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OPINION ON

SACCHARIN AND ITS SODIUM, POTASSIUM AND CALCIUM SALTS

(expressed on 2 June 1995)

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Terms of reference

To re-evaluate the safety in use of saccharin and its sodium, potassium and calcium salts in the light of additional information.

Background

Saccharin and its sodium, potassium and calcium salts were first evaluated by the Scientific Committee for Food (SCF) in 1977 when a temporary ADI of 0-2.5 mg/kg bw was allocated.[1] The Committee reviewed saccharin again in 1985[2] and decided to maintain the temorary ADI set in 1977. The SCF stated at that time "that the situation should be kept under review and the ADI should be reassessed after the Committee had evaluated the results of ongoing studies on:-

(a) the report to be published on the outcome of the two-generation study in hamsters recently completed,

(b) the mechanism of the effect of saccharin on the bladder in the male rat,

(c) the comparability of the rat and human bladder in relation to differences in metabolism and local effects."[2]

In August 1990, the SCF was informed that the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment had recently reviewed saccharin and recommended that it should be allocated a full ADI of 0-5 mg/kg bw.[3] In September 1990 industry submitted further data and requested re-evaluation of the temporary ADI.[4]

On the basis of the above information the SCF considered saccharin at its 76th meeting in December 1990. The Committee felt that the recent toxicological studies might be sufficient to allow a full ADI to be assigned, but considered that it would need to carry out a comprehensive review of the data before contemplating changing the existing temporary ADI.[5]

Subsequently comprehensive reviews were published on biological risk assessment of sodium saccharin.[6,7] Industry has also submitted further information for the re-evaluation of saccharin[8] together with a copy of the papers given at a meeting in 1993, organised by the International Life Sciences Institute (ILSI), to review saccharin research.[9] Furthermore, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at its 41st meeting reviewed saccharin and its salts.[10,11]

Current review

The following information has been received which relates to the points raised by the SCF in its 1985 evaluation.

Two-generation study in hamsters

On point (a) above, the Committee understands that the two-generation study in hamsters was terminated before completion as it was of poor quality and evaluation was not possible. A long-term, one-generation study in hamsters given saccharin in the drinking water has been published.[12] Tumour types were similar in the control group and in the groups given 0.156, 0.312, 0.625 and l.25% of saccharin in the drinking water and no urinary tract tumours were found in any group. Negative findings for bladder tumours have also been reported in long-term studies in mice and monkeys.[10] Given the evidence (reviewed below) that the male rat seems to have a particular susceptibility to bladder tumours induced by sodium saccharin, the Committee considers it is no longer necessary to have further studies on hamsters.

Mechanism of action of saccharin on the male rat bladder

On point (b) above, the submission and the JECFA review give a considerable amount of new information[3,8,10,11] and detailed reviews of the literature. It is apparent that whilst a definitive mechanism concerning all the steps involved in male rat bladder carcinogenesis following treatment with saccharin is not yet available, a number of important factors can be identified which give rise to the crucial cell proliferation in the bladder of male rats. These are a high concentration of sodium ions, elevated urinary pH, and perhaps also factors like bladder distension, osmolality of the urine and silica content of the diet (crystaluria). The potential role of α-2μ-globulin has also been studied by comparison of a rat strain which does not synthesise this urinary protein with one which does.[13] This protein is produced in low amounts in humans, but is produced in amounts around 100 times higher in rat strains such as the Fischer 344. The study indicates some role for α-2μ-globulin by increasing precipitation of saccharin crystals in the urine, but it is clearly not the sole influence. Many bladder tumour promotion studies, using well known initiators of bladder carcinogenesis, have shown that both increased urinary sodium ion content and a high urinary pH are essential for the promotion of bladder tumours in the male rat by sodium salts of several different organic acids, including saccharin.[6] The initiation factor(s) involved in bladder tumour induction by sodium saccharin in neonatal male rats are not determined as yet.

Relevance for man of the rat bladder tumours

The evidence on point (c) above makes it clear that saccharin is not metabolised in man or in the rat. So the difference between man and male rats is presumably in the local effect on the bladder epithelium. Here the evidence submitted points to a special susceptibility of the male rat bladder, not only compared to man, but also compared to female rats and the bladder of mice, hamsters and monkeys. In these latter species no bladder tumours are induced, even by administration of high doses of saccharin. It should be noted that the studies in mice included neonatal exposure, which has been shown to be critical for the effects of sodium saccharin on the male rat bladder.

Both the JECFA[10,11] and the ILSI[9] meetings discussed the relevance to man of the tumours observed in the male rat bladder in the pivotal two-generation, long-term study in the rat.[14] In both cases it was stated that it would be inappropriate to consider the bladder tumours induced in male rats by sodium saccharin to be relevant to the assessment of a toxicological hazard in humans. The JECFA, in basing its ADI on other effects, concludes "In reassessing the ADI, the Committee considered that the 1% dietary level in the most recent 2-generation long-term feeding study in rats, equivalent to 500 mg/kg bw/day, was appropriate for establishing an intake causing no relevant toxicological effect".[10] At the next higher dose level (3%) and above a marked

disturbance in homeostasis was demonstrated with a decrease in body weight gain in the presence of increased feed consumption.

