litters subsequently produced $F_3a$ and $F_3b$ generations. Some special attention was devoted to examining the testicles and spleens of the male rats.

In a special aspect of this experiment, 10 males and 10 females were selected from the $F_1b$ and $F_2b$ generation litters for 90-day feeding studies.

Results:

1. Health and mortality were reported as not being affected.

2. No adverse effects of triphenyltinhydroxide were reported for various aspects of fertility including number of females which cast a litter, average birth weight of the young, and average body weight of the young. All males were reported as being fertile.

3. Spleen weights of the $F_1b$ and $F_2b$ generation rats were significantly increased (see Table below).

4. Testicle weights of the $F_2b$ generation were lower (14%) than controls at 1.0 ppm and above. These weight differences were not accompanied by pathological lesions, but decreased maturation of the testicle was noted. The weight differences were statistically significant (see TABLE Below).

Average relative testicle and spleen weight of P, $F_1$b and $F_2$b generation male rats, at week 28, 24 and 28 respectively

| ppm TPTH in the ration | organ weights in g per 100 g rat | | | | | |
|---|---|---|---|---|---|---|
| | P-generation | | $F_1$b-generation | | $F_2$b-generation | |
| | testicle | spleen | testicle | spleen | testicle | spleen |
| 0.0 | 0.75 | --[1)] | 0.78 | 0.140 | 0.86 | 0.134 |
| 0.5 | 0.80 | -- | 0.80 | 0.156 | 0.78 | 0.148 |
| 1.0 | 0.74 | -- | 0.79 | 0.158** | 0.74* | 0.158** |
| 2.0 | 0.76 | -- | 0.78 | 0.155* | 0.81 | 0.147* |
| 5.0 | 0.77 | -- | 0.77 | 0.153* | 0.73** | 0.177** |

1) --: not determined

* significantly different from controls according to the test of Wilcoxon, $0.01 < P < 0.05$
** idem, $0.001 < P < 0.01$
*** idem, $P < 0.001$

Inspection of this TABLE calls into question whether or not adverse effects on the spleen are not also present at the 0.5 ppm level. For example, for the $F_1b$ generation at the 0.5 ppm level, a figure is given that is higher than the figure given for 2.0 or 5.0 ppm. However, the figures for 2.0 and 5 ppm are statistically significant. An independent statistical analysis of the data could not be performed by TOXICOLOGY BRANCH because no raw data were presented.

CONCLUSION: This test is INVALID (provisionally). No raw data were presented and TOXICOLOGY BRANCH was unable to concur with the result that suggested a NOEL of 0.5 ppm for adverse effects on spleen development.

Discussion: Triphenyltin derivatives have been reported elsewhere to have adverse effects in testis in rats (see Pate and Hays, J. Econ. Entomol. 61:32-34 (1968).

The adverse effects on spleen development cannot be ignored because other studies with triphenyltinhydroxide have demonstrated decreases in white blood cells and the lymphopietic system has been suggested as the more sensitive index of toxic action of triphenyltin compounds.

14. Observations on a possible effect of TPTH on testicular development in rats.

Central Instituut Voor Voedingoenderzock, February, 1968

This study was designed to follow-up the observations noted in the three generation rat reproduction study where a NOEL of 0.5 ppm was noted relative to apparent adverse effects on testicles and maturation of this organ.

Three successive experiments were carried out. Newly weaned rats were dosed with 0, 0.5, 1.0, 5.0 or 25.0 ppm of TPTH in groups of 10 or 20 male rats. In the first experiment, the rats were sacrificed after two weeks of feeding. In the second and third experiments, the rats were sacrificed at either 2 or 4 weeks after weaning. The weights of the testicles (relative to total body weight) were recorded. Following necropsy, the testicles were stained and examined microscopically.

Results:

1. There were no consistent dose dependent changes in relative testicle weight reported.

2. Testicular descent (relative to the body weight at descent) was not consistently affected.

3. No effects were noted in microscopic examination of the testicles.

Conclusion:

SUPPLEMENTARY DATA: This test does not resolve if TPTH can cause adverse effects on testicular development as was reported in the previous experiment. If TPTH is given while the pup is in utero or during suckling the effect may be realized.

5. Histological Studies of Testis in Rats Treated with Certain Insect Chemosterilants

B.D. Pate and R.L. Hays
J. Ecn. Etom. 61:32-34 (1968)

Dept. of Zoology and Entomology, Clemson University, Clemson, SC

The compounds triphenyltin acetate and triphenyltin chloride produced several degenerative changes in testicular tissue at doses of 20 mg/kg/day for 19 days. These lesions were described as decreases in the number of cell layers per seminiferous tubule, decrease in tubule diameter, and overall testicular size, depletion of the more advanced cell forms from the tubules and a closing of tubule lamina.

