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

Coswell # 159

MAR 15 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Toxicological (Developmental toxicity) of animal and plant metabolite of Captan: 1,2,3,6-tetrahydrophthalimide (THPI)

TO: Reto Engler, Ph.D.
Chair, HED Metabolism Committee
Health Effects Division (7509C)

FROM: James N. Rowe, Ph.D., Section Head *James N. Rowe 3/10/94*
Section III/Toxicology Branch II (7509C)

and
Alberto Protzel, Ph.D. *Alberto Protzel 3/10/94*
Metabolism Committee, Section III

THRU: Marcia Van Gemert, Ph.D., Chief *Marcia Van Gemert 3/11/94*
Toxicology Branch II (7509C)

THPI, an animal and plant metabolite of Captan and structurally related to thalidomide, is a developmental toxicant in mice producing embryonic resorptions and malformations (Fickentscher et al., 1977). As such, it is our opinion that it should be included in the tolerance expression for Captan.

Inbred line (SWS 54/65) of mice were administered a single intraperitoneal injection (5-10 pregnant females; 6.25 to 200 mg/kg) of THPI on day 9 of gestation. On day 18 of gestation the animals were killed and the fetuses removed, macerated in potassium hydroxide solution and the skeletons stained with alizarin red and evaluated for skeletal anomalies. The embryotoxic effect, as measured by the embryo-lethal dose for 50% of the fetuses to be resorbed (ELD₅₀) and the teratogenic activity, as measured by the teratogenic dose which produces a 50% malformation* rate (TD₅₀), were lower (more potent) than for thalidomide under the conditions of the bioassay:

	ELD ₅₀		TD ₅₀	
	mg/kg	nmoles/kg	mg/kg	nmoles/kg
Thalidomide	305.7	1.18	214.7	0.83
THPI	80.0	0.53	58.8	0.39

[* skeletal anomalies were thumb or radial reductions, melted or



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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].

Reference

Fickentscher, K., Kirfel, A., Will, G., and Kohler, F. (1977). Stereochemical properties and teratogenic activity of some tetrahydrophthalimides. *Mol. Pharmacol.* 13: 133-141.

cc K. Baetcke