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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: RfD/Peer Review Report of Carbaryl

CASRN. 63-25-2
EPA Chem. Code: 056801
Caswell No. 160

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

TO: Jack Housenger, Chief
Special Review Branch
Special Review and Re-registration Division (H7508W)

Dennis Edward, PM 19
Insecticide and Rodenticide Branch
Registration Division (H7505C)

The Health Effects Division RfD/Peer Review Committee met on October 28, 1993 to discuss and evaluate the existing toxicology data in support of Carbaryl registration and to re-assess the Reference Dose (RfD) for this chemical.

The Committee considered the chronic toxicity study in rats **(83-1a)** to be acceptable. The Committee considered the chronic toxicity study in dogs **(83-1b)**, when combined with the subacute (5-weeks) feeding study in dogs, to be acceptable.

The potential of carbaryl to induce deleterious effects on reproductive and developmental parameters has been studied in a wide variety of mammalian systems. These studies showed that carbaryl has the potential to induce developmental toxicity in dogs at dose levels below those causing considerable maternal toxicity. However, the Committee felt that the positive effects in the dog study should be viewed in light of the reported unusual metabolism in this species. Although, the reproductive/developmental toxicity study in rats **(83-4)** does not conform to the current Guideline for reproductive toxicity testing, a new study is not required. The Committee recommended that the classification of the rat reproductive toxicity study remains unchanged as Core-

supplementary data. The developmental toxicity study in monkeys **(83-3)**, though not conforming to the current Guideline for developmental toxicity testing, was considered adequate for regulatory purposes. The Committee recommended that the classification of the developmental toxicity study in monkeys remains unchanged as Core-supplementary data. The developmental toxicity study in Guinea pigs **(83-3)** does not conform to the current Guideline for developmental toxicity testing and was considered inadequate due to multiple deficiencies. The Committee recommended that the classification of the developmental toxicity study in Guinea pigs remains unchanged as Core-supplementary data. Furthermore, the Committee recommended to revise the no-observable effect level (NOEL) for maternal toxicity in the Guinea pig study from 100 mg/kg/day to 50 mg/kg/day.

In view of the above, the Committee concluded that a developmental neurotoxicity study should be submitted. This recommendation was based on the fact that none of the reproductive/developmental toxicity studies available conform to the current Guideline for reproductive/developmental toxicity testing, observed reduction of litter size and viability and increased incidence of sciatic nerve degeneration in some of the existing studies.

Acute and subacute neurotoxicity studies, to include studies on cholinesterase inhibition and sciatic nerve degeneration, are also required.

The carcinogenicity studies in rats and mice (83-2a and -2b) were not discussed by the RfD Committee. The carcinogenicity issue has been referred to the Health Effects Division - Carcinogenicity Peer Review Committee (HED-CPRC) for a weight of the evidence evaluation.

The RfD for this chemical was assessed by the Agency RfD Work Group on May 31, 1985 on the basis of a two-year feeding study in rats with a NOEL of 9.6 mg/kg/day. Kidney and liver toxicity were observed at the next higher dose level of 15.6 mg/kg/day. An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the RfD was calculated to be 0.096 mg/kg/day. At that time, this chemical had not been reviewed by the Health Effects Division RfD Committee prior to the Agency RfD Work Group meeting and subsequently, additional data were submitted to the Health Effects Division for review. In the meeting of October 28, 1993 the Health Effects Division RfD Committee concluded that the RfD for this chemical should be based on the chronic toxicity and 5-week studies in dogs with an overall NOEL of 1.43 mg/kg/day. An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **0.014 mg/kg/day.** The lowest-effect level (LOEL) in this study was considered to be 3.37 mg/kg/day in males

and 3.73 mg/kg/day in females based on plasma and brain cholinesterase inhibition in both sexes. It should be noted that this chemical has been reviewed and an Acceptable Daily Intake (ADI) of 0.01 mg/kg/day was established by the World Health Organization (WHO) in 1973.

A. Individuals in Attendance

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

William Burnam

Reto Engler

Karl Baetcke

Henry Spencer

William Sette

Roger Gardner

Stephen Dapson

James Rowe

George Ghali

Rick Whiting

2. Peer Review Committee Members and Associates Unable to Attend (Signature indicates concurrence with the peer review unless otherwise stated).

Marcia Van Gemert

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

Ray Landolt

Mike Ioannou

4. Others:

Kerry Dearfield, Susan Makris and John Doherty of HED as observers.

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Marcia Van Gemert
Ray Landolt
Mike Ioannou
James Kariya
Karen Whitby
RfD and Caswell Files

B. Material Reviewed

Material available for review included data evaluation records for two chronic toxicity/carcinogenicity studies in rats **(83-5 or 83-1a and -2a)**, a carcinogenicity study in mice **(83-2b)**, two chronic toxicity studies in dogs **(83-1b)**, developmental toxicity studies in rats, monkeys, Guinea pigs and dogs **(83-3a and -3b)** and a reproductive toxicity study in rats **(83-4)**, and a tox. one-liner.

