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8EHQ-0692-5142

8EHQ-0692-5142 = SUPP June 25, 1992

88920003788 : PDCN

Document Processing Center (TS-790)
ATTN: Section 8(e) Coordinator
Office of Toxic Substances
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

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NOTED IN BRACKETS

Re: TSCA Section 8(e) Submission

CONTAINS NO CBI

Dear Document Control Officer:

On behalf of the [3V Chemical Corporation], I am submitting supplemental information regarding a previous TSCA Section 8(e) submission for the substance:

1,3-Propanediamine, N,N''-1,2-ethanediybis, polymer with 2,4,6-trichloro-1,3,5-triazine, reaction products with N-butyl-2,2,6,6-tetramethyl-4-piperidinamine
CAS# 120498-03-5.

This substance is covered by PMN# P89-632 and a TSCA Section 5(e) Consent Order DCN: 50-891003208.

On April 6, 1992, portions of the draft final report of a subchronic Toxicity Study in rats were filed with EPA. The supplemental information attached is from the "Revised Draft Final Report" which now contains the results following a 4-week recovery period. As noted in the conclusion of the report, recovery from lung and lymph granulomas was not evident in the high dose group animals.

This draft report is still undergoing review and once finalized will be submitted to EPA in its entirety. If any additional information is desired from the draft report or you would like to discuss this submission, please do not hesitate to call.

Sincerely,

Robert J. Fensterheim
Robert J. Fensterheim

CONTAINS NO CBI
Date October 12, 1993
Per John Antonelli of Office May 26, 1993
Name _____

A. Christman

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I. INTRODUCTION:

This study, conducted for 3-V Chemical Corporation, was designed to assess the potential subchronic toxicity of UVASORB HA-88 when administered orally, via gastric intubation, to Sprague-Dawley CD® rats for 3 months and to evaluate reversibility of any effects during a 4-week recovery period.

This study was designed to meet or exceed the requirements of TSCA (Toxic Substance Control Act) of the U.S. Environmental Protection Agency, 40 CFR, Part 798.2650, Subchronic Oral Toxicity.

This study was also conducted in compliance with FDA, Part 58 of 21 CFR principles of Good Laboratory Practice and EPA Good Laboratory Practice Regulations - TSCA, Part 792 of 40 CFR.

Species and strain of test animal, method and route of test substance administration and dose levels were determined by the sponsor. This study was conducted at Bio/dynamics, Inc., Mettlers Road, East Millstone, New Jersey 08875. All raw data, specimens, the original study protocol, the original final report and a sample of the test substance and vehicle are stored in the Archives of Bio/dynamics, Inc.

II. MATERIALS AND METHODS:

A. Study Dates:

Study Initiation Date: (Date Study Director Signs Protocol)	10 May 1991
Experimental Start Date: (First Dose)	23 July 1991
Study Completion Date:	Date final report is signed by Study Director.

III. RESULTS AND DISCUSSION:

A. Mortality (Appendix B):

In the treatment phase of this study, the only death was a high-dose (Group IV) male in Week 2. Based on the results of gross and microscopic evaluations, this death can not be clearly attributed to the test material. During the recovery phase of this study two control animals (one male and one female) died.

B. In-Life Physical Observations (Appendix C):

All of the noted observations are common to laboratory rats and not test material-related.

C. Ophthalmoscopic Examinations (Appendix D):

There were no indications of treatment-related effects in the eyes.

D. Body Weights (Appendix E):

The body weight values of the low- and mid-dose groups (II and III) and high-dose (Group IV) females were similar to the control group. Body weight gains for Group IV males were statistically significantly decreased compared to values for the control group from Week 3 to 8 and tended to remain decreased during the remainder of the dosing period. However, mean weights for this group were within two percent of the control mean at study termination, and Group IV males had body weight gains similar to or greater than the control group during the recovery period.

III. RESULTS AND DISCUSSION (cont.):

E. Food Consumption (Appendix E):

The high-dose (Group IV) and occasionally the mid-dose (Group III) food consumption values were statistically significantly greater than the control group values. Though these differences appear to be test material-related, increased food consumption values are generally not considered to be an adverse effect. This difference was not seen in the recovery animals.

F. Hematology (Appendices F and G):

At termination, there was a treatment-related increase in the white blood cell counts in the high-dose (Group IV) animals when compared to the control group; this effect was more evident in the females. The increases were due to an increase in the segmented neutrophil portion of the white blood cell population. Although these differences appear to represent an effect of test material administration, white blood cell counts in all of the groups were within the range of Bio/dynamics' normal control values. This effect was not evident at the end of the recovery period.

