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

010603

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SEP 24 1993

MEMORANDUM

SUBJECT: EPA File No.: 009001. Lindane: i. Company response to the Agency's request to provide additional information regarding the adrenal gland for the rat carcinogenicity study; ii. request for a new series 83-2 mouse carcinogenicity study and a series 83-6 developmental neurotoxicity study; and iii. assignment of the RFD and other issues resulting from the RfD committee review of lindane held July 8, 1993.

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FROM: John Doherty, Ph.D., D.A.B.T. 9/14/93
Section IV, Toxicology Branch I
Health Effects Division (H7509C)

TO: Larry Schnaubelt/Robert Richards
Product Manager #72
Special Review and Reregistration Division
(H7508W)

and

Brian Steinwand/Jackie McQueen
Product Manager Team #63
Special Review and Reregistration Division
(H7508W)

and

George LaRocca/Dana Pillet
Product Manager Team #13
Registration Division (H7505C)

KB 9/20/93

THROUGH: Marion Copley, DVM, Section Head
Section IV, Toxicology Branch I
Health Effects Division (H7509C)
Marion Copley 9/16/93

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I. CONCLUSION

1. Rat chronic feeding/carcinogenicity study. Review of the additional histological evaluations of the adrenal gland for the low and middle dose groups treated with lindane together with the historical control information provided allows HED to conclude that there is no evidence of a compound related increase in pheochromocytomas in this gland. The study is upgraded to CORE GUIDELINE for both chronic feeding and carcinogenicity and satisfies the requirement for a series 83-5 chronic feeding/ carcinogenicity study and no additional series 83-5 data are required at this time. Refer to item A under comments.

2. RfD Committee review of lindane and additional toxicity studies required. The HED RfD committee reviewed lindane and determined that a new series 83-2 (carcinogenicity study) with mice and a series 83-6 developmental neurotoxicity study with rats should be submitted to support the toxicity data base for lindane. Refer to items B and C under comments.

3. The RfD. The RfD Committee also determined that the RfD should be 0.0047 mg/kg/day based on systemic effects in the rat 1989 chronic feeding study. The effects on the male rat kidney are not considered appropriate for regulatory purposes. Refer to the Free Standing Toxicity Summary attached.

4. Changes in the "one liners". Due to changes in the interpretation of the kidneys lesions in male rats and updating of other toxicity concepts, several of the "one liners" have been changed. Refer Section III items D and E and Section IV below.

II. Action Requested

Toxicology Branch I (TB-I) previously reviewed the rat chronic feeding/carcinogenicity study (LSR #90/CIL002/0839, November 7, 1989, MRID No.: 418537-01, refer to HED Document No.: 09909 dated December 30, 1992). In that review the registrant was requested to provide additional information on the adrenal gland that included examination of the low and middle dose levels and to provide historical control data for adrenal pheochromocytomas in the Wistar strain rat. The registrant has provided this information (MRID #42572-01) and a supplementary DER has been prepared (attached).

In addition to the response provided by the registrant, HED has held an RfD Committee Peer Review meeting on lindane to address the assignment of the RfD as well as to assess the adequacy of the data base for carcinogenicity testing particularly for mouse studies. This meeting was held July 8, 1992 and several recommendations were made which are discussed below.

The above issues as well as other related issues were considered and the following comments apply.

III. Toxicology Branch Comments

A. Issues related to the rat chronic feeding/carcinogenicity study. Refer to D192793 and S443941.

1. The information submitted by the registrant regarding the additional slide readings for the adrenal gland and the historical control data for this gland was reviewed and a supplementary DER was prepared and is attached. Section IV below describes the "one liner" for the review of this information.

2. The data allow TB-I to conclude that, although the high dose group is still associated with the highest incidence of pheochromocytomas (refer to Table 1 below), the incidence is still within or very close to the historical control range for the Wistar rat and the high dose group is not statistically significantly higher than the control or other dose groups using the most relevant statistical tests. Thus, TB-I does not consider there is sufficient evidence to conclude that the increase in pheochromocytomas in the high dose group is a compound related phenomena.

Table 1. Incidence of adrenal tumors in the rat 1989 carcinogenicity study.

	Incidence[1] Adrenal Tumors		
Dose Level	Benign	Malignant	Total
Control	7	0	7 (14%)
1 ppm	8	0	8 (16%)
10 ppm	8	3	9 (18%)
100 ppm	3	4	7 (14%)
400 ppm	12	1	13 (26%)
Historical Control[2]	4-11	0-1	4-12

1. Data are incidence and in () the percentage based on 50 animals group assessed in each dose group.
2. Charles River publication entitled "Life-Span and Historical Data in Carcinogenicity Testing in Wistar Rats Crl:(WI)BR" J. VanDenBerghe, D.V.M., 1990.

TB-I notes that the incidence of malignant pheochromocytomas is higher in the middle two dose groups than in the historical control. These data, however, did not reach statistical significance and the high dose has a lower rate. The high dose also has the highest frequency of benign tumors but this is not statistically significant and is close to the range for this strain of rat.

3. The study is being upgraded to CORE GUIDELINE for both carcinogenicity and chronic feeding assessment as per this memo. The "one liner" also needs to be changed to reflect the conclusions regarding carcinogenicity and CORE classification. The revised results part of the "one liner" for this study is rewritten in Section IV below.

4. The "one liner" has to be changed to correct an error regarding the direction of the change in the platelets data. The original version of the one liner incorrectly indicated that there was a decrease in platelets whereas the data show there was an increase in the two highest dose levels.

B. Issues related to adequacy of testing in mice for carcinogenicity assessment. Request for a series 83-2 carcinogenicity study with mice.

1. One additional study (Wolff et al, Carcinogenesis 8(12):1889-1892 (1987) was reviewed and this study is listed in Section IV below. The DER for this study is attached. This study demonstrates that certain genetic lines derived from a common strain are more susceptible to induction of liver tumors and possibly also lung tumors. The study, however, is SUPPLEMENTARY and does not satisfy the guideline requirement for a mouse carcinogenicity study (series 83-2).

2. The RfD committee determined that there is no mouse study that meets current Guideline criteria for testing and that an additional study needs to be conducted and submitted to meet the series 83-2 data requirement.

TB-I suggests that a commonly used strain such as the CD-1 mouse strain be used for this new study. The dose levels selected for the carcinogenicity study should be determined by a preliminary dose range finding study. TB-I stresses the standard criteria that the high dose selected for this study should be a dose level at which there are indications of toxicity but not excessive toxicity be met. Alternatively, the registrant may want to consider designing the range finding study to identify the dose level at which the metabolic detoxification system becomes saturated. The study should also consist of at least two lower dose levels (the lowest test dose should not show signs of toxicity) and a control group.

