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UNION CARBIDE CORPORATION 39 OLD RIDGEBURY ROAD, DANBURY, CT 06817-0001



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SP003 12/28/94



December 20, 1994

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Attn: 8(e) Coordinator

ORIGINAL

RE: Union Carbide Corporation's TSCA § 8(e) Submission of
December 21, 1993 Concerning Vinyl 2-Ethylhexanoate
(CASRN 94-04-2)

Dear Sir or Madam:

As a follow-up to the above-noted submission concerning vinyl 2-ethylhexanoate (CASRN 94-04-2), Union Carbide Corporation ("Union Carbide") herewith submits the following report.

"Vinyl 2-Ethylhexanoate: Fourteen-Day Peroral (Gavage) Range-Finding Study in B6CF₁ Mice", Bushy Run Research Center, BRRC Report 93U1319, September 26, 1994 (189 pgs.). [Note: Only the first 17 pages of this report is enclosed. The remainder is available on written request.]

In the attached report the term "Confidential" may appear. This precautionary statement was for internal use at the time of issuance of this report. Confidentiality is hereby waived for purposes of the needs of the Agency in assessing health and safety information. The Agency is advised, however, that the publication rights to the contained information are the property of Union Carbide.

Please contact the undersigned with questions, if any, at 203/794-5230.



89950000097

Very truly yours,

William C. Kuryla, Ph.D.
Associate Director
Product Safety

Attachment

Dom
2/07/95



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STUDY TITLE

Vinyl 2-Ethylhexanoate: Fourteen-Day Peroral (Gavage) Range-Finding Study in B6C3F₁ Mice

TEST SUBSTANCE

Vinyl 2-Ethylhexanoate

DATA REQUIREMENT

Not Applicable

AUTHORS

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STUDY COMPLETION DATE

September 26, 1994

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93U1319

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Vinyl 2-Ethylhexanoate: Fourteen-Day Peroral (Gavage) Range-Finding
Study in B6C3F₁ Mice

CONFIDENTIALITY STATEMENT

This report is Union Carbide Corporation and Shell Oil Company Business Confidential and is not to be released outside of either Corporation/Company without the written consent of the Sponsors.

Vinyl 2-Ethylhexanoate: Fourteen-Day Peroral (Gavage) Range-Finding
Study in B6C3F₁ Mice

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The portions of this study conducted by BRRC meet the requirements of the following Good Laboratory Practice Standards: Toxic Substances Control Act (TSCA), 40 CFR Part 792, and Organisation for Economic Co-operation and Development (OECD), C(81)30(Final).

Study Director:


Steven J. Hermansky, Pharm.D., Ph.D., DABT 9/26/94
Date

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Vinyl 2-Ethylhexanoate: Fourteen-Day Peroral (Gavage) Range-Finding Study in B6C3F₁ Mice

SUMMARY

B6C3F₁ Mice (6/sex/group) were administered vinyl 2-ethylhexanoate in corn oil, CAS No. 94-04-2, by gavage at dosages of 0 (control), 50, 200, 1000, or 2000 mg/kg/day at a dose volume of 4.0 ml/kg/day. Surviving animals were treated for 5 days/week for 2 weeks. Animals in the control group were administered Mazola® corn oil, CAS No. 8001-30-7, at a dose volume of 4.0 ml/kg/day. Monitors for toxic effects included detailed clinical observations, body and organ weights, food consumption, hematologic evaluations, necropsy observations, and microscopic evaluations.

Two female mice from the 2000 mg/kg/day dose group were prostrate approximately 5 hours after the first dose and 1 of these animals died the next day. There were no other chemical-related clinical signs of toxicity or animal deaths observed throughout the remainder of the study. In addition, hepatocellular hypertrophy was observed in all dose groups of both male and female mice. Based upon previous studies that indicated the hydrolysis of the test substance in liver homogenates was enzymatically mediated, the hepatocellular hypertrophy (and resulting increased liver weights in the 1000 mg/kg/day dose group of male mice and 2000 mg/kg/day dose group of both sexes) was likely an adaptive change in response to treatment with the test substance and not a direct toxic effect of the chemical on the liver. Decreased testes weights, but not testicular microscopic lesions, were observed in the 2000 mg/kg/day dose group. Therefore, the significance of the decreased weight of the testes was unknown. The no-observed-adverse-effect level of vinyl 2-ethylhexanoate under the conditions of this study was considered to be 1000 mg/kg/day since the increased liver weights observed in this dose group are considered to be an adaptive change and not a direct toxic effect of administration of the test substance.

