IV. CHRONIC TESTING RESULTS: MICE

A. Body Weights and Clinical Observations

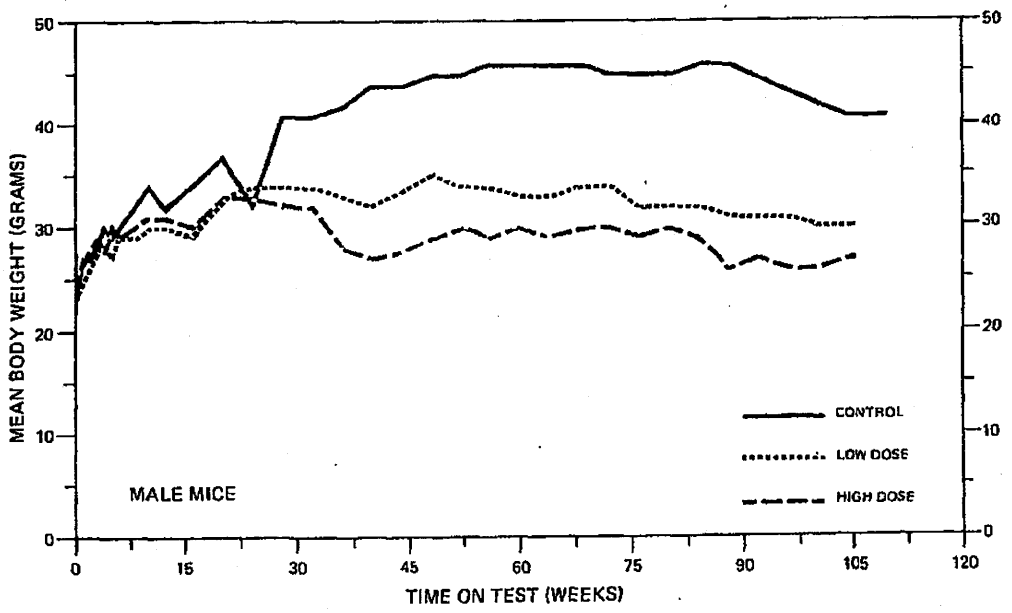
Mean body weight depression was readily apparent in dosed male mice when compared to controls. A similar but less pronounced trend was evident in dosed females (Figure 4).

One low dose male had a soft subcutaneous mass on the leg and two males in this group had palpable abdominal masses. Firm nodular growths developed in one low dose male and two high dose females. Alopecia was observed in 27 control males, 16 low dose males, 4 high dose males, 25 control females, and 3 low dose females. Two low dose and two high dose males experienced noticeable swelling of the eyes. Abdominal distention was observed in one control male and one control female mouse.

B. Survival

The estimated probabilities of survival for male and female mice in the control and 1,5-naphthalenediamine-dosed groups are shown in Figure 5. There was no significant positive association between dosage and mortality for either male or female mice.

Adequate numbers of male mice were at risk from late-developing tumors with 58 percent (29/50) of the high dose, 78 percent (39/50) of the low dose and 66 percent (33/50) of the controls surviving on test until the termination of the study. The 6 control male mice that died in week 11 were autolyzed, as were 2 of the 4 high dose male mice that died in week 41.



