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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: October 4, 1999

MEMORANDUM

SUBJECT: *IMAZALIL*: - REASSESSMENT OF THE REQUIREMENT FOR A DEVELOPMENTAL NEUROTOXICITY STUDY IN RATS - Report of the Hazard Identification Assessment Review Committee.

FROM: Abdallah Khasawinah, Toxicologist *A. Khasawinah*
Reregistration Branch 4
Health Effects Division (7509C)

THROUGH: Pauline Wagner, Co-Chair *Pauline Wagner 10/5/99*
And
Jess Rowland, Co-Chair *Jess Rowland 10/6/99*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Susan Hummel, Branch Senior Scientist
And
Sanjivani Diwan, Senior Toxicologist
Registration Action Branch 2
Health Effects Division (7509C)

PC Code:111901

On September 28 , 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) reevaluated the requirement for a developmental neurotoxicity study as well as acute and subchronic neurotoxicity studies for imazalil based on neurobehavioral effects seen in pups in a published study (Tanaka, 1995) . The Committee recommended that developmental, acute and subchronic neurotoxicity studies be conducted in rats. The Committee's conclusions are presented in this report.

Committee Members in Attendance

Members present on September 28, 1999 were Pauline Wagner, Jess Rowland, Yiannakis Ioannou, Nancy McCarroll, P.V. Shah, Virginia Dobozy, Nicole Paquette, Pamela Hurley, Tina Levine, Dave Andersen Kathy Raffaele, Bill Burnam, and Brenda Tarplee (Executive Secretary). Members in absentia were Sue Makris. Also in attendance were Ed Zager - HED Associate Director, Sanjivani Diwan of Reregistration Branch 4, and Waheeda Tehseen of Registration Action Branch. Data were presented at this meeting by Abdallah Khasawinah of Reregistration Branch 4.

Data Presentation &
Report Preparation:

A. Khasawinah 10-5-99

Abdallah Khasawinah, Ph.D.
Toxicologist

I. BACKGROUND

On June 15 and 22, 1999, the HIARC reevaluated the toxicology data base for imazalil and selected endpoints for acute and chronic dietary as well as dermal and inhalation exposure risk assessments and addressed the potential enhanced sensitivity of infants and children from exposure to imazalil as required by the FQPA (HED DOC. No. 013539). The data base for imazalil was adequate for hazard characterization. The HIARC recommended that the 10x FQPA Safety Factor be retained based on increased susceptibility seen in the two generation reproduction study in rats.

Although neurotoxicity studies were not conducted by the registrant, HIARC in its June 15 and 22 meetings determined that additional neurotoxicity studies including the developmental neurotoxicity study are not required because there was no evidence of neurotoxicity, neuropathology, or abnormalities in the development of the fetal nervous system in the available developmental toxicity studies.

II. FQPA SAFETY FACTOR COMMITTEE CONCERNS

The FQPA Safety Factor Committee in its September 20, 1999 meeting confirmed the retention of the 10x FQPA Safety Factor based on the increased susceptibility of pups in the two generation reproduction study and also the questionable conduct of this study (MRID # 42570701).

The FQPA Safety Factor Committee expressed concern for behavioral effects in offspring following prenatal exposure seen in a published study (Tanaka 1995) and presented previously to HIARC. In this study Imazalil (99%) was administered to Crj:CD-1 mice (10/sex/group) at dietary doses of 0, 0.012, 0.024, or 0.048% (0, 120, 240, or 480 ppm equivalent to 19, 39 and 79 mg/kg/day in males and 26, 45 and 102 mg/kg/day in females during the preconception period) from 5 weeks of age of the F₀ generation to 9 weeks of age in the F₁ generation. In the F₀ generation, Exploratory behavior (number of movements, movement time, total distance and number of turnings) at 8 weeks of age was significantly increased in males of the high dose group. Number of vertical activities was significantly increased in the mid dose group, and number of defecations was increased in the low dose group. These effects did not appear to be dose related. Females were not affected. In the F₁ generation, with regard to neurobehavioral effects, surface righting reflex in all treated females, in the high dose male offspring group on post natal day (PND) 4 and in the mid dose group on PND 7 was significantly affected in a dose related manner. Swimming behavior of head angle in the high dose males and females at PND 4 was significantly affected in a dose related manner. Other neurobehavioral parameters were not affected. The number of turnings (exploratory behavior) in female offspring was significantly increased in the mid dose group, the other groups showed insignificant increase compared to controls. Other exploratory behavior parameters were not affected in males or females. There were some significant effects on multiple water T-maze performance in females, but not in males. By week 8 there were no effects on exploratory behavior in either sex. These results suggest that neurobehavioral effects can occur in mice exposed prenatally to Imazalil in their diet.

