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

CAPTAFILE

APR 19 1984

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Captan and Captafol Metabolite Deferral from Residue Chemistry Branch associated with petitions 3F2893/3H5400, accession # 071623.

FROM: William R. Schneider, Ph.D.
Toxicology Branch
Hazard Evaluation Division (TS-769)

W.R. Schneider

TO: Henry Jacoby, PM 21
Registration Division (TS-767)

THRU: Albin Kocialski, Ph.D., Acting Section Head
Section II, Toxicology Branch
Hazard Evaluation Division (TS-769)

AK 4/19/84
for CC 4/19/84

THRU: William L. Burnam
Branch Chief, Toxicology Branch
Hazard Evaluation Division (TS-769)

Tox Chemicals: Captan 159
Captafol 828

Residue Chemistry Branch has deferred to Tox Branch on the toxicological significance of the metabolites tetrahydrophthalimide epoxide (THPI-epoxide) and 4,5 dihydrohexahydrophthalimide (4,5-dioH HHPI) from both captan (memo, A. Rathman, Nov 12, 1980) and captafol (memo, P. Errico, Oct 1, 1980).

Captan THPI Derived Metabolites.

Hoffman et.al., 1973, showed that tissue residues at 96 hours did not exceed 0.1% of the total ¹⁴C derived from ¹⁴C carbonyl labeled captan given by gavage at 82 mg/kg to rats. The urine was tested for metabolites as shown in the table.

One goat was tested (memo, A. Rathman, 1981) at 50ppm by capsule three times a day for 10 days with ¹⁴C carbonyl labeled captan. Total ¹⁴C "captan" residues 4 hours after the final dose ranged from 0.36 ppm in fat to 2.27 ppm in kidney. Milk showed from 0.13 to 0.63 ppm ¹⁴C "captan". Fifty percent of the activity in milk was shown to be due to 3- and 5-OH THPI. 4,5-dioH HHPI ranged from 5 to 10% of the activity, as did THPI itself. Similar amounts of these metabolites were seen in tissues. 4,5-dioH HHPI was found at 0 to 11% of the activity in tissues. No THPI-epoxide was found in meat and milk in this study.

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Captafol THPI Derived Metabolites.

Rats were administered 10mg/kg ¹⁴C carbonyl labeled captafol orally (memo, P. Errico, Oct.1, 1980). Less than 0.1% of the label was found in tissues 96 hours after dosing. At 24 hours 1.8 to 4.4 % THPI-epoxide and 0.9 to 5.3 % 4,5-diOH HHPI were identified.

One goat (memo, P. Errico, Oct. 1, 1980) was dosed with 80ppm ¹⁴C carbonyl labeled captafol 3 times a day for 10 days. Four hours after the last dose, ¹⁴C residues ranged from 0.04ppm in fat to 1.72ppm in the kidney. Milk contained 0.2% of the label. THPI-epoxide was seen at 0.01ppm and 4,5-diOH HHPI was present at 0.07ppm in the milk. Of the label present in the tissues, 4.5 to 24.1 % was 4,5-diOH HHPI, and 2.6 to 10.6% was present as THPI-epoxide.

THPI-epoxide Metabolism

A rat was orally dosed with ¹⁴C carbonyl labeled cis and trans THPI-epoxides. The trans isomer appeared to be relatively stable with 81.5% excreted in the urine. The cis isomer was metabolized to 4,5-diOH HHPI (61.9%) and the trans THPI-epoxide (31.6%). Two days after dosing, 96 to 99% of the label was excreted in the urine and feces.

Discussion and Conclusions:

Due to the low levels of these metabolites in milk and tissues and considering that other similar metabolites seem to be as persistent, Tox Branch does not feel that THPI-epoxide and 4,5-diOH HHPI are of concern.

These metabolites are derived from the THPI moiety which is identical in captan and captafol. Captan and captafol differ only in their side chain which is hydrolysed from the THPI moiety during metabolism. Since the intestinal tumors seen in the mouse occur only with captan but not with captafol, the side chain is apparently responsible for this tumor induction. The THPI moiety may however be responsible for other toxic effects. Since we have no toxicological data on these metabolites alone, we can not distinguish their toxicity from the parent molecule's toxicity. These metabolites are animal metabolites as determined in several studies performed in rats and goats, therefore they should not cause any unexpected toxicological effects since they would be present in the toxicology test animals.

Except for the intestinal tumor issue, Tox Branch does not have data that allows us to determine the individual toxicological properties of these metabolites.

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HED

Residue Chemistry Branch

Re: Pesticide Petition 3F2898 Chevron's Request to Reduce Captan
Tolerances

Please re-evaluate per Mike Conlon's request the tolerances for residues of Captan in or on detreated seed corn (CFR §561.65); and tolerances for residues of Captan in or on fat, meat and meat-by-products of cattle and hogs fed detreated corn seed (§180.103).

Please include in your review for this petition information needed by HED's Risk Assessment Branch. Please coordinate this with that Branch.

✓ Toxicology Branch

Re: Pesticide Petition 3F2898, Chevron's Request for Reduction of
Tolerance for Residues of Captan

Please consider all metabolites of concern to RCB in this request for reduction of tolerances for Captan, i.e. 4-cyclohexene-1,2-dicarboximide and others named by RCB.

Eugene M. Wilson
May 26, 1983

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