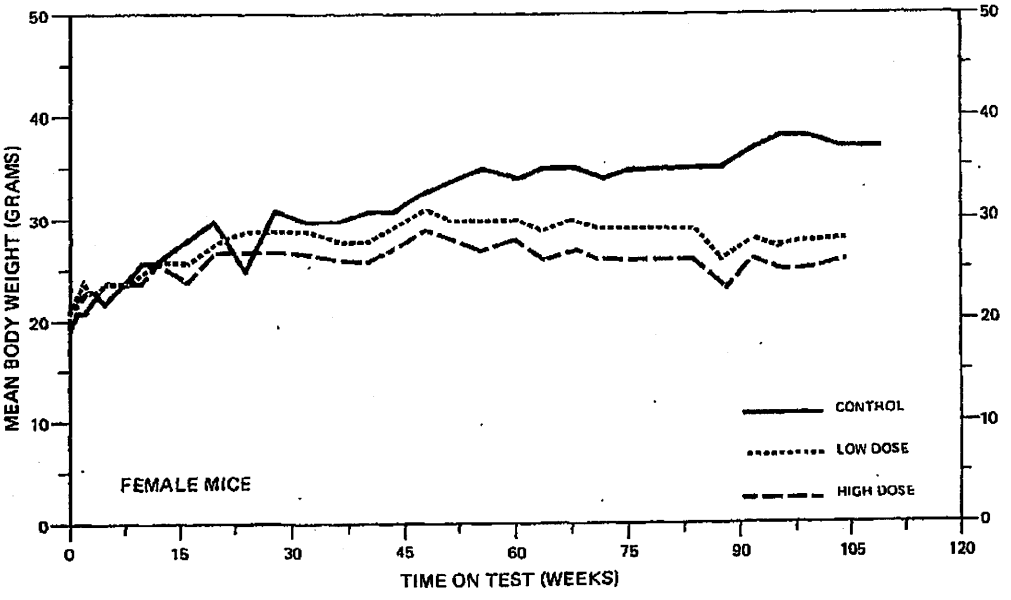
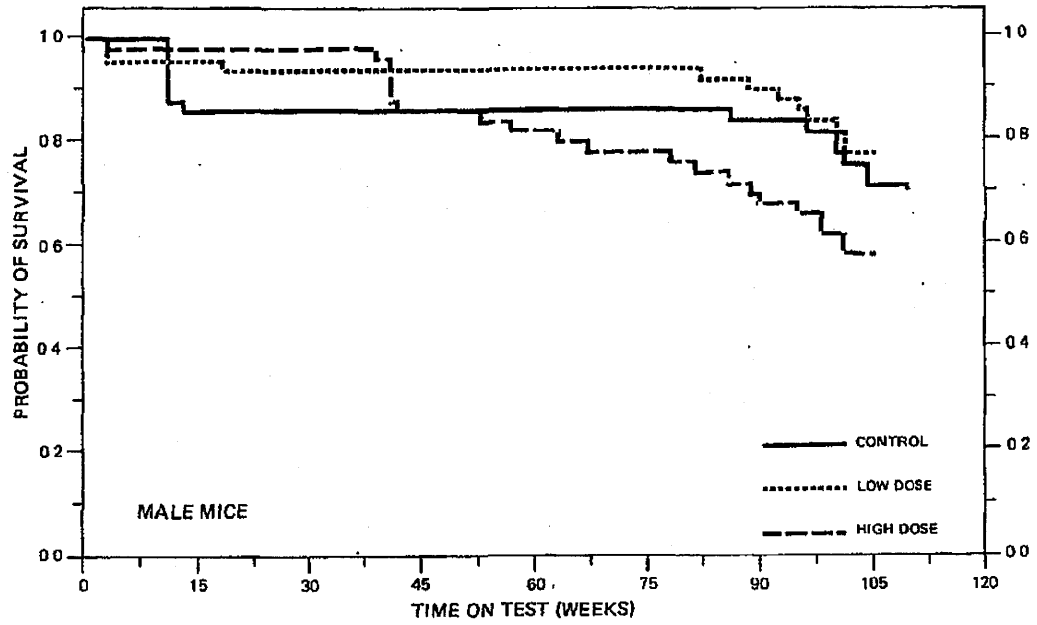


