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

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OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

November 30, 2000

SUBJECT: **1,3-Dichloropropene (1,3-D or Telone):** Review of a 90-Day, Subchronic Oral Toxicity Study in Rats (OPPTS Test Guideline 870.3100) Submitted by Dow AgroSciences for the 3-Chlorallyl Alcohol Metabolite of Telone.

FROM: Michelle M. Centra, Pharmacologist
Reregistration Branch III
Health Effects Division (7509C)

THRU: Steve Knizner, Branch Senior Scientist
Reregistration Branch III
Health Effects Division (7509C)

TO: Phil Budig, Chemical Review Manager
Robert McNally, Branch Chief
Reregistration Branch II
Special Review and Reregistration Division (7508C)

DP Barcode: D265844
Case: 818694
Submission No.: S579498
Chemical: 029001
Caswell No.: None

Purpose of Memorandum: The purpose of this memorandum is transmittal of a Data Evaluation Record (DER) of a 90-day, subchronic oral toxicity study in rats (MRID 45027901) using the 3-chloroallyl alcohol metabolite of Telone.

This study has been reviewed and found to be **Acceptable-guideline**.

The executive summary follows and the DER is attached.

EXECUTIVE SUMMARY: In this subchronic oral toxicity study (MRID 45027901), 3-chloroallyl alcohol (98.6 % a.i.) was administered to 10 Fischer 344 rats/sex/dose in the drinking water at nominal dose levels of 0, 3, 10, or 30 mg/kg/day for 3 months.

No treatment-related findings were observed in the 3 mg/kg group. No mortalities occurred during the study. Clinical signs, functional tests (sensory evaluation, rectal temperature, grip strength, and motor activity), ophthalmoscopic observations, hematology and urinalysis parameters, and gross pathological changes were unaffected by the test substance.

Water consumption was dose-dependently decreased in all treated animals (↓9-58%, $p \leq 0.05$). It is likely that the decreased water consumption was due to unpalatability of the test substance, and was not a toxicological effect. In the kidney, very slight degeneration (with regeneration) of the cortex tubules was noted at 30 mg/kg (males-10/10, females 9/10 vs. 7/20 controls) and 10 mg/kg (males-10/10, females 4/10 vs. 7/20 controls). In addition, increased relative kidney weights were observed at these doses (↑7%-15%, $p \leq 0.05$). It is not possible to determine if the kidney effects are due to decreased water consumption with the additional stress of potentially increased compound concentration or a direct toxicological effect by the test compound.
At 30 mg/kg, body weights decreased progressively throughout the study in the males (↓1-13%). Overall (days 1-92) body weight gains were also decreased in these animals (↓23%). In the females, body weights were only slightly decreased (↓3-8%) and body weight gains were decreased by 15% compared to controls. It was stated that the inverse of body weights was statistically significant for both sexes combined ($p \leq 0.05$). Furthermore, decreased food consumption was noted in the males from day 15 through the end of the study (↓10-18%, $p \leq 0.05$). Alanine aminotransferase (↑240%, raw data), alkaline phosphatase (↑46%, raw data), and aspartate aminotransferase (↑156%, raw data) were found to be increased in the females. It was stated that the inverse of alanine aminotransferase, the square root of alkaline phosphatase, and the log of aspartate aminotransferase were statistically significant ($p \leq 0.05$). In addition, cholesterol was increased ($p \leq 0.05$) in both sexes (↑23-29%, raw data). Relative liver weights were increased in both sexes (↑10%) and corresponded to histopathological changes ($p \leq 0.05$; statistical analyses performed on combined data only). The following histopathological changes were observed in the liver (none of the changes were observed in any control animal): (i) very slight periportal hepatocyte hypertrophy (3/10 males); (ii) slight periportal hepatocyte hypertrophy (males-7/10, females-10/10); (iii) slight chronic periportal inflammation (males-10/10, females 8/10); and (iv) slight multifocal hepatocyte necrosis (1/10 males). In addition, very slight to slight multifocal hepatocyte (individual cells) necrosis was observed (males-8/10, females 10/10 vs. 2/20 controls). In the female hearts, very slight valvular endocardiosis was observed (2/10 treated vs. 0/10 controls).
The only effect noted at 10 mg/kg included very slight periportal hepatocyte hypertrophy (2/10 treated vs. 0/10 controls) in the females.
The LOAEL for this study is 30 mg/kg/day based on changes in body weights, body weight gains, food consumption, clinical chemistry parameters, organ weights, and histopathology of the liver.
The NOAEL for this study is 10 mg/kg/day.

The submitted study is classified as **Acceptable/guideline (§82-1a)** and satisfies the requirements for a subchronic oral toxicity study in rats.

Cc (with attachments): Michelle Centra (RRB III), Steve Knizner (RRB III), Phil Budig (SRRD, RRB II), Robert McNally (SRRD, RRB II).