Using the approach of assessing the effects of lindane at a dose level in excess of the test animals demonstrated capacity to detoxify it may help to classify lindane as a carcinogen with regard to determining the appropriate method of quantitative risk assessment. It is strongly recommended that the protocols for both the range finding and definitive studies be submitted to the

Agency for review prior to initiating the study.

Two publications that TB-I considers relevant to the overall issue of metabolic differences being possibly related to increased susceptibility of mice to liver tumors are as follows:

-R.W. Chadwich et al. "Effects of Age and Obesity on the Metabolism of Lindane by Black a/a. Yellow A^{vy}/a, and Pseudoagouti A^{vy}/a phenotypes of (YS x VY) F_1 Hybrid Mice." Journal of Toxicology and Environmental Health 16:771-796 (1985).

-R.W. Chadwich et al. "Saturation of Lindane Metabolism in Chronically Treated (YS x VY) F_1 Hybrid Mice." Journal of Toxicology and Environmental Health 20:411-434 (1987).

C. Issues related to developmental toxicity testing. Request for a series 83-6 developmental neurotoxicity study.

The rat and rabbit developmental toxicity studies (refer to HED Document No.: 010384 for current DERs) were determined to be CORE MINIMUM. The RfD Committee, requested, however, that a series 83-6 developmental neurotoxicity study be conducted to assess the potential of lindane on development of the nervous system. This study is considered important because lindane is currently regarded to be able to cross the placenta and to be a neurotoxicant.

The study should be conducted with the same strain of rat used for the multi-generation reproduction study (Life Sciences Research, Study No.: 91/CIL004/0948, September 12, 1991, Charles River CD strain rats). In addition to the specified endpoints for a series 83-6 study, special attention should be paid to the onset of tooth eruption and duration for hair coat growth completion. Refer to part D (item 2) below for rational.

It is recommended that the protocol for this series 83-6 study be submitted to the Agency for review.

D. Changes in the "one liner" for the multi generation reproduction study.

The original DER (refer to HED Document No.: 009911) for the rat multi-generation reproduction study (MRID No.: 422461-01, Life Science Research Study No.: 91/CIL0004/0948, September 12, 1991) identified separate parental and reproductive NOEL and LELs and also described extensively the specific lesions in the male rat kidney. In addition, a reference was made to delayed tooth eruption and delayed completion of hair growth as toxicologically

significant endpoints. The expression of the "one liner" was considered in a reassessment of the data subsequent to the RfD meeting. Based on both this reassessment, the following changes in the "one liner" are being made. Refer to section IV below for the revised "one liner". Note: This memeo takes the place of a Supplemental DER.

1. Condensing the commentary on the male rat kidney effects.

Since male rat kidney effects are no longer considered a meaningful endpoint for regulatory toxicology, the effects on the male rat kidney were reduced to a simple statement. Refer to section IV below.

2. Delayed tooth eruption and completion of hair growth.

TB-I recalled the original study and reexamined the data for these parameters. Although TB-I agrees that the data indicate some possible delays in these parameters, tooth development and hair condition appear normal at weaning. These parameters were not presented with individual animal data but the range for each of the litters was presented. It was not possible to tell how many in each group had the later onset. The observation of these parameters is subjective and TB-I would prefer:

-a clear dose response in at least the two highest dose levels
-persistence of the effect (i.e. evidence of the delayed dental or coat development at day 21 or longer)
-individual pup data indicating the number of pups affected.

Since none of these conditions were satisfied, TB-I does not believe that this observation should be included in the final conclusions for definite effects of the test material. The condition should be discussed in the body of the DER for future reference. Since these observations were noted at the high dose where there is other evidence of more significant toxicity, the regulatory aspects of lindane will not be affected by omitting these from the "one liner" expression.

Lastly, in order to clarify the issue of possible delayed onset of tooth eruption and extended duration of hair coat growth, the series 83-6 special developmental neurotoxicity study will be requested to use this same strain of rat and to include in the protocol a specific requirement to include assessments of these parameters for possible effects.

E. Update on the rat series 82-4 subchronic dermal toxicity study with rats and other changes in the "one liners".

The rat 90-day dermal toxicity study (MRID No.: 408217-01, Hazleton, UK, Study No.: 5757-580/2, August 1988, refer to HED Document No.: 007189) was originally classified as SUPPLEMENTARY and the registrant was requested to provide analytical data on the alpha 2u globulin content of the kidneys. This information was not provided but HED no longer considers it necessary to provide it because the nature of the kidney lesion has been characterized from other studies.

As per this memo, this study is reclassified as CORE GUIDELINE and the study satisfies the requirement for a series 82-4 subchronic dermal toxicity study in rats. The "one liner" for this study has also been revised to update NOEL and LEL based on non-kidney effects. Refer to section IV below.

The conclusions for other studies listed in the "one liners" have been revised to relate the current policies toward the interpretation of the male rat kidney effects. Refer to Table IV below.

F. Toxicity Profile for Lindane.

An updated toxicity profile (September 1993 edition) has been prepared and is attached. All of the above changes in the status of the toxicity profile for lindane have been incorporated.

IV. Studies Reviewed and/or changed for the "one liner" files.

Study Identification	Material	MRID No.:	Results	Classification
83-5. Chronic Feeding/ Carcinogenicity rats. Life Science Research Study No.: 90/CIL002/0839, Nov. 7, 1989.	Technical Lindane Batch DA433	418537-01 and 428712-01	NOEL and LEL = 10 and 100 ppm. At 100 ppm: Periacinar hepatocyte hypertrophy and liver weight increase; spleen weight increase; increase in platelets. At 400 ppm: decreased survival in females (trend in males); convulsions in females; decrease in body weight gain (early) and increase in inorganic phosphorous, calcium, urea and cholesterol and decrease in albumin/globulin ratio and decrease in RBC parameters. No evidence of carcinogenicity. Kidney effects: LEL < 1 ppm associated with induction of alpha 2u globulins. Endpoint not to be used for regulatory toxicology. Wistar strain rat. Dose levels tested: 0, 1, 10, 100 or 400 ppm corresponding to 0, 0.05, 0.47, 4.81 or 19.66 mg/kg/day in males and 0, 0.06, 0.59, 6.00 or 24.34 mg/kg.day for females.	GUIDELINES (for both chronic feeding and carcinogenicity testing.

