ROE1970P

289

Fd Cosmet. Toxicol. Vol. 8, pp. 135–145. Pergamon Press 1970. Printed in Great Britain

Research Section

Feeding Studies on Sodium Cyclamate, Saccharin and Sucrose for Carcinogenic and Tumour-promoting Activity

F. J. C. ROE, L. S. LEVY and R. L. CARTER

Chester Beatty Research Institute, Institute of Cancer Research, Royal Cancer Hospital, Fulham Road, London, S.W.3, England

(*Received 4 September 1969*)

Abstract—Groups of 50 female Swiss mice were fed for 18 months on a standard diet containing sucrose (10%), sodium cyclamate (5%) or saccharin (5%), while 100 control mice were fed on the standard diet alone. The survival times were comparable in all groups and no acute toxic effects were encountered. No local tumours in the gastro-intestinal tract, nor excess incidence of distant tumours, were found in animals fed on the various sweeteners. The mice fed on the diet containing 10% sucrose gained more weight than animals in the other groups, but did not show an increased incidence of neoplasms.

Comparable groups of mice were given a single intragastric instillation of 50 μg benzo[*a*]pyrene in 0·2 ml polyethylene glycol 400, 7 days before the start of feeding of the different test diets. Some mice in all these groups developed, as expected, benign and malignant neoplasms of the forestomach epithelium, but treatment with the sweetening agents had no obvious effect on the incidence, number or histological type of these or of any other type of neoplasm.

No neoplasms of the urinary bladder were seen on careful macroscopic examination of mice at necropsy; the bladders were not examined microscopically.

It is concluded that, under the experimental conditions described, the three sweeteners examined showed no carcinogenic or tumour-promoting activity.

INTRODUCTION

The two non-caloric synthetic sweeteners that have found wide use as substitutes for dietary sugars are saccharin (2,3-dihydro-3-oxybenzisosulphonazole) and the sodium and calcium salts of cyclamate (*N*-cyclohexylsulphamate). Until recently saccharin and cyclamate were believed to be relatively inert pharmacologically, and over the wide range of doses that have been studied they produce no acute toxic effects apart from slight softening of the stools (Fitzhugh, Nelson & Frawley, 1951; Richards, Taylor, O'Brien & Duescher, 1951; Schoenberger, Rix, Sakamoto, Taylor & Kark, 1953; Taylor, Richards, Wiegand & Weinberg, 1968). The risks of long-term exposure, however, are still somewhat uncertain. Stein, Serrone & Coulston (1967) saw no haematological, biochemical or pathological changes in monkeys fed sodium cyclamate at 4 g/kg/day for 9 months. In a number of studies no tumours have been reported when cyclamate or its metabolite, cyclohexylamine, have been fed to experimental animals (see Taylor, Richards, Wiegand & Weinberg, 1968, for review) though a related compound—dicyclohexylamine—has been stated to be weakly carcinogenic to rats (Pliss, 1958; Shabad, 1963; Lomonova, 1965). Previously, Fitzhugh *et al.* (1951) had observed an "increased incidence of the uncommon condition of abdominal lymphosarcoma" in rats maintained for life on a diet containing 5% saccharin.

After the present paper had been prepared for publication, we became aware of a report by Bajusz (1969) on the occurrence of myocardial lesions in hamsters given high doses of calcium cyclamate and of the then unpublished observation of an increased risk of neoplasms of the bladder in rats fed on a high concentration of a saccharin–cyclamate mixture (Price, Biava, Oser, Vogin, Steinfeld & Ley, 1970).

