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SUBJECT: Validation Review of IBT Study 623-7924 Reproduction Study with CGA-15324 (Curacron) in Albino Rats.

FROM:

Gary Burin GB
Toxicology Branch, HED (TS-769)

DEC 4/11/80

TO:

Branch Chief
Lab Audits and Regulatory Analysis
SPRD (TS-791)

W. J. Burin

THRU:

M. Adrian Gross, Chief
Toxicology Branch, HED (TS-769)

Discussion

It is concluded that this study should be considered invalid for the purpose of estimating the toxic effect of Curacron in rats. Reasons for this conclusion (listed in order of importance) are the following;

- 1) Respiratory disease appears to be near ubiquitous among both treated and control parental animals. A total of 41 of 288 parental animals died during the course of the study (before sacrifice) and histopathologic diagnoses (when not prevented by excessive autolysis) of these animals found chronic murine pneumonia and/or congestion, acute bronchopneumonia and tracheitis. Mortality can be broken down as follows (from Tables V and VI of the final report):

♂	<u>Deaths</u>		Total
	First Mating	Second Mating	
F ₀	5	3	8
F ₁	1	5	6
F ₂	9	2	11
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F ₀	3	4	7
F ₁	2	2	4
F ₂	4	1	5
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In addition to animals dying outright, the finding of chronic murine pneumonia, often combined with findings such as aggregates of alveolar macrophages, alveolar hemorrhage, bronchiectatic abscesses, congestion, bronchopneumonia and other indications of respiratory disease were reported in almost every animal examined. For example, among males of the F₀ generation surviving to sacrifice, 5 out of 5 control animals examined had mild to moderate CMP and 5 out of 5 treatment animals had moderate to severe CMP.

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The occurrence of respiratory disease to this extent in a population of albino rats less than six months old is an indication of poor animal husbandry and greatly reduces the sensitivity of the assay in detecting compound related effects.

- 2) Complete microscopic examinations were reported for 5 males and 5 females from the control and high dose group. The Ciba-Geigy validation report (p. 6) states that:

"Discussion with IBTL personnel indicated that the method of selecting the surviving animals for histopathologic evaluation was not entirely random but depended on which parental animals first completed their utility in a given generation. That is, those rats which completed the reproductive cycle first were used for histopathologic evaluation; those that weaned their litters last were sacrificed and discarded."

It appears that this procedure may have resulted in a bias in the animals chosen for microscopic examination.

- 3) Original protocol called for a complete histologic examination of all post-mortem animals. Only lung, liver, kidney, spleen, heart, gonads and grossly visible lesions were actually examined.



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

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SUBJECT: EPA (HED) Review of IBT Validation Report

FROM: Gary Burin
Tox.Br./HED (TS-769)

TO: Branch Chief
Regulatory Analysis and Lab Audits Branch
Special Pesticide Review Division

Validation Submitted by: Gary Burin

Date of Validation: 4-8-80

IBT Report Number: 623-7924

Date of Final Report: April 19, 1978

Type of Study: Reproduction Study in Albino Rats

Compound: Curacron (CGA-15324)

EPA Accession Number: 097798
Registrant Validation Report
IBT Report Submitted to EPA

Conclusions:

 X

VALID
INVALID
NO CONCLUSION

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