Saccharin – urban myths and scientific data

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ABSTRACT

It is commonplace among many Romanian people (although proper statistics to estimate the real extent of this are not available) to lament that artificial sweeteners, flavours, colors and other ingredients bearing a mysterious "E number" are dangerous for their health. Saccharin, a rather old sweetener with a contorted history makes no exception. Is this chemophobia well founded and are the competent authorities proving themselves in fact incompetent by allowing the presence of saccharin on the market? Or are negative beliefs about saccharin just urban myths developed through amplification of misjudged evidence? In this mini-review we make a synthetic presentation of the data available on the safety of saccharin to allow an objective and scientific assessment of its risks and benefits and will end with a short look at its benefits in weight-control. The contorted regulatory history of saccharin, from its discovery through its bans and ban removals are presented here, together with the available evidence of carcinogenity and its limits.

In 1986, J.E. Blundell and A.J. Hill published a paper in which reported that consumption of an aspartame solution resulted in an increase in ratings of appetite compared with the control group, which only received water. Following this report, authors from the same group provided new evidence suggesting that aspartame, as well as saccharin and acesulfame can increase hunger ratings compared with water. However, the totality of the non-clinical, epidemiological and clinical studies published up to now have been inconsistent and designs varied considerably regarding study population, duration, type of control, etc., with different limitations. Most of the studies and especially clinical trials, have not found an increase in weight associated with consumption of artificial sweeteners, but studies with contradictory results continue to be published. Uncertainty regarding benefits of artificial sweeteners, including saccharin, will probably continue for at least a few years more.

Key words: saccharin, sweeteners, weight control, cancer

Urban myths?

It is commonplace among many Romanian people (although proper statistics to estimate the real extent of this are not available) to lament that artificial sweeteners, flavours, colors and other ingredients bearing a mysterious "E number" are dangerous for their health. Saccharin, a rather old sweetener with a contorted history makes no exception. For illustrative purposes, we include here a few quotations taken from Romanian web pages (in our own translation):

"*Saccharin is one of the most controversial sweeteners currently available on the market. Although discovered more than a century ago, it is not clear yet whether it is safe for consumption or not. Before choosing to consume saccharin instead of sugar or choosing another 'light' product containing this additive, you must know well what you will be exposed to.*" (9)

"*Some specialists think that consumers (especially pregnant women and children) have been given a false feeling of safety and security*

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against the danger of developing cancer following saccharin use. Although it is a weak carcinogen, saccharin consumption may be a risk for every person." (5)

"*Any sweetener containing saccharin, aspartame or cyclamate (sic) is carcinogen. I use fructose-based Splenda… it is a tiny little bit more expensive but it does not contain all those carcinogenic substances*" (83).

"*Even though it seems harmless, saccharin is not recommended by the food experts. Those who want or need to eliminate sugar from their diet have preferred for a long time saccharin; it is seen as an ideal sweetener, but laboratory studies have proven the existence of harmful side effects not at all negligible. Artificial sweetener derived from toluene (known carcinogen), prohibited in 1977 in USA, it was reintroduced under the condition of strict labeling.*" (10)

"*Produced from oil, saccharin is sweeter than sugar, about 300 times, but energetically or nutritionally your body will use nothing from it, as it does with sugar. If consumed for a long time, various kinds of cancer may occur, especially of bladder, genital apparatus and prostate*." (80)

Similar negative feelings may probably be encountered in most if not every place and culture where artificial sweeteners are used. Such opinions illustrate a deep distrust about the safety of various chemical additives which have become part of modern life and continue to be marketed with the official blessing of the competent authorities. The latter should be presumed to use appropriate (and ideally best) expertise to base their decisions of allowing or prohibiting various additives on the market. Is this chemophobia well founded and are the competent authorities proving themselves in fact incompetent by allowing the presence of saccharin on the market? Or are such ideas as mentioned above just urban myths developed through amplification of misjudged evidence? In this mini-review we make a synthetic presentation of the data available on the safety of saccharin to allow an objective and scientific assessment of its risks and benefits and will end with a short look at its benefits in weight-control. To understand the current fears associated with saccharin we need to look first into its contorted history.