83-2. Carcinogenicity - mouse National Center for Toxicological Research, Arkansas. As published in Carcinogenesis 8:(12):1889-1897(1987).	Lindane	None	Evidence for positive carcinogenic response in the agouti and pseudoagouti mouse lines for both liver (hepatocellular adenoma and carcinoma) and lung (papillary and/or solid) tumors. Clara cell hyperplasia occurs in the lung in all three lines that is apparently irreversible. Liver weight increased (agouti > pseudoagouti > black) and monooxygenase activity is increased in all three lines (pseudoagouti > black > agouti). Three lines of mice from NCTP stocks: black, pseudoagouti and agouti. Dose levels tested 0 or 160 ppm.	SUPPLEMENTARY
82-3. Subchronic dermal-rats Hazleton, UK, Study No.: 5757-580/2, August 1988.	Technical lindane	408217-01	Revised from earlier "[illegible] liner": NOEL and LEL = 10 and 60 mg/kg/day. At 60 mg/kg/day: liver weight increases and centrilobular hypertrophy; serum cholesterol; behavioral changes (minor); body weight increases (both sexes). At 400 mg/kg/day: possible decrease in survival in females. At all doses in males evidence of kidney effects consistent with the alpha 2u globulin model. This endpoint not to be used for regulatory purposes. Wistar strain rat Crl:(WI)BR. Dose levels tested: control, 10, 60 or 400 mg/kg/day.	Revised: GUIDELINES

83-4. Multi-generation reproduction - rats. Life Science Research, England, Study No.: 91/CIL004/0948, Sept. 12, 1991.	Lindane Batch # DA433	422461-01	**Revised from earlier "one-liner":** Parental NOEL and LEL = 20 and 150 ppm. At 150 ppm: decreased bodyweight gain. No effects on parental reproductive parameters noted. Developmental NOEL and LEL = 20 and 150 ppm. At 150 ppm: decreased pup birth weight and weight at weaning; and decreased viability to day 4. At all doses in males evidence of kidney effects consistent with the alpha 2u globulin model. This endpoint not to be used for regulatory purposes. Charles River CD strain rat. Dose levels tested: 0, 1, 20 or 150 ppm corresponding to 0, 0.0865, 1.71 or 13.05 mg/kg/day.	**GUIDELINE**

82-4. Subchronic (3-month) inhalation toxicity - rats. Frau. Inst for Tox and Aerosol, Study No.: 104264; Feb. 28, 1983.	Lindane 99.9%from batch #79044/174	255003 (Acc. No.:	Revised from earlier "one-liner". NOEL and LEL = 0.5 and 5 mg/m^3. At 5 mg/m^3: diarrhea and piloerection; increased liver weight and cytochrome p-450 (males and females). Effects on bone marrow parameters as indicated by myelograms to indicate possible effect on formation of blood elements (females and especially males). At 0.5 and 5 mg/m^3: in males evidence of kidney effects consistent with the alpha 2u globulin model. This endpoint not to be used for regulatory purposes. Wistar HAN/BOE, SPF strain rats. Dose levels tested: 0, 0.1, 0.5 and 5 mg/m^3 generated by meas of a LaMer (NaCl assisted) generator.	MINIMUM.
82-1a. Subchronic Feeding 3-month-rat Res and Consulting Co. Study No.: 005220, February 3, 1983.	Lindane 99.9% purity.	250340 250341 250342 00128356	Revised from earlier "one liner" NOEL and LEL = 4 and 20 ppm. At 20 ppm: hepatocyte hypertrophy. Note at 0.2 ppm: liver microsomal enzyme activity increased. At 20 ppm and above: in males evidence of kidney effects consistent with the alpha 2u globulin model. This endpoint not to be used for regulatory purposes. Wistar strain rat. Dose levels tested: 0, 0.02, 0.06, 0.30, 1.55 or 72.5 mg/kg/day in males and 0.02, 0.06, 0.33, 1.67 or 7.90 mg/kg/day in females.	GUIDELINE.

Free Standing Toxicity Summary

010603

Toxicity Data Base: Lindane
September 1993 Edition

Tox Chem Number: 527
PC Number: 009001

Series. Study Type	Study Status	Results/Comments
81-1. Acute oral - rats Tox. Appl. Pharma. 14:515-554 (1969) MRID No.: 00049330 HED Document No.: 004704	S	LD_{50} = 88 mg/kg (males) = 91 mg/kg (females) Toxicity Category II.
81-2. Acute Dermal - rabbits Tox. Appl. Pharma. 14:515-554 (1969) MRID No.: 00109141 HED Document No.: 004704	S	LD_{50} = 1000 mg/kg (M) = 900 mg/kg (F) Toxicity Category II.
81-3. Acute inhalation - rats Res. Consult. Co. Study No.: 061637, April 16, 1986 MRID No.: 263946 HED Document No.: 005703	G	LC_{50} = 1.56 mg/l (Males and Females) (4 hr exposure). Toxicity Category III.
81-4. Primary eye - rabbits Res. Consult Co. Study No.: 061672, March 20, 1986 MRID No.: 263946 HED Document No.: 005703	G	Primary Irritation Score = 0.6. Transient irritation only. No corneal opacity. Toxicity Category III.
81-5. Primary dermal - rabbits Res. Consult. Co., Study No.: 06661, March 19, 1986 MRID No.: 262946 HED Document No.: 005703	G	Primary irritation score = 0 (4 hr exposure). Toxicity Category III.
81-6. Dermal sensitization - g. pig Res. Consult. Co.: Study No.: 061650, April 18, 1986. MRID No.: 262946 HED Document No.: 005703	G	Negative for sensitization in the maximization test.
81-7. Delayed neurotoxicity - hen	N/A	
81-8. Special neurotoxicity - rat		Expected in September 1993.

82-1a. Subchronic oral - rat Res. Consult. Co.: Study No.: 005220, February 3, 1983. MRID No.: 250340, 250341, 250342 and 00128356. HED Document No.: 005582 and 002993	G	NOEL and LEL = 4 and 20 ppm. At 20 ppm: hepatocyte hypertrophy. Note at 0.2 ppm: liver microsomal enzyme activity increased. Refer also to section 4. C below. Wistar strain rat. Dose levels tested: 0, 0.02, 0.06, 0.30, 1.55 or 7.25 mg/kg/day in males and 0.02, 0.06. 0.33, 1.67 or 7.90 mg/kg/day in females.
82-1b. Subchronic oral - nonrodent		Refer to 83-1b.
82-2. 21-day dermal		Refer to 82-3 below.
82-3. 90-day dermal - rats Hazleton Study No.: 5757-580/2, August 1988. MRID No.: 408217-01 HED Document No.: 007189	G	NOEL and LEL = 10 and 60 mg/kg/day. At 60 mg/kg/day: Centrilobular hepatocyte hypertrophy; serum cholesterol; behavioral changes (minor); body weight increases (both sexes); possible decrease in survival in females. Refer also to section 4. C below. Wistar strain rat: Dose levels tested: 0, 10, 60 or 400 mg/kg/day.
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82-3. 90-day dermal - rabbits Hazleton Study No.: 6164-58016, February 22, 1990. MRID No.: 414276-01 HED Document No.: 008610	G	NOEL and LEL = 10 and 60 mg/kg/day. At 60 mg/kg/day: Centrilobular hepatocyte hypertrophy(both sexes); adrenal weight increase (males). At 320/350/400 mg/kg/day: Tremors, deaths, body weight decreases (both sexes); RBC parameters (<9% for RBC counts, PCV and hemoglobin, in males); alkaline phosphatase and/or glutamic pyruvate transaminase (both sexes). New Zealand White Rabbit: Dose levels tested: 0, 10, 60 or 320/350/400 mg/kg/day.