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DATA EVALUATION RECORD

3-CHLOROALLYL ALCOHOL (TELONE METABOLITE)

Study Type: §82-1(a), 90 Day Oral Toxicity (Drinking Water) Study in Rats

Work Assignment No. 2-01-68A (MRID 45027901)

Prepared for
Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Prepared by
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Date: 6/30/00

Quality Assurance
Steve Brecher, Ph.D.

Signature: Steven Brecher
Date: 6/30/00

Disclaimer

This Data Evaluation Record may have been altered by the Health Effects Division subsequent to signing by Dynamac Corporation personnel.

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3-CHLOROALLYL ALCOHOL (TELONE METABOLITE) **Subchronic Oral Toxicity (§82-1[a])**

EPA Reviewer: Roger Hawks
Reregistration Branch 3/HED (7509C)

Roger Hawks 8/14/00

Work Assignment Manager: Sanjivani Diwan
Reregistration Branch 4/HED (7509C)

Sanjivani Diwan 8/

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DATA EVALUATION RECORD

STUDY TYPE: Subchronic Oral Toxicity [drinking water] - rats
OPPTS Number: 870.3100 OPP Guideline Number: §82-1a

DP BARCODE: D263373, D265844 SUBMISSION CODE: S575429, S579498
P.C. CODE: 029001 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): 3-chloroallyl alcohol (98.6 % a.i.)

SYNONYMS: 3-chloro-2-propen-1-ol; 3-chloroprop-2-en-1-ol; 3-chloroprop-2-en-1-ol isomer mix; telone alcohol; telone alcohol metabolite; telone alcohol degradate

CITATION: Crissman, J.W., Dryzga, M.D., Cieszlak, F.S. (1999) 3-Chloroallyl alcohol: 13-Week Drinking Water Toxicity Study in Fischer 344 Rats. Toxicology & Environmental Research and Consulting, Dow Chemical Company, Midland, MI. Laboratory Project Study ID 991029R, November 10, 1999 (Revised December 9, 1999). MRID 45027901 (MRID of Revision: 45105101). Unpublished.

SPONSOR: Dow AgroSciences (DAS) LLC, 9330 Zionsville Rd., Indianapolis, IN

EXECUTIVE SUMMARY: In this subchronic oral toxicity study (MRID 45027901), 3-chloroallyl alcohol (98.6 % a.i.) was administered to 10 Fischer 344 rats/sex/dose in the drinking water at nominal dose levels of 0, 3, 10, or 30 mg/kg/day for 3 months.

No treatment-related findings were observed in the 3 mg/kg group. No mortalities occurred during the study. Clinical signs, functional tests (sensory evaluation, rectal temperature, grip strength, and motor activity), ophthalmoscopic observations, hematology and urinalysis parameters, and gross pathological changes were unaffected by the test substance.

Water consumption was dose-dependently decreased in all treated animals (↓9-58%, $p \leq 0.05$). It is likely that the decreased water consumption was due to unpalatability of the test substance, and was not a toxicological effect. In the kidney, very slight degeneration (with regeneration) of the cortex tubules was noted at 30 mg/kg (males-10/10, females 9/10 vs. 7/20 controls) and 10 mg/kg (males-10/10, females 4/10 vs. 7/20 controls). In addition, increased relative kidney weights were observed at these doses (↑7%-15%, $p \leq 0.05$). It is not possible to determine if the

kidney effects are due to decreased water consumption with the additional stress of potentially increased compound concentration or a direct toxicological effect by the test compound. At 30 mg/kg, body weights decreased progressively throughout the study in the males (↓1-13%). Overall (days 1-92) body weight gains were also decreased in these animals (↓23%). In the females, body weights were only slightly decreased (↓3-8%) and body weight gains were decreased by 15% compared to controls. It was stated that the inverse of body weights was statistically significant for both sexes combined ($p \leq 0.05$). Furthermore, decreased food consumption was noted in the males from day 15 through the end of the study (↓10-18%, $p \leq 0.05$). Alanine aminotransferase (↑240%, raw data), alkaline phosphatase (↑46%, raw data), and aspartate aminotransferase (↑156%, raw data) were found to be increased in the females. It was stated that the inverse of alanine aminotransferase, the square root of alkaline phosphatase, and the log of aspartate aminotransferase were statistically significant ($p \leq 0.05$). In addition, cholesterol was increased ($p \leq 0.05$) in both sexes (↑23-29%, raw data). Relative liver weights were increased in both sexes (↑10%) and corresponded to histopathological changes ($p \leq 0.05$; statistical analyses performed on combined data only). The following histopathological changes were observed in the liver (none of the changes were observed in any control animal): (i) very slight periportal hepatocyte hypertrophy (3/10 males); (ii) slight periportal hepatocyte hypertrophy (males-7/10, females-10/10); (iii) slight chronic periportal inflammation (males-10/10, females 8/10); and (iv) slight multifocal hepatocyte necrosis (1/10 males). In addition, very slight to slight multifocal hepatocyte (individual cells) necrosis was observed (males-8/10, females 10/10 vs. 2/20 controls). In the female hearts, very slight valvular endocardiosis was observed (2/10 treated vs. 0/10 controls).

