

The Oncogenicity of Two 1,1-Diaryl-2-propynyl *N*-Cycloalkylcarbamates¹

Paul N. Harris, William R. Gibson, and Robert D. Dillard

Division of Toxicology [P. N. H., W. R. G.], Eli Lilly and Company, Greenfield, Indiana 46140, and Division of Chemical Research [R. D. D.], Eli Lilly and Company, Indianapolis, Indiana 46206

SUMMARY

1,1-Bis(4-fluorophenyl)-2-propynyl *N*-cyclooctylcarbamate and 1,1-bis(4-fluorophenyl)-2-propynyl *N*-cycloheptylcarbamate were fed to rats for 3 months, and then all surviving animals were killed for necropsy. With the cyclooctyl compound, 18 of an effective number of 25 rats developed malignant lymphoma; 2 developed malignant lymphoma and colonic adenocarcinoma; and 2 developed ileal adenocarcinoma. The first tumor was found after 55 days. With the cycloheptyl compound, 19 of an effective number of 37 rats developed malignant lymphoma; 1 developed malignant lymphoma and mammary adenocarcinoma; and 2 developed mammary adenocarcinoma. The first tumor was found after 54 days.

INTRODUCTION

Several of a series of acetylenic carbamates synthesized by Dillard *et al.* (1, 2) had high activity against transmissible animal tumors. A 90-day toxicity test of 3 of these compounds showed them to be oncogenic for rats. We present data on 2 compounds with which no further study is planned; the 3rd is still under investigation.

MATERIALS AND METHODS

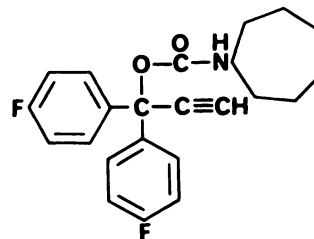
The compounds (Chart 1) were incorporated in the diet of recently weaned, individually caged Harlan rats at levels based upon the LD₅₀ (P. N. Harris, W. R. Gibson, and R. D. Dillard, unpublished data). Weights of the male rats ranged from 80 to 152 g, and weights of the females ranged from 75 to 139 g. The rats were weighed weekly, and the food supply was replenished after consumption for the week had been recorded. The dietary concentrations of the cyclooctyl compound were 0, 0.05, 0.1, and 0.25%, and those of the cycloheptyl derivative were 0, 0.01, 0.025, and 0.05%. There were 10 rats of each sex per group. Necropsy was done on all rats that died spontaneously, and the survivors were killed for necropsy after 90 days.

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RESULTS

The Cyclooctyl Compound. The control rats were tumor free at the end of the study. Chart 2 shows the fate of each treated rat. At all dose levels, males survived better than did females. Fifteen male and 10 female rats lived 55 days or more, and 22 of these developed tumors; 18 had malignant lymphoma, 2 had malignant lymphoma and colonic adenocarcinoma, and 2 had adenocarcinoma of the ileum. Intestinal tumors occurred in males only. The lymphomas were composed of large cells, and all were considered reticulum cell sarcoma.

1,1-Bis(4-fluorophenyl)-2-propynyl *N*-cycloheptylcarbamate



1,1-Bis(4-fluorophenyl)-2-propynyl *N*-cyclooctylcarbamate

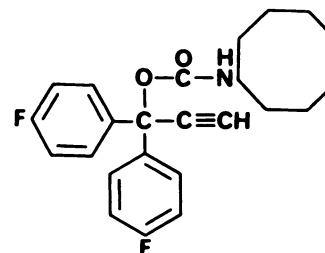


Chart 1.

Lymphomatous infiltration involved the spleen and liver in 20 rats, the adrenals in 19, the lungs in 14, the parathyroid lymph nodes in 6, the upper abdominal lymph nodes in 2, the kidneys in 4, the perirenal fat in 2, and the ovaries in 2. The lumbar vertebrae of 5 rats were sectioned; all were lymphomatous. When not neoplastic, the spleen was usually atrophic, and in only 2 rats was the thymus not atrophic.

