The Carcinogenic Activity of Some 5-Nitrofuran Derivatives in the Rat

J. Emory Morris, J. M. Price, J. J. Lalich, and R. J. Stein


SUMMARY

Three 5-nitrofuran derivatives showed carcinogenic activity when fed to female Holtzman rats at levels of 0.1 to 0.3% in a commercial diet for up to 44.5 weeks, while 2 other 5-nitrofuran derivatives and 5,5-diphenylhydantoin were inactive. Formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]-hydrazide induced benign and malignant tumors of the nonglandular forestomach. 5-Nitro-2-furanmethandiol diacetate and control of wound infections, secondary infections of burns, vaginitis, and urethritis (4, 32).

INTRODUCTION

5-Nitrofuran derivatives have some interesting biologic properties. Some of these derivatives inhibit spermatogenesis at the primary spermatocyte stage in rats (22), and 5-nitro-2-furaldehyde semicarbazone may be radiomimetic (20) and mutagenic (42). 5-Nitro-2-furaldehyde semicarbazone and related 5-nitrofurans may have some antitumor activity, especially against primary and metastatic testicular tumors.

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Table 1

<table>
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<th>Group</th>
<th>Compound and structure</th>
<th>Experiment No.</th>
<th>% of diet</th>
<th>Average (mg per day)</th>
<th>Total (gm)</th>
<th>No. of rats</th>
<th>Mammary</th>
<th>Tumor incidence</th>
<th>Other sites</th>
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<td></td>
<td>2</td>
<td>0.03 3.9</td>
<td>0.81</td>
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Incidence of tumors in female Holtzman rats fed nitrofurans, 5,5-diphenylhydantoin, or N-(2-fluorenyl)acetamide. The expected liver tumors found in the animals of Group 2 have not been tabulated.


In Experiment 1 the chemicals were fed for 36 weeks; in Experiment 2 the chemicals were fed for 44.5 weeks.

This indicates the number of rats surviving to at least 36 weeks of age, except for Group 2, in which it indicates the number of rats surviving to 17 weeks of age (the time when the first gross tumor was discovered).

All mammary tumors were histologically benign except those produced in Group 2 and in 6 rats in Group 4, Experiment 2.

Probability that the observed result might have occurred by chance, as calculated by the exact method for 2 X 2 tables.

This group received the grain diet described by Miller et al. (21).

This group received the test diet for the duration of the experiment (60 weeks).

and spectral properties, was 5-nitro-2-furaldehyde azine. This compound was present to the extent of about 3% in the chemical grade material which was used in these experiments (Dr. James A. Buzard, Eaton Laboratories, personal communication). The same chromatographic and spectral methods did not detect these impurities in the pharmaceutical, medicinal grade material which Dr. Buzard generously donated for comparison with the material used in these studies. The relationship between the results obtained here and the presence of impurities in the samples used is considered in the Discussion section of this paper.

The other compounds used in this study were found, after
Test Animals

Female albino rats (Holtzman Rat Company, Madison, Wisconsin) were housed in raised, screen-bottomed cages in groups of 3 to 6 animals per cage. Animals were allowed food and water ad libitum. In Experiment 1, groups of 20 rats, 60 days of age and averaging 170 to 175 gm in body weight, were started on the test diets. Groups of 30 to 36 rats, averaging 55 to 58 gm in body weight and 22 days of age, were used in Experiment 2.

Diets and Animal Care

Ground Wayne Lab-Blox (Allied Mills, Inc., Chicago, Illinois) was used as the stock diet. Test supplements were prepared by grinding the chemical and glucose together in a glass mortar in proportions such that the test diets could be prepared by the addition of 10 gm of the triturate/kg of ration. The supplement and stock diet were then mixed thoroughly in an institutional food-mixing machine (Hobart Manufacturing Company, Troy, Ohio). Diets were prepared in 5-kg quantities and stored at 8-12°C until needed. In Experiment 1 an additional group of rats was fed a test diet containing 1-[(5-nitrofururylidene)amino]hydantoin which was prepared in the same manner, except that the grain diet described by Miller et al. (21) was used in place of the ground Wayne Lab-Blox diet.