The only effect noted at 10 mg/kg included very slight periportal hepatocyte hypertrophy (2/10 treated vs. 0/10 controls) in the females.

The LOAEL for this study is 30 mg/kg/day based on changes in body weights, body weight gains, food consumption, clinical chemistry parameters, organ weights, and histopathology of the liver.

The NOAEL for this study is 10 mg/kg/day.

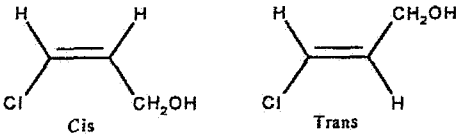
The submitted study is classified as **Acceptable/guideline (§82-1a)** and satisfies the requirements for a subchronic oral toxicity study in rats.

COMPLIANCE: Signed and dated GLP, Quality Assurance, Data Confidentiality, and Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: 3-chloroallyl alcohol
   Description: Amber liquid
   Lot/Batch #: 199801576-46, TSN101692
   Purity (w/w): 98.6 % a.i.
   Stability of compound: The test substance was stable in the drinking water for at least 9 days under experimental conditions.
   CAS #: 542-75-6
   Structure:



2. Vehicle: Tap water

3. Test animals: Species: Rat
   Strain: Fischer 344
   Age and mean weight at the start of dosing: Approximately 7 weeks old; 154.9-157.3 g (males), 108.0-111.7 g (females)
   Source: Charles River Laboratories, Raleigh, NC
   Housing: Individually, in stainless steel cages with wire mesh floors
   Diet: Certified Rodent Lab Diet #5002 (Purina Mills, Inc. St. Louis, MO), ad libitum
   Water: Tap water, ad libitum
   Environmental conditions:
   Temperature: 19-25° C
   Humidity: 40-70%
   Air changes: 12-15/hour
   Photoperiod: 12 hours light/12 hours dark
   Acclimation period: At least one week

B. STUDY DESIGN:

1. In life dates: Start: 3/31/99 End: 7/1/99

2. Animal assignment: The rats were randomly assigned (stratified by body weight) to the test groups shown in Table 1.

Table 1. Study design

Test Group	Dose Levels (mg/kg/day)	Intake [a] (mg/kg/day)		Number of Animals	
		Male	Female	Male	Female
Control	0	0	0	10	10
Low	3	3.1	3.1	10	10
Mid	10	10.2	9.9	10	10
High	30	29.0	27.5	10	10

a Intake values were obtained from the study report Tables 36 and 37, pages 196-197.

3. Dose selection rationale - The dose levels selected for this study were based on the results of a previous 4-week drinking water study in which 5 rats/sex/group received doses of 0, 10, 30, or 100 mg/kg/day. High-dose animals displayed decreased food consumption, water consumption, body weights, and body weight gains, clinical chemistry changes, and minor histopathological effects in the liver and kidneys. Decreased food and water consumption and an adaptive increase in urine specific gravity were observed in the mid-dose animals. The NOAEL was 10 mg/kg/day. Based on the results of this 4-week study, the doses presented in Table 1 were selected.

4. Dose preparation and analysis - Drinking water solutions containing the test substance were prepared weekly by serial dilution of the high dose with tap water. Drinking water concentrations of the test material were calculated from the most recent body weight and water consumption data. Homogeneity (top, middle, bottom) was determined for the 3 mg/k/day female and the 30 mg/kg/day male drinking water solutions. Stability of the test substance in drinking water was determined in a previous study and was found to be stable for up to 12 days at dose levels of 15, 35, 75, and 125 mg/kg/day. Stability of the test substance in the 3 and 10 mg/kg drinking water samples was determined at the beginning of the current study and approximately 24 days later (stored at room temperature, assumed by reviewers). In addition, a 9-day stability analysis was conducted on the 3 mg/kg drinking water. Concentration analyses were performed on all dose preparations at the beginning of the study and twice during the treatment period.

Results -
Homogeneity analysis (range as % relative standard deviation): 0.90-1.73%

Stability analysis (% of day 0): 89-97%

Concentration analysis (range as % of nominal): 94-107%

The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

5. Statistics - All parameters were subjected to Bartlett's test for homogeneity of variances; data were subsequently transformed as necessary. Body weights were evaluated using a repeated measures analysis of variance (ANOVA) with Bonferroni adjustment. Terminal body weight, organ weight, (excluding ovaries, uterus, epididymides, and testes), hematological (excluding RBC indices and differential WBC), clinical chemistry, and urine specific gravity data were evaluated with a two-way ANOVA, followed by Dunnett's test. Data for water and food consumption, and ovary, uterus, epididymides, and testes weights were analyzed by one-way ANOVA followed by Dunnett's test. Rectal temperature and grip performance were analyzed by factorial analysis of covariance (ANCOVA). Motor activity data were transformed by taking their square roots and then analyzed by a factorial repeated-measures design with Bonferroni adjustment. Outliers were identified by the Grubbs test, but were routinely excluded from food consumption only.