The Cycloheptyl Compound. The control rats were tumor free at termination of the test. The outcome for each treated rat is shown in Chart 3. Eighteen males and 19 females lived 54 days or more, and 22 of these (7 males and 15 females)

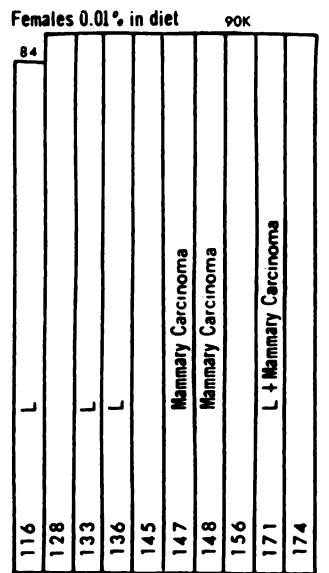
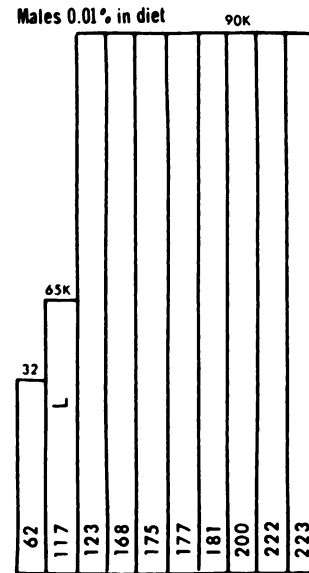
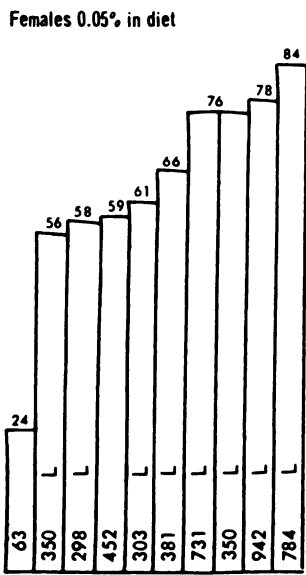
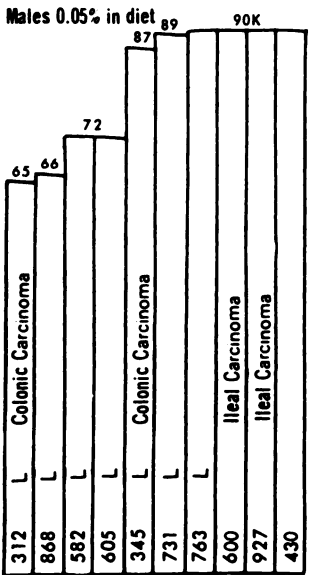
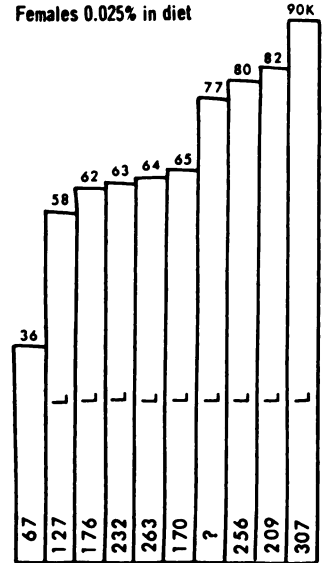
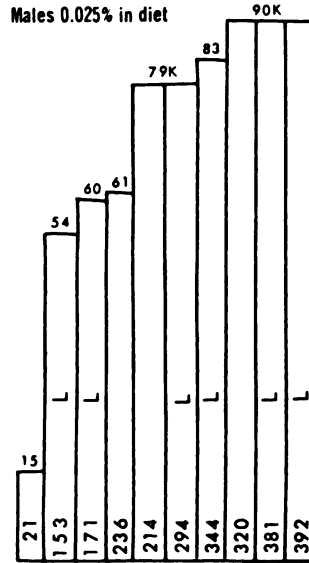
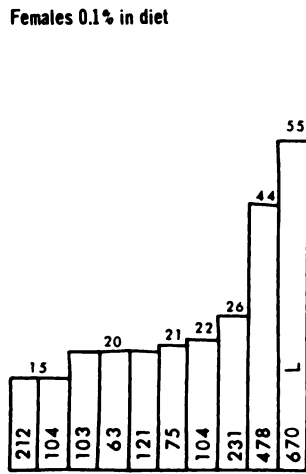
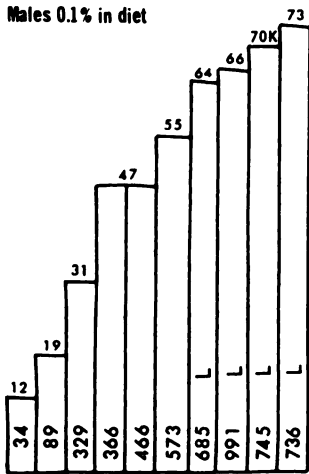
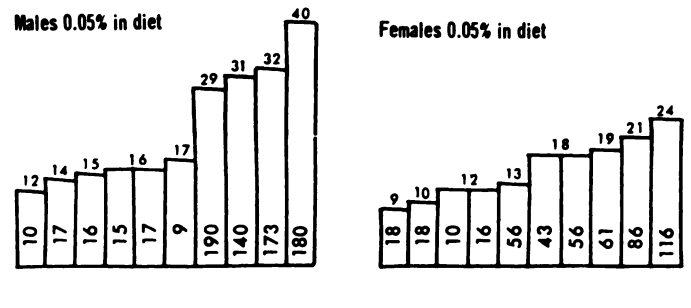
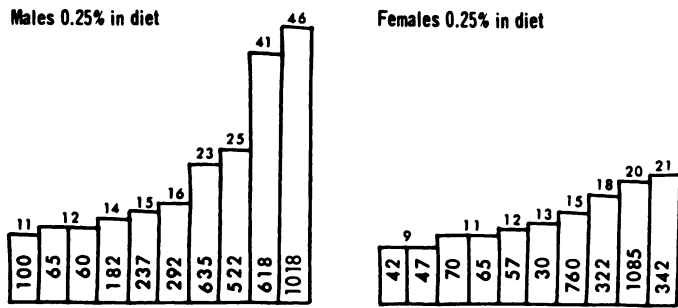


