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OFFICE OF TOXIC SUBSTANCES  
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REV. 7/27/82

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A 04

CHEMICAL MANUFACTURERS ASSOCIATION

FYI-0875

COURTNEY M. PRICE  
VICE PRESIDENT  
CHEMSTAR

June 19, 1998

S 3/1/98

Dr. Lynn Goldman  
Assistant Administrator  
Office of Prevention, Pesticides and Toxic Substances TS-7101  
Environmental Protection Agency  
401 M Street, SW, Room 637, East Tower  
Washington, DC 20460

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Dear Dr. Goldman,

The Chemical Manufacturers Association makes available to the public and appropriate government agencies final reports of environmental, health and safety research that it manages. In keeping with this policy, the following recently completed report addendum is enclosed:

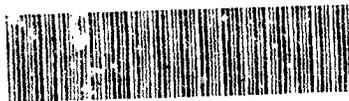
A 28-Day Repeated Dose Oral Toxicity Study of HBCD in Rats.

This report does not include confidential information.

If you have any questions, please call Wendy K. Sherman of my staff at 703-741-5639.

Sincerely yours,

*Courtney Price* / *cp*



FYI-97-001289

Enclosure



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Received  
6/26/98





**ADDENDUM TO THE FINAL REPORT**

**STUDY TITLE**

**A 28-DAY REPEATED DOSE ORAL  
TOXICITY STUDY OF HBCD IN RATS**

**DATA REQUIREMENT**

OECD Guideline, Section 407

**STUDY DIRECTOR**

Christopher P. Chengelis, Ph.D., D.A.B.T.

**DATE**

May 28, 1998

**PERFORMING LABORATORY**

WIL Research Laboratories, Inc.  
1407 George Road  
Ashland, Ohio 44805-9281

**LABORATORY STUDY NUMBER**

WIL-186004

**SPONSOR PROJECT NUMBER**

BFRIP 2.0-WIL HBCD

**SPONSOR**

Chemical Manufacturers Association  
Brominated Flame Retardant Industry Panel  
1300 Wilson Blvd.  
Arlington, Virginia 22209

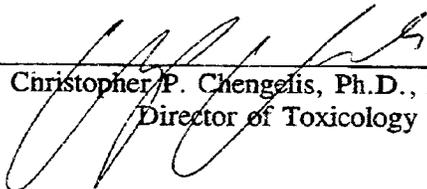
WIL-186004  
CMA BFRIP

A 28-Day Repeated Dose Oral  
Toxicity Study of HBCD in Rats

**COMPLIANCE STATEMENT**

This addendum to the final report, designated WIL-186004, was conducted in compliance with the United States Environmental Protection Agency (EPA) Good Laboratory Practice Regulations (40 CFR Part 792), October 16, 1989, the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice [C (81) 30 (Final)], the Standard Operating Procedures of WIL Research Laboratories, Inc., and the protocol as approved by the sponsor (Chemical Manufacturers Association Brominated Flame Retardant Industry Panel). The protocol was designed and the study was conducted in accordance with the OECD Guidelines for testing of Chemicals, Health Effects Test Guidelines, Section 407, adopted May 12, 1981.

Study Director:

  
\_\_\_\_\_  
Christopher P. Chengelis, Ph.D., D.A.B.T.  
Director of Toxicology

28 May 98  
Date

WIL-186004  
CMA BFRIP

A 28-Day Repeated Dose Oral  
Toxicity Study of HBCD in Rats

**ADDENDUM TO THE FINAL REPORT**

The test article, hexabromocyclododecane (HBCD), in the vehicle, corn oil, was administered orally (gavage) to three groups of CrI:CD<sup>®</sup>(SD)BR rats for 28 consecutive days. Dosage levels of 125, 350 and 1000 mg/kg/day were administered at a dose volume of 5 ml/kg. The treated groups consisted of 6 rats/sex in the 125 and 350 mg/kg/day groups and 12 rats/sex in the 1000 mg/kg/day group. A concurrent control group comprised of 12 rats/sex received the vehicle on a comparable regimen. Parameters that were evaluated included survival, clinical condition, body weights, food consumption, functional observational battery performance, motor activity, hematology and serum chemistry. At the conclusion of the four-week dosing period, 6 rats/sex/group were euthanized and necropsied. The remaining 6 rats/sex in the control and 1000 mg/kg/day groups were euthanized and necropsied following a two-week recovery period. Selected organs were weighed and/or preserved and selected tissues were examined microscopically for each animal.