The dietary concentrations of the chemicals and the resulting dosages are shown in Table 1. In Experiment 1 the test diets were fed for 36 weeks; the stock diet (as pellets) was fed for an additional 17 to 19 weeks in order to allow small tumors to grow to a detectable size, and the surviving rats were then killed. In Experiment 2 test diets were fed for 44.5 weeks; the stock diet (as pellets) was fed for an additional 15 to 17 weeks, and the surviving rats were then killed. The partially emptied food containers were weighed for 3 days at least once every 3 weeks to permit calculation of the amount of chemical consumed.

The rats were palpated approximately biweekly at the time of weighings to detect superficial tumors. The animals were inspected at least once and usually twice a day. Morbid animals were sacrificed when it appeared that they would not survive until the next inspection; nevertheless, some animals were lost because of postmortem autolysis or cannibalism.

Postmortem Examination.

Where possible, all animals were subjected to thorough postmortem examinations. Anesthetized animals were exsanguinated by severing the brachial artery. The brain and the thoracic and abdominal viscera, including the lumen of the gastrointestinal tract and the lumen of the urinary bladder, were grossly examined.

All tissues except the bladders were fixed in 10% formalin, 10% buffered formalin, or formalin acetic acid (2000 ml of distilled water, 1000 ml of 95% ethanol, 300 ml of formalin solution, and 50 ml of glacial acetic acid). All bladders were fixed in Bouin's solution. Specimens of all gross tumors, all bladders, and samples of the livers, kidneys, and spleens were embedded in paraffin, sectioned, and stained with hematoxylin and eosin. With the finding of evidence of respiratory infection, samples of lung tissue were examined microscopically. Other tissues with even slight gross evidence of abnormality were also examined microscopically.

Additional Medication

In an effort to combat the high mortality caused by respiratory infection, animals in Experiment 1 received Terramycin (Pfizer Laboratories Division, Charles Pfizer & Company, Inc., New York, N. Y.) at a concentration of 125 mg/liter in the drinking water for 5 days during the 13th week of feeding. Animals in both experiments received Tetracycline HCl per liter in the drinking water for 11 days beginning the 21st week of feeding in Experiment 1 and the 8th week of feeding in Experiment 2. Neither treatment had an appreciable effect on the mortality rate. Since α-hemolytic pneumococcus was the predominate organism found in cultures of lung tissue from moribund animals, penicillin (Bicillin Long-Acting, a brand of benzathine penicillin G suspension, 300,000 units per ml, Wyeth Laboratories, Inc., Philadelphia, Pennsylvania) was given (0.5 to 1.0 minim per rat i.m.) in the 23rd week (Experiment 1) and 10th week (Experiment 2) of feeding. Penicillin injections were repeated at 3- to 4-day intervals throughout the remainder of both experiments.

During the 33rd and 20th weeks respectively of feeding the test diets, a pinworm infestation was noticed in other rats housed in the same room. Piperazine citrate (3 gm/liter in the drinking water for 7 days) was administered to all animals in the room. This infestation was probably caused by the admission of previously infested animals to the colony without adequate quarantine. Pinworm infestation was not detected in the animals used in these experiments.

RESULTS

Growth, Survival, and Toxicity

Except as noted below, the animals appeared to tolerate the drugs at the levels fed and had no toxic manifestations. Survival was poor in all groups, including untreated control rats, until penicillin therapy was begun.