C. METHODS:

1. Observations - All animals were observed twice daily within their cage for mortality, moribundity, clinical signs of toxicity, behavior, and nervous system function. Detailed clinical examinations (cage-side, hand-held, and open field) were performed weekly, and observations were recorded either categorically or scored (scoring explanation is presented in Appendix A). Functional tests, including sensory evaluation, rectal temperature, grip performance, and motor activity were conducted prior to the study and during the last week of treatment. Motor activity measurements were conducted in a clear plastic circular alley located in a quiet, light-attenuated room. An infrared photobeam crossed the alley in two locations, and activity was monitored by a computerized data collection system. Each 48-minute test session was comprised of six 8-minute intervals. An activity count was defined as a beam break that lasted more than 100 msec, following at least 100 msec since the previous beam break.

2. Body weight and body weight gains - Each animal was weighed once during the pretest interval, twice during the first week of treatment, and weekly for the remainder of the study. In addition, body weight gains were calculated.

3. Food consumption - Food consumption was measured for all animals once during the pretest interval, twice during the first week of treatment, and at least weekly for the remainder of the study. Food consumption was calculated as (g/day).

4. Water consumption - Water consumption was measured for all animals once during the pretest interval, twice during the first week of treatment, and at least weekly for the remainder of the study. Water consumption was calculated as (g/day).

5. Ophthalmoscopic examination - Ophthalmoscopic examinations were performed using indirect ophthalmoscopy on all test animals prior to the start of treatment and prior to study termination.

6. Blood - Upon study termination, all animals were fasted and anaesthetized, and blood was collected from the orbital sinus. The checked (X) hematology and clinical blood chemistry parameters were examined.

a. Hematology

X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)	X	Mean corpusc. volume (MCV)
X	Platelet count		Reticulocyte count
X	Blood clotting measurements		Erythrocyte distribution width
	(Thromboplastin time)		
	(Activated partial thromboplastin time)		
	(Clotting time)		
X	(Prothrombin time)		

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Phosphorus	X	Total Cholesterol
X	Potassium		Globulin
X	Sodium	X	Glucose
			Direct bilirubin
	ENZYMES	X	Total bilirubin
X	Alkaline phosphatase (ALK)	X	Total serum protein (TP)
	Cholinesterase (ChE)	X	Triglycerides
	Creatine phosphokinase		
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase (ALT)		
X	Serum aspartate aminotransferase (AST)		
	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

7. Urinalysis - During the last week of the study, urine was collected from all animals using timed urine volume collection and manual bladder compression. The checked (X) parameters were examined on all urine collected by the compression method. Analyses of the timed urine volume collection samples were for validation purposes only (data not provided).

X	Appearance	X	Glucose
X	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

8. Sacrifice and Pathology - At study termination, all animals were fasted, anaesthetized, euthanized by decapitation, and subjected to a gross pathological examination. The following CHECKED (X) tissues were collected from all animals and preserved in neutral, phosphate-buffered 10% formalin. The tissues from the control and high-dose animals and any animals that died or were sacrificed prematurely were embedded in paraffin, stained with hematoxylin and eosin, and examined histologically. Furthermore, the lungs, liver, kidneys, and relevant gross lesions from the low- and mid-dose groups were examined microscopically. Additionally, the (XX) organs were weighed.

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	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
X	Tongue	X	Aorta	XX	Brain
X	Salivary glands	XX	Heart	X	Periph. nerve
X	Esophagus	X	Bone marrow	X	Spinal cord (3 levels)
X	Stomach	X	Lymph nodes	X	Pituitary
X	Duodenum	XX	Spleen	X	Eyes
X	Jejunum	XX	Thymus		
X	Ileum				GLANDULAR
X	Cecum		UROGENITAL	XX	Adrenal gland
X	Colon	XX	Kidneys	X	Lacrimal gland
X	Rectum	X	Urinary bladder	X	Mammary gland
XX	Liver	XX	Testes	X	Thyroids w/ parathyroids
X	Pancreas	XX	Epididymides		
		X	Prostate		OTHER
	RESPIRATORY	X	Seminal vesicle	X	Bone (including joint)
X	Trachea	XX	Ovaries	X	Skeletal muscle
X	Lung	XX	Uterus	X	Skin
X	Pharynx	X	Vagina	X	All gross lesions and masses
X	Larynx	X	Cervix	X	Harderian gland
				X	Nasal tissues
				X	Auditory sebaceous glands[1]
				X	Coagulating glands
				X	Mediastinal tissues
				X	Mesenteric tissues
				X	Oviducts

1 Collected, but not examined histologically

II. RESULTS

A. Observations

1. Mortality - No mortalities occurred during the study.

2. Clinical signs - No treatment-related clinical signs were noted. Red periocular staining and lacrimation were observed occasionally during the treatment period in the high-dose animals; however, these clinical signs were transient in nature and were considered not to be of toxicological concern.

3. Functional tests - No treatment-related differences from concurrent controls were observed in the sensory evaluation, rectal temperature, grip performance or motor activity measurements. Motor activity data are presented in Table 2.