A SHORT HISTORY

In 1879, Professor Ira Remsen from Johns Hopkins University was supervising a young research fellow, Constantin Fahlberg, in the chemical study of several toluene derivatives. This seems to be the only indisputable fact of the story, for otherwise a whole set of variations on the same theme exists. In one version, while hastening to have dinner (other sources make reference to lunch), Remsen did not wash his hands carefully (he did not wash them at all, in other versions of the story) and in the course of the meal he felt that the food was inappropriately sweet, and later bitter; his wife felt nothing of the sort. This lead Remsen to discover that sweetness came not from the food, but rather from his fingers. But the same story was told by Fahlberg, who not only claimed that he was the sole discoverer of the saccharin, but patented it and made a fortune from its marketing. Moreover, to Remsen's dismay, Fahlberg published several papers claiming his exclusive merits in the discovery of saccharin, although the first paper on the topic was co-authored by both of them. This left Professor Remsen with a very bad taste: "Fahlberg is a scoundrel. It nauseates me to hear my name mentioned in the same breath with him", wrote he, in a letter to an old friend. What he was interested in (he claimed), was not so much the material benefits which Fahlberg reaped, but rather the moral recognition of his contribution: "I did not want his money, but I did feel that I owed to have received a little credit for the discovery" (24, 40, 57).

Soon saccharin was marketed in Europe and then in United States as a good alternative to sugar. Initially, saccharin was manufactured starting from toluene, which was treated with chlorosulfonic acid and the product of this reaction was then oxidized directly to saccharin. In United States this manufacturing process was first used by the Monsanto Chemical Company, started by John F. Queeny in 1901, with saccharin as its first product to be manufactured. In the beginning of the 1950s, a better process was developed by Oliver Senn and George Schlaudecker, starting not from toluene, but from the common grape flavorant methyl anthranilate; the saccharin thas produced was commercialized by the Maumee Chemical Company (which will subsequently be acquired by the Sherwin Williams Company, who later would sold the saccharin business to PMC Specialties Group, Inc.) (43).

Safety of saccharin was investigated relatively soon after its discovery and was questioned before

long after its marketing. In 1886 it was tested in Europe on workers who received single doses of up to 5 grams. Two years later, a French investigator administered the dose of 5 g to diabetic patients for 5 months. Both these investigations were considered as proofs of its safety. In the following years sporadic reports about loss of appetite and gastrointestinal disturbances were reported as associated with saccharin consumption (91). In 1890, the Commission of the Health Association in France declared saccharin to be "harmful," and outlawed its manufacture or importation. Several scientists, especially French hygienists, protested vehemently, attempting to prove the harmless character of saccharin (17). By 1902, governments of Germany, Hungary and Portugal banned the use of saccharin in food and beverages, purportedly because of concern that high level of saccharin might cause digestive problems (112). Other interests may also have played a role in taking these decisions: the German decision, for instance, seems to have been heavily influenced by pressures from the German sugar beet manufacturers (114).

In United States, in the years preceding the famous Food and Drug Act of 1906, saccharin and other sweetener manufacturers were singled out as food adulterators by Harvey Wiley, the nation's leading authority on food and drug adulteration at that time. The first proposal of saccharin banning was made in fact by Wiley, but firmly rejected by President Roosevelt (the other main force behind the adoption of the Food and Drug Act), in a an episode involving a heated exchange of words between two strong personalities. According to Wiley (in its autobiography), in the context of an important discussion on saccharin, Roosevelt asked him: "Doctor Wiley, do you think benzoate of soda is an injurious substance when placed in food?" At this, the not-very-humble Wiley retorted: "Mr. President, I don't think, I know." In his autobiography, Harvey Wiley continues the chronicle of this episode: "When I said this, President Roosevelt turned upon me, purple with anger, and with clenched fists, hissing through his teeth, said: 'You say saccharin is injurious to health? Why, Doctor Rixey gives it to me every day. Anybody who says saccharin is injurious to health is an idiot."(113)

In 1912, saccharin got banned from foods in United States, but it still remained available as a medicine on this market. During World War I, sugar shortages lead to a temporary lifting of the ban, but otherwise it applied up to 1938. From this year, it was available in United States both as a drug (medicinal product) and special dietary supplement available to those patients with special medical needs. Saccharin availability seems to have been similar during this period also in Canada (59). Between 1920 and 1950 numerous attempts to investigate saccharin toxicity in laboratory animals were made. These investigations were of relatively short duration and did not show reasons for concern. In 1951, Fitzhugh et al. reported the occurrence of lymphosarcomas in rats fed with 5% saccharin diet (but not in those fed with 1% saccharin); these results were not considered conclusive because a similar high incidence of tumors was seen in the control group of animals (47, 91).