82-4. 90-day inhalation - rats Frau. Inst for Tox and Aerosol. Study No.: 104264, February 28, 1983. MRID No.: 255003 HED Document No.: 005059	M	NOEL and LEL = 0.5 and 5 mg/m^3. At 5 mg/m^3: clinical symptoms including diarrhea and piloerection (males and females), increased liver cytochrome p450, increased liver weight, Wistar strain rat. Dose levels tested: 0, 0.1, 0.5 and 5 mg/m^3.
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82-4. 14 week inhalation - mice Bushy Run Res. Center, Study No.: 51-524 and 14014, October 7, 1988. MRID No.: 408735-01 HED Document No.: 007304	G	NOEL and LEL = 0.3 and 1.0 mg/m^3. At 1.0 mg/m^3 2 deaths. At 5-10 mg/m^3 20 deaths (5 males and 15 females); increase in liver weight (14%). CD-1 strain mouse. Dose levels tested 0, 0.3, 1.0 and 5-10 mg/m^3.
82-5. 90-day neurotoxicity		Refer to series 82-7 below.
82-6.		
82-7. Neurotoxicity screen		Expected in September 1994.
83-1a. Chronic feeding - rat		Refer to 83-5. Refer also to item 4. C below.
83-1b. Chronic feeding -nonrodent Huntingdon Research Centre, Study No.: 3720/70/532, January 7, 1971, HED Document No.: 004704	M	NOEL and LEL = 50 and 100 ppm. At 100 ppm: macroscopic but not microscopic changes in the liver appearance; changes in EEG. Beagle dogs: Dose levels tested: 0, 25, 50 and 100 (for 104 weeks) and 200 (for 32 weeks. Corresponding estimated levels of to 0, 0.63, 1.25, 2.5 and 5 mg/kg/day.
82-2a. Oncogenicity - rat		Refer to 83-5.
82-2b. Oncogenicity - mouse	DG	Refer to section below. A new study is being required as per the RfD meeting of July 8, 1993. Several studies exist but have reporting and design deficiencies and no study or combination of studies meets current criteria for acceptability. Liver tumors and in one strain lung tumors have been implicated in these studies.
83-3a. Developmental toxicity - rat		
83-3b. Developmental toxicity -		

83-4. Multi generation reproduction Life Science Research, Study No.: 91/CIL004/0948, September 12, 1991. MRID No.: 422461-01 HED Document No.: 009911	G	Parental NOEL and LEL: 20 and 150 ppm (1.71 and 13.05 mg/kg/day). At 13.75 mg/kg/day: decreased body weight in Fo females during gestation. No effects on parental reporductive parameters. Developmental NOEL and LEL: 20 and 150 ppm: At 150 ppm: decreased pup weight gain and decreased viability for postnatal days 1-4 in both generations. Refer also to Section 4. C below. Wistar strain rat. Dose levels tested: 0, 1, 20 or 150 ppm corresponding to 0, 0.09, 1.71 and 13.05 mg/kg/day.
83-5. Combined chronic/onco Life Science Research, Study No.: 90/CIL002/0839, November 7, 1989. MRID No.: 418587-01 HED Document No.: 009909 and	G	NOEL and LEL: 10 and 100 ppm. At 100 ppm: periacinal hepatocyte hypertrophy; liver and spleen weight increase; and platelet increase. At 400 ppm: decreased survival in females (trend in males); convulsions in females; decrease in body weight gain (early); increase in inorganic phosphorous, calcium, urea and cholesterol and decrease in albumin/globulin ratio and decrease in RBC parameters. No evidence of carcinogenicity. Wistar strain rat. Dose levels tested 0, 1, 10, 100 or 400 ppm. Corresponding to 0, 0.05, 0.47, 4.81 or 19.66 mg/kg/day in males and 0, 0.06, 0.59, 6.00 and 24.34 mg/kg/day in females.
83-6. Developmental neurotoxicity		Recommended as per the RfD meeting of July 8, 1993.
84-2. Gene mutation		Refer to section 5 below.
84-2. Chromosome aberration		Refer to section 5 below.
84-2. Other mechanism genetic tox		Refer to section 5 below.
85-1. Metabolism - rats and mice. Multiple studies described and summarized in HED Document No.: 004629.	A	Absorption, distribution, retention, elimination, identification of metabolites of lindane in rats and mice described. Refer to document for details.
85-2. Domestic animal safety		Refer to individual formulations.

85-3. Dermal Absorption - humans Tox. Appl. Pham. 27: 1974. HED Document No.: 004704.	\	9.3 ± 3.7% of lindane applied as an acetone solution was absorbed from human forearms.
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Dermal absorption - rat Hazleton Study No.: 6188-103 MRID No.: 400561-07 HED Document No.: 005914	A	Absorption into body is dependent on time and dose applied as follows Applied / Absorbed 0.5 hrs / 24 hrs 0.1 mg / 0.6% / 27.2% 1.0 mg / 0.96% / 20.9% 10.0 mg / 0.66% / 5.0%
.....	...	.....
Dermal absorption - rabbits Hazleton Study No.: 6188-184 MRID No.: 400561-08 HED Document No.: 005914	A	Absorption into body is dependent on time and dose applied as follows Applied / Absorbed 0.5 hrs / 24 hrs 0.5 mg / 5.96% / 55.68% 5.0 mg / 6.68% / 39.99% 50 mg / 1.99% / 16.56%
85-. Nerve function/operant behavior		Not required at this time.

Data Gaps.

83-2. Carcinogenicity-mouse (specifically with the CD-1 strain).

83-6. Developmental neurotoxicity - rat.

Special Toxicology Issues and Problems.

1. **Labelling.**

No special labeling requirements based on toxicity properties of the technical chemical. The acute toxicity of the individual formulations should govern the label signal word and precautionary statements.

2. **Carcinogenicity.**

Lindane has not been reviewed by the HED Carcinogenicity Peer Review committee.

