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Some Non-Nutritive Sweetening Agents

Summary of Data Reported and Evaluation

Cyclamates (Cyclamic acid, sodium cyclamate, calcium cyclamate, cyclohexylamine and dicyclohexylamine)

Saccharin, sodium saccharin, calcium saccharin and *ortho*-toluenesulphonamide

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CYCLAMATES (CYCLAMIC ACID, SODIUM CYCLAMATE, CALCIUM CYCLAMATE, CYCLOHEXYLAMINE & DICYCLOHEXYLAMINE)

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5. Summary of Data Reported and Evaluation

5.1 Experimental data

Sodium cyclamate has been tested by oral administration in two experiments in mice, one of which was a multigeneration study, and in three experiments in rats. A few benign and malignant bladder tumours were observed in rats, but the incidences were not statistically greater than those in controls in any single experiment. An increased incidence of lymphosarcomas was seen in female but not in male mice in one experiment. Sodium cyclamate was also tested by oral administration in other experiments in mice, rats, hamsters and monkeys, but these experiments could not be evaluated because of various inadequacies or incomplete reporting.

Sodium cyclamate has also been tested in mice by bladder insertion (implantation) in one experiment: it increased the incidence of bladder carcinomas. When administered in one experiment by subcutaneous injection to rats, no tumours were seen at the site of injection.

Calcium cyclamate has been tested by oral administration in one two-generation experiment in rats; no difference in tumour incidence was seen between treated and control animals. Two further experiments in rats showing a few bladder tumours and one in hamsters were considered to be inadequate for evaluation. When administered by subcutaneous injection to rats, tumours were produced at the site of injection.

The combination of sodium cyclamate with sodium saccharin in a ratio of 10:1 has been tested by oral administration in a multigeneration experiment in mice and in two experiments in rats. In one study in rats, transitional-cell carcinomas in the bladder were produced in male animals given the highest dose; in the other study in rats and in the study in mice, there was no difference in tumour incidence between treated and control animals.

In one study in rats fed sodium cyclamate after receiving a single instillation into the bladder of a low dose of *N*-nitroso-*N*-methylurea, transitional-cell neoplasms of the bladder were produced. No such tumours were observed in animals that received *N*-nitroso-*N*-methylurea alone.

Cyclohexylamine has been tested by oral administration in two experiments in mice, one of which was a multigeneration study, and in four experiments in rats; there were no differences in tumour incidence between treated and control animals. A further experiment in rats was considered to be inadequate for evaluation.

The limited number of mutagenicity studies published give no evidence that cyclamates cause point mutations. Both cyclamates and cyclohexylamine cause chromosome damage.

There is no evidence that cyclamates and cyclohexylamine are teratogenic.

5.2 Human data

Mortality from bladder cancer has been investigated in two studies by examination of time trends in the United States and in England and Wales. These have shown no marked increase in incidence or mortality from bladder cancer following a substantial increase over a few years in the use of cyclamates and saccharin, but such studies are too insensitive to exclude completely a carcinogenic effect.

In two studies of cancer mortality in patients with diabetes mellitus (who, as a group, have been shown to consume larger quantities of artificial sweeteners than the general population), lower mortality from cancer at all sites was observed as compared with the general population; there was no excess of bladder cancer in particular. in a further study, the frequency of the mention of diabetes mellitus in death certificates of persons who had died of bladder cancers was compared with that in those of controls who had died of other cancers (excluding those of the lung and pancreas); in the presence of diabetes mellitus, there was no increase in the risk of bladder cancer. As there are differences other than artificial sweetener use between diabetics and the general population, such studies cannot exclude a small carcinogenic effect of these sweeteners.

Seven case-control studies were considered by the Working Group. Only two of these studies examined confounding factors in detail. Of these two, one suggested that use of nine or more tablets of artificial sweeteners per day was positively associated with risk for bladder cancer in men, but not in women, although in these small groups the results may have been due to chance, to unsuspected confounding factors, or to residual effects of those confounding factors that were considered in the analysis and could be shown to reduce the magnitude of the association. The other study that considered confounding factors suggested that there was no effect of the use of artificial sweeteners on the incidence of bladder cancer; the observed relative risk was 1.0 (indicating no increase in risk), but a relative risk below 1.4 could not be excluded. The other five case-control studies also showed no association, although they were limited by some inadequacies in experimental design.

In six of the seven case-control studies, women with bladder cancer showed a tendency to consume less artificial sweeteners than female controls. This observation suggests that there is no association between use of artificial sweeteners and bladder cancer in women.

5.3 Evaluation

The experimental data provide *limited evidence* for the carcinogenicity of cyclamates in mice and rats. There is no conclusive evidence that cyclamates alone are carcinogenic when given by the oral route. There is evidence that they can promote the local action of a known carcinogen in the bladder. The available experimental data provide no evidence for the carcinogenicty of cyclohexylamine.

