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19 pp

8EHQ-1091-1377 UNIT
8892000022

October 15, 1991



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

ATTN: 8(e) Coordinator (CAP Agreement)

Dear Sir:

SUBJECT: A LIST OF STUDIES AND OR REPORTS OF INFORMATION WHICH IS SUBMITTED UNDER UNIT II.B.3 OF THE COMPLIANCE AUDIT PROGRAM PURSUANT TO THE TERMS OF AGREEMENT BETWEEN SHELL OIL COMPANY AND THE ENVIRONMENTAL PROTECTION AGENCY AND DEFINED BY UNIT II.B.1.C. OF SAID AGREEMENT.

IDENTIFICATION NUMBER: 8ECAP-0050

REFERENCE: SHELLCAP-5

The enclosed information was found in an audit being conducted within Shell Oil Company under the Terms of Agreement of EPA's Compliance Audit Program. It is being submitted pursuant to the TSCA 8(e) Compliance Audit Program and the EPA-Shell CAP Agreement (ID. No. 8ECAP-0050).

The enclosed information is entitled: HSE-77-0244, Status Report on the 2 Year Study Incorporating Acrylonitrile in the Drinking Water of Rats.

The Category of the information: the enclosed information is categorized as Category (ii), i.e., received by the Office of Toxic Substances (OTS) on a "For Your Information" ("FYI") basis and included in the formal OTS "FYI" filing system.

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The date of the submission: 04/04/1977

The EPA OTS FYI filing number: OTS -0477-0150 (initial)
OTS-0280-0062 (final)

The associated chemical substance is: Acrylonitrile

CAS No. 000107-13-1

The listed information (an interim report on a 2-year bioassay of Acrylonitrile) indicates an increased incidence of dose-related "proliferative lesions in CNS", polyps in stomach, and "masses" in several organs.

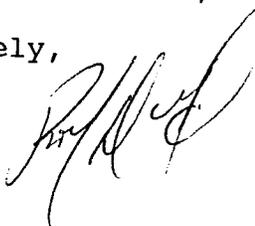
No TSCA 8(e) reports have been submitted on this chemical by Shell; nor has a Premanufacture Notice been sent by Shell to the Agency on this chemical.

This information is not considered confidential business information.

For further discussion, please contact the following:

J.C. Willett
Manager, Product Safety and Compliance
Shell Oil Company
P.O. Box 4320
Houston, TX 77210

Sincerely,



GTY:mak

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HSE-77-0224
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January 14, 1977.

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H.S. & E. REPORTS
FILE COPY

To all members of: The Plastic Bottle Institute
Food, Drug and Cosmetic Packaging
Materials Committee
Plastic Beverage Container Group
Acrylonitrile Safety Group

Ladies and Gentlemen:

Enclosed herewith please find an Interim Thirteen Month Status Report on the Two Year Feeding Study being conducted by the Manufacturing Chemists Association (MCA) on Acrylonitrile. This Status Report was delivered to the Food and Drug Administration Staff in a meeting held today at MCA's request; Dr. Dixler, Peter Smith and I were present throughout the session. In addition to the FDA staff, personnel from the National Cancer Institute, National Institute of Occupational Safety and Health, the Environmental Protection Agency's Office of Toxic Substances and the Occupational Safety and Health Administration attended.

As you will note, the Two Year Feeding Study underway by MCA is being conducted at levels of 300 ppm, 100 ppm, and 35 ppm with a suitable control. The highest feeding level is far in excess of the "Maximum Tolerated Dose" level recommended by the National Cancer Institute for carcinogenicity testing; the middle level is somewhat in excess. This may raise problems in the ultimate assessment of the final study. For example, assuming the final report shows no significant toxicological impact at the 35 ppm level, FDA and the other agencies could conclude that even carcinogenicity at the levels above NCI's "Maximum Tolerated Dose" of 85 ppm need not be determinative because the animals were stressed beyond normal limits.

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January 4, 1977
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The status report indicates an increased incidence of masses in the mammary region in females at all dose levels, increased incidence of ear canal masses in males and females at 300 ppm and in females at 100 ppm, central nervous system lesions in males and females at 100 ppm and 300 ppm, and stomach polyps in some male and female animals at 300 ppm and females at 100 ppm.