At the time the experiments reported in this paper were begun, the evidence relating to the carcinogenicity of sugars and sweeteners in general was difficult to interpret. This applied particularly to the induction of subcutaneous sarcomas in rats by repeated subcutaneous injections of various sugars, including sucrose (Hueper, 1965; Grasso & Golberg, 1966; Carter, 1970). Hueper (1965) suggested that such tumours arose because the test carbohydrate was contaminated with polycyclic aromatic hydrocarbons during preparation, while Grasso & Golberg (1966) stressed that non-specific physico-chemical factors such as repeated injection of hypertonic solutions played an important part in sarcoma development. Few, today, would accept that such tumours reflect 'inherent' carcinogenic activity in the sugars themselves. On a more general level, there is some evidence that increased caloric intake *per se* may favour the development of tumours in experimental animals (Tannenbaum & Silverstone, 1953). In theory, therefore, the substitution of non-caloric sweeteners such as saccharin and cyclamate for sucrose should lead non-specifically to a reduced risk of neoplasia.

In view of these conflicting observations, it seemed worthwhile to re-appraise the possible carcinogenic activity of cyclamates and other sweeteners added to the diet of experimental animals. In addition to the tests for complete carcinogenic activity, we explored the possibility that the addition of sweetening agents to the diet promoted tumour development after oral treatment with a known carcinogen (benzo[*a*]pyrene; BP). The need to examine food additives for co-carcinogenicity as well as for carcinogenicity has been stressed elsewhere (Roe, 1968) but sweetening agents have not, to our knowledge, been tested from this viewpoint.

EXPERIMENTAL

Materials. The sweetening agents used were sucrose (British Drug Houses Ltd., Poole, Dorset), saccharin (British Saccharin Sales Co. Ltd., Nottingham) and sodium cyclamate (Abbott Laboratories Ltd., Sittingbourne, Kent). BP was obtained from Koch-Light Laboratories, Ltd. (Colnbrook, Bucks.) and polyethylene glycol (PEG) of average molecular weight 400, from British Drug Houses Ltd. (Poole, Dorset).

Animals and diets. Female mice of a random-mated Swiss albino strain (9–14 wk of age) were used. The standard diet used for both control and treated groups was Oxoid Breeding Diet, as supplied by Oxo Ltd. (London). This diet included crude oil (3·8%), crude protein (20·5%), crude fibre (2·6%), digestible crude oil (3·1%), digestible crude protein (17·9%) and digestible crude fibre (1·2%). It also contained a mixture of vitamins, including A, B_1, B_2, B_6, B_{12}, D_3, E, nicotinic acid, pantothenic acid, biotin and the 'essential nutritional factors', inositol and choline, and necessary minerals. Test diets were prepared by blending the standard diet and sweeteners in a powdered form in a food mixer. Approximately 5 g dry powdered food, moistened with water, was allocated daily to each mouse, this being rather more than the amount they regularly consumed.

Experimental design and conduct. The mice, divided into eight groups, received various treatments which are summarized in Table 1. On day 0, animals were given a single intra-

gastric instillation of either 0·2 ml PEG or 50 μg BP in 0·2 ml PEG after overnight starvation. All mice then received the standard diet only (i.e. without sweeteners) for 7 days, before being transferred to their various test diets. Throughout, water was given *ad lib.* They remained on these diets until the experiment terminated 18 months after pretreatment with BP or PEG. The mice were weighed fortnightly for the first 4 months of the experiment and monthly thereafter. After the first 6 wk all mice were examined at weekly intervals for obvious tumour development and daily for general health. Sick animals were killed. Post-mortem examinations were carried out on mice killed or found dead during the experiment

Table 1. *Survival of mice given various sweetening agents in the diet with or without oral pretreatment with BP*

Group no.	No. of mice/group	Pretreatment* plus dietary sweetener (%)	No. of survivors at month 12	15	18
1 H†	100 48	PEG only	88 40	77 35	65 32
1 L†	100 52		88 48	77 42	65 33
2 H	100 39	BP + PEG only	90 33	81 31	61 21
2 L	100 61		90 57	81 50	61 40
3	50	PEG + 5% cyclamate	45	42	34
4	50	BP + PEG + 5% cyclamate	48	45	41
5	50	PEG + 10% sucrose	45	34	27
6	50	BP + PEG + 10% sucrose	47	40	35
7	50	PEG + 5% saccharin	44	40	36
8	50	BP + PEG + 5% saccharin	38	37	32

* Mice were pretreated with an oral dose of 50 μg BP in 0·2 ml PEG or with 0·2 ml PEG alone, followed 7 days later by diets containing added sweetener.

