The Oncogenicity of Two 1,1-Diaryl-2-propynyl N-Cycloalkylcarbamates

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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.

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.

**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) developed malignant lymphoma; 1 developed malignant lymphoma and mammary adenocarcinoma; and 2 developed mammary adenocarcinoma. The first tumor was found after 54 days.

**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.

**MATERIALS AND METHODS**

The compounds (Chart 1) were incorporated in the diet of recently weaned, individually caged Harlan rats at levels based upon the LD$_{50}$ (P. N. Harris, W. R. Gibson, and R. D. Dillard, unpublished data).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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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.
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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 in-
volved; in 3 cases, only these 2 organs were affected. In 6 rats,
the liver involvement was less advanced than the spleen in-
volvement. 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 com-
pounds 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.

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