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MEMORANDUM **NOTE DE SERVICE**

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TO / A: Dr. C.T. Miller,
Co-ordinator,
Task Force for Re-assessment
of Chemical Safety

FROM / DE: Dr. J.H. Kinzell,
Task Force for Re-assessment
of Chemical Safety

SECURITY - CLASSIFICATION - DE SÉCURITÉ:

OUR FILE – N / REFERENCE:

YOUR FILE – V / REFERENCE:

DATE: August 11, 1981

SUBJECT / OBJET: Audit And Validation of Rat Teratology Study With Prometon:

NAME OF LABORATORY:	INDUSTRIAL BIO-TEST LABORATORIES, INC.
LABORATORY REPORT NO.:	B-904
PETITIONER:	CIBA-GEIGY
COMMON NAME OF COMPOUND:	PROMETON
OTHER NAME:	PROMITOL
FORM OF TEST MATERIAL:	PROMETONE TECHNICAL (FL-17507)
TYPE OF STUDY:	TERATOLOGY
SPECIES, BREED AND STRAIN:	ALBINO RAT, CHARLES RIVER
FILE UNDER:	PROMETON
RECOMMENDATION:	INVALID* (SUPPLEMENTARY DATA)

OVERALL COMMENTS:

In general, the information presented in the final report is supported by the raw data. However, because of several inadequacies this study should be considered invalid, and used as supplementary data only. There are no daily dosing records for days 6-15 when the dams were exposed to the compound. The high dose of 50 mg/kg per day does not appear to be sufficiently high to produce any effects in the dams.

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AUDIT

REPORT'S TITLE: Teratogenic Study with Prometone Technical in Albino Rats.

REPORT'S NUMBER & DATE: IBT No. B 904; March 28, 1972

SPONSOR: Ciba-Geigy (Geigy Agricultural Chemicals Division)

PROTOCOL: No protocol either written by the sponsor or test laboratory is available.

TEST MATERIAL: A shipping order dated 22-11-71 indicates J.R. Forsythe requested 1 kg of Prometone Technical (FL-17507) be sent to M.L. Keplinger of IBT. According to a memo from M.L. Keplinger dated January 17, 1972, the sample from Ciba-Geigy was labelled prometryne. The melting point of the compound was checked (at IBT) and found to correspond to the published values for prometone. The error was discussed with J. Forsythe (Ciba-Geigy) and hence the corrections in the name of the compound on the raw data sheets.

TEST ANIMALS: According to the final report female Albino Rats (approx 200 gm in weight) were acquired from Charles River Breeding Laboratories, North Wilmington, Mass. There is no information to confirm the source or age of animals.

RAW DATA: There are no records for dosing on days 6-15 reactions or daily observations. Also, there are no individual records on the day the contro dams were killed, giving the results of the examination of the reproductive tract, final body weights of dams, and litter weights.

VALIDATION

1. DATES

Actual start of study: December 8, 1981 (date first dose given which was also day 6 of gestat
Actual termination: December 22, 1981 (necropsy date)

2. PROTOCOL:

Pregnant rats (confirmed by sperm positive results of vaginal examinations and shipped to IBT on day one of gestation) were assigned to each of 2 treatments, 21 animals per treatment.

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VALIDATION

PROTOCOL - CONTINUED

On day 6 of gestation (and for 10 days thereafter) rats were given either 25 or 50 mg prometone/kg. A third group of female rats served as untreated controls and were dosed with water. All animals were allowed food and water ad libitum. Body weights were recorded on days 6,9,12,15, and at sacrifice. Mortality and reactions were maintained on a daily basis. All females were sacrificed on day 20 of gestation and both uteri in each female examined for the numbers of fetal swellings, implantation sites, resorption sites, uterine abnormalities and viable fetuses. Fetuses were removed, litter weights taken and individual fetuses examined for any external and internal abnormalities.

TEST MATERIALS AND QUALITY CONTROL

Technical Prometon was made up as 1% solution (w/v) in corn oil. There are no data indicating the purity of the test material.

PERSONNEL:

Report prepared by: Sandra Haley, Assistant Toxicologist, Rat Toxicity

Approved by: James B. Plank, Senior Group Leader, Rat Toxicity

P.L. Wright, Ph.D., Section Head, Toxicology

M.L. Keplinger, Ph.D., Manager, Toxicology

EXECUTION

1. DOSING - There are no records showing that the rats were dosed according to their body weights during days 6-15. Control dams were dosed with water rather than corn oil as stated in the final report.

2. BODY WEIGHTS - The raw data support information presented in the final report. Data are not signed or initialed but are dated. The body weight data for control dams are from another study (IBT No.B700) run prior to the prometon teratology study (see MF 3/7 page 22.)

3. REACTIONS - There are no raw data indicating reactions were observed for on a daily basis during the course of the study. It is unlikely there were any since the acute LD_{50} study on this compound showed only hypoactivity at 177 mg/kg and hypoactivity and salvation at 600 mg/kg. The acute oral LD_{50} for prometone is about 2900 mg/kg.

4. MORTALITY - Information in the final report is supported by the raw data. No individual sacrifice data sheets are available for the control dams.

5. REPRODUCTIVE EFFECTS - The raw data for offspring in the treated groups agree with the final report. The data are dated but not signed. No individual raw data sheets are available for the control offspring.

FETAL DEVELOPMENT

a) Body Weights - unsigned but dated raw data support the information in the final report. No individual raw data are available for the control offspring.

b) External development - information in the final report agrees with the raw data which are dated but not signed. One incident of gastroschsis in a female put in T-II was not included in the final report (malformation not observed in 22, 292 Charles River rat pups; observed in 1 out of 8, 036 New Zealand White rabbit offspring, data from report on Effects of Drugs on Reproductive Processes, Huntington Research Center, Huntington, UK). No raw data are available for the control offspring.

c) Skeletal Development - The raw data and final report agree. The data are dated, but not signed. No raw data are available for the control offspring.

d) Internal Development - The number of fetuses examined in T-I and T-II were 100 and 78 respectively rather than the 90 and 68 reported. However, the effect of this on the percentage incidence of the various findings is insignificant. The raw data are dated, but not signed or initialled. Raw data are not available for the control offspring.

OVERALL COMMENTS

In general, the information presented in the final report is supported by the raw data. However, because of several inadequacies, this study should be considered invalid, and used as supplementary data only. There are no daily dosing records for days 6-15 when the dams were exposed to the compound. The high dose of 50 mg/kg per day does not appear to be sufficiently high to produce any effects on the dams.

AUDITOR'S REPORT

Accurately accounted for the differences between the raw data and the final report. The auditor also noted the deficiency in recording of the dosing information in the raw data.

1ST REVIEWER: J. H. Kinzell

2ND REVIEWER: W. J. Cunningham

C.T. MILLER,
CO-ORDINATOR S. M. Charbonneau