# Health Effects of Artificial Sweeteners

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## Artificial Sweeteners and Carcinogenicity

Saccharin, aspartame, and acesulfame-K have generated most concerns over potential carcinogenicity. In relation to saccharin, concerns arose from early animal toxicology studies in the 1970s in which bladder cancer developed in rats administered high doses. However, further research found that the carcinogenic mechanisms identified in rodents were not applicable to humans, and subsequent studies have found no associations between saccharin consumption and cancer in humans[1, 2].

Research on aspartame is generally controversial due to the strong associations between study outcomes and funding source. Analysis of this issue found that industry funded studies all attest to safety, while 92% of independently funded studies report adverse health effects, particularly in relation to body weight, diabetes or glucose regulation[4]. These inconsistencies mandated the need for an unbiased evaluation of empirical evidence in relation to aspartame and carcinogenesis. A 2015 meta-analysis of carcinogenic bioassay animal studies concluded there was no significant relationship between various experimental doses of aspartame and occurrence of cancerous tumours[4]. This is consistent with observational epidemiology in humans[3].

It is important to note that much of the controversy regarding aspartame stems from 3 studies from the same research group in Europe, all of which purported to show carcinogenicity in rats and mice[5, 6, 7]. The 2015 meta-analysis included these studies, lending weight to its conclusions[4]. The European Food Standards Agency have rejected the findings of the latest study[7] on the basis that the tumours observed in mice were not mechanistically relevant to humans[8]. More concerningly, the researchers misdiagnosed hyperplasia as malignant tumours and violated OECD testing protocols by administering aspartame during fetal development[4, 8]. Unfortunately, these studies generate unscientific assertions that run contrary to the fact that there is no strong evidence that aspartame is carcinogenic[9, 10]. This should be interpreted in the context of

recent re-analyses of aspartame by the EFSA which concluded that the current ADI is appropriate having regard to potential risk and current levels of consumption[8].

Sucralose is one of the most comprehensively researched AS with a strong safety profile, including for consumption during pregnancy and in children[1]. A recent review of toxicology research found no evidence of carcinogenicity in long-term animal models or in human studies[17]. The research on sucralose highlights an important factor to consider: toxicology programs are designed to induce a toxic response, and there is substantial regulatory oversight in ensuring rigorous standardisation of the toxicology models[17]. To date, numerous international agencies and scientists working in the field continue to support the safety of AS for human consumption. There is often criticism levelled at the regulatory framework in which AS are approved for us, posited as: "who regulates the regulators". It is important to point out that the EU has banned over 1,300 compounds from use in personal care and cosmetic products based on even preliminary evidence of toxicology[18]. The criticism fails to stand up to an unbiased, objective assessment of the regulatory framework in which the safety of AS are analysed.

Nonetheless, using animal bioassays to inform health risks of long-term human consumption will always carry a margin of uncertainty. It is thus difficult from a scientific standpoint to consider the carcinogenic potential of AS a closed case. However, within current toxicology monitoring programs and at average consumption levels in the population, the evidence does not currently support a carcinogenic effect of authorised AS in humans.

## Artificial Sweeteners & Body Weight

Several observational human studies have observed a relationship between high or regular diet soda consumption and increased adiposity and cardiometabolic risk[19]. Teasing this apart, it is clear that the increase in cardiometabolic risk factors is a consequence of increasing adiposity[19]. The relevant question is the relationship between non-calorically sweetened beverage consumption and weight gain. Closer scrutiny of the observational research reveals that the relationship is in fact the other way around: higher adiposity is associated with high levels of AS intake. This is known as "reverse causality", i.e. those with high AS consumption are more likely to have a poor, high calorie diet and have higher adiposity.

There is a clear distinction between observational research and controlled trials, and there are multiple randomised controlled trials looking at this issue. A recent meta-analysis of 15 RCT's found that use of AS was clearly associated with lower body weight, BMI and waist circumference[20]. The included RCT's comprised a large sample size, including 4 studies in children, with no study finding that AS led to negative weight outcomes[20]. This is consistent with the expected purpose of AS substituting for sugar and/or calories in beverages and food products, which is to reduce total energy intake and contribute to weight loss. This is consistently observed in RCT's[20].

It should be stressed that this effect assumes that compensations are not made in energy intake by substituting AS and increasing calories from other sources: the reverse causality observed in observational studies. This is a behavioural issue and cannot be specifically attributed to AS. Controlled data supports basic energy balance fundamentals, and when AS products substitute for calorie-containing products, individuals lose weight[20]. However, certain research has suggested other mechanisms by which AS may contribute to weight gain, including stimulating blood glucose and "tricking" the brain through activation of brain-reward circuitry which responds to sugar/sweet taste, in turn stimulating appetite[21, 22]. These concerns warrant closer scrutiny.

