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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Memorandum

Subject: EPA ID No.: 009001. Lindane: Request for a waiver from the requirement for a series 83-2b carcinogenicity study with mice.

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I. Conclusion

Toxicology Branch II (TB-II) has considered the resubmission sponsored by the Centre Internationale d'Etudes du Lindane (CIEL) for a waiver for the series 83-2b mouse carcinogenicity study and has determined that a sufficient basis for a waiver has not been provided by the registrant. HED has determined that none of the existing studies or combination of studies is considered sufficient to provide a basis for risk assessment or even if quantitative carcinogenic risk assessment is appropriate for lindane. A new study that will be conducted consistent with current guidelines for testing and including assessing dose levels below and above the dose level at which metabolic detoxification of lindane is saturated will help to resolve

unsettled questions regarding lindane's potential to induce liver tumors in mice. The CIEL's documents discussed the issues related to liver tumors noted in at least two mouse studies but did not also discuss the possible inducement of lung tumors as indicated by TB's review of the Wolff 1987 study. The new study is also expected to clarify the issue of possible induction of lung tumors.

II. Background and Action Requested

Health Effects Division (refer to the memo for EPA File No.: 009001 and dated September 24, 1993) requested that a series 83-2b carcinogenicity study in mice be provided for completion of the toxicity data base for lindane. The need for this study was determined by HED's RfD committee¹ and is based on the fact that there is no mouse study that meets the current GUIDELINE criteria for an acceptable study for carcinogenicity evaluation in this species. Although HED recognized the existence of nine studies with mice submitted from various laboratories, none of these studies alone or combination of studies was determined to meet the criteria for an acceptable study. The existing data base was considered to indicate that lindane is associated with liver tumors in some strains of mice. A previous review of the cancer issues by the Agency's Carcinogenicity Assessment Group (CAG, refer to memo dated July 23, 1985 from R.E. McGaughy to Anne Barton) classified lindane as a "B2-C". Since that time issues related to the dose levels being excessive and causing competing toxicity or overwhelming the metabolic defenses of the mouse have been reconsidered. At least one study received since that time also suggested lindane is associated with increases in mouse lung tumors. HED determined that the diversity of the results of these nine studies did not render any confidence in classifying lindane as a carcinogen or selecting a statistical model for risk assessment.

The September 24, 1993-memo specifically advised the registrant that a commonly used mouse strain be used for this requested study. The 1993 memo also advised that a range finding study be conducted to determine the appropriate dose levels and in particular the dose levels at which the metabolic detoxification system becomes saturated and that the doses used for the definitive study include doses above and below the metabolic saturation dose level.

A previous waiver request, based mainly on the low potential for lindane residues to remain in food as a result of seed treatment, for the mouse carcinogenicity study was also submitted but denied by Toxicology Branch (refer to the memo dated November 28, 1995, for DP Barcode D212372).

The McKenna & Cuneo, L.L.P. law firm on behalf of their client Centre Internationals d'Etudes du Lindane (CIEL) has resubmitted a request for a waiver from this requirement for a series 83-2 mouse carcinogenicity study (refer to letter dated August 15, 1997 from Charles A. O'Connor, III). This resubmission of the waiver request was supported mainly by revised

¹Refer to the RfD Committee report dated August 25, 1993.

documentation as prepared by Dr. Gary Burin (see report dated April 15, 1997) that addresses the existing carcinogenicity and mutagenicity data base for lindane. In addition to Dr. Burin's report, additional documents prepared by Carlton and Blacker, 1993, Vesselinovitch and Carlborg, manuscript published in 1983 and Vesselinovitch, 1980 were also submitted but these documents were considered on prior occasions by HED.

Toxicology Branch II (TB-II) has reviewed this resubmission and the following comments apply.

III. Toxicology Branch Comments

1. Carcinogenicity Issues in the Rat and Mutagenicity Issues.

The CIEL has provided a carcinogenicity study (MRID No.: 41853701 and 42871201 refer to HED Documents No.: 009909 and 010603) with rats and this study was reviewed and classified as GUIDELINE and HED concluded that there was no evidence of lindane induction of neoplasms in rats in this study. Thus, lindane is not considered carcinogenic in the rat by HED. TB-II does not consider that the weight-of-evidence from mutagenicity studies indicates a mutagenicity concern for lindane. The issues regarding carcinogenicity potential in the rat and mutagenicity should not require further comments from HED in this memo since HED does not consider lindane carcinogenic in the rat or to have a mutagenicity concern.