† H and L refer to mice weighing >36 g and <36 g respectively at the start of the experiment (see text).

or killed terminally. Some 449 out of 500 mice were so examined; the remainder were either found in a state of advanced autolysis or had been eaten by cage mates. Post-mortem examination was carried out by a standardized procedure which involved the completion of a form by the entry of negative as well as positive findings (Roe, 1965). All major organs including the urinary bladder but excluding the brain, pituitary gland and spinal cord, were examined macroscopically in the present experiment. All neoplasms, or lesions suspected of being neoplasms, were removed and fixed in Bouin's fluid. Paraffin sections were prepared and stained with haematoxylin and eosin.

Because of a misunderstanding, mice were not allocated randomly to the eight treatment groups. The oldest, and therefore heaviest, mice were included mainly in the control groups (groups 1 and 2) while the lightest and youngest mice were allocated to test groups 3–8. In order to see if initial body weight influenced the subsequent incidence of tumours, a distinction was made between heavier (above 36 g) and lighter (below 36 g) animals, designated H and L, respectively, in the two control groups. The observations for these H and L sub-groups are recorded separately in the tables.

RESULTS

Survival

The numbers of survivors at 12, 15 and 18 months are shown in Table 1. Neither treatment with BP nor subsequent treatment with any of the sweetening agents appeared to

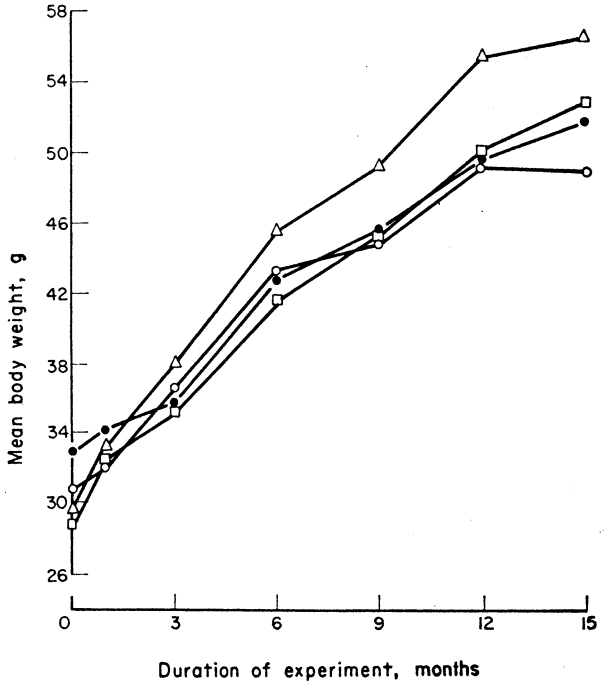

FIG. 1. Growth of female mice fed a basic diet containing 10% sucrose (△), 5% saccharin (□), 5% sodium cyclamate (○) or no added sweetener (●). Values for mice weighing more than 36 g or less than 26 g at the start of treatment were excluded.