The comments generally made by FDA staff members to us informally subsequent to the meeting were to the effect that these interim results should not be a cause for over-reaction where indirect additives are concerned. It was also indicated that in those applications (e.g. beverage containers) where Food Additive Regulations have, in essence, been premised on the concept of no reasonable expectation of migration of AN to foods, the new data should not lead to any radical changes in present status.

Collaterally speaking, it has come to our attention that many in the plastics industry may have misinterpreted a February 10, 1977 Food Chemical News article concerning a recommendation that small size plastic beverage containers be banned on environmental grounds. This article mis-reported the memorandum in question to include plastic bottles for all food contact uses. In fact, the now in dispute memorandum was written solely in response to questions concerning plastic beverage containers and was limited to that application. The recommendation does, however, have substantial impact as a precedent for all food packaging containers and materials.

You will undoubtedly be hearing from us again shortly after FDA has decided what posture it will take in light of the just given MCA toxicology status report. In the meantime, should you have any questions or comments concerning this matter, please do not hesitate to contact us.

Cordially yours,

Norman W. Wickman

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STATUS REPORT ON THE 2 YEAR STUDY INCORPORATING
ACRYLONITRILE IN THE DRINKING WATER OF RATS

J. M. NORRIS
HEALTH AND ENVIRONMENTAL RESEARCH H.S. & E. REPORTS
THE DOW CHEMICAL COMPANY FILE COPY.
MIDLAND, MICHIGAN 48640

January 12, 1977

An investigation of the long-term effects of the administration of acrylonitrile (AN) in the drinking water of rats is being administered by the Manufacturing Chemists Association and funded by American Cyanamid Company, Borg-Warner Chemicals, The Dow Chemical Company, E.I. duPont de Nemours & Co., Monsanto Company, Standard Oil Company of Ohio, Tennessee Eastman Company, Uniroyal, Incorporated and Gulf Oil Corporation. The investigation is being conducted in the Toxicology Research Laboratory of The Dow Chemical Company. This 13-month interim report has been prepared to communicate current findings of the study. The study is scheduled to run for 2 years.

The concentrations of AN in the drinking water of the rats are 0, 35, 100, or 300 ppm.* These concentrations are equivalent to daily dosages, of approximately 4, 10, and 30 mg/kg body weight, respectively. Statistically significant dose-related decreased water consumption of the rats on all concentrations was observed as well as lowered food consumption of the rats on the highest concentration and of the

*ppm = mg/l

females, only, at the intermediate concentration. The decreased food and water consumption was associated with statistically significant decreased body weight of the animals at the higher two concentrations. The body weight of the animals on the lowest concentration was decreased, but not statistically significantly, when compared with the controls. No treatment-related effects were noted in the hematology or in clinical chemistry determinations, which included kidney and liver function tests. The various urinalyses that were conducted showed nothing other than an increase in specific gravity in the urine of the rats of both sexes at the 300 ppm concentration throughout the study and in the females at the 100 ppm concentration in the 12th month of the study. This effect is probably related to the lower water intake.

As of thirteen months into the study there is a higher incidence of (a) subcutaneous masses in the mammary region of females at all concentrations of AN, and (b) masses of the ear canal among both sexes at the highest concentration, and among females, only, at the intermediate concentration.

Gross pathologic examination of some of the rats dying spontaneously and in those rats sacrificed after one year of

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administration of AN revealed focal areas of hyperplasia and/or polyp formation in the nonglandular portion of the stomach of a number of animals at the two higher concentrations. No gross pathologic changes were observed in the stomachs of the animals at the lowest concentration.

Microscopic examination of the brain of the animals sacrificed at the 12 month interim kill revealed proliferative lesions, not observed on gross examination, in rats on the 300 and 100 ppm concentrations. A similar lesion was seen in the spinal cord of one rat on the 100 ppm concentration.

It is concluded that administration of AN under the condition of this study has significantly lowered body weight, produced pathologic changes in the gastric epithelium, increased the incidence of masses of the ear duct and produced proliferative lesions in the central nervous system of rats. The significance of the higher incidence of subcutaneous masses in the mammary region of the rats is less clear, and its resolution will have to await further progress of the study.