Variations in total drug intake (Table 1) mainly reflect differences in dietary concentrations or duration of feeding (as with rats fed N(2-fluorenyl)acetamide and 5,5-diphenylhydantoin in Experiment 2). The method for estimating diet consumption, however, was only semiquantitative since it was not possible to correct for diet spilled by the rats. Therefore, all of the values given for drug consumption in Table 1 must be regarded as maximal estimates. Rats that received fomivic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide ate approximately 70% as much food as untreated controls. An attempt to increase the intake of this compound by increasing the dietary concentration to 0.5% was unsuccessful. During exposure to the higher concentration, the rats lost weight, probably because the amount of food eaten decreased by
about 50%. Presumably this decreased food consumption was due to a lowered palatability of the diet since doses more than twice as large (on the basis of weight of chemical per unit of body weight) were well tolerated when administered by stomach tube (R. J. Stein, unpublished data).

5-Nitro-2-furaldehyde semicarbazone caused a high degree of irritability within 24 to 48 hr after the initiation of feeding. Treated rats showed a marked tendency to attack, to squeal, to resist handling, and to be extremely restive during weighings. Hyperirritability was previously observed in acute toxicity testing of this drug (17), and peripheral neuritis has been a limiting factor in the use of this drug in cancer chemotherapy (12, 37). In the present experiments the hyperirritability disappeared within several weeks after withdrawal of the drug. Similar abatement of the peripheral neuritis in patients receiving large doses of the drug has been reported (37). These rats also experienced generalized seizures which seemed to be initiated by loud noises, handling, or other excitement. No fatalities appeared to result from such convulsive episodes.

Neoplastic Reactions

Table 1 shows the incidence of neoplastic reactions observed in these experiments. Brief descriptions of the various tumors follow.

Gastrointestinal Tract. Acetone [4-(5-nitro-2-furyl)-2-thiazolyl] hydrazone and formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazone were the only agents which induced lesions of these organs. The former compound induced multiple squamous papillomas of the forestomach, and the latter compound induced carcinomas of the small and large intestine. Carcinomas of the esophagus and of the tongue were also seen in rats fed the acetone hydrazone derivative.

The forestomach lesions varied from squamous hyperplasia to papillomas with invasion of the submucosa and muscularis. These alterations were associated with numerous mitotic figures (up to 7 per high-power field) (Figs. 1, 2). Since these tumors did not penetrate the serosal surface, they have not been classified as carcinoma in accordance with the criterion of Stewart et al. (36).

The intestinal lesions were polypoid adenomas or adenocarcinomas (Figs. 3, 4). The larger lesions showed some tendency toward annular growth and were moderately necrotic. Mitotic activity was increased considerably, with glands and nests of epithelial cells invading the muscular layers of the intestinal wall, and some tumors were actively secreting. Lung lesions in one rat were interpreted to be metastatic, but it could not be resolved if they had originated from the intestinal tract.

Kidney. Kidney tumors were found only in rats which received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazone. These tumors varied from less than 1 mm to about 9 mm in diameter (Figs. 5, 7, 9). They were located in the cortex, usually near the corticomedullary junction. The larger tumors were visible on the surface of the intact kidney. The smaller lesions were visible only on the cut surface, and some were found only microscopically. The lesions were circumscribed, uniform in appearance, and white or grayish-pink in color. They occurred as single or multiple tumors of one kidney or bilaterally.

Microscopically, the tumors grew as solid alveolar masses of cells or in a papillary cystic pattern (Figs. 6, 8—10). They were circumscribed and contained only small amounts of connective tissue. The tumor cells resembled tubular epithelial cells. Compared to the surrounding tissue, the tumor cells stained more intensely, and the nuclei were somewhat larger and usually contained a single prominent nucleolus. Mitotic figures were rare. The adjacent kidney tissue was usually compressed (Figs. 5, 6, 10). Frequent complications were distention of the renal tubules with hyaline casts and interepithelial deposition of an unidentified golden-brown pigment. Several kidneys which did not contain tumors also had tubular atrophy with pigment deposition. Only the clearly invasive lesions (Figs. 7, 8) were regarded as carcinomas.