The only test article-related effect observed in the originally-scheduled portion of the study was dose-related increases in liver weights in the treated groups at the primary necropsy (week 4). An increase in mean liver weight was also observed for the 1000 mg/kg/day group females at the recovery necropsy (week 6). However, the magnitude of the increase was less pronounced at the recovery necropsy, suggesting the effect was reversible. In the absence of test article-related liver histopathology and serum chemistry changes, the increases in liver weight observed in the treated groups were considered to be an adaptive response, rather than a toxic response, and were most likely the result of microsomal induction.

After the release of the final report, the sponsor requested that the thyroid glands of all animals from the primary and recovery necropsies be examined histopathologically. After fixation, the thyroid glands were trimmed as described by Thompson<sup>1</sup>. Trimmed specimens were placed in appropriately labeled and numbered cassettes. The tissue samples were processed into paraffin blocks. The labeled paraffin blocks were sectioned

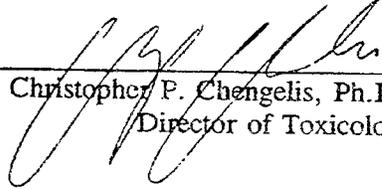
WIL-186004  
CMA BFRIP

at five to eight microns, and paraffin ribbons of the sectioned tissue were placed on clean glass microscope slides labeled with the appropriate study, animal, group, and cassette numbers. Upon completion of staining with hematoxylin and eosin (AFIP Manual of Histological Staining Methods<sup>2</sup>), cover slips were placed on the slides. Microscopic examinations were performed by Carney B. Jackson, D.V.M., D.A.C.V.P., D.A.C.V.P.M., Assistant Director of Pathology and Veterinary Medicine. The results were peer-reviewed by other pathologists on staff at WIL Research Laboratories, Inc.

Colloid loss was observed with similar frequency in the control and treated groups at the primary and recovery necropsies. The severity grading in the 1000 mg/kg/day group males was slightly increased relative to that in the control group. Differences in the severity gradings were less pronounced at the recovery necropsy. No similar increases in the severity of colloid loss were observed in the 1000 mg/kg/day group females at either necropsy. Given that it was slight and reversible in nature, occurred in only one gender and was not accompanied by other histologic indicators of increased thyroid activity, the slightly increased severity grading of the colloid loss in the 1000 mg/kg/day group males is probably not of toxicological significance.

Other histopathological findings, such as follicular cell hypertrophy, cytoplasmic vacuolation, inflammation, ultimobranchial cysts and autolysis, were observed in all treated groups infrequently or at an incidence similar to that in the control group.

Approved and Submitted By:

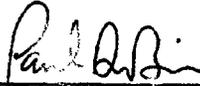
  
\_\_\_\_\_  
Christopher P. Chengelis, Ph.D., D.A.B.T.  
Director of Toxicology

28 May 98  
Date

A 09

WIL-186004  
CMA BFRIP

Report Prepared By:



J. Paul DuBois, B.S.  
Report Writer II

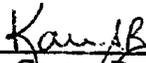
28 May 1998  
Date

Reviewed By:



Chandikumar S. Elangbam, M.V.Sc., Ph.D.,  
D.A.C.V.P., D.A.B.T.  
Senior Pathologist

5/28/98  
Date



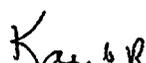
Carney B. Jackson, D.V.M.,  
D.A.C.V.P., D.A.C.V.P.M.  
Assistant Director of Pathology and Veterinary Medicine  
Study Pathologist

5/28/98  
Date



Jozef J.W.M. Mertens, Ph.D., D.A.B.T.  
Assistant Director of Toxicology

5/28/98  
Date



Karen S. Regan, D.V.M., D.A.C.V.P., D.A.B.T.  
Director of Pathology and Veterinary Medicine

5/28/98  
Date

# A 10

WIL-186004  
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## QUALITY ASSURANCE UNIT STATEMENT

| <u>Date(s) of<br/>Inspection(s)</u> | <u>Phase<br/>Inspected</u>                  | <u>Date(s) Findings<br/>Reported to<br/>Study Director</u> | <u>Date(s) Findings<br/>Reported to<br/>Management</u> |
|-------------------------------------|---|--|--|
| 10/27/97                            | Study Records (H-1/P-1,<br>Additional Data) | 10/28/97   | 11/26/97   |
| 10/28/97                            | Report Addendum                             | 10/28/97   | 11/26/97   |

This addendum to the final report was conducted and inspected in accordance with the Good Laboratory Practice Regulations, the OECD Principles of Good Laboratory Practice, the Standard Operating Procedures of WIL Research Laboratories, Inc., and the sponsor's protocol and protocol amendment(s). Quality Assurance findings, derived from the inspections of the raw data and addendum, are documented and have been reported to the study director. A status report is submitted to management monthly.