## Artificial Sweeteners & Blood Glucose Regulation

The hypothesis is that the intense sweet perception of AS alters glycemic and insulin responses, and sweet-taste receptors in the gut are activated in response to AS, increasing glucose uptake. In relation to glycaemia and insulin, a trial in morbidly obese subjects but with normal insulin sensitivity [assessed by HOMA-IR] found greater peak plasma glucose levels and insulin response to an oral glucose tolerance test [OGTT] given 10-mins after a pre-load with 48mg of sucralose[23]. This study has challenged previous research on sucralose, which was considered to have no impact on carbohydrate metabolism from multiple studies looking at glycemic responses[24].

It is difficult to reconcile the current literature on sucralose in relation to glycaemic or insulin responses. In the E.U. SCF review of sucralose safety, one 6-month study in Type-2 diabetics found a consistent increase above baseline in HbA1c [a marker of long-term glycemic control] in subjects given 667mg sucralose daily, however, this occurred in the absence of any impacts on insulin or blood glucose levels[25]. The SCF review ultimately concluded that the doses administered were significantly greater than consumption levels, such that any actual effect at population levels of consumption would be so small as to be clinically insignificant[25]. In this context, note that in the trial which found greater peak plasma glucose and insulin responses to an OGTT, the responses still remained within normal range for OGTT and amounted to nominal differences between sucralose group and controls[26]. The inconsistencies in the research are evident in trials on sucralose: one study found higher blood glucose levels, one study reported lower blood glucose levels, and nine studies have found no effect[26]. A recent systematic review of 28 trials of aspartame, sucralose, saccharin, and acesulfame-K confirmed these inconsistencies[26]. Certain trials have found effects of AS on glucose metabolism, most have not found any interaction, and the significant differences in the studies between subjects, the AS used, the placebo, and outcome variables, limits comparisons[26]. Of these issues, perhaps the most important is the comparison of AS to placebo, often water, where arguably the appropriate trial design is a comparison with a caloric sweetener. This is because, if we assume AS do stimulate glucose uptake, then this would occur in the context of low concentrations of glucose in the digestive tract, while a caloric sweetener like sucrose would result in a greater

amount of glucose absorbed[27]. This may explain why in trials using OGTT the observed differences in absorption between an AS beverage and water are largely nominal[28].

The second arm of the hypothesis is that AS activate glucose transporters in the gut, with one proposed mechanism being activation of glucagon-like peptide-1 [GLP-1]. This research is also equivocal, evident in a systematic review including 11 studies which assessed GLP-1: aspartame has been shown to lower GLP-1, while sucralose and acesulfame-K found to increase GLP-1 concentrations[36]. Yes again, this is not consistent. In a trial administering 72mg aspartame and 24mg sucralose before a 75g OGTT, no effect of either AS on GLP-1, insulin or glucose in Type-2 diabetics was found[29]. For more confusion, the healthy control subjects had a significantly higher GLP-1 area-under-the-curve from sucralose, but not aspartame[29].

The real issue here is arguably trial design, an example of which is evident in two trials. The first used diet soda containing 46mg sucralose plus 26mg acesulfame-K as the intervention in healthy humans, and found GLP-1 increased in response to OGTT compared to water[30]. However, the trial failed to control for other compounds in the diet soda – citric acid, phosphoric acid, potassium benzoate, potassium citrate, natural colourings and flavourings – which may have influenced the results[30]. Consequently, a subsequent trial administered 46mg sucralose plus 26mg acesulfame-K, or 52mg sucralose, or 200mg acesulfame-K alone, to healthy subjects and found no effect of either treatment on GLP-1, blood glucose, or insulin concentrations[31]. This is consistent with another trial showing no effect of sucralose administered through intraduodenal glucose feeding on GLP-1 or glucose uptake[32].

Taking this research as a whole, a couple of trials show some effect of AS on GLP-1 and glycemic response[29,30],while other studies[31, 32]and a systematic review of 11 studies measuring GLP-1[27] suggest the majority of human studies have found no effect of AS on intestinal sweet-taste receptors and glucose uptake. The biological basis for the limited studies finding such effect in humans remains unexplained, and the clinical significance of the findings remains questionable[25, 27]. On the basis of in vitro [cell culture] and animal model studies, some authors and commentators have reached outside the data to make speculative assumptions on the consequences of sweet-taste receptor activation on glucose regulation[27]. While potential mechanisms have been elucidated in vitro and in animal models, with limited supporting human data, the nominal effects may be

of no clinical relevance. The overall body of evidence for a direct effect of AS on glycemic control is limited. It would be an overreach from the current evidence to say that AS influence blood glucose, insulin, or GLP-1 in humans: equally, it would be an overreach to say that AS are biologically inert.

