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FINAL REPORT (6 COPIES), 104-WEEK DIETARY CARCINOGENICITY STUDY WITH 1,2,4-TRICHLOROBENZENE IN RATS, WITH COVER LETTER DATED 6/15/94			
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1,2,4-TRICHLOROBENZENE			

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CHEMICAL MANUFACTURERS ASSOCIATION

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June 15, 1994

VIA MESSENGER

ATTN: TSCA Section 4
Mike Gerel
TSCA Public Information Office
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Room N.E. Mall G102
401 M Street, SW
Washington, D.C. 20460

REC'D
JUNE 27, 1994
TSCA PICIC

RE: Chlorinated Benzenes Final Test Rule: Oncogenicity Testing of 1,2,4-Trichlorobenzene (40 CFR 799.1053); Final Report

Dear Sir/Madam:

The Chemical Manufacturers Association submits six copies of the final report entitled:

"104-Week Dietary Carcinogenicity Study with 1,2,4-Trichlorobenzene in Rats."

The study report is submitted on behalf of the test sponsor, Standard Chlorine Chemical Company, Inc.

Any questions regarding this submission should be directed to the Chlorobenzenes Panel Manager, Dr. Carol R. Stack, at (202) 887-1196.

Sincerely,

Langley A. Spurlock, Ph.D., CAE
Vice President, CHEMSTAR

Enclosures (6)

cc: Michael Stahl, Director, Office of Compliance Monitoring
Roger Nelson, OPPT/CCD/CTIB
Chlorobenzenes Panel, 1,2,4-TCB Task Group

2501 M Street, NW, Washington, DC 20037 Telephone 202-887-1100 Fax 202-887-1237

Responsible Care® A Public Commitment

HAZLETON
WASHINGTON

Sponsor:

Standard Chlorine of Delaware, Inc.
Governor Lee Road
Delaware City, Delaware 19706

FINAL REPORT

Study Title:

104-Week Dietary Carcinogenicity Study with 1,2,4-Trichlorobenzene in Rats

Author:

Michael R. Moore, Ph.D., D.A.B.T.

Study Completion Date:

June 10, 1994

Performing Laboratory:

Hazleton Washington, Inc. (HWA)
1330-B Piccard Drive
Rockville, Maryland 20850

Laboratory Project Identification:

HWA 2603-103

Volume 1 of 4

HAZLETON WASHINGTON

HWA 2603-103

COMPLIANCE STATEMENT
104-Week Dietary Carcinogenicity Study
with 1,2,4-Trichlorobenzene in Rats

This study was conducted in compliance with the Good Laboratory Practice Regulations as set forth in Title 40 of the U.S. Code of Federal Regulations Part 792, issued November 29, 1983 (effective December 29, 1983), and with any applicable amendments. All deviations from the protocol and/or GLPs are listed in Appendix II. There were no deviations from the aforementioned regulations which affected the quality or integrity of the study or the interpretation of the results in the report.

Study Director:

Michael R. Moore 6/10/94

Michael R. Moore, Ph.D., D.A.B.T. Date
Department of Toxicology

HAZLETON
WASHINGTON

QUALITY ASSURANCE STATEMENT

Study Title: 104-Week Dietary Carcinogenicity Study with 1,2,4-Trichlorobenzene in Rats

Project No.: 2603-103

Quality Assurance inspections and reviews of this study were conducted according to the standard operating procedures of the Quality Assurance Unit and according to the Good Laboratory Practice regulations of the Environmental Protection Agency (EPA - TSCA), Title 40 of the U.S. Code of Federal Regulations Part 792, issued November 29, 1983 (effective December 29, 1983) and with any applicable amendments. These inspections and reviews were performed and findings were reported to the Study Director and management as follows:

Dates of Inspection/Review	Dates Findings Reported to Management/ Study Director	Inspector/Reviewer
Protocol Review:		
3/13/91	3/15/91	M. Aderiye
Inspection and/or Data Review:		
4/12,26,30;5/1,4,13,14/91	5/22/91	B. Munch
7/11,23,29-31;8/2,5/91	8/22/91	B. Munch
10/7,8,9,11,14,15,24/91	10/31/91	B. Munch
1/10,16,17,20,21;2/3,4/92	2/21/92	B. Munch
4/23,24,27-29/92	5/11/92	B. Munch
7/15-17,23/92	7/23/92	S. Ballenger
10/1,15,16,19,20;11/2,3/92	11/9/92	P. Tillotson
1/8,11,12/93	2/8/93	D. Mullett
4/5,12-14/93	5/17/93	M.J. Robertson
Report and Data Review:		
10/27-29;11/1-3,8,9,11,12, 15,16/93	11/16/93	K. Butler
6/10/94	6/10/94	L. Cassell

Lois Cassell 6/10/94
Lois Cassell — Date Released
Quality Assurance Unit

HAZLETON
WASHINGTON

STUDY IDENTIFICATION
104-Week Dietary Carcinogenicity Study
with 1,2,4-Trichlorobenzene in Rats

HWA Study Number:	2603-103
Test Material:	1,2,4-Trichlorobenzene
Sponsor's Representative:	Carol R. Stack, Ph.D. Chemical Manufacturers Association 2501 M Street N.W. Washington, D.C. 20037
Sponsor:	Standard Chlorine of Delaware, Inc. Governor Lee Road Delaware City, Delaware 19706
Study Director:	Michael R. Moore, Ph.D., D.A.B.T. Hazleton Washington, Inc. (HWA) 9200 Leesburg Pike Vienna, Virginia 22182-1699 (703) 893-5400
Study Timetable	
Study Initiation:	December 14, 1990
Initiation of Dosing:	April 5, 1991
Completion of Terminal Necropsy:	April 9, 1993