OBJECTIVES

The objectives of this study were to evaluate the toxicity of 4 dose levels of vinyl 2-ethylhexanoate in B6C3F₁ mice when administered by gavage and to establish dose levels for a potential 90-day gavage study.

BACKGROUND INFORMATION

Several acute studies were conducted with vinyl 2-ethylhexanoate at BRRC (BRRC Report 53-130). Vinyl 2-ethylhexanoate was considered to be slightly toxic when administered perorally; the LD₅₀ for the male rat was 9.54 ml/kg and for the female rat was 5.47 ml/kg. When administered percutaneously, vinyl 2-ethylhexanoate had an extremely low order of toxicity; a 24-hour occluded dose of undiluted dose of 16.0 ml/kg killed 1 of 5 male rabbits and 2 of 5 female rabbits. When 5 male and 5 female rats were exposed to substantially saturated vapor (static) for 6 hours, there were no deaths. Minor to moderate erythema and edema occurred on all 6 rabbits that were occluded for 4 hours following the application of 0.5 ml of vinyl 2-ethylhexanoate to the clipped skin of the back. Minor irritation persisted 3 days after treatment, and the skin appeared normal 7 days after treatment. No corneal injury or iritis occurred in any of 6 rabbit eyes after instillation with 0.1 ml. Minor conjunctival irritation developed in all 6 eyes but resolved by 48 hours after treatment.

Vinyl 2-ethylhexanoate was also tested for potential mutagenic activity using the Salmonella/microsome (Ames) assay (BRRC Report 53-133). No indication of mutagenic activity was observed with any of 5 bacterial strains tested with or without metabolic activation. Vinyl 2-ethylhexanoate was not considered to be mutagenic under the conditions of this in vitro screening test.

A study to measure the rates of hydrolysis of various vinyl ester compounds in rat liver homogenates was conducted at BRRC (BRRC Report 92U1149). Analytical methodology for the hydrolysis work was developed and validated in an independent study (BRRC Report 92U1097). The following vinyl ester compounds were investigated in the study: vinyl acetate (CAS No. 108-05-04), vinyl propionate (CAS No. 105-38-4), vinyl pivalate (CAS No. 3377-92-2), vinyl 2-ethylhexanoate (CAS No. 94-04-2), divinyl adipate (CAS No. 4074-90-2), vinyl laurate (CAS No. 2146-71-6), vinyl neononanoate (CAS No. 54423-67-5), and vinyl neodecanoate (CAS No. 51000-52-3). The disappearance of each of the compounds in Fischer 344 male rat liver homogenates was measured. The autohydrolysis of selected compounds was also evaluated at pH 2, as well as evaluation of the effect of heat treatment on enzymatic hydrolysis. The nonenzymatic degradation rate of vinyl 2-ethylhexanoate at pH 2 was measured and was found to be 2 to 3 orders of magnitude slower than the metabolic degradation rates measured using rat liver homogenates. Furthermore, heat-inactivation (70°C/20 min) of liver homogenates inhibited hydrolysis. The nonenzymatic degradation rate would, therefore, not be expected to substantially influence the overall breakdown of vinyl 2-ethylhexanoate in vivo when compared to the enzymatic rates of degradation.

The Michaelis-Menten, first-order rate constants (K_m) and maximum velocities (V_{max}) of hydrolysis of vinyl 2-ethylhexanoate were measured in 3% (or less, w/w) rat liver homogenates with an incubation period of 1 minute or less. The

results from these studies indicated that vinyl 2-ethylhexanoate was metabolized by rat liver homogenate but not as readily as other vinyl esters that do not contain a neo group.