Consumption of saccharin and other artificial sweeteners (especially cyclamates) increased after 1950s on the North-American continent after manufacturers of artificially sweetened foods extended their marketing efforts to include not only diabetics, but also dieters. When in 1958 the Food Additives Amendment to the Food, Drug, and Cosmetic Act was passed by the Congress, saccharin was one of the substances "generally recognized as safe" (GRAS) (73). During this period the use of saccharin and cyclamates increased substantially, and after 1969, when FDA banned the use of cyclamates (because ingestion of large amounts were shown to be associated to some extent with cancer in some animals), the use of saccharin, left as the sole artificial sweetener available in US, escalated to unprecedented levels. By 1977, in the United States the diet soft drinks market was estimated to about 1.5 billion $ and 15% of the soft drink market (112).

In 1970, the US National Academy of Sciences (NAS) adopted the no-effect level of 1% recommended by FAO/WHO committee, but held that the use of a 100:1 safety factor was "unduly conservative" and instead recommended a safety factor of only 30:1, leading to an ADI of about 1 g per day for the average adult; NAS also recommended further studies on saccharin safety (112) (in 1993, A.G. Renwick would propose a safety factor of 50) (96). Soon after this, investigation of two-generation, chronic toxicity in animals was initiated. A study on male rats, sponsored by the Winsconsin Alumni Research Foundation (WARF, 1972), revealed an increase incidence of bladder tumors, particularly in the second generation. These findings lead FDA to remove saccharin from the GRAS list, where it had belonged for over 10 years. In that same year (1972) FDA introduced restrictions on saccharin, aimed to discourage its general use by consumers and asked the NAS to perform a new review of the toxicological data available for saccharin. In this review (fi-

nalized in 1974), NAS concluded that evidence was not concluding regarding carcinogenicity and suggested that orthotoluensulfonamide (OTS), a common impurity in commercial saccharin might play a role in tumour induction and recommended reassessment after further data would become available (91). In the following years OTS was found not to be responsible for the carcinogenicity (16, 67).

When a 1977 study sponsored by the Canadian government (16) showed that saccharin administered as 5% in the food of animals was carcinogenic (but OTS was not), both Canadian and American authorities decided to take regulatory actions. Both countries announced on 9 March 1977 that they intended to prohibit the sale of foods containing saccharin (but the sweetener as such was to continue to be available in pharmacies) (7,59). FDA proposed an immediate ban on saccharin, because the so-called Delaney Clause (an 1958 amendment of the food and drug legislation) requires removal from the market of any additive shown to cause cancer in animals or humans. However, the FDA announcement provoked a wave of uproar and legal protests, later to be called by an author "the 1977 saccharin rebellion": about 50,000 letters reached FDA and 100,000 reached Congress; thousands of letters were received by President Carter; James Martin, a Representative from North Carolina alone received around 6,000 letters and in a statement at the time said that "legislators have heard from a million angry citizens" (41). Congress responded by adopting the Saccharin Study and Labeling Act, which introduced a two-year moratorium on saccharin ban and a compulsory label warning: "*Use of this product may be hazardous to your health. This product contains saccharin, which has been determined to cause cancer in laboratory animals*." The moratorium was intended to allow performance of additional studies investigating saccharin safety and has been extended five times since (73).

Evidence of carcinogenicity and its limits

While the contorted history of saccharin continued after 1977, we would like to stop here for a while to discuss the strength of the evidence supporting a carcinogenic effect for saccharin. It is undisputed that a number of experiments showed that saccharin may induce bladder tumours in rats, alone (15, 17, 25, 30, 42, 63, 66, 102) or after initiation with other substances (although it is only a weak co-carcinogen) (33, 110) and, in rather peculiar experimental conditions, also in mice (21). It is interesting to note that in mice, saccharin was able to potentiate lung carcinogenicity of urethane (106, 115). The crux of the problem, however, is whether these findings are relevant for the human species and for the substantially much lower doses commonly used by humans.