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Table 2. Mean motor activity (square root of total counts) in rats treated with 3-chloroallyl alcohol for 3 months (mean ± standard deviation).[a]

Treatment interval (weeks)	Dose (mg/kg)			
	0	3	10	30
Males				
Pretest	10.05±1.60	9.15±0.75	10.30±1.36	8.97±1.45
13	11.12±1.86	10.59±1.18	11.28±1.31	10.31±2.10
Females				
Pretest	9.25±2.10	10.04±1.13	9.80±1.45	10.12±1.58
13	13.32±1.89	12.36±1.87	11.83±2.42	12.49±1.18

a Data obtained from the study report Table 22, page 171; n=10.

B. Body weight and body weight gain - Body weights decreased progressively throughout the study in the high-dose males (↓1-13%; Table 3a). Overall (days 1-92) body weight gains were also decreased in these animals (↓23%; Table 3c). In the high-dose females, body weights were only slightly decreased (↓3-8%, Table 3b); however, body weight gains were decreased by a greater magnitude (↓15%) in these animals. It was stated that the inverse of body weights was statistically significant for both sexes combined ($p \leq 0.05$).

Table 3a. Selected body weights (g) in male rats treated with 3-chloroallyl alcohol for 3 months (mean ± standard deviation).[a]

Days	Dose (mg/kg)			
	0	3	10	30
1	157.3±11.5	156.4±9.1	154.9±7.9	156.0±12.8 (↓1)
33	261.2±13.9	259.2±15.1	253.8±17.9	241.6±23.5 (↓8)
61	299.1±15.7	297.3±16.6	292.1±20.8	269.7±24.7 (↓10)
82	322.7±20.3	320.4±16.3	310.2±21.9	281.1±24.1 (↓13)
92	322.3±19.0	320.5±14.2	311.1±21.9	282.5±22.1 (↓12)

a Data obtained from the study report, Table 27, pages 176-177; n=10. Percent difference from controls is listed parenthetically.

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Table 3b. Selected body weights (g) in female rats treated with 3-chloroallyl alcohol for 3 months (mean ± standard deviation).[a]

Days	Dose (mg/kg)			
	0	3	10	30
1	111.7±2.9	108.0±3.8	110.2±4.9	108.7±3.7(-3)
33	155.9±8.0	151.8±8.2	154.5±5.8	147.1±5.2 (-6)
61	169.5±8.9	166.4±8.9	169.1±9.2	159.6±5.6 (-6)
82	180.5±10.9	177.0±10.1	177.9±9.3	166.6±5.2 (-8)
92	179.4±9.9	176.4±8.9	177.2±9.6	166.1±4.5 (-7)

a Data obtained from the study report, Table 29, pages 181-182; n=10. Percent difference from controls is listed parenthetically.

Table 3c. Overall (days 1-92) body weight gains (g) in rats treated with 3-chloroallyl alcohol for 3 months (mean ± standard deviation).[a]

Dose (mg/kg)			
0	3	10	30
Males			
165.0±14.5	164.1±10.0	156.2±18.1	126.5±13.3 (↓23)
Females			
67.7±8.8	68.3±6.6	67.1±6.7	57.3±4.3 (↓15)

a Data obtained from the study report Tables 28 and 30, pages 180 and 185; n=10.

C. Food and water consumption and compound intake

1. Food consumption - Treatment-related decreased food consumption (Table 4) was noted in the high-dose males from day 15 through the end of the study (↓10-18%, $p \leq 0.05$). In the mid-dose males, food consumption was decreased (↓7-8%, $p \leq 0.05$); however, these decreases were sporadic and minor and considered not to be treatment-related. Decreases ($p \leq 0.05$) in food consumption were also observed in the high- (↓8-12%) and low- (↓7-8%) dose females; however, the decreases were sporadic and generally not dose-dependent and, therefore, considered unrelated to treatment.

Table 4. Selected mean food consumption (g/day) in rats treated with 3-chloroallyl alcohol for 3 months.[a]

Interval (days)	Dose (mg/kg)			
	0	3	10	30
Males				
1-5	15.8	15.5	14.9	14.6
22-29	17.0	16.6	16.0	15.3* (↓10)
43-50	16.8	16.3	15.5* (↓8)	14.1* (↓16)
64-71	16.5	16.2	15.4	13.5* (↓18)
71-78	16.2	15.8	15.0* (↓7)	13.5* (↓17)
85-92	16.4	16.4	16.3	13.9* (↓15)
Females				
1-5	11.3	10.7	10.9	10.6
5-8	11.8	11.0* (↓7)	11.4	10.4* (↓12)
8-15	11.9	11.0* (↓8)	11.6	10.7* (↓10)
15-22	12.0	11.4	11.5	10.6* (↓12)
64-71	10.9	10.8	10.7	9.9* (↓9)
85-92	10.4	10.1	10.0	9.6* (↓8)

a Data obtained from the study report, Tables 32 and 33, pages 188-191; n=8-10. Percent difference from controls is listed parenthetically.