1. Hamada, N. N. (1993). Combined chronic toxicity and oncogenicity study with carbaryl technical in Sprague-Dawley rats. MRID No. 42188901, 42918801, HED Doc No. 010638, 010092.

Core Classification: Core-minimum data.

Committee's Conclusion and Recommendations:

The chemical was tested in Sprague-Dawley rats at 250, 1500 and 7500 ppm (10, 60.22, 349.5 mg/kg/day in males and 12.6, 78.6 and 484.6 mg/kg/day in females). The NOEL/LOEL were considered to be 250 and 1500 ppm in both males and females based on decreased brain and red blood cell cholinesterase activity. The high dose tested was considered adequate for carcinogenicity testing based upon decreased body weight gain, decreased food efficiency and alterations in hematological and clinical chemistry parameters. Degeneration of the sciatic nerve was observed in the high dose males and females accompanied by skeletal muscle degeneration. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. The carcinogenicity phase of the study was not discussed. The carcinogenicity issue has been referred to the HED-CPRC. The study was considered to be acceptable and the data evaluation record was considered to be adequate. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats.

2. Hamada, N. N. (1987). One-year oral toxicity study in beagle dogs. MRID No. 40166701, 40901401, HED Doc No. 006401, 007086, 009776.

3. Hamada, N. N. (1991). Subchronic toxicity study in dogs with carbaryl technical. MRID No. 42022801, HED Doc. No. 009776.

Core Classification: The chronic toxicity study is considered to be Core-minimum data when considered together with the 5-week feeding study in dogs.

Committee's Conclusion and Recommendations:

The chemical was tested in beagle dogs at 125, 400 and 1250 ppm (3.37, 11.23 and 33.83 mg/kg/day in males and 3.73, 12.17, and 34.43 mg/kg/day in females) for one year, and at 20, 45 and 125 ppm

(0.59, 1.43 and 3.83 mg/kg/day in males and 0.64, 1.54 and 4.11 mg/kg/day in females) for 5 weeks. The overall NOEL/LOEL were considered to be 45 and 125 ppm in both males and females based on significant decrease in plasma (23%) and brain (20%) cholinesterase activity. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. The study was considered to be acceptable and the data evaluation records were considered to be adequate. This chronic feeding study, when considered together with the 5-week study in dogs, satisfies data requirement 83-1b of subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in dogs.

4. Weil, C. S. and Carpenter, C. P. (1972). Sevin (Carbaryl) comparative study of dietary inclusion versus stomach intubation on three-generations of reproductive, on teratology and on mutagenesis. MRID No. 00139647, HED Doc. No. 000000

Core Classification: Core-supplementary data.

Committee's Conclusions and Recommendations:

The chemical was tested in rats at 3, 7, 25 and 100 mg/kg/day by intubation and at 7, 25, 100 and 200 mg/kg/day by incorporation in diet. For the reproductive toxicity phase of the study, the systemic toxicity NOEL/LOEL were considered to be 25 and 100 mg/kg/day and the NOEL for reproductive toxicity was considered to be 100 mg/kg/day. For the developmental toxicity phase of the study, the maternal toxicity NOEL/LOEL 25 and 100 mg/kg/day and the developmental toxicity NOEL was considered to be 100 mg/kg/day. The Committee generally agreed with the reviewer's evaluation and interpretation of data and the classification of the study. Although, the reproductive/developmental toxicity study in rats does not conform to the current Guideline for reproductive/developmental toxicity testing, new studies are not required. The Committee recommended that the classification of the rat reproductive/developmental toxicity study remains unchanged as Core-supplementary data. This study does not satisfy data requirement 83-3a or 83-4 of subpart F of the Pesticide Assessment Guideline for developmental and reproductive toxicity testing in rats.

5. Coulston, F. et al. (1974). Teratogenic evaluation of carbaryl in the Rhesus monkey (Macca mulatta). MRID 00139648, 00139658, HED Doc. No. 000000.

Core Classification: Core-supplementary data.

Committee's Conclusions and Recommendations:

The chemical was tested in Rhesus monkeys at 0.2, 2.0 and 20 mg/kg/day. Maternal, developmental and reproductive toxicity NOEL

was considered to be 20 mg/kg/day, the highest dose tested. The Committee agreed with the reviewer's evaluation and interpretation of data and classification of the study. The developmental toxicity study in monkeys (83-3), though not conforming to the current Guideline for developmental toxicity testing, was considered adequate for regulatory purposes. The Committee recommended that the classification of the developmental toxicity study in monkeys remains unchanged as Core-supplementary data.

6. Weil, C. S. (1971). Study of Guinea pigs teratology of Sevin fed in the diet versus stomach intubation. MRID 00080675, 00125162, HED Doc. No. 000000.

Core Classification: Core-supplementary data.