6. Investigation of Teratogenic and Toxic Potential of Technical Triphenyltinhydroxide (in rats).

Cannon Laboratories, Inc., October 12, 1976

5 groups of Sprague-Dawley rats were dosed with 0, 1.25, 5.0, 8.75 or 12.5 mg/kg b.w. of triphenyltinhydroxide on days 6 through 15 of gestation. Each group, except the 5.0 gm/kg dose group, consisted of 20 pregnant rats. The 5.0 gm/kg group consisted of 19 pregnant rats.

Results:

A. Maternal effects. There was one abortion in the 8.75 mg/kg dose group and 3 abortions in the 12.5 mg/kg dose group. These abortions were considered to be test chemically related. Body weight gain in the two highest dose groups was lowered (31% and 47%). At the two highest doses the % live fetuses, % dead fetuses, resorptions, and mean fetal weight were all adversely affected.

B. Fetal examination (1/3 of pups).

1. External - No dose dependent abnormalities were noted (all pups reported as being examined).

2. Visceral examination (Wilson technique). Increases in hydrocephalus and hydronephrosis were realized as indicated in the following table.

| Dose Level mg/kg | Hydrocephalus % | Hydronephrosis % |
|---|---|---|
| 0 | 1.6% (1/94) | 2.1% (2/94) |
| 1.25 | 20% (15/75) | 6.6% (5/75) |
| 5.0 | 10.9% (8/73) | 16.4% (12/73) |
| 8.75 | 14.8% (7/47) | 34% (16/47) |
| 12.5 | 30% (6/20) | 36% (6/20) |

3. Skeletal observation (2/3 of pups), Alizorin technique. No truly dose dependent abnormalities were reported.

CONCLUSION:

No NOEL for the fetotoxic/teratogenic effects of hydrocephalus and hydronephrosis was obtained. This test is CORE MINIMUM - no concurrent positive control was included.

17. Chronic (two-year) toxicity study with triphenyltinhydroxide (TPTH) in beagle dogs.

Central Instituut Voor Voedingoenderzock, July, 1968.

Thirty-four beagle dogs were used in this test. They were grouped as controls (5 males and 5 females) and four test groups (3 males and 3 females). All dogs were started in the experiment within 3 months of each other, and were fed the test diet for 2 years. Hematological, biochemical, urinalysis tests were determined at weeks 13, 26, 52, 78, and 102. Other tests were conducted at termination. Four weeks were allowed from the last test dose diet day to sacrifice. Dose levels were 0, 0.5, 2.5, 5 and 10 ppm.

1. General appearance and behavior. - There were no consistent dose dependent abnormalities noted.

2. Growth and food consumption. There were no dose dependent effects noted.

3. Clinical and biochemical observations and urine analysis. No differences in hematological (blood cell count), biochemical values (BUN, blood sugar, SAP, SGPT, and SGOT, or urine analysis were reported.

4. Liver function test. (sulphobromophthalein method) at week 103 and kidney function test (phenol red excretion method) at week 103 did not indicate a dose dependent effect.

5. Hair color - Indicated a more rapid hair growth in dogs in test levels of 5 and 10 ppm than in controls and 0.5 and 2.5 ppm.

6. Organ weights - Possibly some effects at 5 and 10 ppm. Thyroids were lower at all levels, but dose response is questionable.

7. Water content of the brain. The laboratory report states that the water content of the cerebrum, frontal and parietal lobe was slightly higher in the two highest test dose groups than in the other groups.

8. Pathology - Gross examination. No consistent pathological lesions reported.

9. Histopathology - No consistent pathological lesions reported.

Note: Because there were only 3 dogs per sex per test group, pathology and histopathology are of limited value.

CONCLUSION:

This test is CORE SUPPLEMENTARY, only three dogs of each sex at each dose level. Organ weight differences are not interpretable. The four week "recovery period" should not have been allowed because the nature of this chemical suggests transitional edema of internal organs. A NOEL of 2.5 ppm is assigned.

Chronic toxicity study with triphenyltinhydroxide in rats for two years.

Central Instituut Voor Voedingoenderzock, August, 1970

Six groups of 50 Wistar rats (25 males and 25 females) were segregated and fed diets containing 0, 0.5, 1.0, 2.0, 5.0 and 10.0 ppm of TPTH for 2 years.