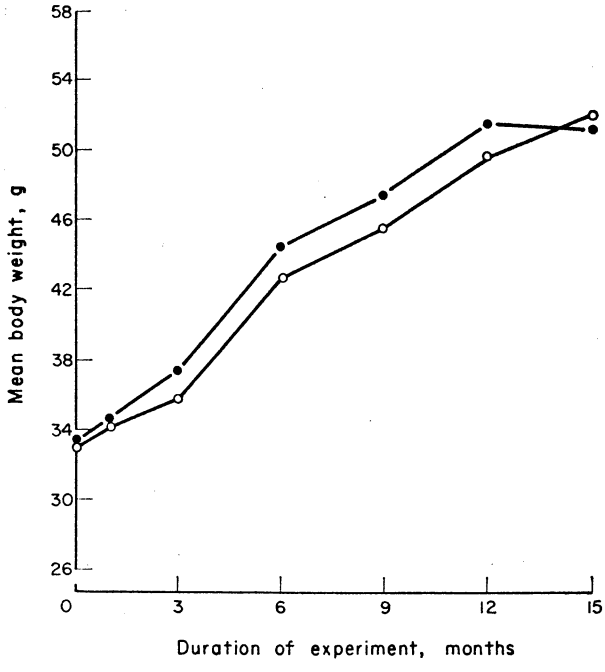

FIG. 2. Growth of female mice fed a basic diet with (●) or without (○) previous administration of a single intragastric dose of 50 μg benzo[*a*]pyrene. Values for mice weighing more than 36 g or less than 26 g at the start of treatment were excluded.

Table 2. *Incidence of forestomach neoplasms and other neoplasms in mice that survived for 18 months* from the start of treatment*

Group	Treatment	No. of mice examined at autopsy at 18 months	No. of mice with: Squamous papillomas of forestomach	Squamous carcinomas of forestomach	Pulmonary tumours	Hepatomas	Malignant lymphomas	Other neoplasms
1 H†	PEG	65 32	2 0	0 0	15 8	5 3	3 0	1 1—subcutaneous sarcoma
1 L†		33	2‡	0	7	2	3	0
2 H	BP/PEG	61 21	20 8	1 1	18 6	9 3	0 0	2 2—subcutaneous sarcoma and sarcoma of uterus
2 L		40	12	0	12	6	0	0
3	PEG/Cyclamate	34	1	0	6	1	1	0
4	BP/PEG/Cyclamate	41	4	0	10	6	0	2—subcutaneous sarcoma and mammary carcinoma
5	PEG/Sucrose	27	0	0	5	1	3	2—both spindle-cell tumours of uterus
6	BP/PEG/Sucrose	35	8§	2§	5	4	0	1—haemangioma of liver
7	PEG/Saccharin	36	0	0	8	1	2	2—haemangioma of liver and retroperitoneal sarcoma
8	BP/PEG/Saccharin	32	10*§	1§	7	2	1	2—granulosa cell tumour of ovary and haemangioma of liver

* In addition, one mouse of group 8 that died after 15·5 months had a small papilloma of the forestomach. Otherwise no stomach neoplasms were seen in any group before 18 months.
† H and L refer to mice weighing >36 g and <36 g respectively at the start of the experiment (see text).
‡ Total includes one mouse with a solitary keratoacanthoma.
§ Totals include one mouse with both a papilloma and a carcinoma.

Table 3. *Incidence of neoplasms in mice that failed to survive for 18 months from start of treatment*

Group	Treatment	No. of mice dying between 0 and 18 months without post-mortem examination	No. of mice dying					
			Before 12 months		Between 12 and 15 months		Between 15 and 18 months	
			No. examined *post mortem*	No. with neoplasms	No. examined *post mortem*	No. with neoplasms	No. examined *post mortem*	No. with neoplasms
1 H*	PEG	5	3	2 (malignant lymphoma)	4	1 (lung adenoma)	7	2 (lung adenoma) 2 (hepatoma) 1 (undifferentiated tumour of lung)
1	PEG	9	9		8		9	
1 L*	PEG	4	6	2 (malignant lymphoma)	4	1 (subcutaneous sarcoma)	2	1 (reticulum cell sarcoma and hepatoma)
2 H	BP/PEG	5	3	0	6	2 (lung adenoma) 1 (hepatoma) 1 (localized lympho-sarcoma)	7	3 (lung adenoma) 1 (malignant lymphoma)
2	BP/PEG	9	6		8		16	
2 L	BP/PEG	4	3	1 (malignant lymphoma)	2	1 (pulmonary adenoma)	9	1 (malignant lymphoma) 1 (hepatoma) 1 (granulosa cell tumour) 1 (subcutaneous haemangioendotheliosarcoma)

