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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

DATE: May 10, 2006

TXR: 0053729

MEMORANDUM

SUBJECT: Waiver Request for Triazole Chronic/Oncogenicity Studies.
DP# 321328 PC Code 600074
Related PC codes: 109901, 113961, 120603, 122101, 123909, 125620, 127201, 128847, 128857, 128997, 129011, 600074

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Background: This memo addresses a data waiver request for chronic/oncogenicity studies in male rats and female mice 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 chronic/oncogenicity studies in male rats and female mice be waived (MRID 45575501). The Triazole *Ad Hoc* HED Peer Review Committee evaluated that waiver request and reaffirmed the requirement for chronic toxicity/oncogenicity studies (8/5/03 memo, TXR 0052012).

The US Triazole Task Force recently submitted another data waiver request (August 3, 2005, MRID 46616401). Although this memo also discussed the requirement for an acute neurotoxicity study, that requirement will be discussed in a separate memo.

The waiver request for the chronic/oncogenicity studies discussed in this memo was evaluated by Triazole Team members Steve Dapson, Kit Farwell, Kathleen Raffaele and

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Senior Scientists/Branch Chiefs Bill Burnam, Vicki Dellarco, Jess Rowland, and Gino Scarano.

Carcinogenic risks were evaluated in the triazole risk assessment since the waiver request was submitted, and it was determined that a margin of exposure or RfD approach should be used to assess carcinogenic risk using the most sensitive endpoint with appropriate database uncertainty factors. (See triazole risk assessment for more details, February 7, 2006. D322215.) Therefore a carcinogenicity study is not required at this time.

There are currently no adequate long term studies to evaluate triazole. The triazole risk assessment accounted for these data gaps using database uncertainty factors. However, new uses and new conazoles are rapidly being submitted which will result in greater exposure and risk.

Conclusion: There are no long-term toxicity studies with triazole and a 1-year rat study is needed to refine the risks which will result from new chemicals and new uses. The study should be a 1-year chronic rat study in males and females (not a carcinogenicity study).

The study should be performed in rats rather than mice because of the greater sensitivity in rats compared to mice in the previously submitted studies. The target organ in mice is the testes with toxicity occurring at higher doses than the doses at which other toxicity occurred in rats. The testes will undergo a detailed evaluation in the required rat study (see below).

The 1-year chronic rat study should follow 870.4100 chronic toxicity guidelines and should also include detailed evaluation of target organs identified in the subchronic and reproductive studies. The nervous system should be evaluated following neuropathology procedures described in 870.6200 neurotoxicity screening battery guideline. Timepoints evaluated in the previous subchronic neurotoxicity study need not be repeated. Pathological evaluation of the reproductive system including testes, sperm, and ovaries shall be conducted as described in 870.3800 reproduction and fertility guideline; mating of animals is not required. It is recommended that the Task Force consult with the Agency before beginning this study.

Responses to specific Task Force comments: The waiver request presented rationales as to why toxicity noted in the subchronic triazole studies would be unlikely to lead to cancer in a long-term study. Carcinogenicity concerns have already been addressed in the triazole risk assessment. Parent conazoles do not appear to drive a tumor response by direct interaction with DNA. A margin of exposure or RfD approach to assess carcinogenic risk was recommended using the most sensitive endpoint with appropriate database uncertainty factors. (See triazole risk assessment, February 7, 2006, D322215.)

Task Force: The Task Force argued that triazole is a mammalian metabolite and has therefore already been tested in chronic toxicity studies.

HED Response: With few exceptions, the toxicological effects and target organs of triazole are fundamentally different from those of the parent conazoles. Even in parent compounds with high conversion to triazole, the equivalent doses of triazole were low because liver toxicity from the parent compounds limited the doses which could be given. Therefore triazole toxicity was generally not seen in chronic studies with parent compounds and triazole was not adequately tested in chronic studies with parent conazoles.

Task Force: The chronic endpoint used in the risk assessment is decreased body weight in adults and offspring and decreased brain weight in offspring which occurred at the LOAEL of 15 mg/kg/day in the reproductive study. Based on NOAELs and LOAELs from subchronic studies, the Task Force predicts a NOAEL of 5-10 mg/kg/day in a chronic rat study, which is not more protective than the chronic endpoint used.

HED Response: The Agency disagrees with the Task Force. In the requested chronic study, lower doses (than used in the subchronic studies) would be tested. There may be more severe effects at lower doses or changes in the dose-response curve not predicted by the subchronic studies which could result in a NOAEL lower than those established in the subchronic studies. Furthermore, an adequate dose response evaluation of the reproductive and neurotoxicity following long-term exposure is needed for proper hazard characterization and hazard assessment. Potential changes in the use pattern and registration of new chemicals of this class mandates the need for an adequate chronic toxicity study in rats.

Task Force: Toxicity to Purkinje cells in the cerebellum occurred only with high doses and represented a threshold effect. Triazole is a polar, water-soluble compound which would not bioaccumulate in the brain and cause nervous system damage such as occurs with the non-polar, fat-soluble compounds as with the organochlorine pesticides.

HED Response: Chronic toxicity often occurs with repeated exposures without bioaccumulation. Triazole clearly does not have the potential for bioaccumulation of the organochlorine pesticides, however, cerebellar toxicity in rats, as shown by tremors and staggering occurred after only 30 days exposure and decreased brain weight occurred after only 90 days exposure. Incidence and severity of neurobehavioral findings such as tremor and incoordination increased over the course of the study, raising the possibility that effects might be seen at lower doses with continuing exposure.

Task Force: Ovaries in the reproduction study had increased number of corpora lutea accompanied by increased ovarian weight. The Task Force contended that increased corpora lutea would be unlikely to occur at lower doses in a chronic study than occurred in the reproduction study because dosing lasted up to 252 days in the reproduction study.

HED Response: Dosing in the reproduction study lasted for a much shorter period of time than would occur in a chronic study. Dosing lasted for approximately 119 days in the F0 generation and for approximately 98 days in the F1 generation. No individual animals were dosed for 252 days.

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Chemical: 1H-1,2,4-Triazole (A metabolite of tebuconazole & metabolite of acaricidal & fungicidal compounds)

PC Code: 600074
HED File Code: 11000 Chemistry Reviews
Memo Date: 5/10/2006
File ID: TX0053729
Accession #: 412-06-0194

HED Records Reference Center
7/27/2006