CASWELL FILE

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

JUN 19 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review Committee on Cyanazine (Bladex)
Caswell No. 188 C Tox Proj No.: N/A

TO: Janet Auerbach, Chief
Special Review Branch
Registration Division (TS-767C)

FROM: Quang Q. Bui, PhD., DABT. Quang Q. Bui
Acting Head, Review Section V
Toxicology Branch/HED (TS-769C)

THRU: Theodore M. Farber, PhD., DABT. Theodore M. Farber 6/19/87
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

At the request of the Toxicology Branch, a peer review committee consisting of representatives from different Offices met on June 5, 1987 to discuss the comments raised by the FIFRA Scientific Advisory Panel relative to Cyanazine. Recommendations from the peer review committee are attached to this memorandum.

Committee Members in Attendance:

David G. Anderson,	TOX/HED/OPP
Quang Q. Bui,	TOX/HED/OPP
Gary Burin,	SIS/HED/OPP
William Burnam,	TOX/HED/OPP
Laurence D. Chitlik,	TOX/HED/OPP
Carole Kimmel,	REAG/ORD
Gary Kimmel,	REAG/ORD
Curt Lunchick,	EAB/HED/OPP
Guillermo Millicovsky,	Dynamac Corporation

Committee Member in Absentia:

Theodore M. Farber,	TOX/HED/OPP

cc. Anne Barton (TS-769C)
Joanna Dizikes (TS-767C)
Reto Engler (TS-769C)
James Yowell (TS-767C)

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PEER REVIEW DOCUMENT FOR CYANAZINE (BLADEX)

BACKGROUND

Oral administration of Technical Cyanazine induced developmental toxicity (including malformations) in rabbits and rats. From the rabbit oral developmental toxicity data, both maternal and fetal developmental toxicity NOELs were established at 1 mg/kg and both LELs at 2 mg/kg.

Dermal application of Technical Cyanazine produced irritation in rabbits at all doses tested (96, 283, 573, and 955 mg/kg) but, frank maternal toxicity (body weight depression and food consumption reduction) was observed only at 283 mg/kg and above. A maternal NOEL was established at less than 96 mg/kg based upon dermal irritation. Developmental toxicity (delayed ossification) was found at 955 mg/kg (LEL) and a dermal developmental toxicity NOEL was established at 573 mg/kg

In the rat, a dermal absorption rate of 2% was demonstrated.

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) met on March 24, 1987 to discuss the scientific issues related to Cyanazine. Recommendations and issues raised by the SAP were addressed in the final report dated March 31, 1987 and are highlighted in this document. A Peer Review Committee (PRC) was convened on June 5, 1987 to discuss the issues raised by the SAP and recommendations from the PRC are presented as follows:

Issue # 1

SAP Comment:

The Panel believes that the toxic endpoint that should be used is systemic toxicity. The latter only occurred at doses that were maternally toxic and maternal systemic toxicity occurred at lower exposures. Thus a lower margin of safety exists for adult animals than for the developing fetus.

Peer Review Committee Response:

The PRC believes that the panel recommendation applies only to the dermal and not to the oral developmental toxicity data. In the latter, developmental toxicity occurs at a dose which is also maternally toxic (both maternal and developmental toxicity LELs are 2 mg/kg). In the dermal study, developmental toxicity occurs at a dose higher than that producing maternal toxicity. Consequently, if the margin of safety (ratio of NOEL to estimated human exposure) is calculated based upon the dermal maternal NOEL instead of the developmental toxicity NOEL, as suggested by the SAP, a lower margin of safety would result. However, the use of the maternal NOEL, regardless of the route of exposure,

in calculating the margin of safety may not be justified since:

a. Maternal toxicity end points determined from a developmental toxicity study (body weight, organ weight, food consumption, clinical signs) are insensitive parameters which require scientific judgement on a case-by-case basis. To be helpful, end points of maternal toxicity should extend to clinical chemistry, hematology, histopathology, etc. These parameters are presently not required in a conventional teratology study.

b. Developmental toxicity manifestations may or may not be associated with maternal toxicity.

c. As a screening test, a developmental toxicity study does not allow characterization of subtle changes in systemic toxicity and the length of exposure (10 days) is not adequate to detect every possible systemic effects.

d. Manifestations of maternal systemic toxicity may result from repeated exposures whereas manifestations of developmental toxicity are more likely resulted from single exposure.

e. To truly protect human workers, a lowest systemic NOEL from the most sensitive species should be used. This lowest systemic NOEL may be obtained from a chronic or subchronic study and not necessarily from a developmental toxicity study. However, if the maternal NOEL is the lowest, then, it may be used to assess risk associated with adult human exposures.

