



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

OCT 07 1997

OFFICE OF  
PREVENTION, PESTICIDES  
AND TOXIC SUBSTANCES

MEMORANDUM:

SUBJECT: **Captan (N-trichloromethylthio-4-cyclohexene-1,2-dicarboximide):**  
Hazard Identification Committee Report.

CASRN: 133-06-2

PC Code: 081301

Caswell: 159

FROM: George Z. Ghali, PhD. *G. Ghali*  
Executive Secretary, Hazard Identification Committee  
Health Effects Division (7509C)

Thru: Clark Swentzel *K. Clark Swentzel 10/7/97*  
Chairman, Hazard Identification Committee  
Health Effects Division (7509C)

To: Joanne Miller, PM 23  
Fungicide-Herbicide Branch  
Registration Division (7505C)

The Health Effects Division-Hazard Identification Committee met on August 07, 1997 and again on September 05, 1997 to evaluate the existing and/or recently submitted toxicology data in support of captan re-registration, identify toxicological endpoints and dose levels of concern appropriate for use in risk assessments for different exposure routes and duration, and assess/reassess the reference dose for this chemical.

### Individuals in Attendance

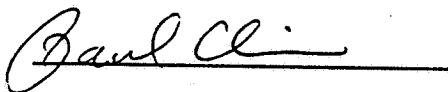
Hazard Identification Committee members present were David Anderson, Karl Baetcke (Senior Science Advisor, HED), William Burnam (Chief, SAB, HED), George Ghali (Executive Secretary, Hazard Identification Committee, HED), Susan Makris, Kathleen Raffaele, John Redden, Jess Rowland, and Clark Swentzel (Chairman, Hazard Identification Committee, HED).

Hazard Identification Committee member(s) in absentia: Nancy McCarroll.

In attendance on August 7, 1997 also were Al Nielsen, Joycelyn Stewart, and Virginia Dobozy, HED, OPP as observers.

Scientific reviewer(s) (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report and concurrence with the hazard identification assessment review unless otherwise stated.

Paul Chin

A handwritten signature in cursive script, appearing to read "Paul Chin", is written over a horizontal line.

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## I. TOXICOLOGY PROFILE:

### A. Carcinogenicity:

Captan was classified by the HED-Carcinogenicity Peer Review Committee as a "Group B", probable human carcinogen or likely to be carcinogenic in humans. The  $Q_1$  value of  $2.4 \times 10^{-3}$  (mg/kg/day)<sup>-1</sup> should be used in the cancer risk assessment.

Captan was associated with an increased incidence of intestinal neoplasms in B6C3F1 mice; in ICR-derived CD-1 mice; in Charles River CD-1 mice. Captan was also associated with an increased incidence of renal cortical/tubular cell neoplasms in male Charles River CD rats and an increased incidence of uterine sarcomas in Wistar rats.

Captan demonstrated positive mutagenic activity and is structurally related to known oncogens/mutagens, i.e. captafol and folpet.

### B. Reproductive and Developmental Toxicity:

#### 1. Reproductive Toxicity

In a three-generation reproductive toxicity study, captan was administered to COBS CD rats at 25, 100, 250 or 500 mg/kg/day (MRID# 00125293). In a one-generation reproductive toxicity study, captan was administered at 6, 12.5 or 25 mg/kg/day (MRID# 00120315).

In the three-generation reproduction study in rats, evidence of toxicity was noted in the offspring at dietary levels at 25 mg/kg/day and higher (LDT). Pup weights were significantly decreased at  $\geq 25$  mg/kg/day (93% to 61% of control in F1a, F1b, F2a, F2b, F3a and F3b). The report listed decreased litter size in F1b pups, only, decreased fertility in F1 males and F1 females at 250 and 500 mg/kg/day. Parental toxicity {decreased body weights in the P0, F1 and F2 generations (85%-95% of control)} was observed at 100, 250 and 500 mg/kg/day, with a NOEL of 25 mg/kg/day. Since the one-generation study showed no effects on parents or pups at 6, 12.5 and 25 mg/kg/day, the NOEL for pups was determined to be 12.5 mg/kg/day as a more protective endpoint for pups. The one and three-generation studies are acceptable together. However, the two studies also show that pups and parents are equally sensitive.

#### 2. Developmental Toxicity

Developmental toxicity in hamsters - Hamsters were dosed at 0, 50, 200 or 400 mg/kg/day after implantation and major organogenesis (MRID# 00078622, 00078623,

00086803, 00126348 & 00130848). The studies were accepted as adequate at a previous meeting and were not discussed in this meeting. The study showed a NOEL/LOEL of 50/200 mg/kg/day based on reduced body weight gain and mortality in dams and a NOEL/LOEL of 200/400 mg/kg/day based on delayed ossification and post-implantation loss.

