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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.: 429272-01

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.

Quality 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 comments 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.

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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.

Supplemental DER dated 9/13/93

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