3	PEG/Cyclamate	3	5	0	1	0	7	3 (lung adenoma) 1 (lung adenocarcinoma) 1 (subcutaneous fibromyxosarcoma) 1 (reticulum cell sarcoma) 1 (localized lymphoma)
4	BP/PEG/Cyclamate	4	0	—	1	0	4	1 (malignant lymphoma) 1 (subcutaneous sarcoma and lung adenoma)
5	PEG/Sucrose	7	2	0	8	1 (lung adenoma) 1 (malignant lymphoma) 1 (granulosa cell tumours of both ovaries)	6	2 (lung adenoma) 1 (hepatoma) 1 (subcutaneous sarcoma)
6	BP/PEG/Sucrose	3	2	0	5	1 (lung adenoma)	5	1 (malignant lymphoma) 3 (lung adenoma)
7	PEG/Saccharin	8	3	0	1	0	2	0
8	BP/PEG/Saccharin	8	6	0	0	—	4	1 (lung adenoma) 1 (granulosa cell tumour of ovary) 1 (hepatoma) 1 (forestomach papilloma)

* H and L refer to mice weighing >36 g and <36 g respectively at the start of the experiment.

influence survival up to 18 months, nor was there any consistent difference in survival between the L and H sub-groups of groups 1 and 2.

Body weight

Mice fed on the sucrose diet gained weight faster than mice fed on other diets (Fig. 1): at 15 months, sucrose-fed mice weighed on average 4 g more than was to be expected on the basis of their average weight at day 0. A single dose of BP had no effect on the rate of weight gain in mice fed the standard diet (Fig. 2). Pretreatment with BP did not influence the weight gain in mice fed on diets containing added sucrose or cyclamate but was associated with reduced weight gain in saccharin-fed mice. At the start of treatment the average weight of mice in group 7 was 29·0 g and of mice in group 8, 28·9 g; at 6 months, mice in group 7 weighed 41·7 g on average, but those in group 8 only 38·7 g; and at 12 months the average weights were 50·1 g and 44·8 g, respectively. We can think of no logical explanation of this finding and believe it may be spurious.

Neoplasms and hyperplastic changes in the forestomach

The incidence of forestomach neoplasms in mice that survived for 18 months is given in Table 2. Clearly, treatment with BP alone increased the incidence of neoplasms arising in the forestomach epithelium. The addition of various sweetening agents did not increase the incidence of such tumours, whether BP was given or not. Focal and more generalized epithelial hyperplasia and hyperkeratosis were seen in some BP-treated mice but the sweetening agents exerted no obvious effect on the incidence or severity of these changes.

Neoplasms at sites other than the forestomach

The incidence of histologically-confirmed neoplasms, other than those of the forestomach, in animals killed at 18 months is also shown in Table 2, and of those in animals dying before 18 months, in Table 3. The incidence of hepatomas was greater in animals treated with BP, but the incidence of pulmonary tumours and malignant lymphomas was similar in all groups. It is noteworthy that none of the treatments appeared to influence tumour incidence in the oesophagus, glandular stomach and small or large intestine. Careful macroscopic examination of the bladder revealed no abnormality in any mouse from any group.

