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

JUN 14 1995

#900AA JUN 14 1995

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: **THIODICARB: Historical Control Data Supplemental Data to Rat Combined Chronic Toxicity/ Carcinogenicity Study**

TO: Bonnie Adler
PM Team Reviewer (52)
Reregistration Branch, SRRD, (7508W)

FROM: Linda L. Taylor, Ph.D. 6/6/95
Toxicology Branch II, Section II,
Health Effects Division (7509C)

THRU: K. Clark Swentzel 6/7/95
Section II Head, Toxicology Branch II
Health Effects Division (7509C)

and

Marcia van Gemert, Ph.D.
Chief, Toxicology Branch II/HFAS/HED (7509C)

Registrant: Rhône-Poulenc Secteur Agro
Chemical: Thiodicarb
Synonym: Larvin
Submission No.: S484338
DP Barcode: D213593
Caswell No.: 900AA
Case: 816454
Identifying No.: 114501
Shaughnessey No.: 114501
MRID No.: 435964-01
Action Requested: Please review the historical rat onco data submitted by Rhone Poulenc per our 2/8/95 meeting.

Comment: The Registrant has submitted a "detailed statistical analysis of the rat historical control data as well as the raw rat historical control data from Inveresk Laboratories in Scotland."

In THIODICARB 104 Week Dietary Carcinogenicity Study in Rats - C Atkinson, P Hudson, J Willerton, and V Iswariah [MRID # 433082-01], high-dose [900 ppm] males displayed an increased incidence of interstitial cell tumors in the testes compared to the concurrent and historical control males. Additionally, increases in tubular atrophy [mid- and high-dose levels] and interstitial cell hyperplasia [all dose levels] were observed in the testes, although

statistical significance was not attained, and the incidence of hyperplasia was not strictly dose-related.

The Registrant contends that the reported increase in benign interstitial cell testicular tumors is not treatment-related, based on the facts that: (1) There is clear evidence that exposure to 900 ppm Thiodicarb resulted in **increased** survival [58%] relative to controls [45%], and statistical tests not adjusting for differential mortality can be expected to have an increased rate of false positive findings. Even under these circumstances, statistical significance was not found for the testicular tumors. (2) Using an appropriate test such as the logistic regression analysis, which is the method of choice when differential survival is observed and the lesions are not considered to be rapidly lethal, according to the Registrant, statistical significance was not attained. (3) Because benign interstitial cell tumors are very common age-related tumors and the high-dose males showed a 1.3 times higher survival rate than controls, one would expect to see a higher raw incidence of these tumors at the high dose. (4) These tumors should not be considered appropriate for human risk assessment because they do not transform into a more aggressive form with time, and although they are very common in rats, they are highly uncommon in humans. Additionally, epidemiological evidence that Leydig cell tumors in rats are relevant for human health risk assessment is absent. (5) The % of tumors at the high dose [24.5%] is "near to the historical control range of the performing laboratory [0-10%]. (6) Both sexes at the high-dose level displayed fewer tumors and fewer had multiple benign and malignant tumors. Additionally, there was a significant <u>decrease</u> in the incidence of pituitary tumors in the high-dose males, which was not considered biologically significant, but it demonstrates that spurious differences in tumor incidence can occur.

As stated previously, Thiodicarb is to be presented to the HED Carcinogenicity Peer Review Committee, and these data and arguments along with the additional data and arguments submitted for the mouse carcinogenicity study [D214346; S485444; MRID #'s 436193-01 and 436117-01] will be presented as part of the data package provided to the Committee for their consideration. Additionally, the statistical analysis provided in this submission will be forwarded to Statistics along with the tumor incidence data from both the rat and mouse studies for analysis. Prior to the Cancer Peer Review Committee meeting, Thiodicarb will be presented to the HED RfD/Peer Review Committee for an assessment of the data base.