Developmental Toxicity in Rabbits - New Zealand rabbits were administered captan at 0, 10, 30 or 100 mg/kg/day from day 7 to 19 of gestation (MRID# 41825901). There was evidence of developmental toxicity at 30 and 100 mg/kg/day based on odontoid partially ossified, 27 pre-sacral vertebrae and 13th rib with a NOEL of 10 mg/kg/day and at 100 mg/kg/day additional ossification delays, fetal wt decrement and post implantation loss (encephalocoele and dilated brain ventricles all possibly in the same fetus). Maternal toxicity was expressed by greater than 148 g body wt gain decrement at 30 mg/kg/day and food consumption decreases with a NOEL of 10 mg/kg/day. Thus, developmental toxicity was expressed at maternal toxic dose levels.

### 3. Developmental Neurotoxicity

There was no developmental neurotoxicity study available for consideration by the Committee. Although the HED-RfD Committee recommended a developmental neurotoxicity study (HED-RfD Committee report dated January 31, 1994), after reevaluation of data, it was determined that the developmental neurotoxicity study is unnecessary. Upon reevaluation of the rabbit and hamster brain defects, it was determined that the encephalocoele and dilated brain ventricles noted in one rabbit fetus and one exencephally in one hamster fetus were inadequate evidence to require a developmental neurotoxicity study at this time.

### 4. Other Issues

The developmental toxicity potential of THPI (1, 2, 3, 6-tetrahydrophthalimide), an animal and plant metabolite of Captan was reevaluated (HED-Metabolism Committee, memo dated May 30, 1997). It was concluded that a toxicological concern for developmental effects of THPI, the major metabolite of captan, by the oral route is not expected. This conclusion also did not indicate developmental concerns for captan, since developmental toxicity occurred only at maternally toxic doses in the rabbit.

Based on the subgroup meeting of the HED-Hazard ID committee on Sept. 5, 1997, the following issues have been resolved:

The Draft Risk Assessment Guidelines for Developmental Toxicity [FR 56:63798, December 5, 1991] indicate that developmental effects at maternally toxic doses are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity. Thus, in the specific case of captan, the developmental

toxicity at maternally toxic doses should not necessarily be ignored.

Because orally administered THPI is a major metabolite in rats and presumably so in rabbits, it appears plausible to conclude, as before, that THPI by the oral route may share in some of the toxicological properties of captan in these species. Thus, one may conclude that developmental toxicity concerns about THPI by the oral route may not be automatically discounted.

#### C. FQPA Considerations:

Under the Food Quality Protection Act (FQPA), P.L. 104-170, which was promulgated in 1996 as an amendment to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency was directed to "ensure that there is a reasonable certainty that no harm will result to infants and children" from aggregate exposure to a pesticide chemical residue. The law further states that in the case of threshold effects, for purposes of providing this reasonable certainty of no harm, "an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. Notwithstanding such requirement for an additional margin of safety, the Administrator may use a different margin of safety for the pesticide residue only if, on the basis of reliable data, such margin will be safe for infants and children."

Pursuant to the language and intent of the FQPA directive regarding infants and children, the applicable toxicity database for captan was evaluated by the Committee.

The Committee determined that adequate data available on captan provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to captan. Therefore, an additional uncertainty factor under FQPA for risk assessment purposes is not warranted.

#### D. Mutagenicity:

The mutagenicity issue had already been addressed earlier by the HED-Carcinogenicity Peer Review Committee.

#### E. Dermal Absorption:

"In a dermal absorption study (85-2, MRID No. 00117083, Memo of R. Zendzian to J. Redden dated June 20, 1996), male Sprague-Dawley rats were dermally exposed to 2 doses (0.5 or 5 mg/animal) of ring <sup>14</sup>C-labeled captan. At 1, 2, 4, and 8 hours after dosing, 4 animals from each dose were sacrificed. The skin of the application site, blood sample, total urine and feces and residual carcass were collected and analyzed for

radioactivity. A maximum daily dermal absorption rate of captan was approximately 10% based upon 1.3% per hour for 8 hours at 5 mg/animal. At 0.5 mg/animal, captan was absorbed at 0.9% per hour".

