



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

CASWELL
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MAY 30 1997

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: Reevaluation of Developmental Toxicity Potential of THPI (1, 2, 3, 6-tetrahydrophthalimide), an animal and plant metabolite of Captan (N-trichloromethylthio-4-cyclohexene-1,2-dicarboximide)

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5/30/97

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BACKGROUND

The Health Effects Division Metabolism Committee determined that both captan and THPI, an animal and plant metabolite of captan, will be considered for the risk assessment of reproductive and developmental effects (memorandum from C. Olinger and P. Chin to E. Zager, dated April 1, 1994). This decision was based on preliminary indication in the scientific literature [Fickentscher et al. (Mol. Pharmacology 13: 133-141, 1977)] that TPHI could be of concern for developmental effects (memorandum from J. Rowe and A. Protzel to R. Engler, dated March 15, 1994).

In June 1985, the Agency issued a Position Document (PD 2/3) which concluded that "The Agency dose not have sufficient data on residues of THPI to perform a risk assesment and will therefore be requesting such data pursuant to FIFRA 3(c)(2)(B).

EXECUTIVE SUMMARY

The developmental toxicity potential of THPI was re-evaluated and it was concluded that THPI does not present a developmental toxicity concern by the oral route in rabbits and hamsters based on the following considerations:

1) The aforementioned study of Fickentscher et al. (1977) was conducted by the intraperitoneal (IP) route and thus it does not correctly measure the potential for developmental toxicity by the oral route.

In their study surveying the developmental toxicity potential of several imide derivatives, Fickentscher et al. (1977) reported that THPI is a developmental toxicant in mice. THPI was administered to SWS 53/65 mice in a single IP dose in the range of 6.25 to 200 mg/kg on day 9 of gestation. The incidence of malformations was higher than that observed in vehicle or untreated controls as doses at or above 12.5 mg/kg. The statistical significance of the observations could not be evaluated, because there was no statistical analysis of the data. The malformations attributed to THPI were not specified, but may have included one or more of the following: thumb or radial reductions, melted or forked thoracic vertebrae or ribs, radial and tibial aplasia (sometimes extending to the first or second phalanx) or complete and severe phocomelia of the long bones.

Although the above study of Fickentscher et al. (1977), indicated developmental toxicity in mice after IP dosing, these results may not be plausibly extrapolated to predict developmental toxicity after oral ingestion of THPI because the IP route may result in higher levels of fetal exposure than the oral route. In particular,

- o Intraperitoneal administration is likely to have produced a high direct exposure of the fetuses to the test material as present in the abdominal cavity. Oral administration followed by transplacental transport is likely to produce a more gradual and thus lower exposure to THPI.
- o Ingestion of THPI, with its subsequent metabolism to polar compounds during passage through the liver, will result in decreased exposure because these polar compounds (some conjugated) are less likely to undergo transplacental transport.

2) THPI is extensively metabolized to a series of oxidation products in the rat after oral dosing. As indicated above, these oxidized products are less likely to undergo transplacental transport that may produce the high fetal exposures that could result after IP dosing. Examination of urinary radioactivity in

rats dosed with [¹⁴C]-captan indicated that 79.1% of the urinary radioactivity consisted of oxidation products of THPI and only 10.6% of untransformed THPI. As shown in Figure 1, THPI is metabolized further to its hydroxide, epoxide, and diol in rats dosed orally with [¹⁴C]-captan (see attached Figure 1, MRID No.415054-03, HED Doc, No. 009330).

3) Captan [which produces THPI as a major metabolite in rats] produced developmental toxicity in mice after subcutaneous dosing but not after oral dosing. In a preliminary screening study performed for NCI by Bionetics Research Labs [1968, as cited in Captan, Special Review Position Document 2/3, EPA/OPP 1985] captan at 100 mg/kg was administered subcutaneously or orally to 21 C57BL6 female mice on GD 6-14 and to 13 AKR female mice on GD 6-15. Following subcutaneous injection captan was associated with maternal weight loss, increased fetal mortality, reduced fetuses per litter and reduced fetal weights in both strains of mice. An increased number of abnormal fetuses, largely resulting from microphthalmia, was reported in the C57BL6 strain but not in the AKR strain of mice. Following oral administration of captan, maternal weight loss occurred in mice without prominent signs of fetal toxicity or abnormalities. Were THPI a developmental toxicant by the oral route under the experimental conditions, developmental toxicity resulting from the intermediate THPI would have been expected after dosing with captan.

4) The two studies rated Acceptable and summarized below indicate that captan does not present a developmental toxicity concern by the oral route in rabbits and Golden hamsters. Because THPI is a major metabolite in rats and may be presumed to be so in rabbits and Golden hamsters it appears plausible to conclude that THPI by the oral route, also does not present a developmental toxicity concern.

a) A developmental toxicity study of captan in rabbits showed that the developmental toxicity of captan [which produces THPI as a major metabolite in rats] is observed at the maternally toxic dose of 30 mg/kg/day. The maternal toxicity was 30 mg/day based upon reduced body weight gain, decreased food consumption and anorexia in the dams. The developmental toxicity NOEL for captan was not established. The developmental toxicity LEL for captan was considered to be 30 mg/kg/day based upon increased post-implantation loss, and reduced mean fetal weight. At 100 mg/kg/day (the highest dose tested), encephalocoele and dilation of brain ventricles was found in one fetus. In addition, at this HDT captan caused increased skeletal defects which were limited to fused maxillae in two fetuses from one litter (MRID Number: 418269-01; HED Doc. 009537).

b) A developmental toxicity study of captan [which produces THPI as a major metabolite in rats] in Golden Syrian hamsters

(MRID No. 00086803) showed that the maternal NOEL/LEL were considered to be 50 and 200 mg/kg/day based upon reduced body weight gain and increased mortality. The developmental NOEL/LEL were considered to be 200 and 400 mg/kg/day based upon increased incidence of delayed ossification, decreased weight and increased resorption. The developmental toxicity studies in both rabbits and hamsters satisfy (a second species) the toxicological data requirements for a developmental toxicity (83-3).

It is noted, however, that there are no Acceptable studies of the developmental toxicity potential of Captan or THPI in rats at the present time.

Additionally, it is noted that in contrast with thalidomide (a known developmental toxicant) which has a planar aromatic pthalimide moiety (Figure 2), THPI and Captan have a non-planar tetrahydro pthalimide moiety.

Captan tox review

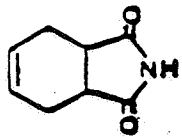
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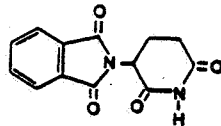
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THPI



Thalidomide

Figure 2. The chemical structures of THPI and thalidomide

cc Beth Doyle, Kathy Martin, Kevin Costello, Metabolism Committee
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