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STATUS REPORT ON 2-YEAR STUDY INCORPORATING ACRYLONITRILE
IN THE DRINKING WATER OF RATS

- SUMMARY OF FINDINGS AS OF 13 MONTHS -

- ① STATISTICALLY SIGNIFICANT DECREASED WATER CONSUMPTION AT ALL DOSE LEVELS.
- ② DECREASED FOOD CONSUMPTION AT 300 PPM IN MALES AND FEMALES AND AT 100 PPM IN FEMALES.
- ③ STATISTICALLY SIGNIFICANT DECREASED BODY WEIGHTS OF MALES AND FEMALES AT 300 AND 100 PPM AND A NONSTATISTICALLY SIGNIFICANT DECREASE AT 35 PPM.
- ④ INCREASED SPECIFIC GRAVITY OF URINE OF MALES AND FEMALES AT 300 PPM AND IN FEMALES AT 100 PPM.
- ⑤ INCREASED INCIDENCE OF MASSES IN THE MAMMARY REGION IN FEMALES AT ALL DOSE LEVELS.
- ⑥ POLYPS IN STOMACH OF SOME MALE AND FEMALES AT 300 PPM AND FEMALES AT 100 PPM.
- ⑦ INCREASED INCIDENCE OF EAR CANAL MASSES IN MALES AND FEMALES AT 300 PPM AND IN FEMALES AT 100 PPM.
- ⑧ PROLIFERATIVE LESIONS IN CENTRAL NERVOUS SYSTEM OF MALES AND FEMALES SACRIFICED AFTER 12 MONTHS AT 300 AND 100 PPM.
- ⑨ INCREASED MORTALITY AMONG FEMALES AT 300 PPM.

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STATUS REPORT (13 MONTHS) ON 2-YEAR STUDY INCORPORATING
ACRYLONITRILE (AN) IN THE DRINKING WATER OF RATS

- ACRYLONITRILE (AN) CONSUMED BY RATS -

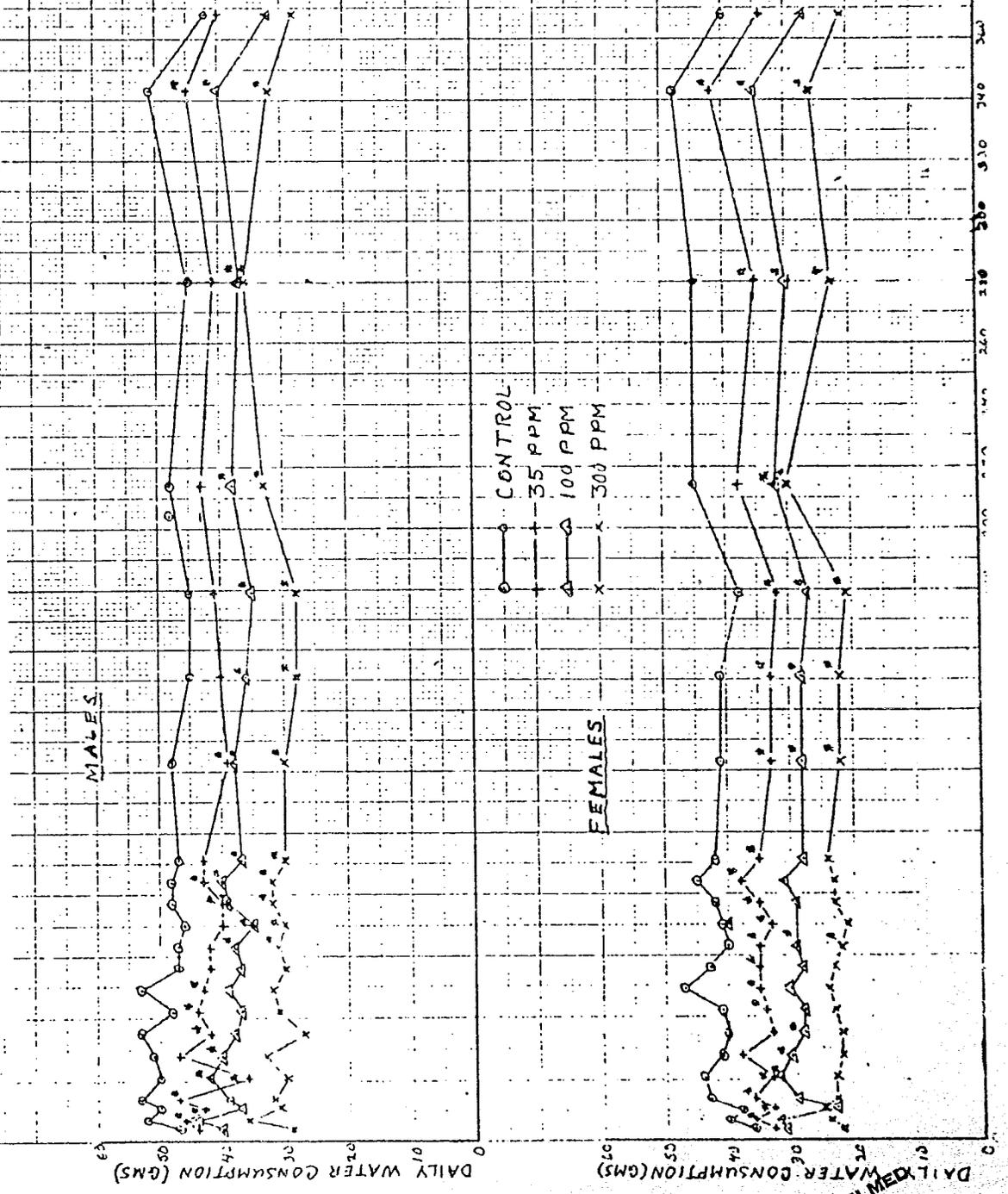
<u>CONCENTRATION (AN) IN DRINKING WATER - PPM*</u>	<u>(AN) CONSUMED - MG/KG/DAY</u>	
	<u>MALE</u>	<u>FEMALE</u>
35	4.8-2.4	5.8-3.6
100	13.8-6.4	15.8-11.1
300	32.7-17.0	37.3-3.0