External Auditory Canal. Tumors of the external auditory canal occurred only in rats that received N-(2-fluorenyl)-acetamide or formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]-hydrazide. The tumors induced with either agent had a similar appearance. They were white, yellowish, or grayish-white in color and generally circumscribed with a freely movable skin. The large tumors exceeded 1 cm in diameter and produced a malocclusion of the mandible or invaded the masseter muscle. The cut surfaces were rough and friable, and a waxy material was frequently expressed from the tumor while it was being cut.

The lesions induced with formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl]hydrazide were squamous cell carcinomas (Fig. 11) with a tendency to keratinize. Whether the tumors originated in the epithelium or the external auditory canal or from the ceruminous glands was not established. However, several of the carcinomas resembled sebaceous glands.

Mammary Glands. 5-Nitro-2-furaldehyde Semicarbazone. Tumors induced with this chemical were glandular in appearance with tough, white connective tissue septa between the lobules, which were pink in color. Because the lobules were freely movable and because of the tough fibrous septa, these tumors were difficult to cut. Although some of the tumors attained a large size (the largest was 240 gm), they never became necrotic or penetrated through the skin. These tumors were always well encapsulated, and they did not invade adjacent tissues. Animals frequently presented multiple tumors of the mammary glands.

Microscopically, these tumors were fibroadenomas, with considerable variation in the proportions of fibrous and epithelial elements. Variants from fibroma (Fig. 12) to fibroma with occasional widely scattered ducts or clumps of epithelial cells (Fig. 13) to adenoma with little fibrous tissue (Fig. 14) were seen. The distribution of epithelial elements within a lobule was primarily either acinar or ductal. Lobules with ductal proliferation usually contained more fibrous tissue. Frequently both types of lobules were present in the same tumor. Usually mitotic activity was slight (not more than 1 to 2 mitotic figures per 5 high-power fields), but occasionally areas of considerably greater activity would be found. Often these tumors exhibited hyaline-like secretions in the ducts and acini, and on occasion these spaces were greatly distended. Frequently the cytoplasm of the acinar cells contained clear secretory vacuoles.

Formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. Many of the mammary tumors induced with this compound...
were similar grossly to those induced with \( N-(2\text{-fluorenyl})\)-acetamide. They were a grayish-pink color and appeared somewhat lobulated. The cut surface was smooth or slightly rough but retained some lobular character. Larger tumors exhibited necrosis and frequently would ulcerate through the skin. The tumors were always well encapsulated and did not appear to invade the adjacent tissues. Animals frequently presented multiple tumors of the mammary glands.

Many breast tumors induced with this agent were similar to those seen in animals fed 5-nitro-2-furaldehyde semicarbazone (Fig. 12–14). They were classified as fibromas or fibroadenomas.

Other breast tumors found in animals fed this compound presented greater cytologic variation on microscopic examination. Some were well-differentiated adenomas with evidence of secretion (Fig. 15). Atypical fibroadenomas (Fig. 16) had both papillary and cystic patterns of growth with markedly irregular stromal trabeculae. Epithelial elements varied from single to multiple cell thickness and showed some tendency both to form acini within the stroma and to grow as isolated clumps of epithelial cells. Some variation in size, shape, and polarity of the nuclei was noted. Frequently basement membranes were absent. Activity of less than 1 mitotic figure per high-power field was common, but occasionally more activity was seen in a few areas. These atypical fibroadenomas were common. The carcinoma was distinguished by greater nuclear pleomorphism, increased mitotic activity, e.g., 6 mitotic figures per high-power field, and frequent hyperchromatic nuclei (Fig. 17). The lesions designated as carcinomas were relatively easy to classify; all doubtful lesions were classified atypical fibroadenomas.

Other Agents. The few mammary lesions occurring in other groups were fibroadenomas, except in the 3 animals which received acetone \([4-(5\text{-nitro-2-furyl})-2\text{-thiazolyl}]\) hydrazone, that presented atypical fibroadenomas.

Controls. Three rats in the control group for Experiment 2 had mammary lesions, 2 of which were clearly benign. One lesion (Figs. 18, 19) was considered to be an atypical fibroadenoma. The atypical lesions always contained small areas suggestive of carcinoma, but the majority of the tumor was too well differentiated to be labeled as malignant.

