CASWELL FILE

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

004629

AUG 26 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Lindane Registration Standard - Addendum to the Toxicology Branch Chapter - Review of Metabolism in Mammals Data.

Tox. Chem No. 527

FROM: John D. Doherty 8/22/85
Toxicology Branch
Hazard Evaluation Division (TS-769)

TO: George LaRocca
Product Manager #15
Registration Division (TS-767)

THRU: Edwin R. Budd, Section Head
Toxicology Branch
Hazard Evaluation Division (TS-769)

Budd 8/22/85

William L. Burnam, Deputy Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

WLB 8.22.85

Theodore M. Farber, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

Background:

The CIEL (Centre International d'Etudes du Lindane) has submitted a summary of the metabolism of lindane entitled "Metabolism of Lindane in Rats and Mice"* prepared by Dr. N. Wilhelm and Dr. F. Pistel in response to a Data Call-In Notice related to the use of lindane as a termiticide. This report cites some 42 references and was accompanied by reprints from the published literature.

The issue of the metabolism of lindane will be addressed in this memorandum especially regarding the adequacy of the available data to satisfy the requirement for metabolism studies.

[*Note: Refer to EPA Accession No. 255001.]

Conclusions and Comments:

1. No additional metabolism study is required.

2. The information provided by CIEL describe and demonstrate the absorption, distribution, deposition and elimination of lindane as well as identify the major metabolites of lindane.

3. Although the data are in the form of reprints from the published literature, most of the major observations were confirmed by separate investigators.

These studies, taken together, are classified as CORE MINIMUM.

The following discusses each of five topics (absorption, distribution, elimination, retention, identification of metabolites) related to the metabolism and pharmacokinetics of lindane. For each section reference is made to the key papers which provided the information; other papers submitted by CIEL are also important.

A. Absorption

1. Distribution and Metabolism of Hexachlorocyclohexane in Mammals. Klaas Van Asperen, Verh. IV. Int. Pflschtzkongr. Hamburg 1957, Vol. II, 1619-1623 (1958).

In this study, following an oral administration of lindane (1200 ug) given by stomach tube to mice, groups of 3 to 4 mice were sacrificed at predetermined intervals (3, 27, 51, and 72 hours) and their blood, brain, skin, muscle, liver, stomach, and intestines were analyzed by gas chromatography for their lindane content.

The results indicated that 40 percent was absorbed in 3 hours, 85 percent was absorbed in 27 hours. Ten percent and 5 percent was unabsorbed after [redacted] 51 and 72 hours respectively.

These data indicate a fairly rapid rate of absorption from the G-I tract.

2. Absorption of Some Organochlorine Compounds by the Rat Small Intestine - In Vivo.
J.C. Turner and V. Shanks. Bull. Environ. Contam. Toxicol. 24:652-655 (1980).

In this paper, an experiment is described which assesses the lymphatic system to take up lindane from the G-I tract. In this experiment, the rats were surgically prepared with

intestinal loops and connalula of the intestinal lymphatic duct. Samples of lindane were injected directly into the intestine and the lymphatic duct was sampled for lindane content. The blood was also sampled for lindane content.

The results indicated, that although lindane was rapidly absorbed into the blood, little was taken up into the lymphatic system. For example, up to 53 percent of the lindane was absorbed from the intestine in 30 min and the blood/lymph concentrations ranged from 151 to 5296, meaning the blood concentration was at least 151-fold higher than the lymph concentration of lindane.

B. Distribution and retention following absorption.

Comparative Study on the Distribution of alpha-and gamma-Hexachlorocyclohexane in the Rat with Particular Reference to the Problem of Isomerization. D. Eichler, W. Heupt and W. Paul, Xenobiotica, 13:639-647 (1983).

In this experiment, male and female albino rats (Chbb: THOM (SPF)) strain, were dosed daily with 15 mg/kg (and later 10 mg/kg/day) of lindane for a total of 56 days. The test material was dissolved in wheat germ oil and appropriate controls were also run. Sets of four males and four females dosed with lindane were sacrificed on days 1, 14, 28, and 56 and additional sets were sacrificed on days 51, 64, and 71 or up to 15 days following the last administration of the test substance.

Following sacrifice (by pentobarbitone), samples of blood were taken and the liver, brain, kidneys, and renal fat were set aside for analysis. The tissues were analyzed by gas chromatography.

Analysis of the tissues indicated that renal fat accumulated the highest concentrations of lindane with the peak concentration (334 mg/kg renal fat in females) being at day 14. Continuous dosing did not result in increased retention of lindane and the fat content actually declined to a lower level of 227 mg/kg at day 56. Following cessation of dosing, the fat content declined thereafter to only 15 mg/kg by day 71.

The kidney itself accumulated a relatively high content of lindane (highest level 115 mg/kg). Whereas the liver (17 mg/kg) and brain (6.8 mg/kg) accumulated less lindane.

C. Identification of Metabolites

The metabolism of lindane in mammals with respect to identification of metabolites has been studied independently by several laboratories. The following selected publications provide descriptive analyses of the metabolism of lindane.