An additional investigation was conducted with male Fischer 344 rats to evaluate the potential for reactive intermediates to be produced during the metabolism of a number of vinyl esters (BRRC Report 92U1190). The depletion of rat liver reduced glutathione (GSH) was considered an indication of the production of reactive intermediates. The results from the investigation provided evidence of a low level of biochemically reactive intermediate production.

DOSE SELECTION

Based upon the above information, dose levels were selected to produce toxicity in the high dose group and no effect in at least one other dose group.

MATERIALS AND METHODS

The protocol and the protocol amendment detailing the design and conduct of this study are included in Appendix 10. Protocol deviations are also included in Appendix 10.

Test Substance

Approximately 1 liter of vinyl 2-ethylhexanoate, CAS No. 94-04-2, Lot No. JGT-1092, was received on August 31, 1993, from Union Carbide Corporation, South Charleston, WV, and assigned BRRC Sample No. 56-348. The test substance was a transparent, colorless liquid and was stored in an amber glass bottle at room temperature. Related correspondence from the supplier stated the purity of the test substance to be 99.9 (wt)%. The purity of the test substance was determined by the GLP Analytical Skill Center at the UCC South Charleston, WV, Technical Center to be 99.8 and the report is included as Attachment 1 of Appendix 1. No corrections for purity were made in any of the calculations. A reserve sample, approximately 8.7 g, was retained in the BRRC archives. This reserve sample will be discarded after issuance of the final report due to the potential for the test substance to form peroxides upon inhibitor depletion with long-term storage.

Vehicle and Control

Twenty-four 8-liter containers of Mazola® corn oil, CAS No. 8001-30-7, Research Lot No. 66580, were received from United States Cold Storage (supplied by Best Foods), Lyons, IL, on September 28, 1993, and assigned BRRC Sample Nos. 56-371-1 through 56-371-24. Sample 56-371-1 was used for the study. The corn oil was stored refrigerated.

Animals and Husbandry

Forty-four male and 46 female B6C3F₁ mice arrived on October 19, 1993, from Harlan Sprague Dawley, Inc. (Indianapolis, IN). They were designated by the supplier to be approximately 35 days old (the birth date was recorded as

September 14, 1993) upon arrival. The females were nulliparous and nonpregnant.

Animals were housed in Room 101 from arrival to termination of the study. Within 1 day of receipt, the animals were examined by a Clinical Veterinarian and a pretest health screen for representative animals was initiated. The health screen included a serology screen, necropsy, and examinations for fecal parasites. Based on the results of these data, the Clinical Veterinarian indicated that these animals were in good health and suitable for use.

All animals were assigned unique numbers and identified by cage tags. Animals considered available for the study were also identified by a toe-clipping procedure.

Upon arrival at BRRRC, the animals, separated by sex, were housed 2/cage (with the exception of 1 cage which housed 3 males) in stainless steel, wire mesh cages (22.5 x 10.0 x 12.5 cm). The purpose of the multiple housing was to help acclimate the animals to their new surroundings. Approximately 7 days later, the animals were individually housed until study termination. DACB® (Deotized Animal Cage Board; Shepherd Specialty Papers, Inc.) was placed under each cage and changed at least 3 times each week. An automatic timer was set to provide fluorescent lighting for a 12-hour photoperiod (approximately 0500 to 1700 hours for the light phase). Temperature and relative humidity were recorded (Cole-Parmer Hygrothermograph® Seven-Day Continuous Recorder, Model No. 8368-00, Cole-Parmer Instrument Co., Chicago, IL). Temperature was routinely maintained at 66-77°F; relative humidity was routinely maintained at 40-70%. Any minor exceptions to these specified ranges were noted in the raw data.