The no-observed effect level from the two-generation study in rats

It is necessary to discuss the dose-response information in the critical two-generation study in rats,[14] in which sodium saccharin was given at doses of 1.0, 3.0, 4.0, 5.0, 6.25 and 7.5%, and whether a no-observed-effect level (NOEL) for bladder tumours can be discerned from this study, especially since a histopathological re-evaluation[15] of the rat urinary bladders from the study has been performed since the SCF's last review.

In the original data submitted to the SCF[16] it was reported that there was a statistically significant positive trend for total primary bladder tumours for the entire dose-response portion of the study (i.e. including the 1% dose). However, it was further reported that the incidence of total primary urinary bladder tumours (benign plus malignant) for the 1% sodium saccharin treatment group in this study was 0.8%, which is the same as the separate mean values for each of benign and malignant primary urinary bladder tumours from the ten historical control groups. In a 1985 report of an Expert Panel[17] it is stated "The tumour incidence at the 1% dose level shows an increase, but not to a statistically significant extent. Thus the effect of the 1% dose level remains equivocal." As mentioned above, the histopathology of the bladders from the pivotal two-generation study was subsequently re-evaluated by Squire. He concluded "no compound-related effects in either the grade or incidence of any lesions were evident in the 1% group."[15]

Considering the evidence as a whole the Committee concludes that a dose of 1% sodium saccharin in the diet should be taken as the NOEL for bladder tumours in the male rat.

Genotoxicity

A further point discussed at the JECFA and ILSI meetings in 1993[9-11] was the question of genotoxicity, as several in vitro and in vivo studies have shown clastogenicity, especially at high concentrations in in vitro studies.[18-24] Sodium saccharin was found weakly positive in several in vitro studies for induction of chromosomal aberrations in Chinese hamster cells[19-23] and in human lymphocytes.[24] Mostly weak responses were observed in some in vitro assays at the chromosomal level.[25-27] However, these responses were only seen in high concentrations and it is probable that they are attributable to ionic imbalances which are known to cause non-specific effects. There are also conflicting reports from in vivo studies,[28-38] but in some cases the material used was known to contain impurities or contaminants from the manufacture of saccharin, and the interpretation of these particular studies is uncertain.

Epidemiology

Further important evidence comes from the now numerous epidemiological studies on saccharin which have included studies of groups consuming relatively high levels of saccharin. Two recent reviews[6,7] indicate that there is no detectable association between artifical sweetener consumption (especially saccharin) and bladder cancer in humans. One review includes discussion of a meta-analysis of all case-control studies up to 1992 which gives a value for relative risk approaching unity (RR=0.97).[7] The large amount of evidence from epidemiological studies indicates no increase in the occurrence of bladder tumours in man from the ingestion of saccharin, including in groups with the highest intakes of artificially sweetened beverages and those using saccharin as a table-top sweetener.

Conclusions and recommendations

Considering the weight of evidence from all the genotoxicity studies, the Committee considers that these indicate saccharin is not a direct acting genotoxin. Support for this view comes also from the fact that it has been shown to be a carcinogen at only one site in only one sex of one species of animal, whereas genotoxic carcinogens tend to be active at more than one site and/or in more than one sex or species.[39]

Although the mechanism of tumour production is not completely understood, a number of important factors involved in the occurrence of tumours in the bladder of male rats given sodium saccharin for prolonged periods, including neonatally, are reasonably well understood. The explanation for the apparent difference between the male rat response and other species including humans is not based on any difference in metabolism, but is probably based on a difference in local effect and response in the bladder wall. The mechanistsic studies, combined with what is known from the epidemiological studies strongly indicate that that saccharin is not related to bladder cancer in humans. While it is unlikely that the tumours in the male rat bladder are of relevance for man, it has not been possible to unequivocally demonstrate this. The Committee therefore wishes, as a matter of prudence, to take these lesions into account in setting an ADI.

The questions concerning mechanism and relevance of male rat bladder tumours, raised by the SCF in 1985, have been satisfactorily addressed to the extent that the Committee can now set a full ADI. In order to establish an ADI for this non-genotoxic, male rat bladder carcinogen, two considerations are relevant, the NOEL from the pivotal two-generation, long-term rat study and the safety factor to be applied. The Committee considers it now reasonable to regard 1% sodium saccharin in the diet as a clear NOEL in relation to male rat bladder tumours. The Committee notes that this is also the NOEL for other non-neoplastic effects of saccharin.

The SCF in 1977 and 1985 allocated a temporary ADI of 0-2.5 mg/kg bw, based on a possible NOEL of 1% in the diet, equivalent to 500 mg/kg bw/day, using a safety factor of 200 because of the temporary nature of the ADI. In response to the new experimental information now available, the extensive epidemiological data with no evidence of any relationship between saccharin intake and bladder cancer in humans, and the information provided in response to the Committee's earlier questions, the Committee concludes that it is appropriate to set a full ADI for sodium saccharin of 0-5 mg/kg bw. This is derived by applying a 100-fold safety factor to the NOEL of 1% in the diet (500 mg/kg bw) for bladder tumours in the rat.

For some purposes it may also be necessary to express the ADI in terms of the free acid, since sodium saccharin is not the only salt used. Taking account of the molecular weight difference between sodium saccharin (MW 241) and the free acid (MW 183), the ADI expressed as the free acid is 0-3.8 mg/kg bw.

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