*PPM = MG/L

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STATUS REPORT (13 MONTH) ON
 2-YEAR STUDY INCORPORATING
 ACRYLONITRILE IN THE DRINKING
 WATER OF RATS

- MEAN DAILY WATER CONSUMPTION
 (GRAM) -



STATUS REPORT (13 MONTHS) ON 2-YEAR STUDY INCORPORATING
ACRYLONITRILE IN THE DRINKING WATER OF RATS

- MEAN DAILY FOOD CONSUMPTION (GRAMS) -

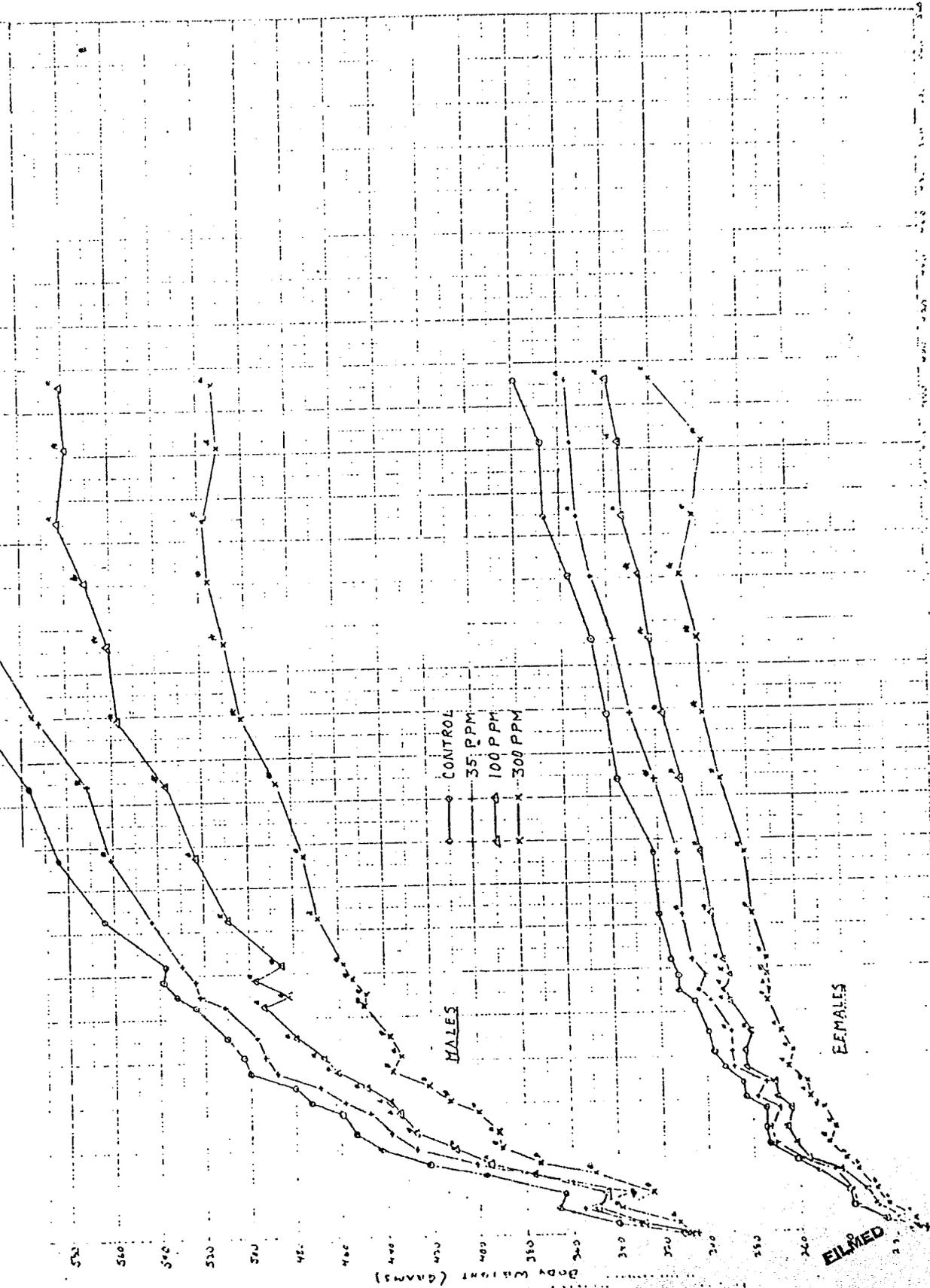
DAYS ON TEST	MALES PPM				FEMALES PPM			
	0	35	100	300	0	35	100	300
4	27	26	25	23*	21	19	20	19
7	27	26	24	24	23	21	19*	20
11	25	24	23	23	18	17	15*	16*
14	24	23	22	21*	18	17	17	16*
21	24	24	26	24	21	18	18	17
28	27	27	25	24*	20	19	19	16*
35	27	25	24	24	19	19	17	16
42	26	24	22	24	19	18	17*	16*
49	26	25	24	23	22	18*	17*	17*
56	-	-	-	-	18	17	17	18
63	25	25	25	22*	18	18	18	17
70	25	24	23	22	20	17*	18	17*
84	26	26	25	24	21	19	19	18
91	25	24	23	22*	20	17	19	17
151	25	24	22	20*	20	16	17	14*
179	24	24	22	21*	19	16*	16*	16*
214	25	24	20*	24	21	18	19	19