Tap water (Municipal Authority of Westmoreland County, Greensburg, PA) was available ad libitum and was delivered by an automatic watering system with demand control valves mounted on each rack. Water analyses were provided by the supplier, Halliburton NUS Environmental Laboratories, Chester Lab, and R. J. Lee Group, Inc. at regular intervals. EPA standards for maximum levels of contaminants were not exceeded. Ground Lab Diet™ The Richmond Standard™ Certified Rodent Diet #5002 (Purina Mills, Inc.; PMI, Inc.) was available ad libitum. Analyses for chemical composition and possible contaminants of each feed lot were performed by Purina Mills, Inc. (PMI, Inc.), and the results were included in the raw data.

Animal Acclimation

The acclimation period was approximately 2 weeks. During this period, the animals were weighed at least 2 times at scheduled intervals. Detailed clinical observations were conducted in conjunction with body weight measurements. Cage-side animal observations were conducted at least once daily, and mortality checks were conducted twice daily (morning and afternoon). The animals were examined just prior to the end of the acclimation period by a Clinical Veterinarian.

Study Organization

Following the second pretest body weight, the animals were assigned to 4 treatment groups and a control group using a stratified randomization procedure based on body weight. At the time of group assignment, only animals with body weight within $\pm 20\%$ of the population mean for each sex were included. The body weight range on the day of first treatment was 21.1 to 24.6 g for males and 17.6 to 21.1 g for females. The following table summarizes the organization of the study.

Group	Number of Animals		Vinyl 2-Ethylhexanoate	
	Male	Female	Volume (ml/kg/day)	Dosage (mg/kg/day)
Control	6	6	4.0	0
Low	6	6	4.0	50
Mid-1	6	6	4.0	200
Mid-2	6	6	4.0	1000
High	6	6	4.0	2000

The treatment began on November 1, 1993 (Study Day 1). Animals were treated for 5 days/week for 2 weeks. All surviving animals were sacrificed on November 15, 1993.

Administration of Test SubstanceDosing Solution Preparation

Dosing solutions were prepared by adding the appropriate amount of vinyl 2-ethylhexanoate (grams) to a volumetric flask and diluting to volume with corn oil. Each solution was mixed manually by repeated inversions. After mixing, the solutions were transferred to 30 ml Nalgene® dosing bottles specifically designed for use with a Hamilton® Microlab 900 automatic diluter/dispenser. The lids of the bottles had a small hole drilled through the top so Teflon® tubing, connected to the diluter dispenser and used for gavaging the animals, could be placed directly into the solution without removing the lid from the bottle. The hole was covered with electrical tape until needed for dosing. Each dosing bottle contained a sufficient quantity for a single day of dosing. These procedures minimized the potential for evaporation of the test substance from the solutions. Details of the dosing bottle design are included in Appendix 1.

Dosing

A fresh 30 ml bottle of dosing solution was utilized daily for each dose group. The dosing solutions were administered to the animals by gavage using an 18 gauge stainless steel animal feeding needle connected to the automatic diluter/dispenser via Teflon® tubing. The concentrations of the dosing solutions for each sex were graduated, 0, 12.5, 50, 250, and 500 mg/ml (which correspond to the dosages 0, 50, 200, 1000, and 2000 mg/kg, respectively), and

the dose volume (4.0 ml/kg/day) remained constant. Control animals were administered corn oil at a volume of 4.0 ml/kg/day. Individual dose volumes were calculated by a computer program based upon the most recent body weight of each animal.

Dosing Solution Analysis

The concentrations of vinyl 2-ethylhexanoate in corn oil were analyzed using a Gas Chromatograph (GC). A standard stock solution of vinyl 2-ethylhexanoate in toluene (1.52 mg/ml for Study Week 1 and 1.46 mg/ml for Study Week 2) was prepared and standards ranging from 0.456 to 1.52 mg/ml and 0.438 to 1.46 mg/ml for Study Week 1 and 2, respectively, were prepared by diluting the stock solution (v/v) with toluene. Dosing solutions were diluted for analysis using the automatic diluter/dispenser unit to ensure that concentration measurements were conducted under conditions identical to those utilized to dose the animals. Furthermore, procedures for priming and purging the dosing unit were recommended and validated utilizing this analytical methodology. For homogeneity and stability (Days 0 and 8) and concentration verification analyses (Study Weeks 1 and 2), dosing solutions were diluted for analysis using glass transfer pipettes.

