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

JAN 31 1994

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: RfD/Peer Review Report of **Captan**

CASRN. 133-06-2
EPA Chem. Code: 081301
Caswell No. 159

FROM: George Z. Ghali, Ph.D. *G. Ghali*
Manager, RfD/Peer Review Committee
Health Effects Division (H7509C)

TO: Joanne Miller, PM 23
Fungicide-Herbicide Branch
Registration Division (H7505C)
and
Lois Rossi, Chief
Re-registration Branch
Special Review and Re-registration Division (H7508W)

The Health Effects Division RfD/Peer Review Committee met on September 23, 1993 to discuss and evaluate the existing toxicology data in support of Captan re-registration and to reassess the Reference Dose (RfD) for this chemical.

The RfD for this chemical was first assessed by the Health Effects Division-RfD Committee on March 7, 1986 and was then verified by the Agency RfD Work Group on March 26, 1986. The RfD was then reassessed by the Health Effects Division -RfD Committee on December 12, 1988 and verified by the Agency RfD Work Group on January 18, 1989. The RfD was based on a no-observable effect level (NOEL) of 12.5 mg/kg/day for decreased pup body weight observed at 250 mg/kg/day in reproductive toxicity studies (one- and three-generations). An uncertainty factor (UF) of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis the RfD was calculated to be 0.13 mg/kg/day. In the meeting of September 23, 1993 the Committee recommended that the RfD remains unchanged. It should be noted that a regulatory value of 0.1 mg/kg/day has been established for this chemical by the World Health Organization (WHO) in 1990.

Since this chemical was last discussed by the HED-RfD Committee as recently as January 1989, and since the carcinogenicity issue had been already addressed by the HED



Carcinogenicity Peer Review Committee (CPRC), a re-evaluation of the chronic toxicity or carcinogenicity data was not necessary. This chemical is currently classified as a "Group B2", probable human carcinogen (HED-CPRC report dated July 20, 1988).

The Committee concentrated their effort on addressing the developmental and reproductive toxicity issues. The Committee considered the two reproductive toxicity studies together to be adequate to satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing. The data evaluation records for these two studies were considered adequate. However, the Committee recommended that summary tables for reproductive indices, parental and pup body weights and viability/survival be included for both studies. The Committee considered the developmental toxicity study in rabbits (83-3a) to be acceptable and the data evaluation record to be adequate. The data record for the developmental toxicity study in hamsters (83-3b) was considered inadequate to verify the NOEL/LOEL established in this study. The Committee recommended reevaluation of the study and updating the data evaluation record with adequate summary tables to allow independent verification of the effects reported. A monkey developmental toxicity study was also available for review. However, the study was considered unacceptable and the data evaluation record was considered to be inadequate.

The Committee recommended that a developmental neurotoxicity study be conducted. This recommendation was based on the findings in the rabbit of encephalocoele, dilation of brain ventricles and exencephaly in hamsters.

A. Individual in Attendance

1. Peer Review Committee Members and Associates (Signature indicates concurrence with the peer review unless otherwise stated).

Reto Engler

Reto Engler

Marcia Van Gemert

Marcia van Gemert

Karl Baetcke

Karl Baetcke

Henry Spencer

Henry Spencer

James Rowe

James N. Rowe

David Anderson

David Anderson

John Tice

J. Tice

George Ghali

G. Ghali

Rick Whiting

R. Whiting

William Burnam*

W. Burnam

William Sette*

William Sette

3. Scientific Reviewer(s) (Committee or non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report).

Joycelyn Stewart

Joycelyn Stewart

Paul Chin

Paul Chin

Marion Copley

marioncopley

4. Others:

K. Dearfield, A. Protzel, L. Hansen, L. Kutney and V. Dobozy of HED as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Marion Copley
James Kariya
RfD File
Caswell File

* Permanent committee members unable to attend.

B. Material Reviewed

Material available for review included data evaluation records for a chronic toxicity/carcinogenicity study in rats (83-5 or 83-1a and -2a), a long-term toxicity study in dogs (83-1b), a carcinogenicity study in mice (83-2b), developmental toxicity studies in rabbits, monkeys and hamsters (83-3a and -3b) and a reproductive toxicity study in rats (83-4), an RfD summary document and a tox. one-liner. The Committee focused the discussion on the following studies.