280	25	24	24	21*	22	18*	18*	16*
336	26	26	24	22*	20	18*	17*	16*
368	20	20	18*	17*	15	14	13	13*

*SIGNIFICANTLY DIFFERENT FROM CONTROLS BY DUNNETT'S TEST,
P<0.05.

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2-YEAR STUDY INCORPORATING
ACRYLONITRILE IN THE DRINKING
WATER OF RATS

- MEAN BODY WEIGHT (GRAMS) -



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STATUS REPORT (13 MONTHS) ON 2-YEAR STUDY INCORPORATING
ACRYLONITRILE IN THE DRINKING WATER OF RATS

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- OBSERVATION OF PALPABLE MASSES IN MAMMARY GLAND REGION -

	MALES			TOTAL		FEMALES			TOTAL	
	A	B	C	#	%	A	B	C	#	%
CONTROLS	4/73 ⁽¹⁾	0/10	1/7	5/90	5.5	12/79	2/10	0/1	14/90	15.5
35 PPM	0/44	0/10	0/3	0/57	0.0	11/45	0/10	3/4	14/59	23.7
100 PPM	3/46	0/10	1/1	4/47	7.0	9/42	3/10	3/5	15/57	26.3
300 PPM	3/41	0/10	0/7	3/58	5.2	11/32	1/10	8/15	20/57	35.1

(1) #MASS BEARING ANIMALS/# ANIMALS IN GROUP A, B OR C.