A previous review by the ORD Carcinogenicity Assessment Group (CAG) classified lindane as "B2-C" (refer to memo from Robert E. McGauhy dated July 23, 1985) and provided a Q1* of 1.1 $(mg/kg/day)^{-1}$ for risk assessment. The critical endpoint for carcinogenicity was liver tumors in mice. Several strains or lines of mice have been reportedly susceptible to liver tumor

induction by lindane but the studies demonstrating this observation all suffer from both reporting and/or procedural deficiencies. There is no mouse carcinogenicity study which meets current criteria for acceptability for regulatory purposes.

HED has since (July 8, 1993) presented the mouse data base to the RfD committee to determine if the studies are adequate to submit to the HED Carcinogenicity Peer Review Committee for reclassification under current criteria for classification. The RfD committee concluded that "The mouse carcinogeniciity data (83-2b) were considered insufficient because of major deficeincies associated with all studies available". In addition, the RfD committee "concluded that another carcinogenicity study in a commonly used strain of mice should be submitted". 010603

The carcinogenic potential for lindane was not classified by the RfD Peer Review Committee. Reclassification of lindane for carcinogenicity is pending receipt and review of a new mouse carcinogenicity study as recommended by the HED RfD Committee.

In the meanwhile, lindane is not considered carcinogenic in the rat. HED thus defers to Registration Division the need for supporting individual registrations of lindane with quantitative carcinogenic risk assessements.

3. **RfD.**

As per the July 8, 1993 RfD meeting, the RfD is 0.0047 mg/kg/day. Refer to the RfD Committee report dated August 25, 1993.

This is based on the NOEL of 10 ppm (0.47 mg/kg/day) from the rat chronic feeding carcinogenicity study (Life Science Research, 1989, MRID No.: 418587-01) together with a 100 fold uncertainty factor. The critical toxicity endpoints at the LEL of 100 ppm (4.81 mg/kg/day) are periacinal hepatocyte hypertrophy, increase liver and spleen weight and increase in platelets.

4. **Non carcinogenic risk assessment and other toxicity issues.**

A. There is no other toxicity endpoint which HED recognizes at this time that requires risk assessments.

B. Lindane has been implicated in causing blood dyscrasia in humans. The reports of these incidents are rare and cannot be conclusively linked to lindane use. There is no animal model to assess for this phenomenon. It is, however, possible that blood dyscrasia result in certain hypersensitive individuals as an idiosyncratic response. Currently there are no specific regulatory restraints for lindane regarding this issue.

C. Lindane affects the male rat kidney through a specific mechanism mediated through an interaction with alpha 2u globulins based on several rat subchronic and chronic studies. The kidneys of other species are not affected. Agency policy on this issue provides that chemicals that affect the male rat kidney should not be regulated on this endpoint. Refer to J. Doherty memo to Brian Steinwand/Nancy Zahedi dated Jun 8, 1993.

011603

5. **Mutagenicity/genetic toxicity comments.**

The weight of evidence for the mutagenicity/genetic toxicity data base dose not indicate a concern. Refer to HED Document No.: 4704 (the Toxicology Branch Chapter for the registration standard for lindane).

6. **Dermal absorption.**

The dermal absorption factor should be selected based on the expected dermal exposure with regard to the amount of exposure and time the lindane will be in contact with the skin. Samples of time and dose dependency are given in the above table (P.5) under part 85-2.

[83-5 \Supplemental-Lindane/1993] 010603

Reviewed by: John Doherty
Section IV, Toxicology Branch I (H7509C)
Secondary reviewer: Marion Copley, DVM
Section IV, Toxicology Branch I (H7509C) 9/13/93

SUPPLEMENTAL DATA EVALUATION REPORT
[Refer to HED Document No.: 009909 for initial DER]

STUDY TYPE: 83-5. Chronic Feeding/Carcinogenicity-rats

MRID NO.: 428712-01 TOX. CHEM. NO.: 527
PC No.: 009001

TEST MATERIAL: Lindane

STUDY NUMBER(S): LSR 93/0353 addendum to LSR Report 90/0839

SPONSOR: CIEL

TESTING FACILITY: Pharmaco-LSR Ltd, ENGLAND

TITLE OF REPORT: "Lindane: Combined Oncogenicity and Toxicity Study in Dietary Administration to Wistar Rats for 104 Weeks Addendum to Final Report (Adrenal Histopathology-Additional Investigations)"

AUTHOR(S): S.J. Amyes

REPORT ISSUED: June 2, 1993

STUDY DATES: Original study October 28, 1987 to October 31, 1989

CONCLUSIONS:

The data submitted satisfy TB-I's request for additional information for this study. The data do not indicate that pheochromocytomas are induced by lindane administration.

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Revised CONCLUSION for the entire study:

NOEL and LEL = 10 and 100 ppm. At 100 ppm: Periacinar hepatocyte hypertrophy and liver weight increase; spleen weight increase; increase in platelets. At 400 ppm: decreased survival in females (trend in males); convulsions in females; decrease in body weight gain (early) and increase in inorganic phosphorous, calcium, urea and cholesterol and decrease in albumin/globulin ratio and decrease in RBC parameters.

No evidence of carcinogenicity.

Kidney effects: LEL < 1 ppm associated with induction of alpha 2u globulins. Endpoint not to be used for regulatory toxicology.

Wistar strain rat. Dose levels tested: 0, 1, 10, 100 or 400 ppm corresponding to 0, 0.05, 0.47, 4.81 or 19.66 mg/kg/day in males and 0, 0.06, 0.59, 6.00 or 24.34 mg/kg.day for females.

Classification: CORE-GUIDELINE for both chronic feedign and carcinogenicity assessment. (revised study classification). No additional series 83-5 rat chronic toxicity or carcinogenicity data are required at this time.

)uality Assurance Statement: Provided.
Good Laboratory Practice Statement: Provided.

REVIEW

This study was reviewed previously and the DER is in HED Document No.: 009909 dated December 30, 1992. The DER indicated that additional microscopic evaluation of the adrenal gland was necessary to complete the review. In addition the registrant was requested to provide historical control data for the Wistar strain rat used for this study. This information was provided and the following comment~ address the pathological findings in the adrenal gland.

The adrenal glands from the males in the low, and two middle dose groups (oncogenicity phase) were processed and examined microscopically. A total of 8 new animals were identified as having pheochromo-cytomas. These included 4 in the 1 ppm low dose group, 3 in the 10 ppm and 1 in the 100 ppm dose groups. Table 1 below illustrates the findings with respect to adrenal pheochromocytomas as revised as a result of the additional readings.

Table 1. Pheochromocytomas in the adrenals in male rats dosed with lindane.