For the first time, an association between saccharine and bladder carcinogenicity was seen in mice in 1957, when workers at the Chester Beatty Institute implanted, intravesically, pellets containing saccharin and cholesterol (1:4) and reported the occurrence of one papilloma and three carcinomas. A second similar experiment was published in 1970; this time, a control group of mice received pellets of pure cholesterol, and had a lower incidence of carcinomas (13% and 12%, versus 47% and 52% for the saccharin-containing pellets) (21). While such evidence is convincing (that saccharin may cause bladder cancer if administered intravesically as pellets), it is of little scientific relevance for the common use of saccharin, which is not implanted intravesically, but ingested orally. It is known that mouse bladder is rather sensitive even to pellets of pure excipients (22), as also shown in this experiment, and therefore this effect is likely to be limited to this particular route of administration. Besides, an experiment in which 50 mice were given 5% saccharin in diet and a control of 100 animals were fed on standard diet, revealed no neoplasms of the urinary bladder on careful macroscopic examination in the saccharin group (98).

In experiments on rats, sodium saccharin increased the occurrence of bladder tumors when the animals were fed over two generations beginning either at conception or at the time of birth and continuing for the rest of their lifetime (15, 25, 66, 102). Its sodium salt also promotes bladder carcinogenesis in the rat following initiation with various substances such as MNU (110), N-butyl-N-(4-hydroxybutyl)nitrosamine or FANFT (N(4-(5-nitro-2-furyl)-2-thiazolyl)formamide) (33). Studies in rats used very high doses, usually 2.5%-5% (5% being the most commonly utilized) in the diet of animals. Hicks et al. (1973) used a dose of 2 g/kg, but a carcinogenic effect was only seen in the presence of methylnitrosourea (MNU); saccharin alone induced only mild hyperplasia of the bladder epithelium in 2 out of 12 animals that received the sweetener alone (65, 66). In a dose-response experiment involving 2,500 second-generation male rats, 1% the 1.0% dietary level (fed to 700 rats) was determined to be a no-effect level for bladder

tumours (102); this NOAEL was also supported by other experiments (112, 56). In a study, the incidence of bladder tumors in the OTS-treated groups and in the female rats fed the 5% saccharin diet was not significantly different from that in control animals (15). In other experiments also tumour response was greater in male compared to female rats (30, 33). Tumorigenic effects were seen with the sodium and to a lesser extent with potassium salts, but not with the calcium salt or the acid form of saccharin (even 7.5% dietary levels of acid saccharin were not able to induce proliferative responses in rat bladder), despite similar levels of urinary excretion for all forms of saccharin (33, 60). Studies of long duration involving administration of sodium saccharin in mice (50, 98), hamsters (1,50) and monkeys (105, 107) have not shown any tumorigenic activity (33). In monkeys, after 22 years of continuous dosing, saccharin has shown no evidence of carcinogenic effects (101, 107) (the dose used in this experiment was 17.9 mg/kg, a dose equal to or close to the usual daily dose in humans, making some critics to deny any relevance of the study) (76). When sodium saccharin is given in rats after 5 or 6 weeks of age, tumorigenicity is generally not detected (33).

Sodium saccharin seems to be just one member of a large group of sodium salts able to act as tumor promoters on rat bladder in high doses. This group also includes sodium ascorbate (extensively investigated for its bladder tumorigenicity in rat) (32, 34, 51, 53), glutamate (38), erythorbate (52), citrate (72) and bicarbonate (75, 38); as in the case of saccharin, the acidic forms of these salts did not trigger proliferative responses on the rat urinary bladder (38, 52). The available evidence suggests that the anionic portion is less important for tumorigenicity than the physiological changes in the urine triggered by the administration of those sodium salts. It seems that the essential factors involved in the preneoplastic and neoplastic changes at bladder level are represented by elevated urinary pH (over 6.5) and high urinary sodium concentration (while urinary calcium must be equivalent to or below normal values) (53, 55, 111). Acidification of urine (e.g. by administering NH_4Cl) inhibits the proliferative activity of sodium saccharin on rat urinary bladder (55, 92). But inhibition of certain enzymes or other mechanisms have also been proposed to explain the carcinogenicity of saccharin on rat bladder (31). In 1988, it was suggested that "in rats with an inherently high urine output, the diuresis associated with NaS (sodium saccharin) ingestion combined with the increasing diuresis that occurs with age in male rats results in a chronic demand for a bladder-volume increase that is met by excessive cell division of the bladder epithelium", finally leading to bladder hyperplasia and tumours (3). Sodium saccharin is not mutagenic and does not bind to DNA (28), which lead to its classification as a non-genotoxic carcinogen (108).