The FQPA Safety Factor Committee also expressed concern for structurally related compounds that have shown increased developmental toxicity. In the structurally related fungicide,

TEBUCONAZOLE (PC Code 128997), the HED Hazard Identification Review Committee (HIARC) determined that on the basis of comparative NOAELs and LOAELs, there was no indication of increased susceptibility of mice, rats or rabbits *in utero* and /or postnatal exposure (HED Doc. No. 012534). However, HIARC determined that a postnatal developmental neurotoxicity study in rats with this chemical is **required** based alterations in the nervous system seen in developmental studies. In the developmental toxicity studies with tebuconazole, there was evidence of alterations to the development of the fetal nervous system in mice (increased malformations of the brain and spinal cord and exencephaly), in rats (anophthalmia) and in rabbits (neural tube defects characterized as meningocele and spina bifida and hydrocephalus) at doses 10 fold higher than the developmental toxicity NOAEL.

With the exception of Etoconazole and Hexaconazole, other structurally related compounds (Triadimefon, Triademenol, Bitertanol, Uniconazole, Propiconazole, Azaconazole, and Cyproconazole) have been shown to cause developmental toxicity at levels below those that are maternally toxic.

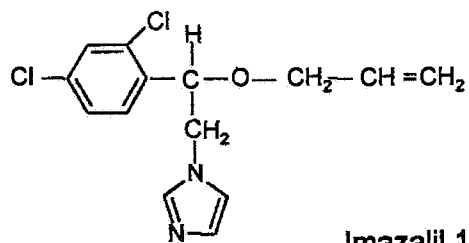
Figure 1 shows the structures of imazalil and structurally related fungicides. Figure 2 shows the structure of imazalil and some human antimycotic therapeutic agents that are **more structurally related**.

The FQPA Safety Factor Committee, in its September 20, 1999 meeting, recommended that HIARC re-evaluate the requirement for a developmental neurotoxicity study (DNT) in light of the Tanaka study and the SAR, as well as the need for acute and subchronic neurotoxicity studies for comparison in adult animals.

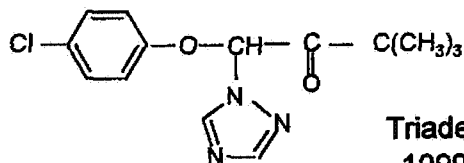
III. HIARC RE-EVALUATION

Based on the positive neurobehavioral effects seen in mice offspring in the Tanaka study described above, the HIARC determined that a DNT study in rats should be required for imazalil. HIARC also determined that Acute Neurotoxicity and Subchronic Neurotoxicity studies in adult rats should be required based on the positive effects seen in the Tanaka study and for comparison to DNT results. HIARC also noted that the experimental design of the Tanaka study differs from the developmental neurotoxicity study and therefore, the DNT is required to assess the potential effects of this chemical in the developing fetuses.

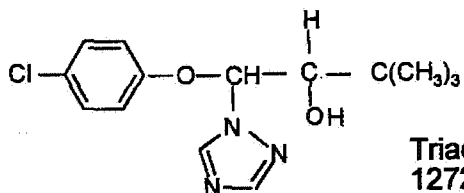
In regard to structural activity similarities to other related fungicides, it was pointed out that imazalil is an imidazole ring based chemical. All other -conazole agricultural fungicides are triazole compounds. Imazalil is more structurally related to some human therapeutic antimycotic agents with an imidazole ring structure. However, there were no data available on the developmental effects of these agents. Therefore, HIARC determined that the results of the Tanaka study provided sufficient concern to require the DNT.



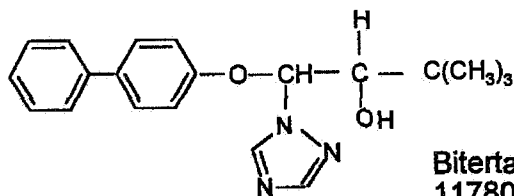
Imazalil 111901



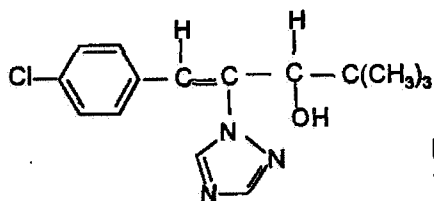
**Triademefon (Bayleton)
109901**



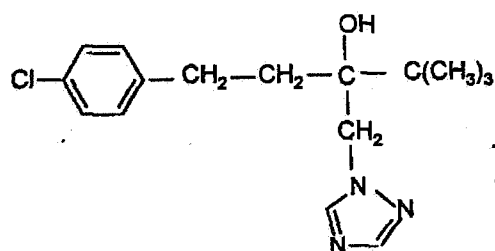
**Triademenol (Baytan)
127201**



**Bitertanol (Baycor)
117801**

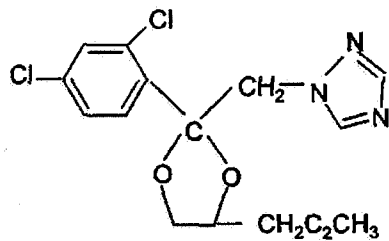


**Uniconazole (Prunit)
128976**

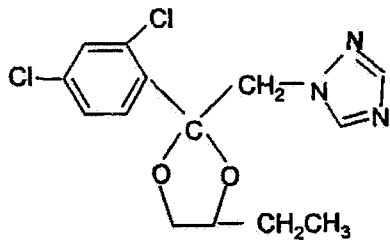


**Terbuconazole (Folicur)
128997**

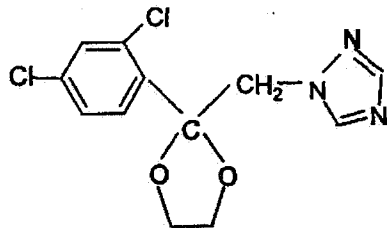
Figure 1. Structure of imazalil and related compounds