No adequate epidemiological data on cyclamates alone were available to the Working Group (see also monograph on saccharin).

For definition of the italicized terms, see Preamble Evaluation.

NOTE:

After the meeting of the Working Group, two epidemiological investigations (Morrison & Buring, 1980; Wynder & Stellman, 1980) were reported.

The study by Morrison and Buring evaluated the relation between cancer of the lower urinary tract and the use of artificial sweeteners in a case-control study of 592 patients with lower-urinary-tract cancer (94 per cent of whom had a bladder tumour) and 536 controls chosen from the general population of the study area. A history of use of artificial sweetenera and exposure to other known or suspected risk factors was determined by interview. In those who had used dietetic beverages and in those who had used sugar substitutes, the relative risk of lower-urinary-tract cancer was estimated as 0.9 (0.7 to 1.2), 95% confidence interval), as compared with 1 in nonusers of artificial sweeteners. Among men, the relative risk was 0.8 (0.6 to 1.1) in those who had used dietetic beverages and 0.8 (0.5 to 1.1) in those who had used sugar substitutes. Among women, the corresponding relative risks were 1.6 (0.9 to 2.7) and 1.5 (0.9 to 2.6). Increasing frequency or duration of use of artificial sweeteners was not consistently associated with increasing relative risk. This study suggests that, as a group, users of artificial sweeteners have little or no excess risk of cancer of the lower urinary tract [Authors' summary].

The study by Wynder and Stellman was a case-control study of 302 men and 65 women with bladder cancer

and an equal number of controls matched for age, sex, hospital and hospital-room status. No association was found between the use of artificial sweeteners or diet-beverage consumption and bladder cancer. The relative risk of bladder cancer (95% confidence interval) among men was 0.9 (0.7-1.3) for artificial sweetener use and 0.8 (0.6-1.2) for diet-beverage consumption; among women, the relative risks were 0.6 (0.3-1.4) and 0.6 (0.3-1.3), respectively. These relative risk estimates did not vary appreciably when a number of potential confounding variables were controlled for, namely, history of diabetes, obesity, occupation, education, religion and coffee or tea consumption. No dose-response relationships between consumption of artificial sweeteners or diet beverages and quantity or duration of use were observed.

Subsequent evaluations: Suppl. 7 (1987); Vol. 73 (1999)

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SACCHARIN (SACCHARIN, SODIUM SACCHARIN, CALCIUM SACCHARIN & *ortho*-TOLUENESULPHONAMIDE)

VOL.: 22 (1980) (p. 111)

5. Summary of Data Reported and Evaluation

5.1 Experimental data

Saccharin has been tested by oral administration in mice, rats and hamsters. In mice, saccharin produced no difference in tumour incidence between treated and control animals in one single and in one multigeneration study. Two further studies by oral administration in mice and three in rats were considered to be inadequate for evaluation. A study in hamsters by oral administration and one study in mice by skin application could not be evaluated. A study in mice by bladder insertion provided evidence for the induction of bladder carcinomas.

Sodium saccharin has been tested by oral administration in mice, rats and monkeys. One study in mice was inadequate for evaluation. One single-generation study in rats showed an increased incidence of bladder tumours in males; two further studies showed a few bladder tumours; one other study showed no difference in tumour incidence between treated and control animals; and two others were inadequate for evaluation. In three two-generation studies in rats, sodium saccharin produced a statistically significant increase in bladder tumours in F_1 males. Sodium saccharin has also been tested in mice by bladder insertion (implantation): it increased the incidence of bladder carcinomas. It has also been tested by oral administration in monkeys and by intraperitoneal administration in mice, but these experiments were considered to be inadequate for evaluation.

The combination of sodium saccharin with sodium cyclamate in a ratio of 1:10 has been tested by oral administration in a multigeneration experiment in mice and in three single-generation experiments in rats. In one study in rats, transitional-cell carcinomas in the bladder were produced in male animals given the highest dose; in a further study in rats and in the study in mice, there was no difference in tumour incidence between treated and control animals. The other study in rats was inadequate for evaluation.

In one study, female rats were administered sodium saccharin in the drinking-water or diet after receiving a single instillation into the bladder of a low dose of *N*-nitroso-*N*-methylurea (NMU): a high incidence of transitional-cell neoplasms of the bladder was found compared with animals that received NMU alone. Sodium saccharin was also tested in male rats pretreated with *N*-[4(5-nitro-2-furyl)-2-thiazolyl] formamide, resulting in an increased incidence of carcinomas of the bladder over that seen in rats given the latter compound alone.

ortho-Toluenesulphonamide was tested by oral administration in rats in a two-generation study: no increase in bladder tumour incidence was noted in animals of either generation. In one of two single-generation studies in rats, benign and malignant bladder tumours were found.

