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

26 AUG 1993

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Lindane: RfD/Peer Review Report
CASRN. 58-89-9
EPA Chem. Code: 009001
Caswell No. 527

FROM: George Z. Ghali, Ph.D. G Ghali 7.14.93
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Health Effects Division (H7509C)

TO: George LaRocca, PM 13
Insecticide-Rodenticide Branch
Registration Division (H7505C)

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

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The Health Effects Division RfD/Peer Review Committee met on July 8, 1993 to discuss and evaluate the existing toxicology data base on Lindane with special emphasis on the reproductive/ developmental toxicity and carcinogenic potential. The Committee was also requested to re-assess the Reference Dose (RfD) for this chemical.

The Committee recommended that a Reference Dose (RfD) be established on the basis of a NOEL of 10 ppm (0.47 mg/kg/day) demonstrated in a chronic toxicity study in rats for periacinar hepatocyte hypertrophy, increased liver and spleen weight and increased platelets observed at 100 ppm (4.81 mg/kg/day) and higher dose levels. 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 **0.0047 mg/kg/day.** The Committee agreed that kidney effects associated with alpha 2u globulins observed at 1 ppm (0.05 mg/kg/day, lowest dose tested, and above) should not be used for regulatory purposes. This specific type of lesion in male rat kidney is not currently regarded as being relevant to human health risk assessment.

The Committee considered the chronic toxicity study in rats (83-1a), the chronic toxicity study in dogs (83-1b), and the reproductive toxicity study in rats (83-4) to be acceptable for regulatory purposes. The developmental toxicity studies in rats and rabbits (83-3a and -3b) were considered marginally acceptable. There was no evidence, based on the available data, that the chemical was associated with significant reproductive or developmental toxicity under the testing conditions. However, because of neurotoxicity signs observed in several species and because Lindane, like other organochlorines, is known to cross the placenta, the Committee concluded that a developmental neurotoxicity study in rats (83-6) must be submitted to further evaluate any potential developmental neurotoxicity of this chemical.

The Committee recommended that the classification of the carcinogenicity study in rats (83-2a) should remain as Core-supplementary until the additional data requested (histopathological data on adrenal glands in the low, mid-low and mid-high dose groups and historical control data on pheochromocytoma in this strain of rats) are evaluated. However, it should be emphasized that the high dose tested in the rat study was adequate for carcinogenicity testing in this strain of rats for both sexes. The mouse carcinogenicity data (83-2b) were considered insufficient because of major deficiencies associated with all studies available. The Committee concluded that another carcinogenicity study in a commonly used strain of mice should be submitted and the Agency should be consulted on the protocol of the study before initiation.

The carcinogenic potential of this chemical was not therefore classified by the RfD/Peer Review Committee. However, the carcinogenic potential of this chemical had been classified by the Cancer Assessment Group of the Office of Research and Development as B2/C based on increased incidence of mouse liver tumors. It should be noted that the 1991 Environmental Health Criteria for Lindane (No. 124, page 20) issued by the IPCS of the World Health Organization concluded that "long-term carcinogenicity tests conducted according to present-day standards should be conducted".

A. Individual in Attendance

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

William Burnam

Reto Engler

Marcia Van Gemert

Karl Baetcke

Henry Spencer

William Sette

Roger Gardner

James Rowe

Kerry Dearfield

George Ghali

Rick Whiting

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

Marion Copley

John Doherty

3. Others:

Marion Copley and Virginia Dobozy of the Health Effects Division as observers

CC: Penny Fenner-Crisp
Richard Schmitt
Kerry Dearfield
Karl Baetcke
Marion Copley
John Doherty
Rick Whiting
James Kariya

B. Material Reviewed

Material available for review included a chronic toxicity/ carcinogenicity study in rats (83-5 or 83-1a and -2a), a long-term toxicity study in dogs (83-1b), several published carcinogenicity studies in mice (83-2b), developmental toxicity studies in rats and rabbits (83-3a and -3b), a reproductive toxicity study in rats (83-4) and the tox. one-liners. The following are the Committee's conclusions and recommendations:

1. Amyes, S. J. (1989). Combined oncogenicity and toxicity study by dietary administration to Wistar rats for 104 weeks. MRID No. 41853701, HED Doc. No. 009909.

Core Classification: According to the data evaluation record the study was classified as Core-supplementary.

