



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

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 5-chloro-2-(2,4-dichlorophenoxy)phenol [Triclosan]: Review of preliminary results from a hamster chronic bioassay submitted under FIFRA 6(a)(2).

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03-30-99

Submitter: Ciba Specialty Chemicals Corporation

Action Requested: Review of previously unobserved toxic effects from administration of Triclosan to hamsters in a chronic bioassay.

Background

The Consumer Care Division of Ciba Specialty Chemicals Corporation ("Ciba") submitted preliminary results of a chronic oral hamster bioassay to the Antimicrobials Division, U.S. Environmental Protection Agency, under FIFRA 6(a)(2). These data were submitted under this statute due to previously unobserved toxic effects which were observed in the hamster bioassay. This particular submission (S556955) is in addition to previously submitted 6(a)(2) data on this same study (S541796).

I. Hamster Bioassay

In the chronic hamster bioassay, groups of 60 male and 60 female hamsters received Triclosan in the diet at doses of 0, 0, 12.5, 75, and 250 mg/kg/day for either 95 weeks (males) or 90 weeks (females). These termination times were based on FDA survival criteria which indicate that study termination should occur when survival approaches 20 animals in any dose group. It is noted that these criteria differ from OECD survival criteria for carcinogenicity studies (Guideline 451), which state a termination date of 24 months for hamsters, or when survival reaches 25 percent in lower dose groups or control. A negative test is only acceptable if no more than 10 percent of the animals are lost to cannibalism, autolysis, or management problems, or survival of all groups is no less than 50 percent at 18 months.

The results as presented in this submission do not appear to contain all of the animals used in this study. There are varying numbers of tissues reported as having been examined in the various dose groups; thus, the true significance in the absence of the final report is unknown. However, it is certain that effects on the kidneys, epididymides, testes, and stomach are observed at a dose of 250 mg/kg/day. Whether effects are also observed at lower doses cannot be determined on the basis of the preliminary data reported in this submission.

The following effects were reported in this submission (data appear for approximately half of the animals in each dose group):

- 1) Decreased survival was observed in high dose male hamsters vs control and lower dose groups (35% survival vs. 65-80% survival in other groups). Female hamsters showed no differences in survival when comparing treated and control groups. There were no reported adverse clinical signs in this submission.
- 2) Decreased group mean body weight in both sexes at the high dose beginning around week 13 of the study and continuing until study termination. Decreased group mean body weight was also observed in male hamsters at the 75 mg/kg/day dose level.

3) Increased urinary volume ($p < 0.01$) and decreased specific gravity ($p < 0.01$) in male and female hamsters at the high dose vs. control and lower dose groups. Other effects noted included decreased group mean urinary protein values at weeks 13 and 65 for the 250 mg/kg/day dose group, and altered urinary pH values at various time points of the study.

4) Hematologic effects in male hamsters, including: decreased prothrombin time at 12.5, 75, and 250 mg/kg/day ($p < 0.05$); decreased mean corpuscular hemoglobin concentration at 75 and 250 mg/kg/day; increased mean corpuscular volume at 75 and 250 mg/kg/day; and increased white blood cell count and neutrophil count at 250 mg/kg/day ($p < 0.05$). Hematologic effects in female hamsters including decreased packed cell volume, hemoglobin, red cell count, mean corpuscular volume, and reticulocyte count at 250 mg/kg/day ($p < 0.05$ or 0.01); increased total white blood cell count, leukocyte count, and eosinophil count at 250 mg/kg/day ($p < 0.05$ or 0.01).

5) Serum biochemistry effects in male hamsters, including decreased SGPT at 250 mg/kg/day ($p < 0.01$); increased potassium and calcium at 250 mg/kg/day ($p < 0.05$); increased serum triglyceride at 75 and 250 mg/kg/day ($p < 0.01$); and increased urea nitrogen at 250 mg/kg/day ($p < 0.05$). In females, decreased SGPT and decreased A1 and A2 proteins at 250 mg/kg/day ($p < 0.05$ or 0.01).

6) Decreased absolute weight of the heart, lungs, liver, prostate, and salivary glands in male hamsters at 250 mg/kg/day ($p < 0.05$ or 0.01); in female hamsters, increased weight of the adrenals at 12.5, 75, and 250 mg/kg/day ($p < 0.05$), decreased weight of the uterus ($p < 0.01$).

In addition to the above effects, the submitted data cited adverse effects on the testes and epididymides of male hamsters at the 250 mg/kg/day dose, and adverse effects on the kidney and stomach in male and female hamsters at the 250 mg/kg/day dose.

The effect in the testes was characterized as partial depletion of one or more generations of germ cells. Total incidence of this effect for animals examined at study termination (based on number of testes examined, NOT number of animals) was 7/39, 7/43, 6/6**, 6/6**, and 9/21*, for the 0, 0, 12.5, 75, and 250 mg/kg/day dose groups, respectively. Incidence for those dying or killed on study was 5/21, 5/17, 5/17, 3/14, and 32/39* for the 0, 0, 12.5, 75, and 250 mg/kg/day dose levels respectively. The severity of this lesion appeared to be increased from 12.5 mg/kg/day upward. The effect in the epididymides was characterized as abnormal spermatogenic cells, reduced numbers of spermatozoa and absence of spermatozoa. These effects appeared increased primarily at 250 mg/kg/day, but effects at lower doses cannot be ruled out until a final report is obtained.

Kidney nephropathy (total incidence) was reported in male hamsters as 34/39, 33/43, 31/44, 34/46, and 21/21 for those examined at study termination, and 7/21, 5/17, 4/17, 2/14, and 35/39** for those killed or dying during the study for the 0, 0, 12.5, 75, and 250 mg/kg/day dose groups, respectively. The number of male hamsters with moderate and marked nephropathy

appeared increased at the 75 and 250 mg/kg/day dose levels. In female hamsters, incidence of kidney nephropathy was reported for hamsters examined at study termination as 11/24, 13/22, 14/28, 10/35, and 27/29** and for hamsters killed or dying during the study as 8/36, 8/39, 12/31, 9/25, and 23/31** with an increase in number of female hamsters characterized with moderate and marked nephropathy at the 75 and 250 mg/kg/day dose level. Note again that these numbers are preliminary and a final report has not been reviewed, AND that incidence is based on number of kidneys examined, NOT numbers of animals.

In the stomach, focal hyperplasia and focal atypical hyperplasia were reported in increased incidence in male and female hamsters. Doses lower than 250 mg/kg/day did not appear to cause any significant incidence of this lesion.

Conclusions

The submitter has stated that the true significance of the histopathological effects observed in this study (testes, epididymides, kidneys, stomach) is uncertain, pending completion of microscopic examination of the remaining dose groups and consideration of the historical incidence of spermatogenesis data in hamsters. A 2-generation reproduction study conducted in rats, previously reviewed by the Agency, did not show any adverse effects on fertility or reproduction.

The Risk Assessment and Science Support Branch, Antimicrobials Division, concludes the following from the submitted data:

1) Preliminary results of the hamster bioassay indicate potential effects of Triclosan on the testes and epididymides of male hamsters, and effects on the kidney and stomach of male and female hamsters. These effects have not been previously observed in any of the studies reviewed by the EPA. A final determination as to the significance of these findings will have to await receipt and review of the final report from the submitter.