## Artificial Sweeteners and Activation of Brain Reward Circuits & Appetite

The hypothesis proposed here is that the intense sweetness of AS activates responses in brain regions that control energy balance. The evidence suggests, however, that for hypothalamic responses to occur there must be a coupling of sweet taste with actual energy content. Interestingly, this has been shown in sports nutrition research investigating the effects of carbohydrate mouth rinsing on performance, which found that the presence of glucose was necessary to elicit a brain response[33]. The trial used functional magnetic resonance imaging [fMRI] to determine activation of brain-reward regions in response to either glucose, maltodextrin [a simple sugar] or saccharin intake[33]. While both of the carbohydrate-containing solutions activated dopaminergic pathways that mediate reward-responses to food, these circuits which were unresponsive to saccharin[33]. This is consistent with another trial comparing sucrose [table sugar] to sucralose [AS] which showed only sucrose led to brain activation responses[34]. This research indicates that the presence of sweet taste alone is insufficient to activate brain regions with a role in appetite or food-reward behaviours, and requires the coupling of energy content to sweet taste as would be found in simple sugars[33, 34].

Notwithstanding the studies using fMRI to determine brain responses, arguments remain that the disconnect between sweetness and energy content diminish control over energy intake and precipitate further energy intake[35]. This is not supported in the literature. A systematic review and meta-analyses on the effect of AS consumption on energy intake found that in studies using pre-loads of AS beverages followed by ad libitum test meal, consumption of AS resulted in a reduction in overall energy, an effect consistent with longer-term RCT's[35]. This is corroborated by another systematic review which identified 7 studies investigating subjective appetite scores, none of which found any effect of AS consumption on subjective appetite[26]. Cumulatively, the literature does not support any direct effect of AS on hunger and either subjective or objective appetite[26, 35, 36]. That AS "trick the brain" into a response in the absence of carbohydrate is also unsupported[33, 34].

## Artificial Sweeteners & the Microbiome

Research on the human gut microbiome has demonstrated that the composition of bacteria in the gut, which is strongly impacted by diet, influences host health[37]. The primary driver of change in the microbiome is the presence or absence of dietary fibre, which undergo selective fermentation by bacteria species which specialise in the degradation of indigestible plant matter[38]. Concerns over the impact of AS on the gut microbiome have been generated largely from in vitro studies, and there is limited quality human evidence[39]. A recent study in mice found that saccharin, aspartame, and sucralose intake led to alterations in the gut microbiome that resulted in increased glucose intolerance[40]. These results may not extrapolate to humans. For example, aspartame is comprised of the amino acids phenylalanine and aspartic acid, and is broken down into its component parts in the human small intestine: the individual component parts are absorbed, not aspartame itself. More particularly, the conclusions of the study were based on interpretation of data from faecal samples in rodents extrapolated to humans, and the findings should be interpreted with caution[39].

An issue with this emerging area of research is the lack of established models, and research designs have yet to be determined[39]. There is evidence that sugar alcohols commonly used as AS may have "prebiotic" effects, increasing concentrations of beneficial bacterial populations in humans[41]. Nonetheless, suggestive mechanisms for metabolic consequences from altered bacterial composition as a result of AS intake have been identified in animal models[42]. The identified bacterial compositions correlate with alterations observed in the microbiome in humans with metabolic disease[42]. While there can be no conclusion on cause vs. consequence yet, these effects warrant further investigation in well-controlled human studies with recognised models.

This area of research serves as an indictment of the hyperbole surrounding AS: those against AS use liberally cite limited and questionable animal model data as concrete evidence of a negative effect in humans, while others casually assume a benign effect. The reality is equivocal: at this moment in time, we cannot say definitively either way.

## Conclusion

Can we definitively say that artificial sweeteners are benign?

Can we say concretely that there are no long-term consequences for human health from AS consumption?

In relation to both questions, the answer – which many people don't want to hear – is that we can never be 100% certain. Objectively and considering the totality of evidence, it does appear that much of the profoundly negative effects are exaggerated. Arguably at current habitual population levels of consumption, AS use would not appear to negatively impact on human health to any identifiable degree. Yet, having regard to grey areas in the literature and the reliance on animal models from toxicology to the microbiome, which cannot be stated with absolute authority.

Can we as healthcare professionals recommend artificially sweetened beverages and/or foods as a means to improve health? AS can certainly be an effective substitution for caloric-containing foods and beverages, provided those calories are not compensated for elsewhere in the diet. Insofar as weight loss may be required for clinically meaningful reductions in lifestyle disease risk, if the targeted use of AS use leads to a reduction in energy intake, that must be considered a positive intervention. However, I do think healthcare professionals should err on the side of caution and avoid recommending overly liberal use. On the other hand, fear-mongering over moderate AS consumption is counterproductive and, importantly for healthcare professionals, is not evidence-based advice. Eating more vegetables is more important than the odd Diet Coke.

In sum, artificial sweeteners can be included in the context of overall nutritional best practices. They should be a tool, not a crutch. In my opinion, that is a responsible position stand having regard to the overall literature.

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