DISCUSSION

The four main findings in this investigation are negative. First, the addition of 10% sucrose, 5% sodium cyclamate or 5% saccharin to a standard diet given to female mice was not associated with an increase either in local tumours arising in the gastro-intestinal tract or in distant tumours at other sites. Secondly, none of these sweetening agents showed any co-carcinogenic activity when tested as promoters in mice which had previously received a single oral dose of 50 μg BP. Predictably, animals treated with BP alone developed benign and malignant tumours of the forestomach epithelium (Field & Roe, 1965), but the incidence, number and degree of malignancy of such tumours were not increased in mice fed on any of the sweetening agents. Thirdly, animals on diets containing 10% sucrose showed a greater rise in body weight than the other groups because of the greater calorific content of the sucrose diet. This rise was independent of pretreatment with BP and was not accompanied by any increase in tumour incidence. The observations by Tannenbaum & Silverstone (1953), mentioned earlier, might have led to the prediction that tumours would be more common in these groups. Lastly, none of the test agents gave rise to detectable toxic effects and none

appeared to have an adverse effect on survival up to 18 months from the start of the experiment.

In spite of the non-random allocation of mice to the various treatment groups, other experience with this strain and consideration of the results as a whole strongly suggest that the three sweetening agents tested possess neither carcinogenic nor tumour-promoting activity under the conditions of the experiment.

Differences between species in susceptibility to cyclamate have not been adequately explored. The need for such work is illustrated by the recent report by Bajusz (1969) which showed that large doses of calcium cyclamate, given orally to hamsters for only 6 days, rapidly induced calcification and necrosis of cardiac and skeletal muscle, coronary sclerosis of the Mönckeberg type and nephrocalcinosis. Equimolecular amounts of calcium given as chloride, aspartate, acetate and ascorbate were inactive. It would seem that the cyclamate part of the calcium cyclamate molecule is necessary for the production of this toxic effect. But at present it appears that the effect is species-specific since calcium cyclamate, given in equivalent doses to rats, did not lead to ectopic calcification. We recorded no evidence of ectopic calcification in the mice of groups 3 and 4.

The findings reported in the present paper are consistent with the view that neither saccharin nor cyclamate are carcinogenic for mice when administered by mouth. This would have been our conclusion had it not been for our becoming aware of the observed increase in the incidence of bladder tumours in rats fed on a sodium cyclamate–sodium saccharin (10:1) mixture in high concentration (Price *et al.*, 1970) and the suspicion that *in vivo* conversion of cyclamate to cyclohexylamine (Kojima & Ichibagase, 1966; Leahy, Wakefield & Taylor, 1967; Oser, Carson, Vogin & Sonders, 1968) was involved in the induction of these tumours. By the time this new information became available, all the mice in our experiment were dead, but Unilever Research Ltd. (Colworth House, Sharnbrook, Bedfordshire) kindly examined mice from our colony of the same strain for ability to convert cyclamate to cyclohexylamine. Four female and eight male mice were fed from the age of 6–8 wk for a period of 2 months on a basic laboratory diet (Spital) and given water containing 0·5% sodium cyclamate. Urine from all 12 mice contained cyclohexylamine at a level indicative of a 2–3% conversion rate.

In view of these later studies, it is likely that mice of groups 3 and 4 in the main experiment also converted some cyclamate to cyclohexylamine. We cannot be sure of this, nor can we exclude the possibility that neoplasms of microscopic dimensions were present in the bladders of the mice of any group. We can, however, with full confidence state that our use of a systematic necropsy regime excludes the possibility that bladder tumours of a size visible to the naked eye were present in any of the 449 mice that were examined *post mortem*.

Acknowledgements—We are indebted to Mrs. Norma Barron for technical assistance, and to Miss Janice Hotham for her help and patience in the preparation of the manuscript.

This investigation was supported by grants to the Chester Beatty Research Institute by the Medical Research Council and the British Empire Cancer Campaign for Research.

REFERENCES

Bajusz, E. (1969). Myocardial lesions: A reassessment of the toxicology of calcium cyclamate. *Nature, Lond.* **223**, 406.

Carter, R. L. (1970). Induced subcutaneous sarcomata. In *Metabolic Aspects of Food Safety*. Edited by F. J. C. Roe. Blackwell Scientific Publications, Oxford–Edinburgh.