For homogeneity and stability analyses, the measured concentration of each sample was determined by obtaining a value calculated by comparing the peak area or peak height of the sample to the peak area or peak height of the appropriate standard. For concentration verification analyses (Weeks 1 and 2), the measured concentration of each sample was determined by the equation for the standard curve developed by linear regression. Homogeneity and stability analyses were conducted for a study in rats (BRRC Report No. 93U1318) with this test substance. The data are presented in this report for completeness. The details of these procedures are included in Appendix 1.

Observations and Measurements

In-life Evaluations

Observations for mortality and overt signs were made twice daily (a.m. and p.m.). Detailed clinical observations were performed prior to dosing on Study Days 1 (first day of dosing), 4, and 8 and shortly after dosing on all other dosing days. In addition, following the first dose, all animals were observed for any overt clinical signs of toxicity at approximately hourly intervals for approximately 5 hours and the results recorded in the raw data.

Body weight data were collected for all animals on the morning prior to the initiation of dosing (denoted as Study Day 1 in the tables) and on Study Days 4, 8, and 15 (prior to sacrifice).

Food consumption measurements were collected for intervals 2-4, 4-8, and 9-15.

Clinical Pathology Evaluations

Prior to final sacrifice following the end of treatment, blood was obtained from all surviving animals for hematology determinations. Blood was obtained from the orbital sinuses of methoxyflurane anesthetized animals. The order of

bleeding and analysis was alternating (1 animal from each dose group then repeating) in order to reduce handling and time biases.

The following were measured or calculated:

Hematology

hematocrit	mean corpuscular hemoglobin
hemoglobin	concentration (MCHC)
erythrocyte count	total leukocyte count
mean corpuscular volume (MCV)	differential leukocyte count
mean corpuscular hemoglobin (MCH)	platelet count

Details of the hematology procedures are included in Appendix 3.

Anatomic Pathology Evaluations

At the end of treatment, all surviving animals were anesthetized with methoxyflurane and sacrificed by severing the brachial vessels. On the day of sacrifice, body weights were obtained to allow expression of relative organ weights. A complete necropsy was performed on all animals. The liver, kidneys, brain, adrenals, spleen, ovaries (females), and testes (males) were weighed for all sacrificed animals. The order of sacrifice and necropsy was randomized in advance in order to reduce observation and handling biases. The following tissues were collected and retained in 10% neutral buffered formalin:

<u>gross lesions</u>	vagina
lungs (with mainstem bronchi)	uterus (corpus and cervix)
<u>brain</u>	aorta
<u>cerebral cortex</u>	skin
<u>cerebellar cortex</u>	gall bladder
<u>medulla/pons</u>	esophagus
pituitary	stomach
thyroid/parathyroid	duodenum
thymic region	jejunum
trachea	ileum
heart	cecum
bone, sternum (including marrow)	colon
salivary gland	rectum
<u>liver</u>	urinary bladder
spleen	lymph node, mesenteric
<u>kidneys</u>	lymph node, other
adrenal gland	mammary gland
pancreas	skeletal muscle (gastrocnemius)
<u>testes</u>	<u>nerve, sciatic</u>
epididymis	<u>nerve, tibial</u>
prostate	eyes
seminal vesicles	femur
ovaries	spinal cord

Feet were saved for identification purposes.

The underlined tissues from the control and high dose groups were processed histologically and examined by light microscopy. In addition, gross lesions, liver, brain, sciatic and tibial nerves were examined microscopically from the low and mid dose groups.

Details of the anatomic pathology procedures are included in Appendix 2.

Data Analyses

The data for quantitative continuous variables were intercompared for the 4 treatment groups and the control group by use of Levene's test for equality of variances, analysis of variance (ANOVA), and t-tests. The t-tests were used when the F value from the ANOVA was significant. When Levene's test indicated similar variances, and the ANOVA was significant, a pooled t-test was used for pairwise comparisons. When Levene's test indicated heterogeneous variances, all groups were compared by an ANOVA for unequal variances followed, when necessary, by a separate variance t-test for pairwise comparisons.