Committee's Conclusions and Recommendations:

The chemical was tested at 1, 10, 100 and 400 ppm (equivalent to 0.05, 0.47, 4.81, 19.66 mg/kg/day for males and 0.06, 0.59, 6.00, 24.34 mg/kg/day for females). The Committee generally agreed with the reviewer's evaluation and interpretation of data. The Committee recommended to treat the two phases of the study (chronic toxicity and carcinogenicity) separately for the purpose of classification. The Committee recommended that the chronic toxicity phase be upgraded to a Core-minimum status and agreed with the reviewer that the carcinogenicity phase of the study should remain as Core-supplementary until data requested in the data evaluation record (histopathological data on adrenal glands in the low, mid-low and mid-high dose groups and historical control data on pheochromocytoma in this strain of rats) are evaluated. The Committee considered the high dose tested in this study to be adequate for carcinogenicity testing based on decreased survival in both males and females, and convulsion observed in females. This study satisfies data requirement 83-1a of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in rats. The acceptability of the carcinogenicity phase of this study (83-2a) will be determined upon the evaluation of additional data recently submitted by the registrant.

2. Merck, A. G. Company (1971). Lindane toxicity study in Beagle dogs. MRID No. 470279025, HED Doc. No. 004704.

Core Classification: According to the data evaluation record the study is classified as Core-minimum.

Committee's Conclusions and Recommendations:

The chemical was tested at 25, 50 and 100 ppm (equivalent to 0.84, 1.71 and 3.51 mg/kg/day in males and 0.95, 2.07 and 4.03 mg/kg/day in females) in the diet for 104 weeks. Another group was

administered the test material at 200 ppm (equivalent to 8.3 and 8.7 mg/kg/day for males and females, respectively) for only 32 weeks. The Committee agreed with the reviewer evaluation and interpretation of the data and classification of the study. The no-observable effect level was determined to be 50 ppm. At 100 ppm there was indication of some liver changes which, according to the reviewer, might be adaptive rather than actually a toxic response. At this dose level, EEG changes were also apparent. This study satisfies data requirement 83-1b of Subpart F of the Pesticide Assessment Guideline for chronic toxicity testing in non-rodent species.

3. Carcinogenicity studies in mice.

Core Classification: All studies were classified as Core-supplementary

Committee's Conclusions and Recommendations:

Several mouse carcinogenicity studies were available for the Committee's consideration. The Committee agreed with the reviewer's evaluation and interpretation of data. The Committee concluded that none of these studies meet the current Agency Guideline criteria for carcinogenicity testing. All studies were deficient in conduct and/or reporting. Because of numerous major deficiencies associated with all of these studies, all mouse studies were considered insufficient for the purpose of classification of the carcinogenic potential and/or quantification of human risk. These studies are inadequate to fulfill the Guideline requirement 83-2b of Subpart F for carcinogenicity testing in mice.

4. Anthony, K. et al. (1971). Effect of lindane on pregnancy of the rat. MRID No. 42808001, HED Doc. No. 010384.

Core Classification: According to the data evaluation record the study is classified as Core-minimum.

Committee's Conclusions and Recommendations:

The Committee generally agreed with the reviewer's evaluation and interpretation of data. The chemical was tested at 5, 10 and 20 mg/kg/day. The NOEL and LOEL for maternal toxicity were considered to be 5 and 10 mg/kg/day respectively, and for developmental were considered to be 10 and 20 mg/kg/day respectively. The Committee considered the study to be marginally acceptable. The data evaluation record was considered adequate as presented. This study satisfies data requirement 83-3a of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rats.

5. Reno, F. R. (1976). Teratology study in rats with lindane. MRID No. 00062656, HED Doc. 010384.

Core Classification: According to the data evaluation records the study is classified as Core-supplementary because the material was administered subcutaneously. Such a route of administration is not recommended by the Guideline.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's evaluation and interpretation of data. This study does not meet the Agency Guideline criteria and therefore is not acceptable. The data, however, are considered useful in supporting the conclusions of the oral rat study.

6. Palmer, A. K. and Neuff, A. M. (1971). Effect of lindane on pregnancy of the New Zealand white rabbit. MRID No. 42808002, HED Doc No. 010384.

Core Classification: According to the data evaluation record the study is classified as Core-minimum.

Committee's Conclusions and Recommendations:

The Committee generally agreed with the reviewer's evaluation and interpretation of data. The chemical was tested at 5, 10 and 20 mg/kg/day. The NOEL for maternal and developmental toxicity was considered to be > 20 mg/kg/day, the highest dose tested. The Committee considered the study to be marginally acceptable. <u>This study satisfies data requirement 83-3b of Subpart F of the Pesticide Assessment Guideline for developmental toxicity testing in rabbits</u>.