Field, W. E. H. & Roe, F. J. C. (1965). Tumor promotion in the forestomach epithelium of mice by oral administration of citrus oils. *J. natn. Cancer Inst.* **35**, 771.

Fitzhugh, O. G., Nelson, A. S. & Frawley, J. P. (1951). A comparison of the chronic toxicities of synthetic sweetening agents. *J. Am. pharm. Ass.* **40,** 583.
Grasso, P. & Golberg, L. (1966). Subcutaneous sarcoma as an index of carcinogenic potency. *Fd Cosmet. Toxicol.* **4,** 297.
Hueper, W. C. (1965). Are sugars carcinogens? An experimental study. *Cancer Res.* **25,** 440.
Kojima, S. & Ichibagase, H. (1966). Studies on synthetic sweetening agents. VIII. Cyclohexylamine, a metabolite of sodium cyclamate. *Chem. pharm. Bull., Tokyo* **14,** 971.
Leahy, J. S., Wakefield, M. & Taylor, T. (1967). Urinary excretion of cyclohexylamine following oral administration of sodium cyclamate to man. *Fd Cosmet. Toxicol.* **5,** 447.
Lomonova, G. V. (1965). Toxicity of cyclohexylamine and dicyclohexylamine. *Fedn Proc. Transl. Suppl.* **24,** T96.
Oser, B. L., Carson, S., Vogin, E. E. & Sonders, R. C. (1968). Conversion of cyclamate to cyclohexylamine in rats. *Nature, Lond.* **220,** 178.
Pliss, G. B. (1958). The carcinogenic activity of dicyclohexylamine and its nitrite salt. *Probl. Oncol.* **4,** 659.
Price, J. M., Biava, C. G., Oser, B. L., Vogin, E. E., Steinfeld, J. & Ley, H. L. (1970). Development of bladder tumours in rats fed cyclohexylamine or high doses of a mixture of cyclamate and saccharin—A preliminary report. *Science, N.Y.* **167,** 1131.
Richards, R. K., Taylor, J. D., O'Brien, J. L. & Duescher, H. O. (1951). Studies on cyclamate sodium (sucaryl sodium), a new non-caloric sweetening agent. *J. Am. pharm. Ass.* **40,** 1.
Roe, F. J. C. (1965). Spontaneous tumours in rats and mice. *Fd Cosmet. Toxicol.* **3,** 707.
Roe, F. J. C. (1968). Carcinogenesis and sanity. *Fd Cosmet. Toxicol.* **6,** 485.
Schoenberger, J. A., Rix, D. M., Sakamoto, A., Taylor, J. D. & Kark, R. M. (1953). Metabolic effects, toxicity and excretion of calcium N-cyclohexylsulfamate (sucaryl) in man. *Am. J. med. Sci.* **225,** 551.
Shabad, L. M. (1963). Blastomogenic substances in human environment and principles of prevention. *Acta Un. int. Cancr.* **19,** 458.
Stein, A. A., Serrone, D. M. & Coulston, F. (1967). Ultrastructural and biochemical studies of sodium cyclamate. *Toxic. appl. Pharmac.* **10,** 381.
Tannenbaum, A. & Silverstone, H. (1953). Nutrition in relation to cancer. *Adv. Cancer Res.* **1,** 451.
Taylor, J. D., Richards, R. K. & Davin, J. C. (1951). Excretion and distribution of radioactive S^{35}-cyclamate sodium (sucaryl sodium) in animals. *Proc. Soc. exp. Biol. Med.* **78,** 530.
Taylor, J. D., Richards, R. K., Wiegand, R. G. & Weinberg, M. S. (1968). Toxicological studies with sodium cyclamate and saccharin. *Fd Cosmet. Toxicol.* **6,** 313.