The raw data, and the original addendum to the final report will be stored in the Archives at WIL Research Laboratories, Inc., or another location specified by the Sponsor.

  
for: Deborah L. Little, B.S.  
Manager of Quality Assurance

5/28/98  
Date

# A 11

WTL-186004  
CMA BFRIP

## REFERENCES

1. Thompson, S.W. (1966) Tissue processing and embedding. In: Selected Histochemical and Histopathological Methods. Charles C. Thomas, Springfield, IL, pp. 29-37.
2. American Registry of Pathology (1968) Manual of Histologic Staining Methods of the Armed Forces Institute of Pathology, 3rd Ed., (Luna, L.G., ed.) McGraw-Hill Book Co., New York, NY, pp. 38-39.

WTL-186604  
CMA BFRIP

A 28-Day Repeated Dose Oral  
Toxicity Study of HBCD in Rats

**INDEX OF TABLES**

|   | <u>Page</u> |
|---|-------------|
| 1. Histomorphological Diagnosis - Summary Incidence<br>(Week 4 Primary Necropsy)        | 10          |
| 2. Histomorphological Diagnosis - Summary Incidence<br>(Week 6 Recovery Necropsy)       | 12          |
| 3. Individual Gross and Microscopic Description of Organs<br>(Week 4 Primary Necropsy)  | 14          |
| 4. Individual Gross and Microscopic Description of Organs<br>(Week 6 Recovery Necropsy) | 84          |

**INDEX OF APPENDICES**

|                           |     |
|---------------------------|-----|
| A. Protocol Amendment III | 128 |
|---------------------------|-----|

**A 13**

**WIL-186004  
CMA BFRIP**

**A 28-Day Repeated Dose Oral  
Toxicity Study of HBCD in Rats**

**Tables 1-4**

TABLE 1 (WEEK 4 PRIMARY NECROPSY)  
 A 28-DAY REPEATED DOSE ORAL TOXICITY STUDY OF HBCD IN RATS  
 HISTOMORPHOLOGICAL DIAGNOSIS -- SUMMARY INCIDENCE

PROJECT NO.: WIL-36004  
 SPONSOR: CMA BFRIP

----- MALL -----

|   | GROUP: |    |    |    |
|---|--------|----|----|----|
|   | 1      | 2  | 3  | 4  |
| NUMBER OF ANIMALS IN DOSE GROUP           | 12     | 6  | 6  | 12 |
| NUMBER OF ANIMALS EXAMINED                | 6      | 6  | 6  | 6  |
| THYROID GLANDS                            |        |    |    |    |
| TOTAL NUMBER EXAMINED                     | 6      | 6  | 6  | 6  |
| EXAMINED, UNREMARKABLE                    | 0      | 0  | 0  | 0  |
| YES, ULTIMOBRANCHIAL                      | 1      | 0  | 0  | 2  |
| PRESENT                                   | 1      | NA | NA | 2  |
| INFLAMMATION, ACUTE                       | 0      | 2  | 0  | 0  |
| MINIMAL                                   | NA     | 2  | NA | NA |
| ATYPIC                                    | 0      | 1  | 0  | 0  |
| MINIMAL                                   | NA     | 1  | NA | NA |
| HYPERPLASIA, FOLLICULAR CELL              | 6      | 6  | 6  | 6  |
| MINIMAL                                   | 6      | 3  | 4  | 5  |
| MILD                                      | NA     | 3  | 2  | NA |
| COLLOID LOSS                              | 5      | 4  | 6  | 6  |
| MINIMAL                                   | 5      | 3  | 5  | 5  |
| MILD                                      | NA     | 1  | 1  | 1  |
| AGGREGATION, CYTOPLASMIC, FOLLICULAR CELL | 6      | 6  | 6  | 5  |
| MINIMAL                                   | 6      | 6  | 6  | 5  |

1- 0 MG/KG/DAY 2- 125 MG/KG/DAY 3- 3.0 MG/KG/DAY 4- 1000 MG/KG/DAY  
 NA = NOT APPLICABLE