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CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
JUL 12 1985 WASHINGTON, D.C. 20460

004542

MEMORANDUM

SUBJECT: PP# 2F2618; Propazine in/on sorghum; revised Section B and Section F
Caswell No. 184

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Robert Taylor
Product Manager (25)
Registration Division (TS-767)

and

Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

6/7/85

THRU: Robert P. Zendzian, Ph.D.
Acting Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William Dykstra, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

5/20/85

WAD 7.1.85

Requested Action:

Request to complete risk assessment for revised Section F, deleting sweet sorghum, and revised label adding restriction, "Do not use on sweet sorghum."

Conclusions:

1. The submitted studies are acceptable as core-minimum data. The oncogenic mouse study is negative for oncogenicity at doses up to 3000 ppm. The NOEL for the 3-generation reproduction study is 100 ppm.

2. In the two-year chronic feeding study in rats, propazine is considered oncogenic in female rats at the high-dose level of 1000 ppm. A significantly increased incidence of mammary gland tumors was observed.

Recommendation:

1. A quantitative risk assessment for dietary and applicator exposure is needed to complete the requested action.

Background:

Propazine was identified as a positive oncogen in female rats, producing a significant increase in tumor bearing animals at the high-dose of 1000 ppm.

On this basis, the review of propazine was referred to the Ad Hoc Committee on 6/16/84. The concesus of the committee was that a decision could not be reached based on the review of the studies. The committee requested that additional re-evaluation of the studies be performed and new reviews be presented. The presentation to the committee has been scheduled for May, 1985.

Review:

Section F Proposed Tolerances

Tolerances for residues of Propazine: 2-chloro-4,6-bis (isopropylamino)-s-triazine and its dealkylated metabolites determined as 2-amino-4-chloro-6-(isopropylamino)-s-triazine and 2,4-diamino-6-chloro-s-triazine in or on the following raw agricultural commodities are proposed;

| | |
|---|---|
| 1.0 ppm | Sorghum forage and fodder |
| 0.02 ppm | Milk and eggs |
| 0.05 ppm | Meat, fat and meat byproducts of cattle, goats, hogs, horses and sheep, excluding kidney and liver |
| 0.10 ppm | Liver and kidney of cattle, goats, hogs, horses, poultry, and sheep |
| 0.25 ppm | sorghum, grain |

1. Tolerances have been established in 40 CFR 180.243.

2. Two-year carcinogenicity study in mice with technical propazine (IRDC #: 382-004; April 24, 1980).

Test material: propazine technical; ARS No. 2046176; Batch No. FL-761357; 35 lbs., white powder.

Details of the materials and methods are attached as Appendix A.

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a. Study Author's results, and conclusions:

"No signs of overt toxicity were observed for any of the treated mice. No compound-related effects were observed with respect to the incidence of palpable masses, survival, group mean body weights or food consumption."

"No compound-related gross or microscopic changes were observed. The inflammatory, degenerative, proliferative and/or neoplastic changes described were considered of spontaneous nature, the prevalence of which were generally similar for both control and treatment groups and unrelated to compound administration. The slight increased incidence of lymphoreticular tumors seen initially among female mice at 3000-ppm treatment group was eliminated upon reevaluation of the data and examination of affected tissues in the 3 and 1000 ppm dietary levels." end of quote.

b. Reviewer's results and conclusions:

No compound-related toxic signs were recorded. Toxic signs observed most frequently in controls and test groups were pale skin, alopecia, tremors, corneal opacity, soft stools, altered posture, material on abdomen, ulcerations, and labored breathing. Mortality, body weight, and food consumption were unaffected by treatment.

The number of survivors in each group is shown below:

Survival at Termination of Study:

| ppm | Males | Females |
|---|---|---|
| 0 | 27 | 33 |
| 3 | 35 | 34 |
| 1000 | 37 | 27 |
| 3000 | 37 | 23 |

Palpable masses recorded did not display any compound-related findings.