Committee's Conclusions and Recommendations:

The chemical was tested in Guinea pigs at 50, 100 and 200 mg/kg/day by gastric intubation and at 100, 200 and 300 mg/kg/day by dietary inclusion. For the dietary phase of the study, maternal toxicity NOEL/LOEL were considered to be 200 and 300 mg/kg/day and developmental toxicity NOEL was considered to be 300 mg/kg/day. For the oral intubation phase of the study the NOEL/LOEL for maternal toxicity were considered to be 100 and 200 mg/kg/day and developmental toxicity NOEL was considered to be 200 mg/kg/day. The Committee generally agreed with the reviewer evaluation and interpretation of data and classification of the study. The Committee recommended to revise the NOEL for maternal toxicity in the gastric intubation phase of the study from 100 mg/kg/day to 50 mg/kg/day. The study does not conform to the current Guideline for developmental toxicity testing and was considered inadequate due to multiple deficiencies. The Committee recommended that the classification of the developmental toxicity study remains unchanged 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.

7. Chernoff, N. (1976, updated 1980). Review of data bearing upon the potential of the pesticide Carbaryl to induce effects on the reproduction and perinatal development of mammals. From N. Chernoff, Ph.D. Neurobiology Branch, Experimental Biology Division, HERL/RTP, to James Benskin, Ph.D., Office of Special Pesticide Review. Includes appendix: "summary critique of available references."

This was apparently a review article of the available unpublished and open literature information on the potential of the pesticide carbaryl to induce reproductive and developmental toxicity in several animal species. General evaluation of this review article indicated that carbaryl has the potential to induce developmental toxicity in dogs at dose levels below those causing considerable maternal toxicity. However, the Committee felt that the positive

effects in the dog study should be viewed in light of the reported unusual metabolism in this species.

C. Conclusions and Recommendations

1. Acute, subchronic and Chronic Toxicity

The Committee considered the chronic toxicity study in rats **(83-1a)** to be acceptable. The Committee considered the chronic toxicity study in dogs **(83-1b)**, when combined with the subacute (5-weeks) feeding study in dogs, to be acceptable.

Acute and subchronic neurotoxicity studies, to include studies on cholinesterase inhibition and sciatic nerve degeneration, are required.

2. Developmental Toxicity

The potential of carbaryl to induce deleterious effects on reproductive and developmental parameters has been studied in a wide variety of mammalian systems. These studies showed that carbaryl has the potential to induce developmental toxicity in dogs at dose levels below those causing considerable maternal toxicity. However, the Committee felt that the positive effects in the dog study should be viewed in light of the reported unusual metabolism in this species. Although, the reproductive/developmental toxicity study in rats **(83-4)** does not conform to the current Guideline for reproductive/developmental toxicity testing, a new study is not required. The Committee recommended that the classification of the rat reproductive/developmental toxicity study remains unchanged as Core-supplementary data. The developmental toxicity study in monkeys **(83-3)**, though not conforming to the current Guideline for developmental toxicity testing, was considered adequate for regulatory purposes. The Committee recommended that the classification of the developmental toxicity study in monkeys remains unchanged as Core-supplementary data. The developmental toxicity study in Guinea pigs **(83-3)** does not conform to the current Guideline for developmental toxicity testing and was considered inadequate due to multiple deficiencies. The Committee recommended that the classification of the developmental toxicity study in Guinea pigs remains unchanged as Core-supplementary data. Furthermore, the Committee recommended to revise the no-observable effect level (NOEL) for maternal toxicity in the Guinea pigs study from 100 mg/kg/day to 50 mg/kg/day.

In view of the above, the Committee concluded that a developmental neurotoxicity study should be submitted. This recommendation was based on the fact that none of the reproductive/developmental toxicity studies available conform to the current Guideline for reproductive/developmental toxicity testing, observed reduction of litter size and viability and increased incidence of sciatic nerve degeneration in some of the existing studies.

The carcinogenicity studies in rats and mice **(83-2a and -2b)** were not discussed by the RfD Committee. The carcinogenicity issue has been referred to the Health Effects Division - Carcinogenicity Peer Review Committee (HED-CPRC) for a weight of the evidence evaluation.

4. Reference Dose

The Rfd for this chemical was assessed by the Agency RfD Work Group on May 31, 1985 on the basis of a two-year feeding study in rats with a NOEL of 9.6 mg/kg/day. Kidney and liver toxicity were observed at the next higher dose level of 15.6 mg/kg/day. An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the RfD was calculated to be 0.096 mg/kg/day. At that time, this chemical had not been reviewed by the Health Effects Division RfD Committee prior to the Agency RfD Work Group meeting and subsequently, additional data were submitted to the Health Effects Division for review. In the meeting of October 28, 1993 the Health Effects Division RfD Committee concluded that the RfD for this chemical should be based on the chronic toxicity and 5-week studies in dogs with an overall NOEL of 1.43 mg/kg/day. An uncertainty factor (UF) of 100 was used to account for the inter-species extrapolation and intra-species variability. On this basis the **RfD** was calculated to be **0.014 mg/kg/day.** The lowest-effect level (LOEL) in this study was considered to be 3.37 mg/kg/day in males and 3.73 mg/kg/day in females based on plasma and brain cholinesterase inhibition in both sexes. It should be noted that this chemical has been reviewed and an Acceptable Daily Intake (ADI) of 0.01 mg/kg/day was established by the World Health Organization (WHO) in 1973.

GG/JB 2.14.94