FIGURE 4
GROWTH CURVES FOR 1,5-NAPHTHALENEDIAMINE CHRONIC STUDY MICE



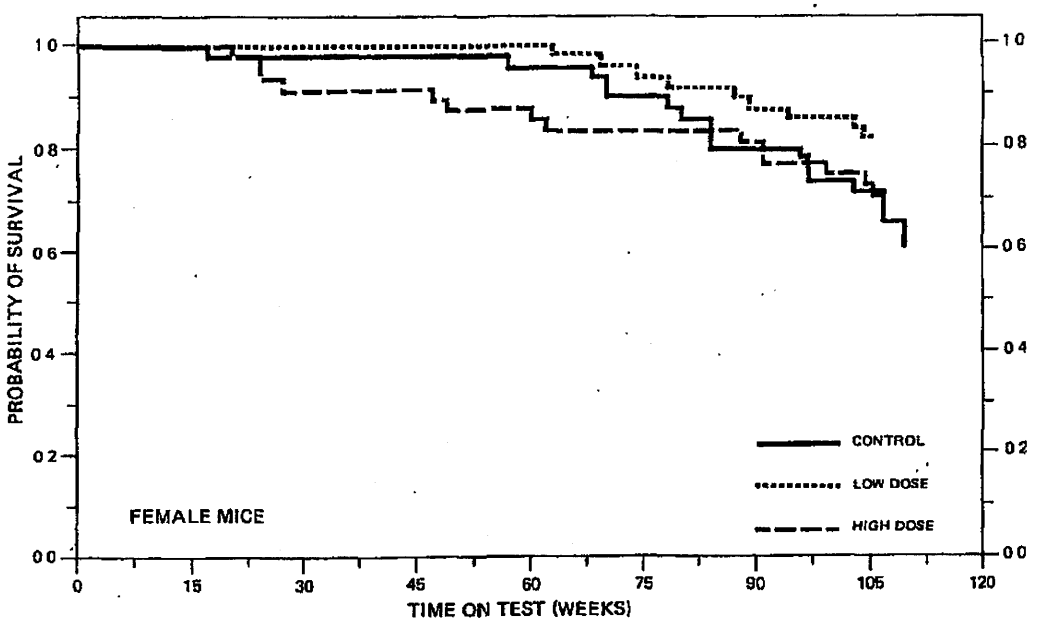


FIGURE 5
SURVIVAL COMPARISONS OF 1,5-NAPHTHALENEDIAMINE CHRONIC STUDY MICE

For female mice, with 68 percent (34/50) of the high dose, 82 percent (41/50) of the low dose and 60 percent (30/50) of the control mice surviving on test until the termination of the study, adequate numbers were at risk from late-developing tumors.

C. Pathology

Histopathologic findings on neoplasms in mice are summarized in Appendix B (Tables B1 and B2); findings on nonneoplastic lesions are summarized in Appendix D (Tables D1 and D2).

Dietary administration of 1,5-naphthalenediamine produced an increase in hepatocellular neoplasms in female mice, and it produced a dose-related increase in thyroid neoplasms and compound-related nonneoplastic thyroid lesions in both sexes. The compound-related lesions are summarized below:

	MALES			FEMALES		
	Control	Low Dose	High Dose	Control	Low Dose	High Dose
LIVER						
(Number of animals with tissues examined histopathologically)	(39)	(45)	(43)	(46)	(49)	(46)
Hepatocellular Carcinoma	12	10	7	1	25	16
Hepatocellular Adenoma	0	3	6	0	3	11
THYROID						
(Number of animals with tissues examined histopathologically)	(38)	(46)	(43)	(44)	(49)	(45)
Follicular-Cell Adenoma (Papillary or Follicular-Cell Adenoma, Papillary Cystadenoma)	0	8	16	2	17	14
Follicular-Cell Carcinoma	0	1	1	2	0	1
Follicular-Cell Hyperplasia	2	12	9	2	1	4
C-Cell Adenoma	0	2	0	0	1	2
C-Cell Carcinoma	0	0	4	0	1	6

In male mice, dietary administration of the compound did not increase the incidence of hepatocellular neoplasms, whereas dosed females showed a striking increase in hepatocellular carcinomas and hepatocellular adenomas.

Grossly, hepatocellular neoplasms appeared as smooth, nodular, rounded masses distorting the normal shape of the liver. Color varied, many neoplasms appearing pale tan or dark red. Microscopically, hepatocellular carcinomas were expansive masses of hepatocytes exhibiting loss of normal architectural pattern, the cells being arranged in sheets or trabeculae instead of the normal lobules. Nuclei were frequently uniform, although variable amounts of pleomorphism did occur. The cytoplasm was either basophilic or acidophilic, sometimes varying from one region of the tumor to another, and was frequently pale. Lesions classified as hepatocellular adenomas were smaller, usually better differentiated, and were less pleomorphic than the hepatocellular carcinomas.