Chart 2. Fate of rats given the cyclooctyl compound. Each bar represents 1 rat. The rats are grouped by sex and dietary level of the compound. Survival in days is given at the top of the bar; K, rat killed for necropsy. Occurrence of neoplasia is shown in the middle of the bar; L, malignant lymphoma. The recorded intake of the carbamate (mg) is given at the base of the bar.

Chart 3. Fate of rats given the cycloheptyl compound. Each bar represents 1 rat. The rats are grouped by sex and dietary level of the compound. Survival in days is given at the top of the bar; K, rat killed for necropsy. Occurrence of neoplasia is shown in the middle of the bar; L, malignant lymphoma. The recorded intake of the carbamate (mg) is given at the base of the bar.

developed tumors; 19 developed malignant lymphoma only, 2 developed mammary carcinoma only, and 1 developed both types of neoplasm. These lymphomas were also reticulum cell sarcoma.

In all 20 lymphomatous rats, the spleen and liver were involved; in 3 cases, only these 2 organs were affected. In 6 rats, the liver involvement was less advanced than the spleen involvement. The adrenals of 17 rats were invaded; in 6 cases, involvement was appreciably less than in the spleen and liver. Lumbar vertebrae of 11 rats were sectioned, and all showed lymphoma. The lungs were invaded in 14 cases, the kidneys in 7, the perirenal fat in 4, the parathymic lymph nodes in 6, the upper abdominal lymph nodes in 7, the ovaries in 2, and the thyroid in 1. There was thymic atrophy in 58 rats and splenic atrophy in 19 of the nonlymphomatous animals.

DISCUSSION

These acetylenic carbamates are representatives of a new class of oncogen. Long-term studies of several related compounds now in progress are yielding a spectrum of tumors with

an indication of specificity related to structure; elaboration must await completion of the experiments.

In some rats, neoplastic infiltration of the spleen was much more advanced than in the liver, which suggests origin in the spleen. There was also a suggestive sequence of microscopic changes; rats that died early showed splenic atrophy; later there was reticuloendothelial hyperplasia and, still later, neoplasia.

ACKNOWLEDGMENTS

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