1. Tinston, D. J. (1991). Captan: teratology study in the rabbit. MRID No. 41826901, HED Doc. 009537.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in New Zealand white rabbits at 10, 30 and 100 mg/kg/day. Maternal NOEL/LOEL were considered to be 10 and 30 mg/kg/day based upon reduced body weight gain, decreased food consumption and anorexia. Developmental NOEL/LOEL were considered to be 10 and 30 mg/kg/day based upon increased post-implantation loss, reduced mean fetal weight, and increased skeletal defects in fetuses. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

2. Palmer, A. K. et al. (1981). Effect of technical captan on pregnancy of the New Zealand white rabbit. MRID No. 00093883, HED Doc. No. 002505.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in New Zealand white rabbits at 6, 12, 25 and 60 mg/kg/day. The study was considered to be unacceptable and the data evaluation record was considered to be inadequate. The Committee recommended to down-grade the study to a core-supplementary status on the tox-one liner for this chemical. This study does not satisfy data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits.

3. Goldenthal, E. I. et al. (1978). Pilot teratology study in hamsters. MRID No. 00078622, 00078623, 00086803, 00126348, 00130848, HED Doc. No. 002447, 004548, 004692.

Core Classification: Core-minimum data.

Committee's Conclusions and Recommendations:

The chemical was tested in hamster at 50, 200 and 400 mg/kg/day. Maternal NOEL/LOEL were considered to be 50 and 200 mg/kg/day based upon reduced body weight gain and increased mortality. Fetotoxicity NOEL/LOEL were considered to be 200 and 400 mg/kg/day based upon increased incidence of delayed ossification, decreased weight and increased resorption. Developmental NOEL was considered to be 400 mg/kg/day, the highest dose tested. The Committee felt that the information included in this study to be very limited. The Committee recommended reevaluation of the study and updating the data evaluation record with adequate summary tables to allow for an independent decision on this study. The data evaluation record as presented was considered to be inadequate. This study, as presented, does not satisfy data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in a second species.

4. Chevron Chemical Co. (1979). Teratology study in hamsters. MRID No. 00078622, 00078623, 00086803, 00126348, 00130848, HED Doc. No. 004692.

Core Classification: Core-supplementary data.

Committee's Conclusions and Recommendations:

This is a journal publication from the open literature. The chemical was tested in golden hamsters at doses ranging from 200 to 2500 mg/kg/day. Maternal NOEL/LOEL were considered to be 50 and 200 mg/kg/day based upon reduced body weight gain and increased mortality. Fetotoxicity NOEL/LOEL were considered to be 200 and 400 mg/kg/day based upon increased incidence of delayed ossification, decreased weight and increased resorption. Developmental NOEL was considered to be 400 mg/kg/day, the highest dose tested. The Committee felt that the information included in this study to be very limited. The Committee recommended reevaluation of the study and updating the data evaluation record with adequate summary tables to allow for an independent decision on this study. The data evaluation record as presented was considered to be inadequate. This study, as presented, does not satisfy data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in a second species.

5. Robens, J. (1970). Teratogenic activity of several phthalimide derivatives in the golden hamster. Toxicology and Applied Pharmacology. 16:24-34. HED Doc. No. 004447, 004454.

Core Classification: Core-supplementary data.

Committee's Conclusions and Recommendations:

This is an open literature study in which the chemical was tested in golden hamsters at doses ranging from 200 to 2500 mg/kg/day. The data evaluation record concluded that the data in this study was insufficient to evaluate the developmental toxicity potential of this chemical. The data evaluation record stated that "this study, as reported, is suggestive for teratogenicity". The Committee felt that the information included in this study is very limited. The Committee agreed with the conclusion of the review and felt that this study should remain as core-supplementary data. This study does not satisfy data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in a second species.