Liver. Aside from the rats which received \( N-(2\text{-fluorenyl})\)-acetamide, only 1 rat, which had received formic acid \(2-[4-(5\text{-nitro-2-furyl})-2\text{-thiazolyl}]\) hydrazide, presented any neoplastic change in the liver. This lesion was a white, hemorrhagic tumor in the left lobe. The tumor grew in a trabecular pattern and compressed the adjacent liver cells to form a pseudocapsule (Fig. 20). Mitotic figures were rare. The lesion was interpreted as a hemangiendothelioma or a hemangioendothelial sarcoma. (In this case the host also bore an atypical fibroadenoma and fibroadenomas of the breast, an adenocarcinoma of the small bowel, a renal adenoma, and a squamous cell carcinoma of the auditory canal. The cytologic pattern in the liver did not resemble any of these other neoplasms.)

Urinary Bladder and Other Sites. No significant pathology was found in any of the sections of the urinary bladder. The only other tumors found were a fibroma of the external ear in a rat treated with formic acid \(2-[4-(5\text{-nitro-2-furyl})-2\text{-thiazolyl}]\) hydrazide and a malignant lymphoma in a rat treated with 5,5-diphenylhydantoin.

DISCUSSION

An unexpectedly large number of animals died early in the experiments. The pathologic findings (13) and the clinical experience that penicillin therapy almost completely controlled these deaths support the opinion that they were usually the result of overwhelming infections superimposed on chronic respiratory disease often seen in rat colonies (26).

The criterion of Stewart et al. (36) for the diagnosis of experimental carcinoma of the stomach, namely, that the carcinoma infiltrates all coats of the gastric wall and extends onto the serosal surface, was adopted. On the basis of this criterion, the gastric tumors observed in these experiments could not be considered carcinomas. Many of them, however, presented histologic evidence suggestive of malignancy.

Only 2 spontaneous squamous cell carcinomas of the stomach have been reported (6, 31, 34, 39). Miller et al. (21) reported that 17 of 20 rats receiving 2-nitrofluorene developed squamous cell carcinomas of the forestomach. In the present study, 15 of 20 rats in Experiment 2 developed papillomas or invasive papillomas of the stomach.

Carcinoma of the esophagus occurs rarely, even in response to chemical carcinogens. One spontaneous squamous cell carcinoma has been reported (5, 34, 39). Only unsymmetric nitrosamines have proved active against the esophageal epithelium (8). Only one spontaneous squamous cell carcinoma of the tongue has been reported in the rat (34).

The lesions of the intestine were classified on the basis of cytologic variation and distortion of the organoid pattern. No evidence of peritoneal seeding or of lymph node involvement was found. Four spontaneous adenocarcinomas of the intestine have been reported (5, 34, 39, 41). A variety of chemicals reportedly induce adenocarcinomas of the intestine (21, 23, 25).

Magee and Barnes (19) have suggested that the renal adenoma represents an early stage of development along a continuum to a frankly malignant neoplasm. Moreover, spontaneous renal tumors in the rat are uncommon (34). Bullock and Rohdenburg (3) observed 10 adenomas in 4300 rats of mixed strain. In the present study renal tumors were only found in rats receiving formic acid \(2-[4-(5\text{-nitro-2-furyl})-2\text{-thiazolyl}]\) hydrazide. Magee and Barnes (19) have induced renal tumors with dimethylnitrosamine, and the lesions of the present study were similar to the adenomas which they describe. Morris et al. (23) induced epithelial tumors in the kidney of rats with \(N-4-(4'\text{-fluoro})\)-biphenylacetonitrile, and, again, the histologic pattern they described was similar.