Nonparametric data were statistically evaluated using the Kruskal-Wallis test followed by the Mann-Whitney U-test. Incidence data were compared using Fisher's Exact Test. For all statistical tests, the probability value of < 0.05 (two-tailed) was used as the critical level of significance.

Various models of calculators, computers, and computer programs may have been used to analyze data for this study. Since various models round or truncate numbers differently, values in some tables may differ slightly from those in other tables or from independently calculated data. The integrity of the study and interpretation of the data were unaffected by these differences.

RETENTION OF RECORDS

All raw data, documentation, the protocol and any amendments, specimens, and a copy of the final report generated as a result of this study will be retained in the BRRC Archives for at least 10 years. Due to the nature of the test substance, a reserve sample will not be retained following submission of the final report.

RESULTS AND DISCUSSION

All references of differences in group mean values in the following text refer to comparisons of statistically significant differences between the dose group and the control group, unless otherwise noted. Repeated reference to the control and the statistical significance will not be made in order to simplify the text.

Analytical Chemistry

Detailed results and discussion of the analytical chemistry measurements are included in Appendix 1.

Homogeneity of each solution (12.5 and 500 mg/ml) was evaluated to ensure that vinyl 2-ethylhexanoate was uniformly distributed throughout the solution. Duplicate samples were analyzed from 3 separate regions (top, middle, and bottom) of the mixing flask for each solution. The mean measured

concentrations (\pm standard deviation) of vinyl 2-ethylhexanoate in the 12.5 and 500 mg/ml solutions were 100.0 (\pm 1.1) and 98.7 (\pm 1.3) % of nominal, respectively. These results indicated that the solutions were uniformly prepared.

Stability analyses were conducted on 12.5 and 500 mg/ml solutions of vinyl 2-ethylhexanoate in corn oil. The solutions were analyzed for concentration of vinyl 2-ethylhexanoate directly after preparation (Day 0) and following 7 and 14 days of storage at room temperature in Nalgene® dosing bottles similar to those used for the dosing procedure. The mean measured concentrations for the 12.5 and 500 mg/ml solutions ranged from 100.0 to 100.2 and 93.6 to 98.9% of nominal, respectively. These results indicated that the solution remained stable at the specified concentrations and conditions for at least 14 days.

Dosing solutions were prepared weekly and analyzed for concentration prior to administration to the animals. The mean measured concentrations of the 12.5, 50, 250, and 500 mg/ml solutions ranged from 99.9 to 102.0% of nominal. Vinyl 2-ethylhexanoate was not detected in any of the control dosing solutions.

Clinical Observations

Summaries of the clinical observations are presented in Tables 1 and 2. Individual animal clinical observation data are included in Appendix 5. Individual animal fate data are included in Appendix 4.

On Study Day 1, there were no clinical signs of toxicity observed during the first 4 hours after treatment. However, 2 female animals from the 2000 mg/kg/day dose group were prostrate approximately 5 hours after dosing while all other animals appeared normal (see Table 4 of Appendix 5). One of these 2 animals was found dead the following day (Study Day 2). Upon examination of this animal at necropsy, there was no indication of a dosing error that may have contributed to the death of this animal. There were no overt clinical signs of toxicity observed in any animal prior to dosing on Study Day 2, including the surviving female animal that was prostrate 5 hours after dosing on Study Day 1.

There were no other clinical signs of toxicity observed in any animal throughout the study that were attributed to treatment with the test substance. One male animal from the control group and 1 female animal from the 50 mg/kg/day dose group died during the study. Necropsy observations of these animals indicated that the deaths were related to the dosing procedure and not due to chemical-induced toxicity. Clinical observations observed in these animals prior to death included limb paralysis, hypoactivity, prostration, cold extremities, labored respiration, urogenital area wetness, and/or lacrimation.

Body Weights

Summaries of absolute body weight and body weight gain are presented in Tables 3 to 6. Individual animal body weight data are included in Appendix 6.

