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

JUL 21 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: EPA ID 018301; Chlorpropham; 6(a)(2) data on an Oncogenicity\Chronic Rat feeding Study/393L-103-055-89 (MRID# 427547-01).

ToxChem No.: 510A. Submission No.: S441606.
PC No.: 018301. DP Barcode.: D191733.

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A. CONCLUSIONS:

Preliminary review of the 6(a)(2) data on the combined oncogenicity/chronic study indicates that benign Leydig cell tumors of males were increased at the HDT of 1000 mg/kg/day (9/60 vs. 1/60 in controls), only. The highest classification for these benign tumors would be a C without a Q*. Thus, inclusion of effects from this study in the regulatory data base for chlorpropham probably would lead to regulation through the RfD rather than a Q*. The study appears to be acceptable, however final evaluation of the study will be determined after the preparation of the review (DER) and after the Carcinogenicity Peer Review is conducted, including the appropriateness of the HDT.

The basis for the current RfD of 0.2 mg/kg/day (uncertainty factor of 300 because of an inadequate data base, 12/13/90) is a NOEL of 50/mg/kg/day for hematological related effects from a study on 2-generations of rat reproduction. A new RfD based on this 6(a)(2) data would be 60% of the current RfD or 0.12 mg/kg/day. This change is not likely to result in an exposure problem, since uses have been removed from the label since the 1990 calculation when only 28.9% of the RfD was used.

Based on a preliminary review of the data, the NOEL for hematological effects is 30 mg/kg/day. The LEL for these

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systemic effects is 100 mg/kg/day for decreased erythrocyte count in both sexes, reduced hematocrit and hemoglobin concentration in females at 100 mg/kg/day and increased MCV, MCH and reticulocytes at higher dose levels in both sexes. Also the blood was darker red from the 100 mg/kg/day animals and higher dose levels than from controls, which may be related to methemoglobin formation. Methemoglobin determinations were not conducted in this study.

B. ACTION REQUESTED:

The following study was submitted under 6(a)(2) data for increased incidence of neoplasms over concurrent controls.

> JA Botta, 24-Months Combined Oncogenicity/Toxicity Evaluation of Chlorpropham in Rats for Chlorpropham Task Force, John Wise & Associates, Ltd. Dated: 4/22/93, Study No.: 393L-103-055-89, by TSP, Inc. 10 Vol. and 3327 pages. (MRID# 427547-01).

Determine whether it will fulfill guidelines 83-1(a) and 83-2(a).

C. BASES FOR THE CONCLUSIONS:

Based on the preliminary review of the data, the NOEL/LEL for the study is 30/100 mg/kg/day for hematological effects. An increased incidence of Leydig cell adenomas occurred at the 1000 mg/kg/day dose level. The 1000 mg/kg/day dose level may be excessive and 500 mg/kg/day, where only hematological parameters were affected, may be adequate to demonstrate the carcinogenicity potential of chlorpropham. The relevance to humans of Leydig cell adenomas in rats dosed excessively is questionable.

Chlorpropham was administered in the feed to 60 Sprague Dawley rats per sex per group at approximately 0, 30, 100, 500 or 1000 mg/kg/day for 24 months.

Toxicologically significant effects on hematological parameters occurred at the 100 mg/kg/day dose level and above. The erythrocyte count was decreased in males and females besides a decrease in the hemoglobin concentration and the hematocrit in females at the 100 mg/kg/day dose level at the 26 week and 53 week intervals. The clinical effects of hematological deficits were compensated by stimulated erythropoiesis and increased erythrocyte size after the 26 and 53 week interval because the parameters showed effects only at the 500 mg/kg/day dose level at the 78 week interval and at termination. Increased splenic extramedullary hematopoiesis and hemosiderosis was found at 100 mg/kg/day and increased hematopoiesis in the liver and bone marrow occurred at 500 mg/kg/day and above.