Using such large doses as 5% of the usual diet is in our view a rather unhappy example of bad science, as even Paracelsus was aware that "*sola dosa facit venenum*" (only the dose makes a substance a poison). The human equivalent would probably be at least 50 grams, corresponding to over 2,700 tablets of 18 mg. An estimation by two of British authors in 1974 was that the amount of sodium saccharin needed to produce bladder cancers in rat was about 2,5 g/kg, that is about 8,300 times the usual human consumption (12). When FDA commissioner Sherwin Gardner announced the saccharin ban, to avoid the potential panic such an announcement could cause, he reminded in public that saccharin had been in use for a long time and that a person would have to drink 800 diet sodas per day to consume de equivalent dosage of saccharin used in the Canadian experiments, a comparison widely exploited by the opponents of the ban at the time (112). R.M. Hicks and J. Chowaniec, who themselves had obtained bladder cancer in rats with saccharin, in a letter to *British Medical Journal* from 1977, following the FDA ban announcement, argued against a similar ban in UK, based on the very high doses needed to generate tumours and stating that "to withdraw saccharin… from the market… could well create more health problems than it could conceivably prevent." (64) Furthermore, with the publication of the large dose-response study of G.P. Schoenig et al. (1985) (102), it was realized that the dose-response function for saccharin was much steeper than was previously assumed based on this, and therefore the risk for humans at the usual low doses is very low (26, 45).

Moreover, all the data showed above indicate that carcinogenicity is limited to male rats given sodium saccharin very early in their lifetime, due to a specific mechanism not relevant for other species. As Bernard Oser put it in a rather memorable phrase in 1981, "Man is not a big rat." (93) Straightforward, unqualified extrapolation of data (irrespective of mechanism, phyisio-pathological context, etc.) from rodents in general, and rat in particular, to man and vice versa, is scientifically unwise (2, 35) (contrary to what was claimed sometimes in the past) (97): for instance, 2-naphthylamine is a strong bladder carcinogen in man, but without effect on the bladders

of rats (8). Data supporting a carcinogenic effect of sodium saccharin in humans are virtually absent. More than 20 epidemiologic studies investigating the relationship between saccharin and cancer were published (4, 11, 12, 13, 20, 23, 27, 29, 54, 68, 69, 78, 79, 83, 85, 86, 88, 89, 103, 116). By 1985, over 5,000 patients with bladder cancer had been included in case-control studies and over 27,000 diabetics had been observed for 234,000 person-years. The summary relative risk calculated by pooling all case-control studies was less than 0,98 (44, 87). In most of these studies the risk ratios (RRs) observed were close to 1 (suggesting no association), and weak inverse associations have been observed at least as often as weak direct ones (89) suggesting absence of any effect or a very weak one. More recent studies have had similar results, not supporting any association between cancer and saccharin use (54). A case-control study from Chine using 254 bladder cancer patients and an equal number of controls reported an odd ratio of 3.9 for bladder cancer patients with a relatively intense use of saccharin; however, its results are to be interpreted with considerable caution, as in this study no elevated risk of bladder cancer in smokers was identified, although large trials have well established the contribution of smoke to bladder cancer (109, 118).