The incidence of palpable masses in the study in shown below:

| ppm | Male palpable masses/no. examined | Female palpable masses/no. examined |
|---|---|---|
| 0 | 10/60 | 10/60 |
| 3 | 18/60 | 11/60 |
| 1000 | 3/60 | 15/60 |
| 3000 | 11/60 | 7/60 |

Only three animals with palpable masses did not have a microscopic evaluation (3 ppm, male 24851 and male 25853; 1000 ppm, female 25062).

A good correlation of gross findings and microscopic findings was observed in all groups.

The incidence of amyloidosis in control and high-dose mice did not show any compound-related effect.

Amyloidosis in control and high-dose male and females is shown below:

Amyloidosis

No. affected/no. examined

| ppm | Male | Female |
|---|---|---|
| 0 | 53/59 | 56/60 |
| 3000 | 58/60 | 57/60 |

Other non-neoplastic lesions occurred at increased incidences in high-dose male and female mice.

In females, myocardial degeneration of the heart was increased as follows:

No. affected/no. examined

| | |
|---|---|
| 0 ppm | 4/60 |
| 3000 ppm | 17/59 |

For males, hemosiderin laden macrophages of the liver occurred in the follow manner.

No. affected/no. examined

| | |
|---|---|
| 0 ppm | 3/60 |
| 3000 ppm | 15/60 |

These non-neoplastic finding are considered compound-related.

Neoplastic lesions did not occur in a compound-related fashion.

Preliminary evaluation of the reticuloendothelial system indicated a significant increase in malignant lymphoma in females at 3000 ppm.

The distribution was as follows as reported in the study.

| ppm | 0 | 3 | 1000 | 3000 |
|---|---|---|---|---|
| No. examined | 61 | 49 | 45 | 59 |
| malignant lymphoma | 16 | 20 | 30 | 32* |

*P<0.01

However, instead of counting the presence of malignant lymphoma as only one per animal, it was erroneously reported in terms of the total number of tumors per group.

A re-evaluation of the incidence of malignant lymphomas in female mice based on one per animal is presented below.

The following table also shows the lack of an effect of latency in tumor development in female mice.

Latency and Incidence of Malignant Lymphoma/Reticulum Cell Sarcoma

(Control)

*Animal number
a weeks on study

Female

| 0 ppm | Weeks | 3 ppm | Weeks | 1000 ppm | Weeks | 3000 ppm | Weeks |
|---|---|---|---|---|---|---|---|
| 24783* | 105[a] | 24903 | 85 | 25027 | 81 | 25149 | 85 |
| 24788 | 105 | 24908 | 76 | 25032 | 88 | 25152 | 89 |
| 24791 | 105 | 24922 | 96 | 25048 | 50 | 25172 | 20 |
| 24806 | 20 | 24923 | 51 | 25056 | 86 | 25174 | 105 |
| 24831 | 83 | 24942 | 105 | 25059 | 105 | 25177 | 27 |
| 24842 | 93 | 24951 | 102 | 25062 | 72 | 25183 | 84 |
| 25203 | 105 | 24952 | 80 | 25064 | 82 | 6 | |
| 7 | | 24960 | 105 | 25065 | 105 | | |
| | | 8 | | 25072 | 90 | | |
| | | | | 25078 | 40 | | |
| | | | | 10 | | | |

Conclusion:

Propazine was not oncogenic in mice. The presence of significant incidences of non-neoplastic lesions in high-dose males were hemosiderin laden macrophages and myocardial degeneration in high-dose females.

Classification: Core minimum data.

3. Two-year chronic oral toxicity study in rats (IRDC # 382-007; 4/28/80).

Test material: Propazine technical; ARS No. 2046/26; Batch No. FL-761357; 35 pounds; white powder.

I. Details of the Materials and Methods are attached as Appendix B.

a. Study author's results and conclusions.

"A slight increase in subcutaneous nodules and masses in female rats from the 1000-ppm group was considered possibly compound-related. No organ weight variations of toxicological significance were observed. There was an increase in the number of adenomas in the mid- and high- dose group, in the number of papillary carcinomas in the low- and high- dose group and in adenocarcinomas in all treated groups without any dose relationship. None of these increases were statistically significant and none were considered treatment related." end of quote.

b. Reviewer's Results and Conclusions.