* Statistically significant at $p \leq 0.05$

2. Water consumption - Water consumption was decreased ($p \leq 0.05$) in the high-dose males (↓14-46%) and females (↓36-58%) throughout the study (Table 5). In addition, water consumption was decreased ($p \leq 0.05$) in the mid-dose males during 13/14 intervals (↓12-30%) and sporadically in the mid-dose females (↓24-36%) and low-dose males (↓9-14%). It is likely that the decreased water consumption was due to unpalatability of the test substance, and was not a toxicological effect.

Table 5. Selected mean water consumption (g/day) in rats treated with 3-chloroallyl alcohol for 3 months.[a]

Interval (days)	Dose (mg/kg)			
	0	3	10	30
Males				
1-5	26.9	27.6	23.6* (↓12)	23.2* (↓14)
22-29	24.6	23.3	19.4* (↓21)	14.5* (↓41)
50-57	23.5	20.9	17.7* (↓25)	12.8* (↓46)
71-78	23.2	21.1* (↓9)	18.0* (↓22)	13.8* (↓41)
78-85	24.8	21.3* (↓14)	17.3* (↓30)	13.7* (↓45)
85-92	21.8	21.9	18.6* (↓15)	13.5* (↓38)
Females				
1-5	23.6	20.3	19.7	15.0* (↓36)
22-29	22.2	20.8	16.9* (↓24)	11.7* (↓47)
50-57	21.3	19.1	13.7* (↓36)	9.7* (↓54)
71-78	22.1	20.9	18.0	9.3* (↓58)
78-85	18.2	17.8	13.6* (↓25)	9.5* (↓48)
85-92	17.7	17.9	15.6	9.7* (↓45)

a Data obtained from the study report, Tables 34 and 35, pages 192-195; n=7-10. Percent difference from controls is listed parenthetically.

* Statistically significant at $p \leq 0.05$

3. Compound intake - Actual intake values are shown in Table 1.

D. Ophthalmoscopic examination - No treatment-related ophthalmoscopic observations were noted.

E. Blood analyses

1. Hematology - No treatment-related differences in hematology parameters were observed. It was stated that minor, but statistically significant ($p \leq 0.05$), differences in red blood cell count (↓3-5%), hemoglobin (↓5-6%), and hematocrit (↓4-6%) were observed in the high-dose animals. The statistical analyses were performed on combined male and female data only.

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Table 6. Selected hematology parameters in rats treated with 3-chloroallyl alcohol for 3 months.

Parameter	Dose (mg/kg)			
	0	3	10	30
Males				
Hematocrit (PCNT)	45.2±1.1	45.0±1.8	44.6±1.1	43.2±1.0
Hemoglobin (G/DL)	15.2±0.5	15.0±0.6	14.9±0.4	14.4±0.4
RBC (10^6)	9.22±0.25	9.2±0.29	9.17±0.19	**8.9±0.27***
Females				
Hematocrit (PCNT)	42.7±1.1	42.1±1.4	41.6±1.2	40±1.3
Hemoglobin (G/DL)	14.6±0.4	14.4±0.6	14.2±0.3	13.7±0.4
RBC (10^6)	8.2±0.23	8.06±0.41	8.11±0.25	7.83±0.24

* $p \leq 0.05$

2. Clinical chemistry - Alanine aminotransferase (↑240%), alkaline phosphatase (↑46%), and aspartate aminotransferase (↑156%) were found to be increased in the high-dose females (Table 7). It was stated that the inverse of alanine aminotransferase, the square root of alkaline phosphatase, and the log of aspartate aminotransferase were statistically significant. In addition, cholesterol was increased ($p \leq 0.05$) in both sexes at the high-dose (↑23-29%). Blood urea nitrogen was increased in the high-dose males and females (↑5-20%); however, this difference was most likely a secondary effect of decreased water consumption on kidney performance and not related to the test substance. In addition, differences ($p \leq 0.05$) in sodium and chloride (↓1-2%) were observed in the high-dose animals; however, these differences were minor and considered not to be of toxicological concern.

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Table 7. Selected clinical chemistry parameters in rats treated with 3-chloroallyl alcohol for 3 months.[a]

Parameter	Dose (mg/kg)			
	0	3	10	30
Males				
Cholesterol (mg/dL)	56.9±9.8	61.6±8.3	63.9±7.4	69.8±7.4 (↑23)
Alanine aminotransferase (U/L)	73±18	75±17	72±16	84±30
Alkaline phosphatase (U/L)	102±10	103±4	99±10	102±4
Aspartate aminotransferase (U/L)	100±14	102±20	101±19	106±26
Females				
Cholesterol (mg/dL)	76.7±5.8	77.7±8.7	72.9±6.5	99.6±18.2 (↑29)
Alanine aminotransferase (U/L)	43±4	39±3	41±5	146±47 (↑240)
Alkaline phosphatase (U/L)	72±5	67±12	69±12	105±21 (↑46)
Aspartate aminotransferase (U/L)	93±7	92±14	89±11	238±70 (↑156)

a Data obtained from the study report, Table 44 and 46, pages 204 and 206; n=10. Percent difference from controls is listed parenthetically.