HAZLETON WASHINGTON

STUDY PERSONNEL
10 ek Dietary Carcinogenicity Study
w i n 1,2,4-Trichlorobenzene in Rats

Study Director:	Michael R. Moore, Ph.D., D.A.B.T.
Study Coordinator:	Julie Bowman, M.S.
Pathologist:	Ricardo V. Quander, D.V.M., Diplomate, American College of Veterinary Pathologists
Clinical Pathologist:	Renée C. Pearson, M.S., D.V.M., Diplomate, American College of Veterinary Pathologists
Biostatistician:	Ajit K. Thakur, Ph.D.
Veterinarian:	Mark D. Walker, D.V.M.
Analytical Chemistry Supervisor:	Janice G. Dorschner, B.S.
Formulations Supervisor:	Danny L. Thomas, B.S., LAT
Laboratory Supervisor:	Preston L. Burlew, B.A., LATq
Laboratory Group Leader:	M. Douglas Jones, A.A., LAT
Laboratory Head Technician:	Charlotte A Ringley, LAT

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SUMMARY

1,2,4-Trichlorobenzene was administered daily in the diet to F-344 rats for at least 104 consecutive weeks to evaluate the oncogenic potential of the test material. There were 50 rats per sex in each study group. For Groups 2, 3, and 4, target dietary concentrations of 1,2,4-Trichlorobenzene were 100, 350, and 1200 ppm. Rats in Group 1 were administered the basal diet alone and served as the concurrent control group. Parameters evaluated were mortality; clinical observations; body weight, food consumption, and compound consumption data; hematology parameters; organ weight data; and necropsy and histopathology findings.

For Groups 2, 3, and 4, during Weeks 1 through 104, the mean daily consumed dose (based on target dietary concentrations) of 1,2,4-Trichlorobenzene was 5.5, 18.9, and 66.7 mg/kg/day, respectively, in the males; and 6.7, 22.9, and 79.3 mg/kg/day, respectively, in the females. The mean daily consumed dose (based on assayed dietary concentrations) was 5.6, 19.4, and 66.5 mg/kg/day, respectively, in the males; and 6.9, 23.5, and 81.4, respectively, in the females of Groups 2, 3, and 4. Therefore, throughout the study, the mean daily dose consumed by females in Groups 2, 3, and 4, was 21.8, 21.2, and 18.9% greater, respectively, than the mean daily dose consumed by males in the same dose groups.

For the administration of 1,2,4-Trichlorobenzene to F-344 rats at dietary concentrations of 100, 350, and 1200 ppm, the high-dose (1200 ppm) proved to be the no-observed-effect-level (NOEL) for carcinogenicity, as well as the Maximum Tolerated Dose (MTD) in males and females. The mid-dose (350 ppm) was the no-observed-effect-level (NOEL) for systemic toxicity in males and females.

The 1200 ppm dietary concentration produced the following treatment-related effects that were indicative of a Maximum Tolerated Dose (MTD): a significant decrease in survival of the males at Week 104; a significant depression of mean body weight gain for Weeks 1 through 24 in

males and females; hepatocellular hypertrophy (generally graded slight to moderate in severity) in 30/49 males and 37/50 females; diffuse fatty change in the liver in 14/49 males and 30/50 females; hepatic focal cystic degeneration in 19/49 males; significantly increased mean absolute liver weight and mean liver-to-terminal-body-weight ratio in males and females; significantly increased mean liver-to-brain-weight ratio in males, with an increased mean value (not significant) in females; enlarged livers noted in 7/50 males at necropsy; renal pelvis mineralization in 49/50 males and 48/50 females, for which the mean severity score was 3.0 (moderate) in males, and 1.3 (minimal to slight) in females; transitional cell hyperplasia of the renal pelvic urothelium, observed only in males, with an incidence of 34/50 and mean severity score of 1.0; chronic progressive nephropathy, for which the severity (mean score of 3.6) was increased only in males; granular/pitted/rough appearance of the kidneys at necropsy in 34/50 males but only 2/50 females; and mean absolute and relative kidney weights that were increased (not statistically significant) in males and females.

The 350 ppm dietary concentration produced no treatment-related effects. In contrast to the 1200 ppm group, the incidence and/or severity of histomorphologic findings in the liver and kidneys of the 350 ppm animals were comparable to control values. For hepatocellular hypertrophy, the incidence was 5/50 and 5/50 in the 350 ppm males and females, respectively, compared to 2/50 and 6/50 in the control males and females, respectively. For diffuse fatty change in the liver, the incidence was 5/50 and 21/50 in the 350 ppm males and females, respectively, compared to 5/50 and 15/50 in the control males and females, respectively. For hepatic focal cystic degeneration (observed only in males), the incidence was 4/50 in the 350 ppm males compared to 9/50 in the control males. For renal pelvis mineralization, the incidence (and mean severity score) was 44/50 (1.0) and 47/50 (1.0) in the 350 ppm males and females, respectively, compared to 34/50 (0.7) and 39/48 (0.8) in the

control males and females, respectively. For transitional cell hyperplasia of the renal pelvic urothelium (observed only in males), the incidence (and mean severity score) was 2/50 (0.0) in the 350 ppm males compared to 2/50 (0.1) in the control males. For chronic progressive nephropathy, the mean severity score was 2.6 in the 350 ppm males compared to 2.7 in the control males.

The 100 ppm dietary concentration also produced no treatment-related effects.