There were no treatment-related effects on mean absolute body weight or body weight gain observed in any dose group of either sex throughout the study. Statistically significant increases in the mean body weight gains of male

animals from the 200, 1000 and 2000 mg/kg/day dose group during the Day 1 to 4 measurement interval were attributed to a slight decrease in the mean body weight gain of the control group. A statistically significant increase in the mean body weight gain in the 2000 mg/kg/day dose group of female mice was not considered to be related to treatment due to the transient nature of the change.

Food Consumption

Summaries of food consumption data are presented in Tables 7 and 8. Individual animal food consumption data are included in Appendix 7.

There were no treatment-related effects on mean food consumption observed in any dose group of either sex throughout the study.

Clinical Pathology Evaluations

Summaries of the hematology measurements are presented in Tables 9 and 10. Individual clinical pathology data are included in Appendix 9. Detailed results and discussion of the clinical pathology measurements are included in Appendix 3.

There were no effects on hematologic parameters observed in any dose group of either sex that were considered to be related to treatment.

Organ Weights, Necropsy Observations, and Microscopic Diagnoses

Summary results of organ weights, organ weights relative to final body weight, and organ weights relative to brain weight are presented in Tables 11 through 16. Summary results of necropsy observations are presented in Tables 17 through 20. Summary results of microscopic diagnoses are presented in Tables 21 through 24. Individual anatomic pathology data are included in Appendix 8. Detailed results and discussion of the anatomic pathology results are included in Appendix 2.

The mean absolute and relative weight of the liver were increased 5 to 8% and 12 to 13% in the 1000 (statistically significant only relative to the final body weight) and 2000 mg/kg/day dose groups of male animals, respectively. A 12 to 13% decrease in the mean absolute and weight of the testes was observed in the 2000 mg/kg/day dose group. There were no microscopic lesions observed in the testes and, therefore, the significance of the decreased weight of the testes was unknown. A statistically significant decrease in the mean weight of the testes relative to the brain weight in the 50 mg/kg/day dose group was not considered to be related to treatment due to the lack of a dose-response relationship.

The absolute and relative weight of the liver was slightly increased (5 to 12%) in the high dose group of female mice but only the weight of the liver relative to the brain weight was statistically significant. There were no other changes or trends in organ weights observed in female mice that were considered to be biologically significant.

There were no gross lesions observed in the study that were attributed to chemical-induced toxicity. Necropsy findings of the thoracic cavity in the

male animal from the control group and the female animal from the 50 mg/kg/day dose group that died on study indicated that effects secondary to errors in the dosing procedure caused the death of these animals.

Hepatocellular hypertrophy was observed in most animals of all dose groups of both sexes. The lesion was not observed in control animals. The severity of the lesion was slightly greater in the higher dose groups. There were no other microscopic lesions observed in any tissues of either sex that were considered to be related to treatment. The hepatocellular hypertrophy (and resulting increased liver weights in the 1000 and 2000 mg/kg/day dose groups of male and/or female mice) was likely an adaptive change in response to treatment with the test substance and not a direct toxic effect of the chemical on the liver.

CONCLUSIONS

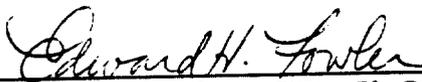
Repeated administration of vinyl 2-ethylhexanoate to mice resulted in prostration in 2 female mice approximately 5 hours after the first dose and death of 1 of these animals the next day. In addition, hepatocellular hypertrophy was observed in all dose groups of both male and female mice with an associated increase in liver weights in the 1000 mg/kg/day dose group of male mice and 2000 mg/kg/day dose group of both sexes. Decreased testes weights were also observed in the 2000 mg/kg/day dose group. The no-observed-adverse-effect level of vinyl 2-ethylhexanoate under the conditions of this study was considered to be 1000 mg/kg/day since the increased liver weights observed in this dose group are considered to be an adaptive change and not a direct toxic effect of administration of the test substance.

REVIEW AND APPROVAL

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