Étude, par des expériences de nutrition, de l'activité carcinogène ou favorable au développement de tumeurs du cyclamate de sodium, de la saccharine et du saccharose

Résumé—Des groupes de 50 souris femelles 'Swiss' ont été soumis pendant 18 mois à un régime alimentaire standard contenant du saccharose (10%), du cyclamate de sodium (5%) ou de la saccharine (5%), tandis que 100 souris témoins recevaient le régime standard tel quel. Les temps de survie dans les différents groupes ont été comparables et aucun effet de toxicité aiguë n'a été observé. On n'a constaté ni tumeurs locales du trajet gastro-intestinal ni fréquence excessive de tumeurs distantes chez les animaux qui recevaient les différents édulcorants. Le gain de poids a été plus considérable chez les souris soumises au régime comportant 10% de saccharose que chez les animaux des autres groupes; la fréquence de néoplasmes n'était cependant pas plus grande.

Des groupes comparables de souris ont reçu, sept jours avant le début des différents régimes d'essai, une instillation intragastrique de 50 μg de benzo[*a*]pyrène dans 0,2 ml de polyéthylèneglycol 400. Des néoplasmes bénins ou malins se sont formés, comme prévu, dans l'épithélium de la partie antérieure de l'estomac chez des souris de chaque groupe; l'administration des édulcorants n'a toutefois pas eu d'effet évident sur la fréquence, le nombre ou le type histologique de ces néoplasmes ni de néoplasmes d'autres types.

Un examen macroscopique attentif n'a fait découvrir, à l'autopsie, aucun néoplasme de la vessie. Les vessies n'ont pas été examinées au microscope.

Les auteurs concluent que les édulcorants en cause n'ont manifesté, dans les conditions d'expérience décrites, aucune activité carcinogène ou favorable au développement de tumeurs.

Verfütterungsversuche mit Natriumcyclamat, Saccharin und Sucrose zur Prüfung auf carcinogene und tumorfördernde Aktivität

Zusammenfassung—Gruppen von 50 weiblichen Schweizer Mäusen erhielten 18 Monate lang ein Standardfutter mit einem Zusatz von Sucrose (10%), Natriumcyclamat (5%) oder Saccharin (5%), während 100 Kontrollmäuse das Standardfutter ohne Zusätze erhielten. Die Überlebenszeiten waren in allen Gruppen vergleichbar, und es wurden keine akuten toxischen Wirkungen beobachtet. Es wurden keine örtlichen Tumoren im Gastrointestinaltrakt und kein übermässiges Auftreten entfernter Tumoren bei Tieren gefunden, die Futter mit den verschiedenen Süssstoffen erhielten. Die mit einem Zusatz von 10% Sucrose gefütterten Mäuse nahmen mehr an Gewicht zu als die Tiere in den anderen Gruppen, zeigten aber kein vermehrtes Auftreten von Neoplasmen.

Vergleichbare Gruppen von Mäusen erhielten 7 Tage vor dem Beginn der Verfütterung der verschiedenen Süssstoffe mit der Magensonde eine einzelne Dosis von 50 μg Benz[*a*]pyren in 0,2 ml Polyäthylenglycol 400. Einige Mäuse in allen diesen Gruppen entwickelten, wie erwartet, benigne und maligne Neoplasmen im Vormagenepithel, jedoch hatte die Verfütterung der Süssstoffe keinen offensichtlichen Einfluss auf Häufigkeit, Zahl oder Histologie dieser oder jeder anderen Neoplasmatype.

Bei der Sektion der Mäuse unter sorgfältiger wurden makroskopischer Untersuchung keine Neoplasmen der Harnblase gefunden; die Blasen wurden nicht mikroskopisch untersucht.

Es wird daraus der Schluss gezogen, dass unter den beschriebenen Versuchsbedingungen die drei untersuchten Süssstoffe keine carcinogene oder tumorfördernde Aktivität zeigten.