The criteria for classification of thyroid neoplasms in mice were the same as those used to classify thyroid neoplasms in rats. The nonneoplastic thyroid lesions found in dosed mice were similar to those in the rats but occurred in higher incidences. Hyperplasia of follicular cells (focal, papillary or adenomatous) were found in 2/38 (5 percent) control, 12/46 (26 percent) low dose, and 9/43 (21 percent) high dose male mice. Abundant golden brown pigment was seen in follicular epithelium, colloid, and macrophages. In the mice,

there were frequent foci of lymphocytes in the thyroid parenchyma and occasional cystic areas filled with amorphous material containing long clefts suggesting cholesterol crystals.

Three transitional-cell papillomas occurred in the bladder or urethra of dosed mice (two high dose males and one high dose female), but none occurred in controls.

Based upon the results of this pathologic examination, 1,5-naphthalenediamine was carcinogenic to B6C3F1 mice, producing hepatocellular neoplasms in females and thyroid neoplasms in both sexes.

D. Statistical Analyses of Results

The results of the statistical analyses of tumor incidence in mice are summarized in Tables 5 and 6. The analysis is included for every type of tumor in either sex where at least two such tumors were observed in at least one of the control or 1,5-naphthalenediamine-dosed groups and where such tumors were observed in at least 5 percent of the group.

For both male and female mice elevated incidences of thyroid tumors were observed in the dosed groups. In female mice the Cochran-Armitage test indicated a significant ($P = 0.005$) positive association between dietary concentration and the incidence of C-cell carcinomas. This was supported by a significant ($P = 0.014$) Fisher exact test for the high dose group. For males the Cochran-Armitage test result was also significant ($P = 0.017$), but the Fisher exact tests were

TABLE 5

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT SPECIFIC SITES IN MALE MICE TREATED WITH 1,5-NAPHTHALENEDIAMINE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	2/39(0.05)	3/46(0.07)	0/45(0.00)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.272	0.000
Lower Limit	---	0.153	0.000
Upper Limit	---	14.686	4.478
Weeks to First Observed Tumor	109	82	---
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	4/39(0.10)	9/46(0.20)	2/45(0.04)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.037	---	---
Relative Risk (Control)[d]	---	1.908	0.433
Lower Limit	---	0.582	0.041
Upper Limit	---	7.882	2.871
Weeks to First Observed Tumor	109	82	105
Hematopoietic System: Malignant Lymphoma[b]	13/39(0.33)	14/47(0.30)	5/49(0.10)
P Values[c]	P = 0.007(N)	N.S.	P = 0.008(N)
Relative Risk (Control)[d]	---	0.894	0.306
Lower Limit	---	0.448	0.094
Upper Limit	---	1.817	0.829
Weeks to First Observed Tumor	100	82	95

TABLE 5 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	12/39(0.31)	10/45(0.22)	7/43(0.16)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.722	0.529
Lower Limit	---	0.318	0.198
Upper Limit	---	1.620	1.306
Weeks to First Observed Tumor	86	88	105
Liver: Hepatocellular Carcinoma or Hepatocellular Adenoma[b]	12/39(0.31)	13/45(0.29)	13/43(0.30)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	0.939	0.983
Lower Limit	---	0.453	0.473
Upper Limit	---	1.981	2.071
Weeks to First Observed Tumor	86	88	105
Thyroid: C-Cell Carcinoma[b]	0/38(0.00)	0/46(0.00)	4/43(0.09)
P Values[c]	P = 0.017	N.S.	N.S.
Relative Risk (Control)[d]	---	---	Infinite
Lower Limit	---	---	0.825
Upper Limit	---	---	Infinite
Weeks to First Observed Tumor	---	---	105

TABLE 5 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Carcinoma or C-Cell Adenoma[b]	0/38(0.00)	2/46(0.04)	4/43(0.09)
P Values[c]	P = 0.044	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.246	0.825
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	105	105
Thyroid: Papillary Adenoma, Follicular-Cell Adenoma, or Papillary Cystadenoma NOS[b]	0/38(0.00)	8/46(0.17)	16/43(0.37)
P Values[c]	P < 0.001	P = 0.006	P < 0.001
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	1.905	4.523
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	105	98

[a]Treated groups received doses of 0.1 or 0.2 percent in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when P < 0.05; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when P < 0.05; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when P < 0.05.

