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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Additional Mutagenicity Study for Cyproconazole

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Chemical: Cyproconazole Tox Chem No. 272E

During the June 20, 1990 HED Peer Review Committee meeting that considered the carcinogenicity classification of Cyproconazole, it was determined that an additional mutagenicity study would be necessary to address an identified mutagenicity concern. A rodent dominant lethal study needs to be performed with this compound. The weight-of-the-evidence discussed at the Peer Review Committee meeting that supports this recommendation is as follows:

1) An assay for potential to induce chromosome aberrations in Chinese hamster ovary (CHO) cells was positive under non-activated and activated conditions. These results indicate that cyproconazole can be clastogenic without metabolic activation (MRID# 411587-01; reviewed in Document# 007632).

2) In the mouse carcinogenicity study (MRID# 411472-01), a decrease in the amount of testicular germinal epithelium in males was noted. In a one-year dietary study with beagle dogs (MRID# 412129-01; reviewed in Document# 007871), one mid-dose male was noted with degeneration of testicular germinal epithelium. These results suggest that cyproconazole is capable of reaching the germinal tissues and causing an effect.

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3) In a rat two-generation reproduction study (MRID#s 406077-23, 412945-00; reviewed in Document#s 007003, 007908), fewer implantation sites, decreased litter sizes, a decreased live birth index and a decreased viability index were noted compared to controls.

4) Among the adverse effects seen in two developmental studies, one in rats (MRID# 406077-21; reviewed in Document#s 007003, 007730) and one in rabbits (MRID# 406077-20; reviewed in Document# 406077-21), decreased total number of fetuses/dam, decreased number of live fetuses/dam, and increased fetal resorptions were found.

5) Cyproconazole was found negative in a mouse micronucleus assay in bone marrow (MRID# 406077-28; reviewed in Document#s 007003 and 007283). However, based on the carcinogenicity studies as well as the other animal studies reviewed during the Peer Review Committee meeting, it was felt that the bone marrow was not a primary target of cyproconazole (e.g. there did not appear to be adverse hematological effects noted in the animal studies). Other targets, such as the liver and as shown in points 2), 3) and 4) reproductive and developmental targets, appear more prominent.

Based on this body of evidence where there is a potential for clastogenic effects and interaction in the germinal tissues, it is recommended that a rodent dominant lethal study be performed before registration of this compound is complete. This is to assay for possible mutagenic effects in a germ line based mutagenicity study. Based on review of the results of this study, further mutagenicity testing may or may not be necessary. Before the commencement of this study, it is advisable that the registrant discuss the protocol and design with the OPP as this type of study can be performed in different ways.

cc: Linda L. Taylor, Ph.D.
Marcia van Gemert, Ph.D.

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