(i) Biodegradation of Lindane (gamma-BHC) and Its Isomers by Mammals and Insects. N. Kurihara and M. Nakajima. Bull. Inst. Chem. Res. Kyoto Univ. 58:390-417 (1980) - a review.

(ii) The Identification of Five Unreported Lindane Metabolites Recovered From Rat Urine. R.W. Chadwick and J.J. Freal. Bull. Environ. Contamin. and Toxicol. 7:137-146 (1972).

(iii) The Identification of Three Unreported Lindane Metabolites From Mammals. R.W. Chadwick, J.J. Freal, G.W. Sovocool, C.C. Bryaen and M.F. Copeland. Chemosphere 8:633-640 (1978).

(iv) Metabolism of Lindane ^{14}C in the Rabbit - Ether-Soluble Urinary Metabolites. J.C. Karapally, J.G. Saha and Y.W. See., J. Agric. and Food Chem. 21:811-818 (1973).

These papers, as well as other publications, indicate that lindane is extensively metabolized in mammals. The metabolic pathways include dechlorination, dehydrogenation, oxidation, and conjugation resulting in cycloalkenes, cyclohexanols, chlorobenzenes, and chlorophenols with various degrees of chlorination and conjugates with N-acetyl cysteine, sulfate and/or glucuronic acid. Both isotope studies with labeled lindane and gas-chromatography-mass-spectroscopy techniques were used to identify the metabolites of lindane.

The major metabolites of lindane in mammals (rats, mice or rabbits, but principally in rats) include:

1,2,3,4,5,6-hexachlorocyclohexane

1,3,4,5,6-pentachlorocyclohexane

3,4,5,6-tetrachlorocyclohexane

2,3,4,5,6-pentachlorocyclohexanol[c]

2,3,4,6
and 2,4,5,6-tetrachlorocyclohexanol[b,c]

1,2,3,4,5,6-hexachlorobenzene

1,2,3,4,5
and 2,3,4,5,6-pentachlorobenzene

2,3,4,5
2,3,4,6 - tetrachlorophenol[b,c]
2,3,5,6

2,3,5
2,4,5 - trichlorophenol[b,c,d]
2,4,6

2,4
3,4 - dichlorophenol[a,b,d]
2,3
2,6

2,3,4,5,6-pentachlorophenol[b]

4-monochlorophenol[d]

a - conjugated with glutathione
b - conjugated with glucuronic acid
c - conjugated with sulfate
d - conjugated with n-acetyl cysteine (nercopturic acids).

The papers mentioned above provide data that lindane is eliminated from the test animals mostly as conjugated material (as above) and that very little lindane is unmetabolized.

D. Isomerization

The possibility that lindane gamma-isomer of hexachlorocyclohexane) isomerizes to the alpha isomer is important because several studies indicate that the alpha-isomer results in liver tumors in both rats and mice. There are two studies available which provide data to indicate that in rats lindane does not isomerize to the alpha-isomer.

1. Comparative Study on the Distribution of alpha- and -gammaHexachlorocyclohexane in Rat With Particular Reference to the Problem of Isomerization. D. Eichler, W. Heupt. and W. Paul. Xenobiotica, 13:639-647 (1983).

Groups of male and female rats (Chbb = THOM (SPF)) were dosed first with 15 mg/kg/day of lindane (later the dose level was reduced to 10 mg/kg/day because of high toxicity) and the rats were sacrificed (4 of each sex) on days 1, 14, 28, and 56. Additional rats were sacrificed in days 61, 64, and 71 or 5, 8, and 15 days after cessation of treatment. After sacrifice (with pentobarbitone), the blood, liver, brain, kidney and renal fat were removed for analysis. Analysis for the different isomers of hexachlorocyclohexane was by gas chromatography.

No evidence of isomerization of lindane to alpha-hexachlorocyclohexane was established by this study in either the blood or the liver, brain, kidney or renal fat.

2. Bioisomerization of Lindane in Rats. M.F. Copeland and R.W. Chadwick. J. of Environmental Pathology and Toxicology, 2:737-749 (1979).

Female Sprague-Dawley rats were dosed with lindane at either 0, 130, 215, or 350 ppm and 6 rats from each group were sacrificed after 1, 2, 4, 8, 16, or 24 weeks of treatment. Note: 24 hours prior to sacrifice each rat was dosed with 1.88 mg of lindane "to ascertain the effect of dose and time on the possible bioisomerization of lindane." Following sacrifice, samples of several tissues were analyzed for lindane content and for the presence of its isomers.

The content of alpha-HCH increased only slightly with dose level of lindane. The slight amount present in fat and liver samples (< 1.0 ppm) was consistent with levels expected from the alpha-HCH, which was a minor contaminant of lindane.

With respect to duration, the liver content of alpha-HCH decreased slightly with time in a manner essentially parallel with the liver content of lindane. This decrease of alpha-HCH content in liver with time is consistent with lack of isomerization and the small amount of alpha-HCH as a contaminant in lindane.