Because of the great number of the epidemiological studies, it is impossible to describe all of them here, even synthetically. Some of them, especially the first ones, were more indirect, comparing time trends of mortality, or persons with diabetes with persons without diabetes. One of such study looked at bladder cancer mortality rates in England and Wales and compared them with figures for consumption (*per capita*) of saccharin and cigarettes. The increase in mortality was attributed to the increase in number of smoking people and no evidence of a break in the continuity of the mortality trends was identified, which might have corresponded to the introduction of saccharin (6, 12). A second British study examined 18,733 patients dying from bladder cancer and 19,709 patients dying from other cancers, with the exclusion of lung and pancreas cancer and looked for the frequency with which diabetes mellitus was mentioned in the death certificates of those patients. Though it was known that diabetics consumed considerably more saccharin than non-diabetics, no evidence of increased risk of bladder cancer was seen in diabetics (11). A third investigation published in that same period in UK, looked at 5,971 members of the British Diabetic Association (99% of whom were suffering of diabetes) and found even a lower overall cancer mortality, as compared with a 10% random sample of all deaths which occurred in England and Wales in 1972 (13). None of these studies detected any association between sodium saccharin consumption and bladder cancer, but due to their inherent limitations it would have been difficult to detect one if it existed (37).

More direct studies, comparing exposed cohorts or cases to non-exposed ones, also had often methodological limitations. Many of the studies, especially those performed in United States, investigated the relationship between artificial sweeteners (not limited to saccharin) and cancer, making difficult to separate the effects of saccharin from those of cyclamates (89). Others (including a Canadian one that found an increased risk of bladder cancer associated with saccharin consumption) were affected by selection bias and small sample size. Most of these studies did not find a positive association between saccharin use and bladder cancer (14, 37). One of them included a high proportion of subjects from UK and Japan who used saccharin in the years during and immediately after World War II, covering thus an "induction period" of 30 years or more. The results showed no association between sodium saccharin and bladder cancer; moreover, an inverse, unexplained relationship was seen between artificial sweeteners and bladder cancer in metropolitan Nagoya, Japan (89). The report of O.M. Jensen and C. Kamby (1982) is also of a particular interest because it assessed the risk of bladder cancer among people exposed to artificial sweeteners in utero and early childhood. In this study the risk of bladder cancer was evaluated in Danish people born during the Second World War, when saccharin use was 4-5 times higher than in pre-war decade, thus the subjects experimenting increased intrauterine exposure. The results provided no evidence of an increased risk of bladder cancer during the first 30-35 years of life after in utero exposure to sodium saccharin (77). These data seem to provide reassurance, considering that it was shown that saccharin crosses the placental barrier and reaches the fetus (36).

In 1991, FDA officially lifted its proposal to ban sodium saccharin based on the results of the newer studies showing no evident link between its consumption and human cancer. The requirement for a special label warning was abolished in United States by the Saccharin Notice Repeal Act in 1996 (48). In 1995, through its Scientific Committee for Food, the European Commission, in line with the joint FAO/WHO Expert Committee on Food Additives (JECFA), set a full ADI for sodium saccharin of 0-5 mg/kg bw (in 1977 and 1985, it

had allocated only a temporary ADI of 0-2.5 mg/kg bw). This was based on a No Effect Level (NOEL) of 1% in the diet, equivalent to 500 mg/kg bw, using a safety factor of 100 (in other words, the ADI is 100 times lower than the level were no effect was seen in animal experiments) (46). In 1999, the International Agency for Research on Cancer, who initially classified sodium saccharin as a class 2B carcinogen, in the light of new data reversed its previous decision and concluded that „saccharin and its salts are not classifiable as to their carcinogenicity to humans" (placing it in group 3) (74). Following a request of the food industry, Health Canada has completed a comprehensive evaluation of sodium saccharin toxicological data and arrived to the same conclusion, that results of the previous studies on rats are not applicable to humans. In 2006, a letter was sent to stakeholders informing them of the results of Health Canada's evaluation and the intention to propose regulatory changes to allow saccharin to be used as a food additive. However, no regulatory amendment regarding sodium saccharin legal status has yet been approved in Canada (62).

Is toluene a known carcinogen?

As mentioned in the introduction of this paper, on one Romanian webpage, it was claimed that saccharin is "derived from toluene (known carcinogen)" (10). The implication is that because toluene as a starting material is a carcinogen, saccharin will also be one. Such reasoning is faulty, as often very slight chemical changes induced in a molecule may transform it from a non-carcinogen in a carcinogen and the other way out. For instance, benzene is a known human carcinogen (82, 90) while phenol is not (70), although the only difference between them is a hydroxyl group (phenol has an additional atom of oxygen in its molecule). Besides, contrary to the statement mentioned, toluene is not classifiable as a human carcinogen (81). The IARC monograph concludes with the following statements: "*There is inadequate evidence in humans for the carcinogenicity of toluene. There is evidence suggesting lack of carcinogenicity of toluene in experimental animals. Overall evaluation: Toluene is not classifiable as to its carcinogenicity to humans (Group 3)*." (71)

Children and pregnant women – a false feeling of safety?