TABLE 6

ANALYSES OF THE INCIDENCE OF PRIMARY TUMORS AT
SPECIFIC SITES IN FEMALE MICE TREATED WITH 1,5-NAPHTHALENEDIAMINE[a]

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Lung: Alveolar/Bronchiolar Carcinoma[b]	0/49(0.00)	1/48(0.02)	3/46(0.07)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.055	0.638
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	89	91
Lung: Alveolar/Bronchiolar Adenoma or Alveolar/Bronchiolar Carcinoma[b]	0/49(0.00)	10/48(0.21)	5/46(0.11)
P Values[c]	N.S.	P = 0.001	P = 0.024
Departure from Linear Trend[e]	P = 0.005	---	---
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	3.037	1.347
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	89	91
Hematopoietic System: Leukemia or Malignant Lymphoma[b]	13/49(0.27)	19/50(0.38)	5/46(0.11)
P Values[c]	N.S.	N.S.	P = 0.045(N)
Departure from Linear Trend[e]	P = 0.011	---	---
Relative Risk (Control)[d]	---	1.432	0.410
Lower Limit	---	0.760	0.124
Upper Limit	---	2.781	1.117
Weeks to First Observed Tumor	57	63	105

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Liver: Hepatocellular Carcinoma[b]	1/46(0.02)	25/49(0.51)	16/46(0.35)
P Values[c]	P = 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P < 0.001	---	---
Relative Risk (Control)[d]	---	23.469	16.000
Lower Limit	---	4.156	2.683
Upper Limit	---	906.346	646.516
Weeks to First Observed Tumor	109	74	99
Liver: Hepatocellular Adenoma or Hepatocellular Carcinoma[b]	1/46(0.02)	28/49(0.57)	27/46(0.59)
P Values[c]	P < 0.001	P < 0.001	P < 0.001
Departure from Linear Trend[e]	P = 0.002	---	---
Relative Risk (Control)[d]	---	26.286	27.000
Lower Limit	---	4.741	4.874
Upper Limit	---	1030.801	1027.943
Weeks to First Observed Tumor	109	74	99
Stomach: Squamous-Cell Papilloma[b]	0/41(0.00)	3/47(0.06)	0/46(0.00)
P Values[c]	N.S.	N.S.	N.S.
Departure from Linear Trend[e]	P = 0.017	---	---
Relative Risk (Control)[d]	---	Infinite	---
Lower Limit	---	0.529	---
Upper Limit	---	Infinite	---
Weeks to First Observed Tumor	---	105	---

TABLE 6 (CONTINUED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Pituitary: Adenoma NOS, Chromophobe Adenoma or Acidophil Adenoma[b]	3/34(0.09)	4/35(0.11)	1/30(0.03)
P Values[c]	N.S.	N.S.	N.S.
Relative Risk (Control)[d]	---	1.295	0.378
Lower Limit	---	0.238	0.007
Upper Limit	---	8.188	4.424
Weeks to First Observed Tumor	109	105	106
Adrenal: Pheochromocytoma[b]	3/46(0.07)	0/44(0.00)	0/44(0.00)
P Values[c]	P = 0.040(N)	N.S.	N.S.
Relative Risk (Control)[d]	---	0.000	0.000
Lower Limit	---	0.000	0.000
Upper Limit	---	1.731	1.731
Weeks to First Observed Tumor	68	---	---
Thyroid: C-Cell Carcinoma[b]	0/44(0.00)	1/49(0.02)	6/45(0.13)
P Values[c]	P = 0.005	N.S.	P = 0.014
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.048	1.574
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	105	105

TABLE 6 (CONCLUDED)