	Incidence[1]			
	Adrenal Tumors			Cortical Fatty
Dose Level	Benign	Malignant	Total	Vacuolation
Control	7	0	7 (14%)	13
1 ppm	8	0	8 (16%)	17
10 ppm	8	3	9 (18%)	16
100 ppm	3	4	7 (14%)	20
400 ppm	12	1	13 (26%)	23
Historical Control[2]	4-11 (8-22%)	0-1 (0-2%)	4-12 (8-24%)	No data

1. Data are incidence and in () the percentage based on 50 animals assessed in each dose group. These data were extracted from Table 3 page 16 of the study report.
2. Charles River publication entitled "Life-Span and Historical Data in Carcinogenicity Testing in Wistar Rats Crl:(WI)BR" J. VanDenBerghe, D.V.M., 1990. Data are the range of incidence for 4 studies and in () the range of incidence in percentage. See also additional discussion below.

010603

The testing laboratory did not have an historical control data base for this strain of rat. Historical control information was, however, provided in the form of a series of publications. In summary, the incidence of pheochromocytoma in males from these assorted references are listed in Table 2 below.

The 10 (3 incidents) and 100 (4 incidents) ppm dose groups have malignant pheochromocytomas in greater excess than the historical control (0 to 1 incident). The high dose group also has a slightly excess incidence of benign (12) and combined benign and malignant (13) than the control (4 to 11 and 4-12 incidents) but this same net tumor incidence was noted for the control group in the Smits-Van Prouge study.

Table 2. Survey of historical control information on the incidence of pheochromocytomas in Wistar rats.

Reference	Incidence and (%) Benign	Malignant
Bomhard, E. et al. JEPTO 7(1/2):35-52 (1986) (10 studies with about 900 males) [An 11th study in this group had 17 benign and 16 malignant incidents and is considered unusual and not included in the range and mean above.]	0-7 Mean % = 3.3%	0-2
Ishmael and Litchfield FAT 11: 308-322 (1988) (1 study/60 males)	2 (3.3%)	
Wester, P.W. et al Fd. Chem. Toxic. 28(3):179-196 (1990). (1 study/50 males)	16 (32%)	
Smits-Van Progue et al Fd Chem Toxic 28(4):243-251(1990) (1 study/50 males)	12 (24%)	1 (2%)
Donaubauer, et al FAT 9:738-752(1987) (1 study/98 males)	1 (1%)	
VanDenBerghe, J. Charles River Publication, 1990 (4 studies/200 males)	4-11 (8-22%)	0-1 (0-2%)

Statistical considerations:

A. Trend tests. The revised data for combined benign and malignant incidence did not reach statistical significance for either the Prevalence or the Cochran-Armitage trend tests giving values of 0.078 and 0.109 respectively. Whereas the original data were positive for trends using the Prevalence test (0.047) but not for the Cochran-Armitage test (0.069). The "life tables" trend test, however, was statistically significant (0.011) for the revised data analysis. This test, however, is considered

irrelevant by the study author because the pheochromocytomas are not thought to be the cause of death except for a single animal in the 100 ppm dose group. [Note: In Appendix 2 which presents the Peto score for the males with pheochromocytomas, this animal is not identified. All decedents are followed by the phrase "Definitely not the cause of death".]

B. Pair-wise comparisons. The results of the statistical analysis using 4 tests are appended. In particular, although the 10 and 100 ppm dose groups have malignant pheochromocytomas in excess of the historical control, these incidents do not reach statistical significance in the Fisher Exact test that is considered most relevent for analyzing the data (as per discussion with the SAB of HED statisticians). The high dose group also has the highest rate of benign pheochromocytomas but this does not reach statistical significance ($p = 0.154$) by Fisher Exact test. This group, however, reaches statistical significance of $p = 0.05$ (for the combined benign and malignant tumors and 0.032 for benign tumors alone) when the "Life Table Test" is used but this test is considered irrelevant because only one pheochromocytoma was considered fatal.

TB DISCUSSION: Pheochromocytomas did not reach a level of statistical significance using relevant tests. In addition, although the occurrence of malignant pheochromocytomas in the middle dose groups is in excess of the historical control data provided, the high dose group has only a single incident. The possibility of competing toxicity was considered but the liver hypertrophy and specific alpha 2 u globulin kidney toxicity are not considered by TB-I to be adequate to change the pattern of increased malignant pheochromocytomas to a lower rate of incidence at the higher dose level. TB-I recognizes that there was also a trend for decreases survival in the males (the high dose group was not statistically lower) but the high dose group had 50% survival to week 93 or longer than the control group which had 50% survival to week 92. Although the incidence of malignant pheochromocytomas in the mid dose groups and the higher frequency of benign pheochromocytomas in the high dose group are disturbing there is insufficient basis to conclude that these tumors are actually related to the test material.

CONCLUSION. The data submitted satisfy TB-I's request for additional information for this study. The data do not indicate that pheochromocytomas are induced by lindane administration.

TH Review 010603

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[83-2. "Agouti" Lindane/1987] 010603

Reviewed by: John Doherty, Ph.D. John Doherty 3/22/92
Section IV, Tox. Branch (H7509C)
Secondary reviewer: Marion Copley, DVM Marion Copley 3/22/92
Section IV, Tox. Branch (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: 83-2. Special study with mice.

MRID NO.: None

TOX CHEM No.: 527
PC No.: 009001

TEST MATERIAL: Lindane (gamma-hexachlorocyclohexane): Obtained from the Hooker Chemicals and Plastics, Niagara Falls, New York.

STUDY NUMBER(S): None (journal article).

SPONSOR: None.

TESTING FACILITY: National Center for Toxicological Research, Jefferson, Arkansas.

TITLE OF REPORT: "Tumorigenic responses to lindane in mice: potentiation by a dominant mutation".

AUTHOR(S): G.L. Wolff, D.W. Roberts, R.L. Morrissey, D.L. Greenman, R.R. Allen, W.L. Campbell, H. Bergman, S. Nesnow and C. H. Firth.

REPORT ISSUED: As published in Carcinogenesis 8(12):1889-1897(1987).

CONCLUSIONS:

Evidence for positive carcinogenic response in the agouti and pseudoagouti mouse lines for both liver tumors (hepatocellular adenoma and carcinoma) and lung (papillary and/or solid) tumors.

Clara cell hyperplasia occurs in the lung in all three lines that is apparently irreversible. Liver weight is increased (agouti > pseudoagouti > black) and monooxygenase activity is increased in all three lines (pseudoagouti > black > agouti).

Dose level tested: 0 and 160 ppm. Species: three mouse lines from the NCTR stocks: "agouti", "pseudoagouti" and black. Females only.