7. Reno, F. E. (1976). Teratology study in rabbits with lindane. MRID No. 00062658, HED Doc. No. 010384.

Core Classification: According to the data evaluation record the study is classified as Core-supplementary because the material was administered subcutaneously. Such a route of administration is not recommended by the Guideline.

Committee's Conclusions and Recommendations:

The Committee agreed with the reviewer's evaluation and interpretation of data. This study is not acceptable because of the route of administration used. The data, however, are considered useful in supporting the conclusions of the oral rabbit study.

8. King, V. C. (1991). Lindane: reproductive performance study in rats treated continuously through two successive generations. MRID No. 42246101, HED Doc. No. 009911.

Core Classification: According to the data evaluation record the

study is classified as Core-minimum

Committee's Conclusions and Recommendations:

The chemical was tested at 1, 20 and 150 ppm (equivalent to 0.0865, 1.71 and 13.05 mg/kg/day). The Committee generally agreed with the reviewer's evaluation and interpretation of data and considered the increase in pup weight to be reproductive/systemic toxicity with a no-observable effect level of 1.71 mg/kg/day. The no-observable effect level for parental toxicity was considered to be 1.71 mg/kg/day. The Committee considered all kidney effects such as increased kidney relative and absolute weight, interstitial nephritis, cortical tubular cell degeneration, tubular necrosis etc. to be related to alpha 2u globulin. A no-observable effect level for effects on the male kidney was established at 0.0865 mg/kg/day. This study is acceptable and the data evaluation record is adequate. The Committee requested that the tooth eruption to be expressed in terms of post-partum days. This study satisfies data requirement 83-4 of Subpart F of the Pesticide Assessment Guideline for reproductive toxicity testing in rats.

C. Conclusions and Recommendations

1. Reference Dose (RfD)

The Committee recommended that a Reference Dose (RfD) be established on the basis of a NOEL of 10 ppm (0.47 mg/kg/day) demonstrated in a chronic toxicity study in rats for periacinar hepatocyte hypertrophy, increased liver and spleen weight and increased platelets observed at 100 ppm (4.81 mg/kg/day) and higher dose levels. 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 **0.0047 mg/kg/day**. The Committee agreed that kidney effects associated with alpha 2u globulins observed at 1 ppm (0.05 mg/kg/day, lowest dose tested) should not be used for regulatory purposes. This specific type of lesion in male rat kidney is not currently regarded as being relevant to human health risk assessment.

2. Data Base

The Committee considered the chronic toxicity study in rats (83-1a), the chronic toxicity study in dogs (83-1b), and the oral reproductive toxicity study in rats (83-4) to be acceptable. The oral developmental toxicity studies in rats and rabbits (83-3a and -3b) were considered marginally acceptable. The Committee recommended that the classification of the carcinogenicity study in rats (83-2a) should remain as Core-supplementary until the additional data requested (histopathological data on adrenal glands in the low, mid-low and mid-high dose groups and historical control data on pheochromocytoma in this strain of rats) are evaluated. However, it should be emphasized that the high dose tested in the rat study was adequate for carcinogenicity testing in this strain of rats for both sexes. The mouse carcinogenicity data (83-2b) were considered insufficient because of numerous and major deficiencies associated with all mouse studies available. The mouse carcinogenicity data are considered inadequate for the classification of the carcinogenic potential and/or quantification of human risk. The Committee recommended that another carcinogenicity study in a commonly used strain of mice be submitted and the Agency should be consulted on the study protocol.

3. Carcinogenic Potential.

The carcinogenic potential of this chemical was not classified by the RfD/Peer Review Committee. However, the carcinogenic potential of this chemical had been classified by the Cancer Assessment Group of the Office of Research and Development as B2/C. It should be noted that the 1991 Environmental Health Criteria for lindane (No. 124, page 20) issued by the IPCS of the World Health Organization concluded that "long-term carcinogenicity tests conducted according to present-day standards should be conducted".

4. Acute and Subacute Concern

There was no evidence, based on the available data, that the chemical was associated with significant reproductive or developmental toxicity under the testing conditions. However, because of some neurotoxicity signs observed in several species and because Lindane, like other organochlorines, is known to cross the placenta, the Committee concluded that a developmental neurotoxicity study (83-6) in rats must be submitted to further evaluate the potential developmental neurotoxicity of this chemical. The Agency should be consulted on the protocol prior to initiation of the study.