6. Courtney, K. D. (1968). Teratological investigation of captan, in *Macaca mulatta*. MRID No. 00043397, 00043398, 00053815, HED Doc. 003520.

Core Classification: This study was not classified under the Core system.

Committee's Conclusions and Recommendations:

The Committee concluded that this data as presented was of little value. There was no real data to review. It should be noted also that the animals in this study were treated with isoniazid along with captan so that the fetal mortality reported at 25 mg/kg/day could be the result of synergistic toxicity. This study does not satisfy data requirement 83-3 of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in a second species.

7. Schardein, J. and Aldridge, D. (1982). One generation reproduction study in rats with captan. MRID No. 00120315, HED Doc. No. 004470.

8. Schardein, J. et al. (1982). Three-generation reproduction study in rats. MRID No. 00125293, HED Doc. No. 004470.

Core Classification: These two studies when considered together are classified as Core Minimum.

Committee's Conclusions and Recommendations:

In both studies, the chemical was tested in COBS CD rats. In the one-generation study dose levels tested were 6, 12.5 and 25 mg/kg/day. In the three-generation study, dose levels tested were 25, 100, 250 and 500 mg/kg/day. Maternal toxicity NOEL/LOEL were considered to be 12.5 and 25 mg/kg/day based upon decreased body weight gain and food consumption. Reproductive toxicity NOEL/LOEL were considered to be 12.5 and 25 mg/kg/day based upon decreased

pup litter weights. Pup survival was reduced at 250 mg/kg/day or higher. The Committee generally agreed with the reviewer's evaluation and interpretation of data and classification of the study. The two studies when considered together were considered adequate. Additional summary data tables for reproductive toxicity indices, parental and pup body weights and viability/survival need to be included in the data evaluation record. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in the rat.

C. Conclusions and Recommendations

1. Reference Dose

The RfD for this chemical was first assessed by the Health Effects Division-RfD Committee on March 7, 1986 and was then verified by the Agency RfD Work Group on March 26, 1986. The RfD was then reassessed by the Health Effects Division -RfD Committee on December 12, 1988 and verified by the Agency RfD Work Group on January 18, 1989. The RfD was based on a no-observable effect level (NOEL) of 12.5 mg/kg/day for decreased pup body weight observed at 250 mg/kg/day in reproductive toxicity studies (one- and three-generations). An uncertainty factor (UF) of 100 was used to account for inter-species extrapolation and intra-species variability. On this basis the RfD was calculated to be 0.13 mg/kg/day. **In the meeting of September 23, 1993 the Committee recommended that the RfD remains unchanged.** It should be noted that a regulatory value of 0.1 mg/kg/day has been established for this chemical by the World Health Organization (WHO) in 1990.

2. Data Base

Since this chemical was last discussed by the HED-RfD Committee as recently as January 1989, and since the carcinogenicity issue had been already addressed by the HED Carcinogenicity Peer Review Committee (CPRC), a re-evaluation of the chronic toxicity or carcinogenicity data was not necessary. The Committee then concentrated their effort on addressing the developmental and reproductive toxicity issues.

3. Developmental/Reproductive Toxicity

The Committee considered the two reproductive toxicity studies together to be adequate to satisfy data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing. The data evaluation records for these two studies were considered adequate. However, the Committee recommended that summary tables for reproductive indices, parental and pup body weights and viability/survival be included for both studies. The Committee considered the developmental toxicity study in rabbits (83-3) to be acceptable and the data evaluation record to be adequate. The data record for the developmental toxicity study in hamsters (83-3) was considered inadequate to verify the NOEL/LOEL established in this study. The Committee recommended reevaluation of the study and updating of data evaluation record with adequate summary tables to allow independent verification of the effects reported. A monkey developmental toxicity study was also available for review. However, the study was considered unacceptable and the data evaluation record was considered to be inadequate.

The Committee recommended that a developmental neurotoxicity study be conducted. This recommendation was based on the findings in the rabbit of encephalocoele, dilation of brain ventricles and exencephaly in hamsters.

4. Carcinogenicity

This chemical is currently classified as a "Group B2", probable human carcinogen (HED-CPRC report dated July 20, 1988).