A - ALIVE AT 13 MONTHS (12/21/76).
B - INTERIM SACRIFICE ANIMALS AFTER 12 MONTHS ON STUDY.
C - DEAD AT 13 MONTHS (12/21/76).

STATUS REPORT (13 MONTHS) ON 2-YEAR STUDY INCORPORATING
ACRYLONITRILE IN THE DRINKING WATER OF RATS

- GROSS PATHOLOGIC EXAMINATION FINDING OF GASTRIC POLYPS IN
NONGLANDULAR PORTION OF STOMACH -

	MALES		FEMALES	
	A	B	A	B
CONTROL	0/10 (1)	0/7	0/10	0/1
35 PPM	0/10	0/3	0/10	0/4
100 PPM	1/10	0/1	0/10	1/5
<2 IN NUMBER				1/5
>2 IN NUMBER	1/10			
300 PPM	7/10	2/7	4/10	2/15
<2 IN NUMBER	6/10	2/7	3/10	2/15
>2 IN NUMBER	1/10		1/10	

(1) # ANIMALS WITH POLYPS/NUMBER ANIMALS IN GROUP A OR B.

A - INTERIM SACRIFICE - AFTER 12 MONTHS ON STUDY
B - DEAD AT 13 MONTHS (12/21/76).

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STATUS REPORT (13 MONTHS) ON 2-YEAR STUDY INCORPORATING
ACRYLONITRILE IN THE DRINKING WATER OF RATS

- SPECIFIC GRAVITY OF URINE -

	DAYS ON STUDY			
	45	85	180	354
CONTROLS	(1)	-	-	-
35	-	-	-	-
100	-	-	-	F ↑
300	M&F ↑	M&F ↑	M&F ↑	M&F ↑

(1) WITHIN NORMAL RANGE

STATUS REPORT (13 MONTHS) ON 2-YEAR STUDY INCORPORATING
ACRYLONITRILE IN THE DRINKING WATER OF RATS

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- EAR CANAL MASSES -

	MALES			TOTAL		FEMALES			TOTAL	
	A	B	C	#	%	A	B	C	#	%
CONTROL	1/73 ⁽¹⁾	0/10	0/7	1/90	1.1	1/79	0/10	0/1	1/90	1.1
30 PPM	1/44	0/10	0/3	1/57	1.7	0/45	0/10	0/4	0/59	0
100 PPM	0/46	0/10	0/1	0/57	0	0/42	2/10	1/5	3/57	5.3
300 PPM	4/41	1/10	1/7	6/58	10.3	4/32	1/10	4/15	9/57	15.8

(1) # MASS BEARING ANIMALS/# ANIMALS IN GROUP A, B OR C.

- A - ALIVE AT 13 MONTHS (12/21/76).
- B - INTERIM SACRIFICE ANIMALS AFTER 12 MONTHS ON STUDY.
- C - DEAD AT 13 MONTHS (12/21/76).

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STATUS REPORT (13 MONTHS) ON 2-YEAR STUDY INCORPORATING
ACRYLONITRILE (AN) IN THE DRINKING WATER OF RATS

- PROLIFERATIVE LESIONS⁽¹⁾ IN BRAIN OF RATS SACRIFICED AFTER 12 MONTHS -

<u>CONCENTRATION AN IN DRINKING WATER - PPM</u>	<u>MALES</u>	<u>FEMALES</u>
CONTROL	0/10	0/10
35	0/10	0/10
100	1/10	3/10 (PLUS 1 SPINAL CORD LESION)
300	1/10	2/10

(1) NOT OBSERVED GROSSLY.

STATUS REPORT (13 MONTHS) ON 2-YEAR STUDY INCORPORATING
 ACRYLONITRILE IN THE DRINKING WATER OF RATS

- PERCENT SURVIVAL -

	<u>CONTROL</u>	<u>35 PPM</u>	<u>100 PPM</u>	<u>300 PPM</u>
MALE	91.3	91.7	95.8	85.4
FEMALE	98.8	93.8	87.5	66.7

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