The tumors of the external auditory canal were similar to those previously described (25, 34). Although the number of these tumors induced with formic acid \(2-[4-(5\text{-nitro-2-furyl})-2\text{-thiazolyl}]\) hydrazide was not statistically significant, the absence of tumors at this site in all other groups is highly suggestive that these tumors do not represent a chance occurrence. Snell (34) observed 5 carcinomas at this site in 488 rats, and in all cases the animals were over 21 months of age.

Spontaneous liver tumors are exceptional. The liver tumor
observed in the present studies was similar to the hemangioendothelial sarcomas which Takayama and Oota (38) produced in the livers of mice with dimethyl- and diethyl-nitrosamine. Toth et al. (40) have also produced hemangiomias and hemangiosarcomas in mice with dimethylnitrosamine. The single tumor observed is not statistically significant, but because this type of tumor is unusual, its occurrence in this study may nevertheless be significant.

The breast tumors induced with 5-nitro-2-furaldehyde semicarbazone were of the type frequently seen even in old, untreated rats, although spontaneous tumors of this type seldom appear in untreated rats before 14 months of age (27). Stewart et al. (35) concluded that, on the basis of transplantability and other considerations, this type of tumor may be considered malignant. Breast tumors induced with formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide or 5-nitro-2-furaldehyde semicarbazone were transplantable to newborn pen-bred rats (Holtzman strain) by subcutaneous implantation of tumor minces (J. E. Morris and J. M. Price, unpublished data).

Because the 5-nitro-2-furaldehyde semicarbazone used in these experiments was not pure, the conclusion that this chemical induces fibroadenomas of the breast tissue is somewhat tenuous. However, the impurity is also a nitrofuran derivative. Whether the semicarbazone or the azine impurity or both are the active agents cannot be determined from these studies. If the azine alone is the active agent, it exerts its effect at a very low level since it was probably present in the diet at a concentration of about 0.003%.

The other 2 compounds in these experiments found to induce significant neoplastic changes, acetone [4-(5-nitro-2-furyl)-2-thiazolyl] hydrazine and formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide, are identical in structure except for the substitution on the terminal nitrogen of the hydrazine side chain. For both of these agents it is difficult to ind the 5-nitrofuran portion of the molecule because thiazole and hydrazine moieties are also present. Numerous thiazole derivatives have been tested and found to be inactive (11, 33). Morris et al. (24) found one adrenal adenoma in 9 rats fed 2-acetamido-4-(2'-fluoryl)thiazole. Kelly and O’Gara (15) found that N-isopropyl-o-(2-methylhydrazino)p-toluamide hydrochloride induced leukemia and multiple mammary carcinomas in both male and female rats. A number of other hydrazine derivatives were inactive or weakly active. Isonicotinic acid hydrazide (isoniazid) has been reported to have some tumorigenic activity (2). Biancifiori and Ribacchi (2) suggested that this activity was due to the formation of free hydrazidine by hydrolysis in vivo, but it is difficult to see how hydrazidine could be readily derived in vivo from the compounds found active in the present study. Nevertheless, the carcinogenic activity of the compounds reported here may be more closely related to the hydrazine or thiazole moiety than to the nitrofuran moiety.

On the other hand, metabolic reduction of the nitro group of 5-nitrofuran derivatives such as 5-nitrofuraldehyde semicarbazone and 5-nitrofuraldehyde acetylhydrazine is well established (29), and other aromatic (benzenoid) nitro compounds which are carcinogenic, e.g., 2-nitrofluorene and 4-nitrobenzhydrol, also undergo metabolic reduction (9, 18). The high tumorigenic activity of acetone [4-(5-nitro-2-furyl)-2-thiazolyl] hydrazine and of 2-nitrofluorene (21) for the forestomach epithelium of the rat may be related in both cases to a reductive metabolic fate, even though the two nitro compounds are only distantly related chemically.

