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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

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HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Imidacloprid (P.C. Code 129099) - Review of Dose-Selection Proposal for a Developmental Neurotoxicity Study in Rats

FROM: Susan L. Makris, M.S. Susan L Makris 6/23/99
Toxicology Branch I
Health Effects Division (7509C)

TO: Tina Levine/Peg Perreault (PM 04)
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THRU: Alberto Protzel, Ph.D., Branch Senior Scientist
Toxicology Branch I
Health Effects Division (7509C)

Alberto Protzel 6/23/99

TASK ID: DP Barcode: D256937
PC Code: 129099

Submission: S563702
Chemical: Imidacloprid.

REGISTRANT: Bayer Corporation

Action requested: Review dose selection proposal for developmental neurotoxicity (DNT) study in rats with imidacloprid

Dose Selection: The information provided indicates that dose selection for the developmental neurotoxicity study will be based upon the results of a two-generation reproduction study (MRID 42256340). In that study, 95.3% imidacloprid was administered to Wistar rats at dietary levels of 0, 100, 250, and 700 ppm (0, 7.3, 18.3, and 52.0 mg/kg/day for males, and 0, 8.0, 20.5, and 57.4 mg/kg/day for females). Parental systemic toxicity was observed in the 700 ppm dietary group and consisted of body weight decrements in both sexes and generations. Offspring toxicity, occurring at the same treatment level, consisted of decreased pup body weights in both generations. These findings were confirmed by the Agency in a Hazard Identification Assessment Review Committee (HIARC) meeting held on September 11, 1997 (memo from J. Rowland to D. Davis, September 22, 1997). The NOAEL for toxicity in the parental animals and offspring was 250 ppm (18.3/20.5 mg/kg/day in M/F). At 700 ppm, F1 male and female PND 21 pup weights were approximately 13% less than control. Additionally at this treatment level, F1 parental female body weights were decreased approximately 13% as compared to control by the end of the premating period, with an average 5-7% lower weight during study weeks 5-13. There were no treatment-related clinical findings, mortality or postnatal viability issues, or postmortem abnormalities. Based upon these results, the Registrant has proposed dietary dose levels of 0, 100, 250, and 750 ppm for the developmental neurotoxicity study. The highest dose level (750

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ppm) was selected to produce evidence of toxicity and represent approximately the maximum tolerated dose, while the lowest dose level (100 ppm) is expected to produce no evidence of toxicity. The mid-dose level (250 ppm) is expected to provide information regarding dose response.

Further review of the toxicology data base for imidacloprid provides information relevant to the selection of the highest dose level. Specifically, it is noted that a 25% decrease in motor activity was observed at the lowest dose tested (42 mg/kg/day) in an acute neurotoxicity study, and that significant alterations to brain weight were noted in both sexes in a 2-year chronic dietary rat study (at treatment levels of 51.3 and 73 mg/kg/day in males and females, respectively). While the route of administration and the duration of treatment are different between these two studies, and in turn are not directly comparable to the proposed DNT protocol, the proposed high dose of 750 ppm is within a dosing range that has been previously noted to result in evidence of neurotoxicity with imidacloprid. Therefore, the proposed dose selection should be adequate to assess the developmental neurotoxic potential of this chemical. This opinion was communicated directly to the study director, Larry Sheets, by the Agency reviewer, in a telephone conversation of June 23, 1999, as requested by the Registrant.

Study Protocol: The protocol for this study was not provided to the Agency for review. The Registrant states that it will closely follow the DNT protocol used for Bayer chemical MKH 3586, which had been previously reviewed by the Agency (memorandum from S. Makris to J. Miller, dated 2/11/99). This plan of action is acceptable.

cc: Donna Davis (7509C)