No treatment-related toxic signs were observed in any group. No compound-related effect on survival was observed. At termination of the study the following animals survived.

| ppm | males | females |
|---|---|---|
| 0 | 31 | 36 |
| 3 | 42 | 37 |
| 100 | 46 | 46 |
| 1000 | 38 | 25 |

Body weight of males and females of the high-dose were significantly decreased in comparison to controls.

Food consumption was significantly decreased in high-dose male and female rats. However, this finding was not considered totally responsible for the decreased body weight differences in these groups.

No compound-related effects were noted in hematology, clinical chemistry or urinalyses in controls and the 1000 ppm groups.

Gross necropsy findings showed an increase of subcutaneous masses and nodules in females of 1000 ppm group. These increased nodules correlated with the increased microscopic finding of mammany gland neoplasms.

Organ weights at terminal sacrifice showed an increased relative liver weight in females 1000 ppm, a decreased absolute kidney weight in 1000 ppm males and a decreased absolute brain weight in females of the 1000 ppm group.

At termination of the study, the following animals were examined.

| Group | Dosage Level | sex | terminal sacrifice | moriburd sacrifice and deaths | total evaluated |
|---|---|---|---|---|---|
| I | control | m | 26 | 18 | 44 |
| | | f | 36 | 19 | 55 |
| II | 3 ppm | m | 36 | 10 | 46 |
| | | f | 37 | 20 | 57 |
| III | 100 ppm | m | 42 | 11 | 53 |
| | | f | 44 | 16 | 60 |
| IV | 1000 ppm | m | 36 | 18 | 54 |
| | | f | 25 | 30 | 55 |

There was a good correlation between gross and microscopic findings.

Neoplasms involving the mammary gland included adenomas, adenocarcinomas, fibroadenomas, papillary adenomas and papillary carcinomas.

Mammary gland tumors were increased in high-dose female rats as follows:

| ppm | No. of tumor-bearing animals/ no. examined |
|---|---|
| 0 | 27/56 |
| 3 | 33/57 |
| 100 | 32/60 |
| 1000 | 39/55 *P<0.05 |

The increase in tumor-bearings animals is significant and considered compound-related.

The most frequent mammary tumor was fibroadenoma.

The distribution and type of mammary gland tumors in control and high-dose female rats is presented in Table I.

Additionally, no treatment-related non-neoplastic lesions were observed.

Conclusion: A compound - related increase in mammary gland tumors in female rats was observed. Other toxicological parameters examined did not show any treatment-related findings. NOEL = 100 ppm; LEL = 1000 ppm; positive for oncogenicity at 1000 ppm.
Classification: Core minimum data. WHO

Table 1

Mammary Tumors in Female Rats Fed Propazine

* Number of tumor-bearing animals

| | Group I - control | | | | | Group IV - 1000 ppm | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Terminal | Moribund | Deaths | Total | % | Terminal | Moribund | Deaths | Total | % |
| No. examined | 36 | 8 | 12 | 56 | | 25 | 15 | 15 | 55 | |
| Papillary carcinomas | 2* | 1 | 0 | 3 | 5.4 | 6 | 1 | 3 | 10 | 18.2 |
| Fibroadenoma | 12 | 0 | 3 | 15 | 26.8 | 8 | 5 | 3 | 16 | 29.0 |
| Papillary adenoma | 1 | 0 | 0 | 1 | 1.8 | 0 | 1 | 1 | 2 | 3.6 |
| Adeno carcinoma carcinoma | 5 | 1 | 0 | 6 | 10.7 | 6 | 3 | 1 | 10 | 18.1 |
| Ductular adenoma | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 1.8 |
| Cystadenoma | 1 | 0 | 0 | 1 | 1.8 | 0 | 0 | 0 | 0 | 0 |
| Adenoma | 1 | 0 | 0 | 1 | 1.8 | 0 | 0 | 0 | 0 | 0 |

4. Three generation reproduction study in rats with propazine technical (IRDC # 382-010; 8/10/79).

Test material: Propazine technical; ARS. No. 2046/76; Batch No. FL-76/357; 35 lbs; white powder.