**Results:**

1. From 10-15 of the 25 males survived the 2-year dosing. Females appeared to survive better, from 15-21 were alive after 2 years. There was no consistent dose related mortality. General health is described as not being adversely affected.

2. No adverse effects on weight gain or food consumption were noted.

3. Hematology - There were statistically significant depressions of WBC (at 6, 13, 26 weeks for males at 5 and 10 ppm and on week 26 at 2 ppm). Other variations were considered incidental.

4. Blood sugar and urea nitrogen showed only incidental variations.

5. Urine analysis - (sampled at weeks 32, 76, and 102). No changes noted.

6. Serum enzymes (SGPT, SGOT, SAP) gave essentially equivalent activity for all dose levels.

7. Body weight and organ weights - (determined on survivors). No differences are reported for heart, kidney, liver, brain, ovary, eye, pituitary, and adrenal. This reviewer notes that the spleens were 18% (females) and 15% (males) lower than controls for the high dose groups. The thyroids for the females were 12% lower and 9% lower for males.

8. No gross pathologic lesions were noted.

9. Histopathology (TAB 18) was conducted on the controls and 10 ppm test group only. 25 males and females from the control group and 24 males and females from the test group were examined. No chemically related lesions were noted. [This reviewer notes that there were 9 incidences of atrophy of the thymus in the high test group vs. 3 incidences in the control group (males)].

   This test is CORE MINIMUM for a chronic feeding study. A NOEL for a 2-year chronic feeding study ~~of~~ is 2 ppm. At 5 and 10 ppm there was noted a decrease in white blood cell formation. This test is CORE SUPPLEMENTARY and does not qualify as an oncogenesis study because only 25 rats of each sex were used and an even lesser number endured the two-year feeding.

Most of the data are in summary tables only without supporting individual animal data.

Bioassay of triphenyltin hydroxide for possible carcinogenicity (in rats and mice).

National Cancer Institute. [Contracted to Litton Bionetics, Inc. Bethesda, Maryland].

DHEW Publication No. (NIH) 78-1394.

Part A - Rats (Fischer 344)

Three groups of rats were dosed with 0, 37.5 or 75 ppm triphenyltin hydroxide for 78 weeks and allowed 26 weeks to recover. Controls consisted of 20 males and 20 females. Test groups consisted of 50 males and 50 females.

Results:

1. Survival was always greater than 75% for both males and females.

2. There was no dose related incidences of tumor pathology reported.

SUPPLEMENTARY DATA for oncogenesis. Not acceptable as a chronic feeding study.

Part B - Mice (B6 C3F1) - Same protocol as with rats.

1. No abnormal clinical signs were reported, body weight was not adversely affected. Male survival rate was 95% (co trols), 74% of the low dose group and 66% of high dose males survived. A dose dependent increase in mortality that was statistically significant resulted. Female mortality was equivalent in all test groups.

2. There was no dose dependent increase in tumors noted.

SUPPLEMENTARY Data for oncogenesis. It is noted that allowing 26 weeks for "recovery" following the last day on the test diet might have obscured transient but serious lesions induced by this chemical.

Note: These studies were classified as CORE SUPPLEMENTARY for the following reasons.

i. Individual pathology reports both gross and histological were not included. The data are in summary form only.

ii. The rats used in these experiments were not kept on their diets for their life span (or at least 24 months). They were fed the test chemical for only 17 months. In addition they were allowed to live for 6 months after cessation of feeding the test chemical.

iii. Organ weight data were neither collected or reported or at least not reported if collected.

iv. There are no signed reports for the various aspects of these studies. Thus, it is not possible to determine the individuals responsible for the observations and conclusions.

v. Other individual animal data are not reported (body weight, death, etc.).

vi. These studies may be upgraded if the above information is provided and the studies when reviewed in their entirety are found to be acceptable to TOXICOLOGY BRANCH.

Screening triphenyl tin hydroxide (Alfa 717) in the Ames Salmonella Typhimrium mutagenicity assay.

By H. E. Bryant, report dated October 4, 1976 (The name and location of this laboratory is not stated).

This report states that triphenyl tin hydroxide was tested in the Salmonella Typhimurium assay system as described by Ames et al. (Mutation Research 31: 347-367 (1975). The strains used were TA-98, -100, -1535, -1537, -1538, and -1978. Both activation (S-9 liver supernatant) and non-activation assays were run. Acetylaminoflurorene was used as a postive control. Both a spot test and a test where TPTH was suspended in the nutrient were run.

The results indicated that TPTH was extremely toxic to the bacteria (1.0 µg/plate was found to be the working range). In no case was there evidence that TPTH was a mutagen in this system.

CONCLUSION:

No CORE assignment.