TOPOGRAPHY:MORPHOLOGY	CONTROL	LOW DOSE	HIGH DOSE
Thyroid: C-Cell Adenoma or C-Cell Carcinoma[b]	0/44(0.00)	2/49(0.04)	8/45(0.18)
P Values[c]	P = 0.001	N.S.	P = 0.003
Relative Risk (Control)[d]	---	Infinite	Infinite
Lower Limit	---	0.267	2.250
Upper Limit	---	Infinite	Infinite
Weeks to First Observed Tumor	---	105	41
Thyroid: Papillary Adenoma, Follicular-Cell Adenoma, or Papillary Cystadenoma NOS[b]	2/44(0.05)	17/49(0.35)	14/45(0.31)
P Values[c]	P = 0.003	P < 0.001	P = 0.001
Departure from Linear Trend[e]	P = 0.025	---	---
Relative Risk (Control)[d]	---	7.633	6.844
Lower Limit	---	1.971	1.709
Upper Limit	---	64.662	58.827
Weeks to First Observed Tumor	80	105	91

[a]Treated groups received doses of 0.1 or 0.2 percent in feed.

[b]Number of tumor-bearing animals/number of animals examined at site (proportion).

[c]The probability level for the Cochran-Armitage test is given beneath the incidence of tumors in the control group when P < 0.05; otherwise, not significant (N.S.) is indicated. The probability level for the Fisher exact test for the comparison of a treated group with the control group is given beneath the incidence of tumors in the treated group when P < 0.05; otherwise, not significant (N.S.) is indicated. For both Cochran-Armitage and Fisher exact tests a negative designation (N) indicates a lower incidence in the treated group(s) than in the control group.

[d]The 95% confidence interval on the relative risk of the treated group to the control group.

[e]The probability level of the test for departure from linear trend is given beneath the control group when P < 0.05.

not. When incidences were combined so that the numerator represented mice with either a papillary adenoma, a follicular-cell adenoma, or a papillary cystadenoma of the thyroid, the Cochran-Armitage test indicated a significant positive association between dietary concentration and tumor incidence for both males ($P < 0.001$) and females ($P = 0.003$). These were supported by significant ($P \leq 0.006$) Fisher exact test results in each sex for comparisons of each dosed group to the control group. Based on these results, the administration of 1,5-naphthalenediamine was associated with the incidence of thyroid neoplasms in both male and female mice.

For females an increased incidence of hepatocellular carcinomas was also observed among the dosed mice. The Cochran-Armitage test indicated a significant ($P = 0.001$) positive association between dose and incidence. This was supported by significant ($P < 0.001$) comparisons of both the high and low dose to the control group using the Fisher exact test. Based on these results the administration of 1,5-naphthalenediamine was associated with the incidence of hepatocellular carcinomas in female mice.

For female mice, when the incidence of alveolar/bronchiolar adenomas and alveolar/bronchiolar carcinomas were combined, an increased incidence in the dosed groups was noted. The Fisher exact test was significant for both the high ($P = 0.024$) and low ($P = 0.001$) dose groups. The departure from linear trend was significant since tumor incidence was increased more in the low dose than in the high

dose group. In historical control data compiled by this laboratory for the NCI Carcinogenesis Testing Program, 17/275 (6 percent) of the untreated female B6C3F1 mice had an alveolar/bronchiolar neoplasm. Based upon these results the administration of 1,5-naphthalenediamine was associated with the incidence of alveolar/bronchiolar neoplasms in female mice.

For females the Fisher exact test comparing the incidence of leukemia or malignant lymphoma in high dose mice with that in the controls had a probability level in the negative direction of $P = 0.045$, a marginal result which was not significant under the Bonferroni criterion.

Also for females the Cochran-Armitage test showed a significant ($P = 0.040$) negative association between dose and the incidence of adrenal pheochromocytomas, but the Fisher exact tests were not significant.

In male mice the possibility of a negative association between dose and the incidence of malignant lymphomas or leukemia was noted.

Based upon these statistical results the administration of 1,5-naphthalenediamine was associated with the increased incidence of thyroid neoplasms in male mice and of thyroid neoplasms, of hepatocellular carcinomas, and of alveolar/bronchiolar neoplasms in female mice.

V. DISCUSSION

There were no significant positive associations between dietary concentrations of 1,5-naphthalenediamine and mortality in either sex of rats or mice. In all groups adequate numbers of animals survived sufficiently long to be at risk from late-developing tumors.

