OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

J V

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

TXR No.: 0054669
Date: August 15, 2007

MEMORANDUM

SUBJECT: CLOTHIANIDIN: HED's Response to Draft Developmental Immunotoxicity Study Protocol. PC Code 044309; DP Number 341978.

TO: Kable Davis, RM 01
Venus Eagle, RM 01
Insecticide/Rodenticide Branch
Registration Division (7505P)

FROM: Kelly Schumacher, Biologist
Registration Action Branch 2
Health Effects Division (7509P)

and

Yung Yang, Ph.D., Toxicologist
Toxicology Branch
Health Effects Division (7509P)

THRU: Richard A. Loranger, Ph.D., Branch Senior Scientist
Registration Action Branch 2
Health Effects Division (7509P)

CONCLUSION: The Health Effects Division (HED) has reviewed the draft protocol for a developmental immunotoxicity (DIT) study on clothianidin submitted by Bayer CropScience LP (Bayer) and Sumitomo Chemical Takeda Agro Company, Ltd. (Sumitomo). The protocol is considered acceptable for the assessment of immune system function in young animals following developmental exposure; however, HED recommends that F1 pup spleen weights are also measured and that the performing laboratory provide data demonstrating its proficiency in performing the selected immunoassays. Additional discussion of the impact of shipping spleens to ImmunoTox, Inc. is also requested.

Recd in RRC
11/2/07

I. BACKGROUND

In previous risk assessments (D331226, D304499), the Health Effects Division (HED) has recommended submission of a developmental immunotoxicity (DIT) study to fully characterize the potential for clothianidin (EPA Reg. No. 74207-1, PC Code 044309) to adversely impact development of the immune system and has retained a 10X UF_{DB} to account for the lack of this study.

Following discussions with EPA and PMRA on July 17, 2007, Bayer CropScience LP (Bayer; 27 W. Alexander Drive, RTP, NC 27709) and Sumitomo Chemical Takeda Agro Company, Ltd. (Sumitomo; 27-1 Shinkawa, 2-Chome, Chuo-ku, Tokyo, 104-8260, Japan) have submitted a draft protocol, dated July 23, 2007, for a DIT study on clothianidin technical.

II. RESPONSE

Although no formal EPA guideline currently exists for a developmental immunotoxicity study, literature published from a number of workshops, symposia, and research laboratories has suggested appropriate experimental designs and tests for evaluating the potential developmental immunotoxic effects of chemical exposure. The protocol submitted for a DIT study on clothianidin reflects this publicly available literature and is well designed and considered acceptable for the assessment of immune system function in young animals following developmental exposure.

Comments from the EPA and PMRA are as follows:

1. The rationale regarding dosage selection of 0, 150, 500, and 2000 ppm is acceptable. These dosages are consistent with the doses selected in the developmental neurotoxicity study (0, 150, 500, and 1750 ppm) and two-generation reproduction study (0, 150, 500, and 2500 ppm), where LOAELs/NOAELs were identified as 500/150 ppm, respectively.

2. In addition to weighing the thymuses of F1 pups, as detailed on page 23 of the protocol, we recommend that the spleens of the F1 pups are also weighed.

3. The performing laboratory should submit information or data demonstrating its proficiency in performing the T-DAR and DTH immunoassays. These data could be shown as tables or graphs of the optimum time to maximum response (*e.g.*, how many days after injection) and the optimum immunized dose of antigen, SRBC, or *Candida albicans* (*e.g.*, how much volume at what concentration is used for injection). These data are part of the laboratory standard operation procedure (SOP) for conducting the immune function assays and would not create extra burden for the performing laboratory. In addition, the concurrently-run positive and negative controls could be used to demonstrate the sensitivity of the assays.

4. There is a concern about the potential effect of shipping spleens across the country to ImmunoTox, Inc. The laboratory should take every precaution to make sure proper packaging and shipping is conducted.

3

13544

R154243

Chemical: Clothianidin

PC Code: 044309
HED File Code: 13000 Tox Reviews
Memo Date: 8/15/2007
File ID: TX0054669
Accession #: 000-00-0122

HED Records Reference Center
11/15/2007