Issue No. 2

SAP Comment:

Developmental toxicity occurred at materrally toxic doses and maternal systemic toxicity occurred at lower exposures. The Panel believes that the EPA is correct in requiring the label changes to reduce applicator exposure, but that it should not state that birth defects are the reason.

Peer Review Committee Response:

The Panel recommendation relative to "maternal toxicity occurred at lower doses than developmental toxicity" applied only to the dermal developmental toxicity data. By the oral route of administration, developmental toxicity and maternal toxicity are observed at the same dose level (both NOELs and LELs are established at 1 and 2 mg/kg, respectively). The Agency's Guideline for the Health Assessment of Suspect Developmental Toxicants (1996) states that "when developmental effects are produced only at maternally toxic doses, the types of developmental effects should be examined carefully, and not discounted as being secondary to maternal toxicity. Current information is inadequate to assume that developmental effects at maternally toxic doses result only from the maternal toxicity; rather, when

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the lowest observed effect level is the same for the adult and developing organisms, it may simply indicate that both are sensitive to that dose level. Moreover, the maternal effects may be reversible while effects on the offspring may be permanent."

There are only four ways (death: structural abnormality: altered growth, and functional deficiency) for a developing organism to signal injury induced by pesticides. Which of the four end points is used to identify adverse effects is not highly relevant since it is the dose and not the types of defects that are important to risk characterization. The developmental toxicity hazard of Cyanazine is identified by the oral route of administration (structural abnormalities) and is confirmed by the dermal route (altered growth: delayed ossification). Stating that "birth defects are not produced by the dermal route" may not be appropriate since one type of developmental toxicity manifestation (altered growth) has been observed in this study. Further, the PRC believes that no definitive conclusion could be made relative to the developmental toxicity potential of Cyanazine by the dermal route due to limitations and restrictions of this type of study design. Based on the questionable reliability and predictability of dermal developmental toxicity study, more effort and emphasis should be directed to this area of reproductive toxicology.

PEER REVIEW COMMITTEE CONCLUSION ON CYANAZINE

From the data available, there is evidence to suggest that Cyanazine is a developmental toxicity. By the oral route of administration, developmental toxicity occurs at maternally toxic doses. This finding simply indicates that both the mothers and developing organisms are sensitive to that dose level and the effects on the offspring cannot be discounted as secondary to the mothers. By the dermal route of administration, developmental toxicity occurs at doses higher than those producing maternal toxicity. However, the use of the maternal NOEL, as suggested by the SAP, to calculate the margin of safety (MOS) for occupational workers is not always justified. Instead, the PRC believes that data from a 90-day dermal rat study or a 21-dog dermal stucy would be more appropriate to assess the question of systemic toxicity in agricultural workers.

At the present time, the Office of Pesticide Programs (OPP) believes that one approach to characterize risk from a developmental toxicant is the margin of safety (MOS), which is the ratio of a NOEL from a developmental toxicity study to an estimated human exposure. Traditionally, OPP prefers the use of an oral NOEL to assess the developmental potential hazard of dietary exposures and a dermal developmental toxicity NOEL for occupational exposure. To be useful, pharmacokinetic information should be incorporated in the design of the dermal study especially for pesticides with minimal dermal absorption or for those which bioaccumulate. In the absence of dermal data, the oral NOEL could be used to assess

risk associated with dermal occupational exposures if dermal absorption data are available. In light of the questionable reliability and predictability of dermal developmental toxicity information, the use of the oral NOEL of 1 mg/kg and a dermal absorption rate of 2% seems justified to calculate the margin of safety for occupational exposures

$$MOS = \frac{\text{Oral developmental toxicity NOEL (1 mg/kg)}}{\text{Human exposure levels (b)}} \times 50\,(a)$$

(a) conversion factor for 2% dermal absorption
(b) data provided by the Exposure Assessment Branch

The Peer Review Committee believes that (1) to enhance our scientific judgement of dermal developmental toxicity studies, considerable effort from the scientific community should be directed to this area of reproductive toxicity and (2) to increase the sensitivity of maternal end points, other parameters should be considered in future Agency Guidelines for developmental toxicity studies.