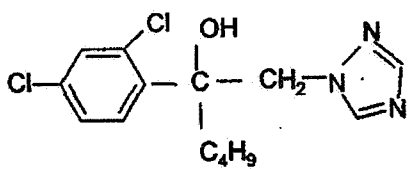
Propiconazole (tilt)
122101



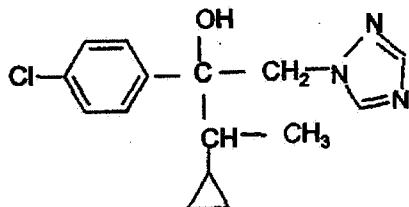
Etaconazole (Vanguard)
120501



Azaonazole
128882



Hexaconazole
128925



Cyproconazole
128993

Figure 1. cont'd. Imazalil structurally related compounds

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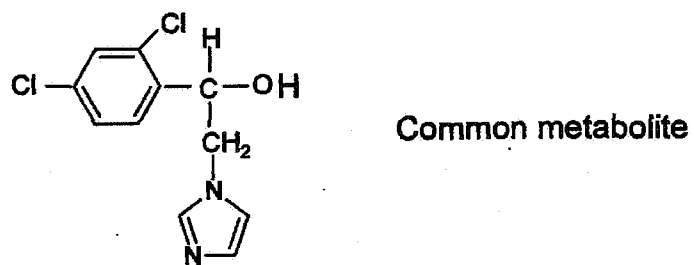
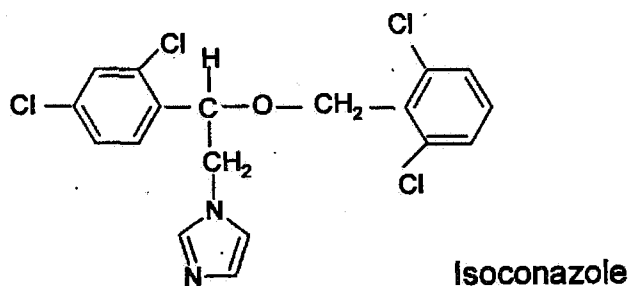
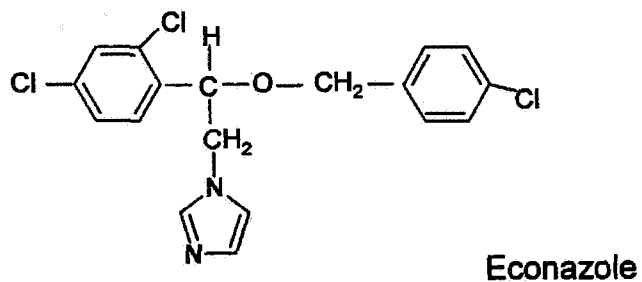
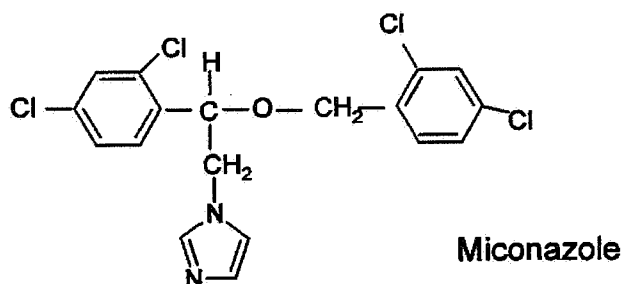
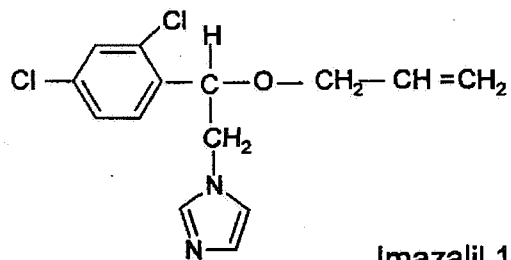


Figure 2. Imazalil and structurally related antimycotic human therapeutic agents

IV. REFERENCES

Tanaka, T. 1995. Reproductive and Neurobehavioral effects of Imazalil Administered to Mice. Toxicology 9 (3): 281-288.

HED DOC. NO. 013539, June 29, 1999. Imazalil - report of the Hazard Identification Assessment Review Committee. Memo from Abdallah Khasawinah to Susan Hummel.