While it was shown that saccharin crosses the placental barrier and reaches the fetus (36), no epidemiological data showed an increase in risk associated with saccharin consumption by children or pregnant women. The report of O.M. Jensen and C. Kamby (1982), mentioned previously, provided no evidence of an increased risk of bladder cancer during the first 30-35 years of life after in utero exposure to sodium saccharin (77). Health Canada, not at all one of the quickest authorities to acknowledge saccharin safety, following its re-assessment of all toxicological data, in a text for the general public on its website, states: "The scientific evidence revealed that saccharin can be safely consumed by humans, including pregnant and breast-feeding women. However, for nutritional reasons, pregnant women should be cautioned against excessive consumption of products containing artificial sweeteners since such foods could be replacing nutrient-dense, energy-yielding foods." (61)

Is saccharin useful for weight-loss?

Saccharin is a low-calorie sweetener and as such is often used by people interested in controlling their body weight, in a pervasive low-calorie culture and obesity epidemic. In the United States, a plan for removing sugar-sweetened beverages from primary and secondary school vending machines and replacing them with diet sodas and other non-nutritively sweetened or unsweetened beverages has been proposed in the fight against the current obesity crisis (104). Delivering sweet taste without sugar calories seems a rational strategy (because artificial sweeteners are several hundred times sweeter than sugar, their contribution to energy intakes is insignificant) (18). But might this be just another myth about artificial sweeteners in general and saccharin in particular?

In 1986, J.E. Blundell and A.J. Hill published a paper in which reported that consumption of an aspartame solution resulted in an increase in ratings of appetite compared with the control group, which only received water (19). Following this report, authors from the same group provided new evidence suggesting that aspartame, as well as saccharin and acesulfame can increase hunger ratings compared with water (99, 100).

However, the totality of the non-clinical, epidemiological and clinical studies published up to now have been inconsistent and designs varied considerably regarding study population, duration, type of control, etc., with different limitations. Most of the studies did not use saccharin, but were focused either globally on artificial sweeteners, or on

aspartame. Some studies have reported that artificial sweetener use – or sweet taste itself – may intensify hunger, cravings, or increase food consumption, but most studies have reported no such increases. A smaller number of studies have reported raised levels of insulin and/or falling glucose levels (49). Most of the studies have not found an increase in weight associated with consumption of artificial sweeteners. A meta-analysis of 16 clinical trials evaluating aspartame (and not saccharin) found the artificial sweetener useful for weight loss, the data estimated from meta-analysis being in agreement with the loss calculated on a theoretical basis: around 0.2 kg/week (39).

Because clinical trials are the most methodologically sound ways of generating evidence, such a meta-analysis should be more convincing than the non-clinical and mere epidemiological data; but some authors seem to have a rather strong bias in selecting only the epidemiological studies supporting the contrary conclusion (117). Evidence has been and continues to be inconsistent. A very recent clinical study compared the effects of a sucrose-rich diet consumed for 10 weeks with those of a diet rich in artificial sweeteners in slightly overweight healthy subjects. Subjects fed with a sucrose-rich diet had significant elevations of postprandial glycemia, insulinemia and lipidemia compared with those fed with a diet rich in artificial sweeteners (95). These results are in agreement with the findings of the previous clinical trials. Instead, a non-clinical study recently published by a group of Hungarian researchers found that mice given water solutions of table top artificial sweeteners (saccharin, cyclamate based, acesulfame-K based, and aspartame) had significantly increased body weight, although the food intake did not change (94). Obviously, comparing the evidence provided by a clinical trial in humans and by a non-clinical study in a different animal species, the former should carry more weight (if both methodologically sound and sensitive). But the diversity of the findings in various studies still leaves the problem open: "*Because the scientific findings are mixed, there is currently no official recommendation about using artificial sweeteners as a tool for weight control",* wrote T. Hampton in a JAMA paper published in 2008 (58). Uncertainty regarding benefits of artificial sweeteners, including saccharin, will probably continue for at least a few years more.

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