F. Urinalysis - No treatment-related differences from concurrent controls were observed in any urinalysis parameter. Log-transformed urine volume data were found to be significantly ($p \leq 0.05$) decreased in the high-dose males and females (↓57-68%, calculated from raw data). Specific gravity was slightly increased in the mid- and high-dose females (↑2-3%, $p \leq 0.05$). These changes in urine characteristics were due to decreased water consumption and therefore considered not to be treatment-related.

G. Sacrifice and Pathology:

1. Organ weight - Increased ($p \leq 0.05$) relative kidney weights were observed in the high-dose males (↑13%) and females (↑15%) and in the mid-dose males (↑7%, Table 8). Relative liver weights were increased in the high-dose animals (↑10%), and corresponded to histopathological changes ($p \leq 0.05$; statistical analyses performed on combined data only). Minor increases ($p \leq 0.05$) in relative epididymis (↑7%) and testes (↑13%) weights observed in the high-dose males were likely due to decreased terminal body weights (↓11%) and were considered unrelated to treatment due to a lack of corroborating histopathological evidence of toxicity. Absolute kidney weights in the high-dose females were slightly increased (↑8%); however, this difference was minor and considered not to be of toxicological concern. It was stated that the log of absolute kidney weight was

statistically significant ($p \leq 0.05$). It was also stated that statistically significant differences in heart (↑3-4%) and spleen weights (↑3-7) were observed in the high-dose animals; however, these differences were minor and statistical analyses were performed on combined male and female data only.

Table 8. Relative organ weights (organ wt./body wt. × 100) in rats treated with 3-chloroallyl alcohol for 3 months. [a]

Organ	Males				Females			
	Dose (mg/kg)				Dose (mg/kg)			
	0	3	10	30	0	3	10	30
Liver	2.700 ±0.189	2.732 ±0.115	2.865 ±0.249	2.996 (↑10) ±0.126	2.639 ±0.139	2.572 ±0.162	2.631 ±0.207	2.913 (↑10) ±0.190
Kidney	0.619 ±0.027	0.651 ±0.41	0.662 (↑7) ±0.028	0.702 (↑13) ±0.029	0.685 ±0.04	0.658 ±0.028	0.716 ±0.038	0.787 (↑15) ±0.051

a Data obtained from the study report Tables 54 and 55, pages 214-217; n=10. Percent difference from controls is listed parenthetically.

Table 9. Absolute organ weights (g) in rats treated with 3-chloroallyl alcohol for 3 months. [a]

Organ	Males				Females			
	Dose (mg/kg)				Dose (mg/kg)			
	0	3	10	30	0	3	10	30
Liver	8.285 ±0.932	8.318 ±0.565	8.518 ±0.961	8.195 (↓1) ±0.912	4.454 ±0.247	4.244 ±0.238	4.424 ±0.459	4.621 (↑4) ±0.366
Kidney	1.895 ±0.137	1.984 ±0.187	1.967 ±0.146	1.912 (↑1) ±0.132	1.155 ±0.047	1.086 ±0.05	1.203 ±0.092	1.247 (↑8) ±0.087

a Data obtained from the study report Tables 54 and 55, pages 214-217; n=10. Percent difference from controls is listed parenthetically.

2. Gross pathology - No treatment-related gross pathological observations were noted.

3. Microscopic pathology - Selected histopathological observations are presented in Table 10. Very slight valvular endocardiosis was observed in the high-dose females (2/10 treated vs. 0/10 controls). In the kidneys, very slight degeneration (with regeneration) of the cortex tubules was observed at the mid- (males-10/10, females 4/10) and high- (males-10/10, females 9/10) doses (vs. 7/20 controls). The following histopathological

changes were observed in the livers of the high-dose animals (none of the changes were observed in any control animal): (i) very slight periportal hepatocyte hypertrophy (3/10 males); (ii) slight periportal hepatocyte hypertrophy (males-7/10, females-10/10); (iii) slight chronic periportal inflammation (males-10/10, females 8/10); and (iv) slight multifocal hepatocyte necrosis (1/10 males). In addition, very slight to slight multifocal hepatocyte (individual cells) necrosis was observed in the livers of the high-dose animals (males-8/10, females 10/10 vs. 2/20 controls). In the mid-dose females, very slight periportal hepatocyte hypertrophy was observed (2/10 treated vs. 0/10 controls).

