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WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

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MEMORANDUM

SUBJECT: Lindane-Special Review - Response to the letter from Mr. C.A. O'Connor and Ms. M.K. Tandy dated October 22, 1985; reply to comments made by Dr. M. Herbst related to interpretation of the rat kidney pathology; review of selected papers related to the health status of workers manufacturing lindane; and current status of the "weight of evidence" with respect to induction of kidney lesions by lindane in test animals.

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Background:

Review of the rat subchronic feeding study with the test chemical lindane (refer to Dr. K. K. Locke review dated June 17, 1983) indicated that the study showed a NOEL of 4 ppm based on pathology of the kidney. It was further indicated in Dr. Locke's review that some aspects of the kidney pathology were still evident six weeks after cessation of dosing with lindane. This led to the prior conclusion that dosing (via feeding) with lindane resulted in "permanent or long-lasting (could not be reversed in 6 weeks) kidney damage".

Subsequently, HED personnel calculated the margins of safety for some applications based on this study which showed a NOEL of 4 ppm and an LEL of 20 ppm based on kidney effects.

In a letter dated October 22, 1985 from Mr. Charles A. O'Connor, III and Ms. Marlene K. Tandy, Counsel for Centre International d'Etudes du Lindane (CIEL) it was indicated that*:

1. The renal changes are reversible.
2. Studies on humans (including occupational exposure) revealed no kidney damage.

*Note only items of this letter related to Toxicology Branch are listed and discussed in this memo.

As justification that the rat kidney lesions were reversible, the registrants provided a report prepared by Manfred Herbst, DVM, Ph.D. who was responsible for conducting the subchronic feeding study. A reprint from the literature (Brassow et al, Int. Arch. Occup. Environ. Health 48:81-87 (1981)) was also provided to show that workers involved in the manufacturing of lindane do not develop adverse kidney effects. These submissions and other related reprints are attached.

Toxicology Branch Responses

1. Classification of the kidney lesion in the rat 90 day study.

Toxicology Branch(TB) concurs with the opinion of Dr. Herbst that the kidney pathology noted in the rat 90 day study and the recovery phase should not be described as permanent or irreversible. Reinspection of the pathology reports indicate that although some signs of pathology of the kidneys are evident after the 6 week recovery period, the intensity (or severity) is much reduced and there is no "tubular degeneration", the lesion that was considered the most serious of the kidney pathology noted.

The term "slowly reversible" should be the more appropriate description of the kidney pathology.

It should also be noted that the NOEL for the rat subchronic feeding study is still 4 ppm. Description of the kidney lesion as slowly reversible as opposed to irreversible does not change the conclusion of the study with respect to determination of the NOEL.

2. Current status of the "weight of evidence" with respect to induction of kidney lesions by lindane in test animals.

The potential for lindane to induce kidney lesions by the oral route in rats will be reevaluated in the chronic feeding/ oncogenicity study which was listed as a data requirement in the Registration Standard.

In addition, Toxicology Branch has recently requested a series of additional studies to further clarify the potential of lindane to cause kidney lesions in various species and by different routes of exposure. Refer to the memo from E.R. Budd to Dana Pilett dated December 5, 1985 attached.

The initial observation that lindane is associated with kidney lesions has apparently been confirmed as indicated by the results of a rat 90 day inhalation study which showed increased incidences of pathological findings in the kidney. This study is written in German and is currently being translated into English by the registrants. More definite statements related to the potential of lindane to cause kidney lesions as indicated by this study will be made by TB when the translated version of this study is reviewed.

TB resurveyed the subchronic and chronic rodent and nonrodent studies with lindane and its metabolite 2,4,6-trichlorophenol in an effort to determine if microscopic slides from these studies could be reexamined for induction of kidney lesions. It was decided that these studies were either too old, were conducted at academic laboratories (and it would not be expected that the tissues were saved), included recovery periods in which no lindane was administered, or were conducted with the evaluation of the liver as the focal point of investigation. Thus, TB will not request that kidney samples preserved from earlier studies be reexamined to reassess for possible kidney effects of lindane.

The current status of the "weight of evidence" with respect to lindane causing kidney lesions is that dietary exposure for 90 days (and probably less) results in lesions that are slowly reversible following removal of lindane from the diet. Inhalation exposure to lindane may also result in pathological responses in the kidney but this conclusion requires further documentation. It is not known if repeated dermal exposure to lindane results in development of kidney lesions. Additional testing has been requested of the registrants to further evaluate the potential for lindane to cause kidney lesions.

3. Overview of reprints reporting the health status of workers manufacturing lindane.

No evidence is available to indicate that exposure to lindane by workers involved in its manufacture results in kidney damage to humans. Although the studies reporting the results of human exposure did not include specific kidney function tests, the available data provide indications that individuals potentially exposed to lindane did not develop overt kidney functional changes.

Some comments on the human exposure studies:

- A. The following table was prepared based on information provided by the literature reports (Samuels and Milby, J. Occup. Med. 13:147-151 (1971), Milby and Samuels, J. Occup. Med. 13: 256-258 (1971) and Brassow et al., Int. Arch. Occup. Environ. Health 48:81-87 (1981)). Of the many tests for changes in levels of blood elements or biochemical endpoints evaluated, the following deviations were noted:

| <u>Endpoint</u> | <u>Study</u> | |
|------------------------------|---------------------------------|----------------------|
| | <u>1971</u> | <u>1981</u> |
| Blood Creatinine | -29% | -8% |
| Reticulocyte Counts | +33% | +37% |
| Total WBC | +23% | (Not changed) |
| Lymphocytes | (Not changed) | -18% |
| Polymorphonuclear Leukocytes | +35% | +14% |
| Lindane Content | 119 x control | (Not available)* |
| Uric Acid | (Not changed) small increase | -15% |
| Monocyte Count | (Not changed) small increase | (No change reported) |

% elevated (+) or % decreased (-)

Of the the above changes, it is noted that blood creatinine (decreased) and reticulocyte counts and polymorphonuclear leukocyte counts (both increased) were different relative to the control groups for both studies.

It should also be noted that although these changes were evident the subjects did not show any obvious associated functional pathology and that the differences may be due to normal variations. It is not conclusive that these changes were the direct result of exposure to lindane per se.

None of the differences in blood content are indicative of kidney damage.

B. It should be noted that these studies have weaknesses as human epidemiological studies. For example,

- i. there were a small number of subjects involved
- ii. the study utilized the healthy subjects or those who reported to work at the time the blood samples were taken and no data on the health status of absentees were provided
- iii. no specific tests were conducted on the workers to assess if subtle changes in kidney function were present
- iv. significant pathological changes in the kidney may also occur in the absence of overt functional changes and the study as designed would not assess this possibility.