Classification: core-SUPPLEMENTARY

Quality Assurance Statement: Not provided.
Good Laboratory Practice Statement: Not provided.

010603

REVIEW

Experimental Constants:

Test Materials

Chemical: Lindane (gamma hexachlorocyclohexane)
Source: Hooker Chemicals and Plastics, Niagara Falls New York
Batch: Lot 6008-425
Purity: Not stated.
Vehicle: None.

Test System:

Species: Three strains of mice as described below. Only females were used.
Supplier: NCTR Breeding Colony
Age: Three to four weeks old at time of allocation to dose groups.
Weight: Initial body weight not provided.
Feed: Purina Laboratory Chow 5010M

The three strains of mice utilized in this study are described as follows:

"Agouti" (A^{vy}/a): This line has increased susceptibility to formation of strain-specific neoplasms (spontaneous as well as virally or chemically-induced), it has a mottled yellow coat color and adult onset obesity.

"Pseudoagouti" (A^{vy}/a): This has the same genotype as the agouti but differs physiologically (it is lean in appearance) apparently because each line has a different degree of mutation expression.

Black (a/a) (YS x VY): This line has a low spontaneous rate of liver tumor formation.

The hybrid mice were produced in the NCTR colony by mating a/a YS females with A^{vy}/a VY males.

B. STUDY DESIGN:

Only control and groups dosed with 160 ppm of lindane were utilized. The dose level of 160 ppm was selected based on a preliminary study which indicated that 160 ppm was the highest dose level which did not result in deaths in a one month study. It is also the dose level tested in the NCI 1977 study in mice. The following experimental intervals were studied.

Continuous feeding:

6 and 12 months: 48 per mouse line for both control and lindane treated.

18 months: 36 of each line for both control and lindane treated.

24 months: 96 of each line for both control and lindane treated.

Discontinuous feeding: (dosed with 160 pm lindane for 6 months and then fed

control diet for 6 or 18 months).

12 months: 48 agouti and black for both control and lindane treated.

24 months: 96 agouti and black for both control and lindane treated.

"Index" "used to detect appearance of hepatic neoplasms for determination of start of terminal sacrifice". 24 black mice for 18 or 21 months.

Analytical Chemistry: No details of the analytical report were provided. The experimental section of the paper states that dose levels in the feed were determined by the NCTR Division of Chemistry.

Statistics:

Test	Parameters Evaluated
One way analysis of variance with Bonferroni multiple comparisons.	Body and liver weight.
Fisher's Exact Test with 2 x 2 subtables of tumor prevalence for pair-wise comparisons. "SAS" procedure CHRONIC for trends.	Tumor data.

C. SPECIFIC METHODS AND RESULTS:

1. Observations. No details were provided. No reactions to treatment were reported. No information on survival within the individual groups was reported.

2. Body weight. No data on body weight during the in-life phase of the study were reported. Carcass weight (body weight minus the liver weight) was reported as not being affects by lindane treatment (no data were provided). The agouti mice were also stated as being 50 to 100% greater in weight than the pseudoagouti and black mice. The pseudoagouti mice were also thought to be consistently heavier than the black mice but no effect of the lindane treatment was implied.

3. Food consumption and compound intake. Some summary data were provided to indicate that the agouti mice consumed about 7 to 10% more feed than the pseudoagouti and black mice meaning that they also ingested more lindane. The lindane intake in terms of mg/kg/day could not be determined since the body weight data were not provided.

4. Ophthalmological examinations. No determinations were

made.

5. Clinical Chemistry and Hematology. No determinations were made except for the special benzo(a)pyrene monooxygenase activity as described as follows.

S-9 fractions of mouse liver obtained from mice from each line that were dosed with lindane for 6 or 12 months were obtained and frozen and shipped to EPA Carcinogenesis and Metabolism Branch RTP, North Carolina. The assay was designed to assess a P-448 enzyme and the method was not described but provided in a reference. Each of the three lines of mice induced the enzyme as indicated in Table 1.

Table 1. Induction of benzo(a)pyrene monooxygenase (P-448) by lindane in three lines of female mice.

	Mouse Line[1]		
Interval	Agouti	Pseudoagouti	Black
6 months	1.84	2.71	2.07
12 months	1.61	2.78	2.09

1. Data are ratio of treated activity to the control activity. The control activity differed slightly for each line.

These data indicated that lindane treatment at both time intervals induced the lowest increase in p-449 in the agouti line and the most increase int eh pseudoagouti line. The black mouse line was probably closer to the agouti line in its susceptibility to induction by lindane.

6. Urinalysis. No urinalysis data were provided.

7. Sacrifice and Pathology: The mice were sacrificed at their scheduled interval by CO_2 asphyxiation. The report states that approximately 35 tissues were necropsied fixed and trimmed for microscopy. The tissues were dehydrated in ethanol, cleared in xylene, embedded in paraffin, sectioned and stained with H&E. Although additional tissues were apparently prepared, only data on the liver and lung were presented in the report.

8. Organ weight: Data on liver weight following 6, 12 18 and 24 months of treatment were presented. The following summarizes the weight differences.

Agouti. Liver weight was increased 22.4%, 31.2%, 14.7% and 30.8% (all $p < 0.05$) for the 6, 12, 18 and 24 month intervals.

Pseudoagouti. Liver weight was increased 13.5%, 20.3%, 22% and 17.4% (all $p < 0.05$) for the 6, 12, 18 and 24 month intervals.

Black. Liver weight was statistically significantly increased at 24 months only (16.4%). Non significant elevations of 12.2%, 12.2% and 15.4% were also noted.

One aspect of these data is that although the pseudo-agouti line indicated the highest level of P-488 induction, this line did not have a larger increase in liver weight as compared to the agouti line.

Data were also presented that indicated that discontinuation of dosing following six months of dosing with lindane resulted in liver weights equivalent to the controls not dosed with lindane.

9. Histopathology-Individual organ discussions.

A. Liver. Liver lesions were classified according to Firth and Ward. In addition, tumors classified as adenomas corresponded to Types I and II and those classified as carcinomas corresponded to types II and IV according to Becker. The occurrence of liver tumors at the various sacrifice intervals is described below.

6 months. No liver tumors reported.

12 months. 2/48 (4%) control and 3/48 (6%) treated agouti mice developed adenomas. No carcinomas were reported. No tumors were reported in the other lines.

18 months. None (0/34) of the control but 33% (12/36) of the lindane treated agouti mice developed adenomas but there was only one incident of a carcinoma each in the control and treated groups for this line.

In the pseudoagouti line, no liver tumors were reported with lindane treatment although there was 6% (2/35) and 3% (1/34) incidents of adenoma and carcinoma in the pseudoagouti control group.