Table 10. Selected histopathological observations noted in rats treated with 3-chloroallyl alcohol for 3 months.[a]

Observation	Males				Females			
	Dose (mg/kg)				Dose (mg/kg)			
	0	3	10	30	0	3	10	30
Heart								
Endocardiosis; valvular (total)	0	0	0	0	0	0	0	2
very slight	0	0	0	0	0	0	0	2
Kidney								
Degeneration; with regeneration; tubule; cortex (total)	6	5	10	10	1	1	4	9
very slight	6	5	10	10	1	1	4	9
Liver								
Hypertrophy; hepatocyte; periportal (total)	0	0	0	10	0	0	2	10
very slight	0	0	0	3	0	0	2	0
slight	0	0	0	7	0	0	0	10
Inflammation; chronic; periportal (total)	0	0	0	10	0	0	0	8
slight	0	0	0	10	0	0	0	8
Necrosis; hepatocyte; multifocal (total)	0	0	0	1	0	0	0	0
slight	0	0	0	1	0	0	0	0
Necrosis; hepatocyte; individual cells; multifocal (total)	2	1	0	8	0	0	0	10
very slight	2	1	0	8	0	0	0	8
slight	0	0	0	0	0	0	0	2

a Data obtained from the study report Table 57, pages 225-232; n=10.

III. DISCUSSION

A. Investigator's conclusions - 3-chloroallyl alcohol was toxic at doses ≥ 10mg/kg. The liver was considered to be the target organ; histopathological changes, increased liver-related clinical chemistry parameters, and increased relative liver weights were observed. Other

treatment-related effects included decreased food consumption and body weight. Histological changes in the kidneys, increased kidney weight, decreased urine volume, and increased urine specific gravity were considered to be adaptive changes to decreased water consumption. The NOAEL for this study was 3 mg/kg.

B. Reviewer's discussion - In this subchronic oral toxicity study, 3-chloroallyl alcohol was administered to 10 Fischer 344 rats/sex/dose in the drinking water at dose levels of 0, 3, 10, or 30 mg/kg/day for 3 months. The analytical data indicated that the mixing procedure was adequate and that the variation between nominal and actual dosage to the study animals was acceptable.

No mortalities occurred during the study. Clinical signs, functional tests, ophthalmoscopic observations, hematology and urinalysis parameters, and gross pathological changes were unaffected by the test substance.

Body weights decreased progressively throughout the study in the high-dose males (↓1-13%). Overall (days 1-92) body weight gains were also decreased in these animals (↓23%). In the high-dose females, body weights were only slightly decreased (↓3-8%); however, body weight gains were decreased by a greater magnitude (↓15%) in these animals. It was stated that the inverse of body weights was statistically significant for both sexes combined ($p \leq 0.05$).

Decreased food consumption was noted in the high-dose males from day 15 through the end of the study (↓10-18%, $p \leq 0.05$). Water consumption was decreased ($p \leq 0.05$) in the high-dose males (↓14-46%) and females (↓36-58%) throughout the study. In addition, water consumption was decreased ($p \leq 0.05$) in the mid-dose males during 13/14 intervals (↓12-30%) and sporadically in the mid-dose females (↓24-36%) and low-dose males (↓9-14%). It is likely that the decreased water consumption was due to unpalatability of the test substance, and was not a toxicological effect.

Alanine aminotransferase (↑240%), alkaline phosphatase (↑46%), and aspartate aminotransferase (↑156%) were found to be increased in the high-dose females. It was stated that the inverse of alanine aminotransferase, the square root of alkaline phosphatase, and the log of aspartate aminotransferase were statistically significant ($p \leq 0.05$). In addition, cholesterol was increased ($p \leq 0.05$) in both sexes at the high-dose (↑23-29%, raw data).

Increased ($p \leq 0.05$) relative kidney weights were observed in the high-dose males (↑13%) and females (↑15%) and in the mid-dose males (↑7%). During the histopathological evaluation, very slight degeneration (with regeneration) of the kidney cortex tubules was observed at the mid- (males-10/10, females 4/10) and high- (males-10/10, females 9/10) doses (vs. 7/20 controls). Relative liver weights were increased in the high-dose animals (↑10%), and corresponded to histopathological changes ($p \leq 0.05$; statistical analyses performed on combined data only). The following histopathological changes were observed in the livers of

the high-dose animals (none of the changes were observed in any control animal): (i) very slight periportal hepatocyte hypertrophy (3/10 males); (ii) slight periportal hepatocyte hypertrophy (males-7/10, females-10/10); (iii) slight chronic periportal inflammation (males-10/10, females 8/10); and (iv) slight multifocal hepatocyte necrosis (1/10 males). In addition, very slight to slight multifocal hepatocyte (individual cells) necrosis was observed in the livers of the high-dose animals (males-8/10, females 10/10 vs. 2/20 controls). In the mid-dose females, very slight periportal hepatocyte hypertrophy was observed (2/10 treated vs. 0/10 controls). Very slight valvular endocardiosis was observed in the high-dose females (2/10 treated vs. 0/10 controls).

The LOAEL for this study is 30 mg/kg/day based on changes in body weights, body weight gains, food consumption, clinical chemistry parameters, organ weights, and histopathology of the liver.

The NOAEL for this study is 10 mg/kg/day.

The submitted study is classified as **Acceptable/guideline (§82-1a)** and satisfies the requirements for a subchronic oral toxicity study in rats.

C. Study deficiencies - The following deficiencies were noted, but do not change the conclusions of this review:

- Statistical analyses were performed on combined (by sex) data only.

APPENDIX A

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Pages ~~28~~ 24 through ~~32~~ 28 are not included.

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