Dr. R. Zendzian, HED, recently reevaluated this dermal absorption study and recommended a dermal absorption rate of 0.4%/hr (instead of 1.3%/hr) for use in risk assessment following dermal exposure to captan. This absorption rate should be applied to cumulative exposure as the best estimate (see comments below).

**Comments about the study and proposed dermal absorption rate:** "Dr. Zendzian stated that "Briefly, I have reexamined the data presented in the captan dermal absorption study particularly the low dose and the eight hour exposure. In this dose the probability and magnitude of error due to sample contamination is apparently less than in the high dose. Recalculation provides dermal absorption mean rates of 4% per 8 hrs for all animals and 3.5%/8 hours omitting rat #261 an obvious outlier (0.5 and 0.45%/hr respectively). I then normalized the low dose of captan in the study as moles/unit area and obtained data on critical physical/chemical properties of captan (state, melting point and solubility in water and various organic solvents). This information was compared with a data base of pesticide absorption in rats and a best match of vinclozolin 70 nmole/cm<sup>2</sup> selected (absorption 4.29%/10 hrs or 0.43%/hr). Overall a rounded value of 0.4% per hour was selected as the best estimate for the rate of captan dermal absorption in the rat model."

A review by California Department of Pesticide Regulation estimated the human dermal absorption by a different process but determined approximately the same final result. "The variability of the dermal absorption results (31 percent in rats in vivo; 8.5 percent in vitro human extrapolation; 1 and 5.8 percent "in vivo" man, 2 percent man and 8 percent rat in vitro) does not allow an exact derivation of a dermal absorption rate. But eliminating both extremes and giving greater weight to the human data for the remaining values, a dermal absorption rate of 6.0 percent per 24 hours (0.25 percent/hour) was used by Worker Health & Safety to estimate absorbed dose for regulatory purposes."

## **II. HAZARD IDENTIFICATION:**

Based on comprehensive evaluation of the toxicology data available on captan, toxicology endpoints and dose levels of concern have been identified for use in risk assessments corresponding to the categories indicated below.

Where no appropriate data have been identified for a particular duration or exposure scenario, or if a risk assessment is not warranted, this is noted. Levels of uncertainties associated with intraspecies variability, interspecies extrapolation, route to route conversion, or extrapolation of data from variable exposure durations extrapolation are also addressed.

Based on the use pattern/exposure profile for captan, the Committee determined that the risk assessments indicated below are required.

**A. Reference Dose (RfD):**

Reference Dose (RfD): 0.13 mg/kg/day.

**Critical Study:** One- and three-generation reproductive toxicity studies in rats (83-4, MRID No. 00120315; 00125293).

**Executive Summary:** In both studies, the chemical was tested in COBS CD rats. In the one-generation study, captan was tested at 6, 12.5 or 25 mg/kg/day. In the three-generation study, captan was tested at 25, 100, 250 or 500 mg/kg/day. The maternal toxicity NOEL/LOEL were considered to be 12.5 and 25 mg/kg/day, respectively, based on decreased body weight gain and food consumption. The reproductive toxicity NOEL/LOEL were considered to be 12.5 and 25 mg/kg/day, respectively, based on decreased pup and litter weights. Pup survival was reduced at 250 mg/kg/day and higher dose levels.

**Endpoint and Dose Level Selected for Use in Risk Assessment:** NOEL of 12.5 mg/kg/day, based on decreased mean litter weights observed at the next higher dose level of 25 mg/kg/day.

**Uncertainty Factor (UF):** An uncertainty factor of 100 was applied to account for both interspecies extrapolation and intraspecies variability. The use of a UF of 100 was justified based on the availability of a two chronic toxicity studies in a rodent (MRID Nos. 00115695, 00126529, 00138179; 00129316, 00129164, 00153284) and non-rodent species (MRID Nos. 40893604, 41472501, and reproductive toxicity studies in rats (MRID No. 00120315; 00125293), the three pivotal studies required in accordance with the rules established by the Agency-IRIS (Integration Risk Information System) Work Group.

**B. Acute Dietary Exposure (one day):**

**Critical Study:** Developmental Toxicity Study - rabbit (83-3, MRID No.:41826901).

**Executive Summary:** In a developmental toxicity study, 20 rabbits per dose group of the New Zealand White strain received either 10, 30, or 100 mg captan/kg/day by oral gavage from gestation days 7 through 19. Maternal NOEL/LEL were considered to be 10 and 30 mg/kg/day based upon reduced body weight gain, decreased food consumption and anorexia. Developmental NOEL/LEL were considered to be 10 and 30 mg/kg/day based upon increased skeletal defects (27 pre-sacral vertebrae) in fetuses at 30 mg/kg/day. There was increased post-implantation loss, reduced mean fetal weight, and increased manus score (altered growth) at 100 mg/kg/day (HDT).