Several uterine neoplasms occurred in dosed female rats at higher incidences than in corresponding controls. There was a significant positive association between dietary concentration of the compound and the incidences of endometrial stromal polyps in female rats. In addition, the high dose to control Fisher exact comparison was significant. Endometrial stromal sarcomas were observed in two low dose and two high dose female rats, but not in controls. Uterine adenocarcinomas occurred at a higher incidence in the high dose female rat group than in the control group, but the difference in tumor incidence was not statistically significant.

The administration of 1,5-naphthalenediamine was associated with an elevated incidence of clitoral gland neoplasms in female rats. There was a significant positive association between the concentration of the chemical added to the diet and the incidence of either adenomas or carcinomas of the clitoral gland in female rats. The incidence of either of these neoplasms in the high dose female rat group was significant relative to the incidence in the control group.

Elevated incidences of thyroid neoplasms were observed among dosed mice. For mice of both sexes there were significant positive

associations between dietary concentration of 1,5-naphthalenediamine and the incidences of thyroid C-cell carcinomas. For the females the high dose to control Fisher exact comparison supported the finding; this was not true for males. When the mice were grouped so that the numerator of the incidence represented those animals with a papillary adenoma, a follicular-cell adenoma, or a papillary cystadenoma of the thyroid, the Cochran-Armitage test was significantly positive for both males and females and all the Fisher exact comparisons supported the findings.

The incidence of hepatocellular carcinomas in female mice was significantly associated with increased concentration of 1,5-naphthalenediamine. In addition, the high dose to control and the low dose to control Fisher exact comparisons were significant. The incidence of alveolar/bronchiolar adenomas was significant, relative to controls, in both the low dose and the high dose female mouse groups.

Under the conditions of this bioassay, 1,5-naphthalenediamine was carcinogenic in female Fischer 344 rats, causing clitoral and uterine neoplasms. 1,5-Naphthalenediamine was also carcinogenic for B6C3F1 mice, producing thyroid neoplasms in males and neoplasms of the thyroid, liver, and lung in females. Insufficient evidence was provided for the carcinogenicity of the compound in male Fischer 344 rats.

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Review of the Bioassay of 1,5-Naphthalenediamine*
for Carcinogenicity
by the Data Evaluation/Risk Assessment Subgroup
of the Clearinghouse on Environmental Carcinogens

June 29, 1978

The Clearinghouse on Environmental Carcinogens was established in May, 1976, in compliance with DHEW Committee Regulations and the Provisions of the Federal Advisory Committee Act. The purpose of the Clearinghouse is to advise the Director of the National Cancer Institute (NCI) on its bioassay program to identify and to evaluate chemical carcinogens in the environment to which humans may be exposed. The members of the Clearinghouse have been drawn from academia, industry, organized labor, public interest groups, State health officials, and quasi-public health and research organizations. Members have been selected on the basis of their experience in carcinogenesis or related fields and, collectively, provide expertise in chemistry, biochemistry, biostatistics, toxicology, pathology, and epidemiology. Representatives of various Governmental agencies participate as ad hoc members. The Data Evaluation/Risk Assessment Subgroup of the Clearinghouse is charged with the responsibility of providing a peer review of reports prepared on NCI-sponsored bioassays of chemicals studied for carcinogenicity. It is in this context that the below critique is given on the bioassay of 1,5-Naphthalenediamine for carcinogenicity.

The reviewer agreed with the conclusion in the report that 1,5-Naphthalenediamine was carcinogenic in treated female rats and in both sexes of mice. He noted that the study was conducted in a room in which other compounds were under test. Based on the experimental findings, he concluded that 1,5-Naphthalenediamine may pose a carcinogenic risk to humans. The reviewer moved that the report on the bioassay of 1,5-Naphthalenediamine be accepted as written. The motion was approved without objection.

Clearinghouse Members present:

Arnold L. Brown (Chairman), Mayo Clinic
Paul Nettesheim, National Institute of Environmental Health Sciences
Verne Ray, Pfizer Medical Research Laboratory
Verald K. Rowe, Dow Chemical U.S.A.
Michael B. Shimkin, University of California at San Diego
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* Subsequent to this review, changes may have been made in the bioassay report either as a result of the review or other reasons. Thus, certain comments and criticisms reflected in the review may no longer be appropriate.

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