In the black mouse line, the control group had a higher incident rate (11%, 4/35) for adenomas than the lindane treated group (6%, 2/36). There were no carcinomas at this time interval for this line.

Ther18 month data indicate the agouti line to be sensitive to the presence of lindane.

24 months. Table 2 below illustrates the findings for liver tumors following 24 months of continuous treatment with lindane

Table 2. Liver tumors (hepatocellular adenoma and carcinoma) in three lines of female mice dosed continuously with lindane as compared to the control.

Tumor Type	Strain[1] Agouti Control	Agouti Lindane	Pseudoagouti Control	Pseudoagouti Lindane	Black Control	Black Lindane
Number examined	93	94	95	95	96	96
Adenoma	8(9%)	33(35%)	5(5%)	11(12%)	6(6%)	3(3%)
Carcinoma	12(13%)	16(17%)	2(2%)	5(5%)	3(3%)	1(1%)
Total	20(22%)	49(52%)	7(7%)	16(17%)	9(9%)	4(4%)

[1] Data are incidents (incidents as a percentage of number examined).

Black line. There was no indication of increases in tumor incidence in this line of mice as a response to lindane treatment. This line had spontaneous rates of adenomas that were equivalent to the control spontaneous rates for the agouti and pseudoagouti lines. The spontaneous rate of carcinomas was, however, higher (13%) for the agouti line than for either the black (3%) or pseudoagouti (2%).

Agouti line. Clearly adenomas were increased (compare 35% incidence with 9% incidence for the treated and control groups) after 24 months and the increase noted at 18 months above. The incidence of carcinomas in this line were only slightly higher for the treated group (17%) when compared to the controls (13%). Thus, the combined total of tumors is higher but the increase in mostly due to adenomas.

Pseudoagouti. Adenomas appear to be higher after 24 months (compare 12% in the treated group and only 5% in the control group. Similarly carcinomas also appear to be higher although there is only 5% incidence in the treated group and 2% incidence in the controls. The combined incidence is correspondingly higher. There was no indication of an increase in this line at the 18 month sacrifice interval.

Note: The statistical analysis provided in the study report is difficult to interpret. There does not seem to be clear evidence that there was a pair-wise comparison between the control and treated group for each line.

The results of discontinuing the lindane treatment after 6 months and sacrificing the mice either 6 or 18 months later indicated a slight increase in hepatocellular adenomas at 24 months in the treated group (14%. 13/95) when compared to the control (9%. 8/93). There were also 13% (12/93) and 14% (13/95) incidence of hepatocellular carcinomas in the control and lindane treated groups. There were no liver tumors in the lindane

treated mice at the 18 month sacrifice interval.

B. Lung. Compound related increases in Clara cell hyperplasia were noted at the 6, 12, 18 and 24 month intervals. Lung tumors were also increased in the later months of the study for the agouti and pseudoagouti mouse lines. Table 3 illustrates the lung pathology data from this study.

Table 3. Lung pathology data in female agouti, pseudoagouti and black female mice dosed with lindane.

Lung Clara Cell Hyperplasia and Lung Tumors[1]

Interval	Agouti		Pseudoagouti		Black	
	Control	Lindane	Control	Lindane	Control	Lindane
	Hyperplasia					
6	17%	77%	8%	50%	10%	56%
12	31%	92%	17%	76%	14%	90%
18	6%	92%	6%	79%	0	89%
24	15%	72%	10%	76%	10%	82%
	Lung tumors					
6	4%(2/48)	2%(1/48)	2%(1/48)	0	2%(1/48)	0
12	0	2%(1/48)	2%(146)	0	2%(1/48)	0
18	0	17%(6/36)	6%(2/35)	6%(2/34)	0	11%(4/36)
24	4%(4/95)	19%(18/95)	6%(6/95)	14%(13/94)	2%(2/96)	3%(3/96)

1. Data are percentage relative to the number examined. For simplicity the number incidents and number of mice examined is omitted from the hyperplasia table. The lung tumor table presents the percentage and in () the number of incidents/number of mice examined. The same denominator applies for both the non-neoplastic lesion (hyperplasia) and the tumor data for each interval.

An increase in the incidence of Clara cell hyperplasia apparently persisted following discontinuation of lindane dosing after 6 months as indicated by 31% vs 75% for the Agouti line and 14% vs 47% for the black line mice affected for the control and treated groups. After 18 months following discontinuation of lindane dosing, the effect was still apparent with their being 15% vs 42% for the Agouti and 22% vs 10% for the black mouse line.

There was also a slight increase in lung tumors in the Agouti line even though the lindane was discontinued from the diets. For example after 6 months there was 1 incident (2%) in treated group but none in the control. After 18 months, there were 10 incidents (10%) in the treated group but only 4 incidents (4%) in the control group. The lung tumor incidence in the black

mouse line was equivalent for both the control and lindane treated groups. [redacted]

In summary, these lung pathology data indicate that there is an increase in the incidence of lung tumors in the Agouti mouse line. This increase in lung tumor incidence may be apparent as early as 18 months in the Agouti line. The pseudo-agouti mouse line also has an apparent treatment related increase but to a lesser magnitude than the Agouti and is only apparent after 24 months. An apparent increase in the incidence of lung tumors in the black line at 18 months was not confirmed at 24 months in a group that had nearly three times as many animals[1].

All three lines are apparently susceptible to lindane dependent increased Clara cell hyperplasia and this condition is apparently irreversible since it was still present even after 18 months after the last lindane dosing.

9. Adequacy of dosing. Since there were no behavioral reactions, in life phase body weight determinations or survival data presented, there is no reliable way to assess if the dose levels were adequate or excessive. Since there was liver weight change, some reviewers may considered that the dose was adequate.

CONCLUSION. The information in this journal article is SUPPLEMENTARY. The data provide a demonstration that the mouse lines (the agouti and pseudoagouti) known to be especially susceptible to spontaneous, viral and/or chemical induction of liver tumors, respond to the dietary presence of lindane by developing more liver tumors. There was no increase in liver tumors in the more standard mouse line (black mouse). The agouti and pseudoagouti mouse lines also had apparent compound related increases in lung tumors. All three mouse lines developed Clara cell hyperplasia in the lungs and this condition is apparently irreversible.

The study is not considered a candidate for upgrading to MINIMUM or GUIDELINE for the following reasons: the protocol included only females, there was only a single dose level tested, only evidence of lung and liver histopathology was presented (no evidence of histopathological examination of the many other tissues was presented), no analytical chemistry report was presented and no individual animal data were presented.

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[1]The mice in the 18 month group were assessed for humoral immune function and the lung tumors were found in this group. The study report suggests that the increase in lung tumors may be somehow related to the immune function testing for the black mouse line.