**Endpoint and Dose Level Selected for Use in Risk Assessment:** Developmental toxicity NOEL of 10 mg/kg/day from the rabbit developmental toxicity study based on increased skeletal defects observed at 30 mg/kg/day.

**Comments and Rationale:** This risk assessment may be necessary for females 13+ years as well as general population (including infants and children) depending upon the type of study/dose/endpoint used. However, no appropriate endpoint was identified for the general population. The use of this end point is limited to females 13+ only.

**C. Short Term Occupational or Residential Exposure (1-7 days):**

**Critical Study:** Developmental Toxicity Study in Rabbits (83-3a, MRID No. 41826901).

**Executive Summary:** In a developmental toxicity study, 20 rabbits per dose group of the New Zealand White strain received either 10, 30, or 100 mg captan/kg/day by oral gavage from gestation days 7 through 19. Maternal NOEL/LEL were considered to be 10 and 30 mg/kg/day based upon reduced body weight gain, decreased food consumption and anorexia. Developmental NOEL/LEL were considered to be 10 and 30 mg/kg/day based upon increased skeletal defects (27 pre-sacral vertebrae) in fetuses at 30 mg/kg/day. There was increased post-implantation loss, reduced mean fetal weight, and increased manus score (altered growth) at 100 mg/kg/day (HDT).

**Endpoint and Dose Level selected for use in risk assessment:** Developmental NOEL of 10 mg/kg/day from the rabbit developmental toxicity study based on increased skeletal defects observed at 30 mg/kg/day.

**Comments and Rationale:** Since this NOEL was for fetuses and dams, it is appropriate therefore to use this NOEL for risk assessments for all subgroups.

**D. Intermediate Term Occupational or Residential Exposure (one week to several months):**

**Critical Study:** Developmental Toxicity Study in rabbits (83-3b, MRID No. 41826901)

**Executive Summary:** See Section II-C, above.

**Endpoint and Dose Level Selected for Use in Risk Assessment:** See Section II-C, above.

**Comments and Rationale:** See Section II-C, above.

E. Chronic Occupational or Residential Exposure (several months to life time):

Critical Study: One- and three-generation reproductive toxicity studies (83-4, MRID No. 00120315 and 00125293)

Executive Summary: See Section II-A, above.

Endpoint and Dose Selected for Use in Risk Assessment: See Section II-A, above.

Uncertainty Factor (UF): See Section II-A, above.

Comments and Rationale: See Section II-A, above.

F. Inhalation Exposure (variable duration)\*:

*\* Use the same format as for the dermal exposure if appropriate studies are available for the 3 exposure time periods. If appropriate studies are NOT available for the 3 time periods, then use the following format.*

Critical Study: 3-Week inhalation toxicity study in rats (82-4, MRID No. 41234401)

Executive Summary: Wistar-derived rats were exposed (nose-only) to captan at levels of 0.8, 5.3 or 24.8 ug/L for 3 weeks (6 hr/day, days/wk). The NOEL for systemic effects is 5.3 ug/L and the LOEL is 24.8 ug/L (HDT) (based on death in two males). The NOEL for local irritation is 5.3 ug/L and the LEL is 24.8 ug/L based on histologic changes in the upper respiratory tract which were treatment related and typical of changes seen with particulate irritants.

Endpoint and Dose Level selected for use in risk assessment: NOEL is 5.3 mg/kg/day, based on treatment-related histologic changes in the upper respiratory tract, effects typical of changes seen with particulate irritants, observed at 24.8 ug/L. Although this inhalation toxicity study provides data on the irritation effects of captan after three weeks of exposure, any inhalation exposure of captan should be combined with dermal exposure to provide an equivalent oral dose which can be used for cancer or developmental/maternal toxicity risk assessment.

The ~~inhalation~~ exposure should be converted to a mg/kg/day dose using a default value of 100% lung absorption factor; the dermal dose should be converted to an equivalent oral dose using the 0.4% dermal absorption rate. The sums of these would be used for a cancer risk assessment using the  $Q^*$  value or a developmental/maternal risk assessment using the NOEL of 10 mg/kg/day.

Comments and Rationale: This risk assessment is required.

cc: Stephanie Irène  
Paul Chin  
Michael Metzger  
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Karen Whitby  
Jess Rowland  
Amal Mahfouz (OW)  
Hazard ID file  
Caswell File