7-4-79 BB-1195 TR-2660

Government of Canada / Gouvernement du Canada

MEMORANDUM NOTE DE SERVICE

001484

SECURITY CLASSIFICATION - DE SÉCURITÉ

OUR FILE - NOTRE RÉFÉRENCE

YOUR FILE - VOTRE RÉFÉRENCE

DATE July 4, 1979

Mr. D. J. Clegg
Head, Pesticides Section

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Dr. H. M. Cunningham

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Validation of Rat Teratogenic Study with Phaltan - IBT No. P-5397.

Overall Comment: The audit and validation of this report indicate that the final report is not supported by the raw data. Of prime significance was a higher than actually found incidence of resorptions reported for the controls and absence of raw data on fetal skeletal and internal development.

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Rat Teratogenic Study with Phaltan - IBT No. P-5397. 001484

A. Audit:

1. Report No. B-5397 dated October 11, 1967.

2. Date of study: Started on 21-5-67 and terminated on 27-7-67.

3. Protocol: No protocol available but procedure indicates that groups of 5-10 pregnant females (17 controls) received levels of 100 and 500 mg/kg of Phaltan suspended in corn oil (total dose = 0.1% of body weight) according to one of two dosing schedules - A = 10 doses from day 6 through 15 of gestation, or B = 3 doses from day 8 through 10. Observations were made on body weight, mortality, reactions and pathologic examination on all females sacrificed on 20th day of gestation. Number of implantation sites, resorption sites, corpora lutea, numbers of fetuses present, their weight and abnormalities in external and internal development and skeletal development were noted. Positive controls received trypan blue at 50 and 25 mg/kg.

4. Test Material: No evidence available to indicate that it was received at IBT.

5. Animal Suitability: Charles River strain albino rats obtained from Charles River Breeding Laboratory Ltd.

6. Raw Data: Initial weights of many rats missing at the 6th day of gestation when treatment started. Data absent on weighing out test material and very few data on mortality and reactions. No raw data to indicate that pathological procedures were actually conducted on gross pathology, internal development and on skeletal development.

B. Validation of Evaluation:

1. Dates: Dosages at the higher level (500 mg/kg) and a few rats at the lower level (100 mg/kg) appear to have been done about a month before the rest of the study and controls. Handwritten dates on summary dosage sheets indicate that the experiment started and finished on the approximate dates indicated above. None of the data sheets were signed.

2. Protocol: The protocol was not followed closely. At least three levels of trypan blue (12.5 mg/kg, 25.0 mg/kg, and 50 mg/kg) were used instead of only 50 mg/kg. The different groups of animals were dosed at different

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times and many observations were not made.

3. Test Material & Quality Control: No shipping invoices or other data to show that the test material was sent to IBT. No data available on mixing the test material with vehicle for dosing although calculations showing the total amount of test material to be administered were available.

4. Personnel:

Report prepared by: Gerald Kennedy, B.S.
Staff Assistant

Report approved by:
Otis E. Fancher, Ph.D.
Director.

J. C. Calandra, M.D., Ph.D.
President

Technicians: No signatures on any of data.

C. Execution of the study:

a. Body weight: Raw data were missing on the body weights on the first day of dosing on many of the rats but those that were available for final body weights agreed with the final report.

b. Dosing: The use of two dosing schedules (10 doses with the lower level and 3 with the higher level) is not good scientific practice.

c. Mortality and Reactions: There was very little raw data on reactions. One death was reported at the high level (500 mg/kg) of Phaltan, supposedly after 3 doses but the raw data indicated that the dosing regime was complete and the rat died 1 day before the others in the same group were sacrificed.

d. Teratogenic and Reproduction Studies: Table II (see appendix) has been corrected according to the raw data. It may be observed that the number of resorptions and abnormalities have been increased in the controls and changed somewhat in the positive controls. There did not appear to be any changes in the test animals.

e. Fetal Skeletal Development: No raw data available.

f. Fetal Internal Development: No raw data available.

g. Progeny Body Weight: Only the average weights of the male and female fetuses in each litter were available in the raw data. The auditor, however, has taken the available data on fetal weights and calculated that statistically significant ~~significant~~ differences existed between the control and test male and female pups ($P < 0.05$) at the 100 mg/kg level, and ($P < 0.01$) at the 500 mg/kg level)

Overall Comment: The audit and validation of this report indicate that the final report is not supported by the raw data. Of prime significance was a higher than actually found incidence of resorptions reported for the controls and absence of raw data on fetal skeletal and internal development.

H. M. Cunningham

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Teratogenic and Reproduction Effects

Albino Rats

Summary of Results

Group	Pregnant Females Examined	Corpora Lutea Total	Corpora Lutea Mean /Female	Implantation Sites Total	Implantation Sites Mean /Female	Resorption Sites Total	Resorption Sites Mean /Female	Fetuses Total	Fetuses Mean /Female	Abnormal Fetuses Total	Per Cent
-I	(10) 7	(135) 76	(13.5) 13.7	(126) 92	(12.6) 13.1	(3) 0	(0.3) 0	(123) 92	(12.3) 13.1	(1) 0	(0.8) 0
-II	(7)	(84) 102	(12.0) 14.7	(80) 92	(11.4) 13.1	(2) 3	(0.3) .42	(78) 82	(11.1) 11.7	0	0.0
C...	10	(129) 138	(12.9) 13.8	(113) 127	(11.8) 12.7	(54)	(5.4)	(64) 57	(6.4) 5.7	(17) 9	(26.7)
ap-I (50 mg/kg)	6	93	15.5	79	13.2	2	0.3	77	12.8	0	0.0
cp-II (0 mg/kg)	7	91	13.0	86	12.3	4	0.6	82	11.7	0	0.0
cp-III (50 mg/kg)	5	49	9.8	49	9.8	4	0.8	45	9.0	0	0.0
cp-IV (00 mg/kg)	5	59	11.8	58	11.6	10	2.0	48	9.6	0	0.0
cp-V (1000 mg/kg)	5	63	12.6	63	12.6	4	0.8	59	11.8	3	5.1
cp-VI (2000 mg/kg)	5	64	12.8	60	12.0	0	0.0	60	12.0	2	3.3
...-I (100 mg/kg)	9	132	14.7	121	13.4	4	0.4	117	13.0	0	0.0
...-II (500 mg/kg)	5	66	13.2	64	12.8	1	0.2	63	12.6	0	0.0
...l-I (100mg/kg)	10	134	13.4	124	12.4	4	0.4	120	12.0	0	0.0
...l-II (500mg/kg)	4	51	12.7	51	12.7	2	0.5	49	12.2	1	2.1

One female died following the three doses. 1/0! it died 1 day [illegible]

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