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WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

DATE: December 14, 2006

TXR: 0054490

MEMORANDUM

SUBJECT: Waiver Request for Triazole Acute Neurotoxicity Study.
DP# 335069 PC Code 600074
Related PC codes: 109901, 113961, 120603, 122101, 123909, 125620, 127201, 128847, 128857, 128997, 129011, 600074

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TO: Michael Doherty, Ph.D., Risk Assessor
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Background: This memo addresses a data waiver request for an acute neurotoxicity study in rats with 1,2,4-triazole, submitted by the US Triazole Task Force.

The US Triazole Task Force submitted a waiver request in 2002 requesting that data requirements for an acute neurotoxicity study in rats be waived (MRID 45575501). The Triazole *Ad Hoc* HED Peer Review Committee evaluated the request and determined that the requirement for an acute neurotoxicity study should be placed in reserve, pending the receipt and review of a subchronic neurotoxicity study in rats (8/5/03 memo, TXR 0052012).

A 90-day combined subchronic/neurotoxicity study in rats has since been received (MRID4647303) and reviewed by HED (TXR #0053214). Based on the results of this and other recently submitted studies, the US Triazole Task Force submitted another data waiver request (August 3, 2005, MRID 46616401). This memo responds only to the request to waive the acute neurotoxicity study. Other aspects of that submission have been addressed separately (TXR #0053729).

The waiver request for the acute neurotoxicity studies discussed in this memo was evaluated by Triazole Toxicology Team members Steve Dapson, Kit Farwell, Kathleen Raffaele, and Kelly Schumacher.

Conclusion: Based on available data, HED has determined that an acute neurotoxicity study in rats will not be required for 1,2,4-triazole at this time. Risk assessments for acute and short term exposure to 1,2,4-triazole are currently based on a NOAEL of 30 mg/kg in a rabbit developmental toxicity study, with a UF of 1000 (including an extra UF of 10x to account for database and FQPA concerns). Based on the findings in other available toxicity studies (including the combined subchronic/neurotoxicity study, in which no neurotoxicity was seen at doses of 33 mg/kg/day), it is unlikely that results of an acute neurotoxicity study would reveal effects of concern at doses lower than current regulatory endpoints.

Responses to specific USTTF comments:

Task Force: The USTTF summarized available data relevant to neurotoxicity of 1,2,4-triazole, and argued that in multiple studies neurotoxicity occurred only following repeated exposure to test compound, with the severity of the toxicity increasing as exposure continued. In addition, a clear neurotoxicity NOAEL of 33 mg/kg was seen across all relevant studies, indicating that the current regulatory endpoint of 30 mg/kg/day would be protective for any neurotoxic effects seen following a single exposure.

HED Response: HED agrees with the USTTF analysis indicating that neurotoxicity in adults is unlikely to be seen at doses lower than the current regulatory endpoint of 30 mg/kg for acute or short term exposure. Although effects were seen in offspring at lower doses in the reproductive toxicity study, concern regarding possible effects at lower doses in developing organisms will be addressed by the required developmental neurotoxicity study and have been accounted for in the current risk assessment by use of an additional uncertainty factor.

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