Thus, the remaining issue is the potential for lindane to be a carcinogen in the mouse.

2. The Existing Mouse Carcinogenicity Data Base.

TB-II and the CIEL² concur that there are nine studies available that assess lindane for potential carcinogenicity in mice. The CIEL maintains that of these there are "four major chronic mouse studies of acceptable duration." These studies are Thorpe and Walker, 1973, Herbst, 1973, NCI, 1977 and Wolfe, 1987. The remaining five studies are of shorter duration (i.e., 24-38 weeks or less than one year) and/or use test material of undetermined composition. Of the four studies considered major, the NCI, 1977 and the Herbst, 1973 studies were not considered positive but some questions remain about the adequacy of dosing. The Thorpe and Walker, 1973 and Wolfe, 1987 studies provide the most convincing data that lindane (defined as >99% pure λ isomer) is associated with increases in liver tumors. The Thorpe study indicates increases in liver tumors at doses of 400 ppm (the only dose assessed), a dose which the CIEL considered to be in excess of the "MTD" or "maximum tolerated dose." The Wolfe study assessed only one dose (160 ppm) and females only but assessed three lines from the same strain of mice (black, pseudo aguiti and yellow lines). In the latter study, lindane increased liver

²CIEL is being used here as a general reference to the registrant and comments in the letter and other documents.

tumors in the pseudo aguti and yellow lines but not in the black line and it was implied that there is a genetic basis for susceptibility and this is related to differences in the ability of each strain to metabolize lindane. Thus, TB-II considers that there are available studies which indicate that lindane under some conditions can induce liver tumors and this may be related to the ability of the mouse to metabolize lindane. The Wolff study also indicated that lindane was associated with increases in lung tumors in the pseudo aguti and yellow lines.

It must also be noted that the Thorpe and Walker study and the Wolff study are available only as publications in the open literature. Such literature reports do not contain sufficient detail or individual animal data to independently verify the summary tables and conclusions.

3. Rationale for the Need for a New Carcinogenicity Study in Mice.

The RfD committee report (dated August 25, 1993) states that "The mouse carcinogenicity data (83-2b) were considered insufficient because of major deficiencies associated with all studies available" and thus concluded that another carcinogenicity study in a commonly used strain of mice should be submitted. It must also be noted that the 1991 Environmental Health Criteria for Lindane (No. 124, page 20) issued by the IPCS of the World Health Organization also concluded that "long term carcinogenicity tests conducted according to present-day standards should be conducted." Thus, the Agency is not alone in its concern for recognizing the need for additional testing in the mouse.

The HED of OPP of the EPA is charged with making determinations with regard to the quality of the data base to use for its regulatory decisions. The existing data base for mouse carcinogenicity testing is not considered of sufficient quality to define the carcinogenicity potential or to justify data for risk assessment models for carcinogenicity. The new study is expected to assess all tissues required for evaluation in a Guideline study. It should be noted that the Wolff '87 study raised the possibility that the lung was also a potential target organ for a neoplastic effect of lindane and this newer issue will also be resolved in the new study. No mention of the lung as a possible target organ was made in the resubmission documents presented by the CIEL.

4. Difference between the 1985 Registration Standard and the 1993 Data-Call-In.

The 1985 decision not to request an additional mouse carcinogenicity study was made by a committee that no longer evaluates the carcinogenicity of pesticides. There was, however, considerable opposition to this decision at the time the decision was made based on the quality of the data available. In 1992-3 TB-I (prior to reorganization) wanted to reevaluate the need for using a Q1* for lindane and tried to present the lindane data base for review by the HED Carcinogenicity Peer Review Committee. This HED Peer Review Committee was formed after 1985 and designed to address carcinogenicity issues related to pesticides. It is common for a chemical that was reviewed previously by the older Carcinogenicity Assessment Group to be

reevaluated by the newer HED Peer Review Group. The carcinogenicity data base is prescreened by HED's RfD Committee for the quality of the studies. When HED's RfD committee assessed the carcinogenicity data base for lindane with mice, it was determined that the quality of the mouse studies made them unsuitable for review by the Carcinogenicity Peer Review group.