The administration of drugs in addition to those under test always complicates the interpretation of results and is to be avoided. In these experiments, however, the use of penicillin must be regarded as essential since without such therapy early deaths would probably have terminated the experiments before the test drugs could have expressed their effects. Dickens and Jones (7) have reported that penicillin G induces sarcomas at the site of repeated injection, but their conditions included subcutaneous injections of much larger doses at more frequent intervals. Nevertheless, the possibility of a cocarcinogenic effect cannot be ruled out. Other medications used during these experiments were inactive or have not been tested (11, 33).

5,5-Diphenylhydantoin was included in the present series because the use of it and closely related hydantoin anticonvulsant drugs in patients have been reported to induce lymphadenopathy, which clinically and histologically mimics malignant lymphomas (30). In patients the lymphadenopathy disappeared in 1 to 2 weeks following cessation of therapy with the inducing drug. Therefore, rats in Experiment 2 were fed the drug until the termination of the experiment. No lymphadenopathy, except 1 malignant lymphoma in the mediastinum, was observed in any of the rats so treated.

The activity of the nitrofuran derivatives studied was less than the activity of N-(2-fluorenyl)acetamide. The total incidence of tumors of the mammary gland was similar, but the latent period was considerably longer even though the dose of the nitrofuran compounds was approximately 8 times greater on a molar basis. If the tumors of the external auditory canal observed in the rats treated with formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide were not chance events, then this compound must be considered much less potent than N-(2-fluorenyl)acetamide for this site also.

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REFERENCES

Carcinogenic Activity of 5-Nitrofuran Derivatives

Fig. 1. Papilloma of the forestomach with prominent keratin pearl formation. Invasion is limited to the submucosa. This rat received acetone [4-(5-nitro-2-furyl)-2-thiazolyl] hydrazine. X 28.

Fig. 2. Papilloma of the forestomach with infiltration of the muscularis. (With less rigorous criteria, this type of lesion might be classified as a carcinoma. See text). This rat received acetone [4-(5-nitro-2-furyl)-2-thiazolyl] hydrazine. X 135.

Fig. 3. Adenomatous polyp of the large intestine. This animal also presented an adenocarcinoma of the small intestine. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 23.

Fig. 4. Adenocarcinoma of the small intestine with infiltration into the serosa. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 28.

Fig. 5. Adenoma of the kidney. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 4.

Fig. 6. An area of the lesion shown in Fig. 5. The tumor was well demarcated and showed no tendency to invade. X 135.

Fig. 7. Papillary adenocarcinoma of the kidney with invasion of the surrounding parenchyma. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 4.

Fig. 8. An area of the lesion shown in Fig. 7. X 28.

Fig. 9. Adenoma of the kidney. Small, benign kidney tumors, visible only in microscopic section or as small whitish-gray dots in gross cut section, were the most frequent kidney lesion. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 85.

Fig. 10. Papillary adenoma or carcinoma of the kidney. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 100.

Fig. 11. Carcinoma of the external auditory canal. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 100.

Fig. 12. Fibroma of the mammary glands. This rat received 5-nitro-2-furaldehyde semicarbazone. X 135.

Fig. 13. Fibroadenoma of the mammary glands. This rat received 5-nitro-2-furaldehyde semicarbazone. X 135.

Fig. 14. Fibroadenoma of the mammary glands. This rat received 5-nitro-2-furaldehyde semicarbazone. X 50.

Fig. 15. Secreting fibroadenoma of the mammary glands. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 100.

Fig. 16. Atypical fibroadenoma of the mammary glands. Irregularity and poor differentiation of the neoplastic glands with frequent mitoses made this type of tumor difficult to distinguish from frank carcinoma. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 50.

Fig. 17. Adenocarcinoma of the mammary glands. In some areas the glandular pattern was completely absent. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 75.

Fig. 18. Atypical fibroadenoma from the mammary glands of a control rat. X 24.

Fig. 19. An area of the lesion shown in Fig. 18. X 100.

Fig. 20. Hemangiendothelioma or hemangiendothelial sarcoma of the liver. This rat received formic acid 2-[4-(5-nitro-2-furyl)-2-thiazolyl] hydrazide. X 135.
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