There was a trend for increased incidence of benign Leydig cell tumors (adenomas). At the 1000, 500, 100 and 30 mg/kg/day dose levels, the incidence was, respectively, 9/60, 4/60, 4/60 and 4/60 vs. 1/60 for controls. Leydig cell hyperplasia was

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reported in 3/60 males at 1000 mg/kg/day vs. 1/60 in controls. The incidence of the Leydig cell adenomas at 1000 mg/kg/day was 15% and in controls it was 2%.

Male body weights at termination were 81% and 75% of control values at 500 and 1000 mg/kg/day, respectively. Food consumption in males was generally statistically significantly increased at 1000 mg/kg/day, but did not differ from control values at 500 mg/kg/day. Female body weights at termination were 77% and 71% of control values at 500 and 1000 mg/kg/day, respectively. Food consumption in females was generally statistically significantly increased at 1000 mg/kg/day and it was frequently statistically significantly increased at 500 mg/kg/day. Body weight decrement and reduced efficiency of food utilization occurred at 500 and 1000 mg/kg/day in both sexes. Probably the 500 mg/kg/day dose group could be considered a sufficient dose to demonstrate the carcinogenic potential of chlorpropham and that the 1000 mg/kg/day dose level was excessive (above a MTD).

No historical control data on Leydig cell tumors were presented from the testing laboratory. However, historical control data from a limited number of animals were reported by Hazleton Laboratories of America. Historical control data for Leydig cell tumors in the Sprague Dawley rat at 104-weeks or more are about 2% to 23% (mean = 10%) in a data base of about 300 rats (Hazleton Laboratories of America, 9200 Leesburg Turnpike, Vienna, VA 22180, 703-893-5400. Historical Control Data, updated 3/5/84). These values were much less than the 90 to 98% for a group of 326 Fisher 344 rats also reported by Hazleton or the 70 to 80% for a group of 60 Wistar rats reported by BASF. The incidence of Leydig cell adenomas in the study was within the historical control range for the Hazleton data on Sprague Dawley rats.

Leydig Cell tumors are frequently seen with anti-androgens or other substances causing hormone imbalance. The increased Leydig cell tumors were accompanied by no effects on adrenal, pituitary, testes or ovarian weight, the only organ weights determined in the study; these organs are frequently susceptible to endocrine imbalances. Thus, there was no evidence that chlorpropham treatment results in any hormonal effects in rats, although hormonal effects were not adequately studied.

At terminal sacrifice the absolute adrenal, splenic ($p \leq 0.01$) and testes weights and organ/brain weight ratios were nominally increased in males over control values at the 1000 mg/kg/day dose level. The absolute splenic weight and organ/brain weight ratios in females were statistically significantly increased at 1000 mg/kg/day. Reduced numbers of corpora lutea at 1000 mg/kg/day were reported in the summary; this was not substantiated by the histological report.

Leydig cell adenomas in rats are an age related phenomena, but Leydig cell tumors in humans are not. They most frequently appear in young men under 30 years of age and are frequently malignant and have a poor prognosis. Leydig cell tumors in rats

are rarely malignant, they generally increase with the age of most strains of rats, and they occur with a higher frequency with prolonged anti-androgen treatment (e.g., the pesticides vinclozolin and procymidone, and the drugs flutamide and cyproterone acetate and spironolactone). There was no indication of any anti-androgen activity from chlorpropham, but organ weights sensitive to anti-androgens such as epididymal, seminal vesicle and prostate weights were not reported.

The latter drugs cause temporary or lower levels of increases in LH in humans than in rats (Neumann, 1991 and Roberts et al., 1989) where prolonged levels of 10 to 20 times normal levels are known to occur. These latter drugs are also used to treat benign prostatic hypertrophy, prostatic and breast cancer, acne and female hirsutism (Schultze and Senge, 1990; Sciarra et al., 1990; Pavone-Macalus et al., 1990; Labrie et al., 1990).

D. Bibliography.

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