There is little evidence that saccharin itself induces point mutations. Dominant lethal effects and unscheduled DNA synthesis have been reported; and it causes sister chromatid exchanges and other chromosomal effects.

In the majority of the studies, no indication for a teratogenic effect of saccharin was found; impurities may be responsible for the occasional effects reported. There is no evidence that *ortho*-toluenesulphonamide is mutagenic, although impurities extracted from some lots of saccharin were mutagenic in the *Salmonella*/microsome test. In one in-vitro test, saccharin was found to enhance the neoplastic transformation of fibroblasts treated with 3-methylcholanthrene.

5.2 Human data

Mortality from bladder cancer has been investigated in two studies by examination of time trends in the United

States and in England and Wales. These have shown no marked increase in incidence or mortality irom bladder cancer following a substantial increase over a few years in the use of cyclamates and saccharin, but such studies are too insensitive to exclude completely a carcinogenic effect.

In two studies of cancer mortality in patients with diabetes mellitus (who, as a group, have been shown to consume larger quantities of artificial sweeteners than the general population), lower mortality from cancer at all sites was observed as compared with the general population; there was no excess of bladder cancer in particular. In a further study, the frequency of the mention of diabetes mellitus in death certificates of persons who had died of bladder cancers was compared with that in those of controls who had died of other cancers (excluding the lung and pancreas); in the presence of diabetes mellitus, there was no increase in the risk of bladder cancer. As there are differences other than artificial sweetener use between diabetics and the general population, such studies cannot exclude a small carcinogenic effect of these sweeteners.

Seven case-control studies were considered by the Working Group. Only two of these studies examined confounding factors in detail. Of these two, one suggested that use of nine or more tablets of artificial sweeteners per day (or more than eight tablets of saccharin per day) was positively associated with risk for bladder cancer in men but not in women, although in these small groups the results may have been due to chance, to unsuspected confounding factors, or to residual effects of those confounding factors that were considered in the analysis and could be shown to reduce the magnitude of the association. The other study that considered confounding factors suggested that there was no effect of the use of artificial sweeteners on the incidence of bladder cancer; the observed relative risk was 1.0 (indicating no increase in risk), but a relative risk below 1.4 could not be excluded. The other five case-control studies also showed no association, although they were limited by some inadequacies in experimental design.

In six of the seven case-control studies, women with bladder cancer showed a tendency to consume less artificial sweeteners than female controls. This observation suggests that there is no association between use of artifical sweeteners and bladder cancer in women.

5.3 Evaluation

Although a small increase in the risk of urinary bladder cancer in the general population or a larger increase in some individuals consuming very high doses of saccharin and cyclamates cannot be excluded, the epidemiological data provide no clear evidence that saccharin alone, or in combination with cyclamates, causes urinary bladder cancer. There are no epidemiological studies on a possible association between use of saccharin and cyclamates and cancer at other sites in humans.

There is *sufficient evidence* that saccharin alone, given at high doses, produces tumours of the urinary tract in male rats and can promote the action of known carcinogens in the bladder of rats of both sexes; and there is *limited evidence* of its carcinogenicity in mice. There is *limited evidence* that *ortho*-toluenesulphonamide is carcinogenic when given orally to rats; but the available data suggest that impurities at the levels normally found in commercial saccharin do not contribute to the carcinogenicity of saccharin.

For definition of the italicized terms, see Preamble Evaluation.

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1 in nonusers of artificial sweeteners. Among men, the relative risk was 0.8 (0.6 to 1.1) in those who had used dietetic beverages and 0.8 (0.5 to 1.1) in those who had used sugar substitutes. Among women, the corresponding relative risks were 1.6 (0.9 to 2.7) and 1.5 (0.9 to 2.6). Increasing frequency or duration of use of artificial sweeteners was not consistently associated with increasing relative risk. This study suggests that, as a group, users of artificial sweeteners have little or no excess risk of cancer of the lower urinary tract [Authors' summary].

The study by Wynder and Stellman was a case-control study of 302 men and 65 women with bladder cancer and an equal number of controls matched for age, sex, hospital and hospital-room status. No association was found between the use of artificial sweeteners or diet-beverage consumption and bladder cancer. The relative risk of bladder cancer (95% confidence interval) among men was 0.9 (0.7-1.3) for artificial sweetener use and 0.8 (0.6-1.2) for diet-beverage consumption; among women, the relative risks were 0.6 (0.3-1.4) and 0.6 (0.3-1.3), respectively. These relative risk estimates did not vary appreciably when a number of potential confounding variables were controlled for, namely, history of diabetes, obesity, occupation, education, religion and coffee or tea consumption. No dose-response relationships between consumption of artificial sweeteners or diet beverages and quantity or duration of use were observed.

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