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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of 8(e)-0729 Submission

FROM: Susan Griffin, Ph.D.
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Susan Griffin

TO: Dave Williams
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THRU: for Stephanie Irene, Ph.D.
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Attached please find my review of the oral toxicity studies on the 8(e) compound ethyl sulfluramid.

Attachment

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Review of 8(e) -0729

The 8(e)-0729 submission consisted of a limited summary and discussion of two separate feeding studies conducted with ethyl sulfluramid, a chemical which is being developed for use as a pesticide. The submitter states that a more detailed draft report is in preparation.

Conclusion

The 8(e) compound, ethyl sulfluramid, was administered orally to beagle dogs in 2 separate 3 month feeding studies. The test compound produced dose-related mortalities and clinical signs of severe toxicity (emaciation, vomiting, diarrhea) at doses as low as 50-100 mg/kg/day. The surviving dogs exhibited toxicity to the male reproductive system as characterized by decreased sperm production and a maturational arrest of spermatogonia. Mature dogs appear to be more sensitive to these toxic effects of the test compound than sexually-immature dogs.

Basis

In the initial 13 week oral toxicity study, 4 juvenile beagles (7-8 months old) /sex/group were administered 0, 100, 300 or 1000 mg/kg/day ethyl sulfluramid either in capsules or dietary admixture. Mortalities and severe clinical signs of toxicity (emaciation, vomiting, diarrhea and depression) were observed after one week of dosing, therefore the doses were reduced to 50, 100 and 300 mg/kg/day. Deaths continued to occur at the mid and

high dose levels until Day 14 and then stopped. Histopathological examination after week 13 revealed an absence of sperm in the seminiferous tubules and epididymis for all treated male dogs. No other toxic effects were noted. The submitters felt this was not a reliable study because (1) the initial doses were too toxic, (2) some dose groups received the test chemical via gelatin capsule while others received it as diet admixtures, and (3) the dogs used in the study were not sexually mature and the absence of sperm production may have been chance rather than treatment-related.

A second 90 day study was conducted in which 10 mature (1.5 - 2 years old) and 10 juvenile (6 months old) beagles were given 100 mg/kg/day ethyl sulfluramid via capsule. Two mature and two juvenile beagles were used as controls. Signs of clinical toxicity similar to those seen in the initial study were observed. One fatality occurred on day 20. The dosage was decreased to 50 mg/kg/day and alternated with weeks wherein the dosing was suspended. Four of the ten mature dogs died by week 13. None of the juvenile dogs died.

After 3 weeks of dosing, a time related decrease in sperm counts was observed with "most" of the treated dogs during the dosing periods. In "some" cases sperm counts returned to normal levels when dosing was suspended and became reduced again approximately 3 weeks after dosing was reinitiated. Sperm counts for the juvenile dogs were variable and no treatment-related effects could be determined.

Unilateral castration was performed on the mature dogs when the sperm counts were low (presumably after the last dosing period). The seminiferous tubules were lined only by Sertoli cells and either one or several layers of spermatogonia in 5 of the 6 remaining dogs. No sperm were seen in the tubules of the epididymis in 4/6 dogs. The remaining testicle was removed at week 32, following the recovery period. Five/6 dogs had recovered full sperm production. Reversal of toxic reproductive effects, however, are not considered meaningful according to the Federal Guidelines for reproductive toxicity (unpublished). Unilateral castration of the juvenile dogs after Week 13 showed 4/10 dogs with 80% or more of the seminiferous tubules lined only with immature spermatogonia and/or Sertoli cells. The rest of the animals exhibited 80-100% normal spermatogonia and Sertoli cells. Nine/10 dogs had sperm within the tubules. Castration following the recovery period (week 32) showed 7/10 dogs with normal seminiferous tubules and 3/10 with less than 10% immature spermatogonia.