Since the 1985 decision, the Agency received and reviewed the publications of Wolfe with the black, pseudo-agouti and yellow lines of mice. These studies assessed only one dose level (160 ppm) in females only but established that there may be a genetic basis for susceptibility to liver and possibly also lung tumor induction by lindane. HED considers that the study by Wolfe raised more questions than it answered. There are questions regarding the potential to induce tumors at lower doses since only one dose was assessed and this dose did not meet HED conventional criteria for adequacy of dosing (i.e., clinical signs or body weight effect or other toxicological response) and only females were tested. The contention that lindane induces liver tumors at dose levels only above doses in excess of the saturation dose for metabolic detoxification can only be implied but not proven from the Wolff study. The Wolff study also indicated lung tumors were associated with lindane treatment and this needs to be verified. Thus, a new study conducted under the more stringent criteria of the recommended CORE guidelines together with a defined basis for dose selection is expected to address some of the issues raised by Dr. Wolfe's study.

Thus, the difference between the 1985 and 1993 position on the need for a new mouse carcinogenicity study is considered justified by HED.

5. CIEL Speculation on the Outcome of the Studies.

The CIEL has implied that conduction of a new mouse study will not change the Q1* for lindane. The CIEL states that if the study is "negative", EPA would still use the Q1* based on the Thorpe and Walker data. The CIEL also states that if the new study is positive, the Thorpe and Walker study would still be used because this study would likely remain the "worst-case study available." In this case, the CIEL is speculating on what they perceive might be the possible outcomes as far as liver tumors are concerned. The CIEL did not mention what the outcome might be if the new study demonstrates lindane induction of lung tumors.

Although, TB-II declines from speculating on the outcome of the study with regard to it being positive or negative or what recommendations will be made based on the outcome of this new study, TB-II believes that the outlook should be more optimistic than the CIEL has portrayed. It is likely that when lindane is eventually reviewed by the HED Carcinogenicity Peer Review Committee (now called the Carcinogenicity Science Advisory Review Committee) the new guidelines for carcinogenicity classification will be used.

6. Other Documents Provided by the CIEL with the August 15, 1997 Resubmission

Mr. O'Connor's letter was accompanied by the following documents:

"Comments on the Weight-of-the-Evidence and the Need for Additional Carcinogenicity testing of Lindane" Prepared by Gary J. Burin, Ph.D., D.A.B.T. and dated August 15, 1997.

"Review of the Carcinogenic Potential of Lindane" Prepared by Betsy D. Carlton, Ph.D., D.A.B.T. and Ann M. Blacker, Ph.D., D.A.B.T. and dated June 1993.

"Lindane Bioassay Studies and Human Cancer Risk Assessment" a reprint appearing in *Toxicologic Pathology* 11:12-22 (1983) and authored by S.D. Vesselinovitch and F.W. Carlborg.

"Lindane and Carcinogenicity" Prepared by D. Vesselinovitch and dated August 1980.

The content of the first item above (Burin document) provided the basis for the discussion that was addressed in items 1, 2, 3, 4 and 5 above. HED staff has already reviewed the remaining three documents (refer to the memo dated October 6, 1993 for Barcode D192975). Dr. Burin's document already conveys the salient features of these three documents. It should be noted that neither of the documents prepared by Vesselinovitch (1983 and 1980) contain a discussion of the Wolff study (1987) which was considered a determining aspect of HED's decision to request a new series 83-2b carcinogenicity study in mice.

7. Additional comment.

None of the nine studies with mice represent conventional approaches with regard to the design, conduction and submission of a study to meet the requirement for carcinogenicity assessment in mice. There are at least two studies (NCI and the Wolff 1987 study) that were conducted at government expense. A NCI study can be used for regulatory purposes when there are no other data to suggest a possible effect. The reservations related to the Wolff study were already discussed above. Since the registrant has not yet had to bear the cost of a mouse carcinogenicity study for lindane which was a major pesticide, there is little weight to the references to the cost and burden to the registrant associated with conducting this study. The CIEL may also want to consider that the new study may allow the reclassification of the carcinogenic potential of lindane to be such that some of its canceled registrations may be restored.