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CASWELL FILE

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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

SUBJECT: Collaborative Review of Prometon Data
Record # S394514, EPA ID # 080804

Tox Chem 096
HED Proj #
1-1026

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I have reviewed the prometon data which were submitted to the OPP. The entire prometon package consists of a one year chronic oral dog study, a 2-generation reproduction study in rats and a two year rat and mouse oncogenicity study. My comments listed below reflect my analysis of the data and the drafts of the contractor-generated Data Evaluation Reports (DER's).

Chronic Rat Toxicity/Oncogenicity Study

The OPP concurs with your overall contractor-generated analysis of the data and Core Guideline classification for this study. Some general comments have been written in the margins of the draft of the DER (see attachment).

Because of our concern for the mammary gland tumors that were seen in the female rats, we obtained a statistical evaluation of the data. Specifically, mammary gland adenomas, adenocarcinomas and fibroadenomas of Sprague Dawley rats administered 0, 20, 500 or 1500 ppm in the diet were the focal

point of this evaluation. It was determined that the incidence of these lesions falls within the range of the available historical control data. There is a statistically significant trend for adenocarcinoma counts ($p < 0.01$) and the combined (adenocarcinoma and adenoma only) tumor counts ($p < 0.01$). The pair-wise comparisons of the adenocarcinomas with the controls and the combined (adenocarcinoma and adenoma only) group with the controls are of borderline significance with p values of 0.089 and 0.072, respectively. The details of our statistical evaluation are provided in the attachment.

As for the systemic toxicity which was seen in this study, mean body weights of the mid and high dose males were significantly ($p < 0.01$) depressed throughout the study when compared to the controls and significant reductions in body weight gains occurred at the mid dose (10-13%) and at the high dose (20-31%). Mean body weights of the high dose females were significantly ($p < 0.01$) depressed throughout the study. There were significant reductions in body weight gain in the mid (10%-18%) and high dose groups (19-37%) throughout the study. The significant reductions in body weight gain indicate that this chemical was tested at adequate dosage. The NOEL and LOAEL for systemic toxicity are 20 ppm and 500 ppm, respectively, as stated in the draft DER.

Mouse Chronic Toxicity/Oncogenicity Study

Your contractor-generated analysis adequately represents the findings of the mouse study. Administration of prometon to CD-1 mice for 88 weeks at levels of 0, 10, 400, 4000 or 8000 ppm failed to demonstrate an oncogenic response. The liver was the primary target organ for systemic toxicity. In the high dose females, the absolute and relative liver weights were increased 17% and 34% over the controls. Hepatocellular hypertrophy, single cell hepatic necrosis or hepatocellular disorganization were increased in the 8000 ppm males and females. Absolute kidney weights were slightly but significantly decreased ($p < 0.05$) in males in the 4000 and 8000 ppm groups and in females in the at the 4000 ppm group. This study was tested at adequate dosage as demonstrated by significant reductions in body weight gains. The NOEL in this study is 400 ppm which is equivalent to 70 mg/kg/d, as stated in your draft DER.

Also note that a typographical error appears on page 2 of the DER; the batch # should be corrected to read FL 841716.

Based on OPP practice, prometon is to be submitted for discussion to the HED Cancer Peer Review Committee since it is a member of the triazine family of chemicals, many of which have demonstrated an oncogenic potential. At that time, the Committee will review the prometon data base (inclusive of the rat and

mouse oncogenicity studies) for consideration of prometon's carcinogenic potential and classification. A final report of that discussion will be issued to your Office following our Peer Review.

Chronic Oral Dog Study

As we discussed previously, my review of this dog study raised concern for the emesis and diarrhea which occurred in both sexes and at all dose levels, including the control animals. These two observations were noted throughout the duration of this study, even though the dose levels were lowered in an attempt to overcome them. The animals also experienced depressed food consumption throughout the 52 weeks, depressed body weights, depressed body weight gains and changes in the clinical biochemistry picture wherein there were reductions in total protein, globulin and cholesterol levels. Contrary to our contractor-generated DER, no NOEL has been established for this study. This study is now classified as Core Supplementary, pending additional information from the sponsor. This dog study may be upgradeable after the requested information has been processed.

The 2-Generation Reproduction Study

Following the review of the data and your contractor-generated DER for this rat study, I concur with the technical evaluation/conclusion that was provided. However, the following comments require your attention:

On Table 7 of the attached DER which lists the ovary wt/body wt, the validity of the value given for the high dose females has been questioned (see attachment).

On page 4 of the DER, this study has been classified as Core Minimum because the purity of the compound was not reported and no protocol was submitted. In my review of the mouse oncogenicity study and this reproduction study, the same lot number, FL 841716, was used for both studies. The mouse oncogenicity study reported the purity as 97-98% and the chemical was also tested for homogeneity and stability. This information obtained by cross-referencing can be used to satisfy the noted deficiency. Although no protocol was provided, the procedure appears appropriate based on the review of the data. The classification of this study should be upgraded to Core Guideline since the deficiencies no longer apply.

As you may know, prometon is a low priority chemical (List B) for the OPP. The shared responsibility for these DER's has been

beneficial to OPP as a time-saving effort and has allowed our two Offices to collaborate and render quality control over shared interests. Please keep me informed of your progress in finalizing the DERs for the rat and mouse oncogenicity studies and the rat reproduction study.

Attachments