G. Clinical Chemistry (Appendix H):

Slight, statistically significant, elevations in serum alanine aminotransferase (SGPT) values and decreases in total protein and serum albumin values were seen in high-dose males at study termination. SGPT values for mid- and high-dose females were also slightly higher than control values, but differences were not statistically significant. Similar differences were not evident at termination of the recovery period. Most individual values were within Bio/dynamics' historical control ranges and, in the absence of microscopic liver pathology, these slight, reversible differences are considered to be of questionable toxicological significance.

III. RESULTS AND DISCUSSION (cont.):

H. Urinalysis (Appendix I):

There were no treatment-related effects evident in the urinalysis values.

I. Terminal Organ and Body Weight, Organ/Body Weight and Organ/Brain Weight Ratios (Appendix J):

Lung weights and/or lung/body and lung/brain weight ratios tended to increase with increasing dose and the increases were greatest in the mid- and high-dose females. This treatment-related increase was consistent with microscopic observations of granuloma formation and edema in the lungs of treated animals. This effect persisted through the recovery period in the high-dose group males, but not in the females.

J. Analyses of Dosing Suspensions (Appendix K):

The analysis results confirmed that the test material dosing suspensions were homogeneous and stable during the dosing period. Weekly analyses confirmed that the dosing solutions were prepared within acceptable tolerances.

K. Pathology (Appendix L, Volume II):

Macroscopic examination revealed changes which occurred sporadically, or otherwise showed similar incidences between the control and the treated groups.

Microscopic examination revealed microgranulomas in the lungs, mediastinal lymph nodes and mesenteric lymph nodes of treated animals killed at the end of the study (males and females, Groups II, III and IV) and high-dose animals killed after a 4-week recovery period (males and females, Group IV).

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III. RESULTS AND DISCUSSION (cont.):

K. Pathology (cont.):

Incidence is tabulated below. Severity is similar in all three dose groups, including the high-dose recovery group.

Incidence of Microgranulomas in the Lung and Lymph Nodes
(N = 10 for all observations)

Group	Dose (mg/kg/day)	LUNGS		LYMPH NODES			
		M	E	Mesenteric		Mediastinal	
				M	E	M	E
<u>Termination</u>							
I	0	0	0	0	0	0	0
II	25	4	1	7	6	2	0
III	75	8	7	8	10	7	2
IV	250	6	7	8	10	3	4
<u>Recovery</u>							
I	0	0	0	0	0	0	0
IV	250	7	3	10	10	5	2

Acute inflammation, purulent exudate, proteinaceous exudate and hyperplasia or squamous metaplasia of the respiratory mucosa were seen in the nasal turbinates of the high-dose males and females at study termination (these tissues were not examined for the low- or mid-dose group or the recovery animals).

The changes in the lungs and nasal turbinates were believed to have been induced by inadvertent aspiration of the test material during the dosing process or by excretion of the test material by the respiratory system. The test material probably provoked an acute inflammatory reaction in the lungs and nasal turbinates, which, in time, became chronic and predominantly granulomatous in the lungs. Prolonged irritation of the respiratory mucosa in the nasal passages apparently led to hyperplasia or metaplastic change in the squamous

III. RESULTS AND DISCUSSION (cont.):

K. Pathology (cont.):

epithelium. Drainage of the inhaled test material from the lungs may have caused the formation of the microgranulomas in the mediastinal and, perhaps, the mesenteric lymph nodes. Absorption of the test material through the gastrointestinal tract probably produced the granulomatous reaction in the mesenteric lymph nodes.

No other treatment-related pathologic findings were seen in the testes, ovaries or any of the other tissues examined.

IV. CONCLUSION:

Oral administration of UVASORB HA-88 to rats for 90 days at doses of 25, 75 and 250 mg/kg/day was associated with granulomas in the lungs and lymph nodes of animals in all dose groups; no recovery was evident in the high-dose recovery group. Elevated lung weights were also seen, primarily in mid- and high-dose animals. Other signs of toxicity were seen in the high-dose group only. However, based on the presence of lung and lymph node microgranulomas at the lowest dose administered, a no effect level was not established in this study.

John M. Mitchell, M.S.
Study Director
Toxicologist

Date

Ira W. Daly, Ph.D., D.A.B.T.
Senior Vice-President and
Director of Toxicology

Date

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