Details of the materials and methods are attached as Appendix C.

a. Study author's results and conclusions:

"No biologically meaningful differences were seen in the food consumption values in all $F_0$, male treatment groups, in the 3 and 100 ppm $F_0$, $F_1$, and $F_2$ females, and in the 1000 ppm $F_1$ females when compared to the control values. A slight reduction in food consumption was observed in the 1000 ppm dosage groups of the $F_0$ and $F_2$ females and in all treatment groups of the $F_1$ and $F_2$ males when compared to the control group."

"No treatment-related differences were seen between the treated and control groups with regard to the male and female fertility indices, length of the gestation periods and the viability and survival of the pups."

"No biologically meaningful differences were seen in the mean pup body weights of the litters in the 3- and 100- ppm treatment groups when compared to the control litters. At the 1000-ppm treatment level, the mean pup body weights of each of the six litters produced were consistently lower than the mean weights of the control pups."

"No gross or microscopic pathological lesions which were considered compound-related were observed in the $F_0$, $F_1$, $F_2$ parental rats or $F_{3b}$ weanling rats. The changes described among these rats were considered of spontaneous nature, not uncommon to rats of this age, and were present in most instances among control and 1000-ppm dose level rats."

"A dose level of 100 ppm Propazine technical or less produced no biologically meaningful signs of parental or pup toxicity when administered in the diet during a three-generation reproduction study in rats. Therefore, the no observable effect level (NOEL) in this study was 100 ppm." end of quote.

b. Reveiwer's Results and Conclusions.

No compound-related effects in toxic signs and mortality were observed during the study.

At 1000 ppm during the study, decreased body weight was observed in male and female parental animals.

Food consumption was reduced at 1000 ppm in the $F_0$ and $F_2$ females and at 3,100, and 1000 ppm of the $F_1$ and $F_2$ male groups.

No compound-related effects in male fetility, female fertility, gestation length, pup viability and pup survival were observed in any litter during the study.

Mean body weights of male and female pups at day 21 of lactation were significantly reduced at 1000 ppm in the $F_{1b}$, $F_{2a}$, $F_{2b}$, $F_{3a}$ and $F_{3b}$ litters. This finding in considered compound-related.

At necopsy of parental animals and 21-day old pups, no treatment-related effects were recorded. Absolute and relative organ weight variations were observed in parental animals.

In the $F_0$ animals, males showed an increased relative testicular and relative heart weight at 1000 ppm.

Males of the $F_1$ parental group at 1000 ppm displayed increased relative liver and heart weight.

In the $F_2$ parental animals at 1000 ppm, males and females had decreased absolute liver weight, males had decreased relative liver weight, decreased relative testicular weight, and decreased absolute kidney weight.

At 100 ppm, females had decreased absolute and relative ovarian weight. This finding is not considered compound-related since it was not observed at 1000 ppm.

At 3 ppm, females had an increased relative liver weight. This finding is not considered compound-related, since females at higher dosage level did not show this finding.

No histological effects were present in parental animals which could further explain the organ weight variations.

Additionally, no effects in incidence or grade of histological findings were present in $F_0$, $F_1$, and $F_2$ parental animals and $F_{3b}$ weanlings at 1000 ppm in comparison to controls.

Conclusion: The NOEL for reproductive parameters is 100 ppm. At 1000 ppm, the LEL, decreased pup body weights at day 21 of lactation were significantly reduced in the $F_{1b}$, $F_{2a}$, $F_{2b}$, $F_{3a}$ and $F_{3b}$ litters of both males and females.

Organ weight variation at 1000 ppm was also recorded in parental animals. No histological findings were obsrved in parental or weanling animals.

Classification: Core minimum data.

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Test for significance of differences between proportions

Female survivor

| ... | ... | ... | ... | One tail z statistic Fisher's |
|---|---|---|---|---|
| ... | 33 | 33 | 33.00+/-(13.42) | |
| ... | 34 | 33 | 33.97+/-(13.37) | -0.510 |
| 1000.000 | 27 | 10 | 45.14+/-(13.42) | $$$$$$ |
| 3000.000 | 23 | 33 | 33.33+/-(13.33) | $$$$$$ |

The linear trend test often gives incorrect results

Test for a linear trend is not significant

PROPAZINE

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