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The review: Effects of acesulfame K on human health

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ABSTRACT

Acesulfame K, a widely used low-calorie artificial sweetener in food and beverages, has raised concerns and sparked controversies regarding its impact on human health. Thus, the objective of this study is to comprehensively review the effects of Acesulfame on human health based on the literatures from the past few decades, providing a scientific basis and reference for promoting accurate understanding and rational utilization of this sweetener. Extensive research has been devoted to investigating the correlation between Acesulfame K and human health over the past few decades. Numerous studies have demonstrated that Acesulfame K can serve as a low-calorie alternative sweetener for weight management and disease prevention, such as diabetes. However, some findings suggest adverse effects of Acesulfame K on the health of cardiovascular, neurological, endocrine, etc. In addition, Acesulfame K is related to some cancers.

KEYWORDS

Acesulfame K; Cardiovascular Health; Neurological Health; Endocrine Health; Gastrointestinal Health; Genotoxic Impacts; Cancer risk

1. INTRODUCTION

Acesulfame K, often abbreviated as ACK, is a prevalent artificial sweetener in modern dietary uses. This non-nutritive sweetener (NNS) is employed to elevate the flavor profile of numerous beverages and food products. Having a sweetness intensity roughly 200 times that of sucrose, ACK serves as a potent agent in sweetening applications. It has been widely utilized over the last several decades. Its discovery can be traced back to 1967 by German researcher Karl Clauss, and subsequent approval by the US FDA granted in 1988 for a variety of food and beverage applications. The ever-growing demand for low-calorie alternatives have significantly incremented its prevalence in the market, thus rendering ACK a common component in human diet.

Generally, ACK is considered as a safe NNS. However, the research surrounding its adverse effects on human health has become one of the academic hot points in recent years. The objective of this review will be to critically examine the potential hazards and health implications of ACK consumption, and provide a robust, factual assessment based on available scientific data.

2. PROPERTIES OF ACK

ACK carries the chemical formula C4H4KNO4S. It belongs to the class of sulfamate esters derived from the structure of 1,2,3-oxathiazin-4(3H)-one 2,2-dioxide, which is substituted by a methyl group at position 6 [1]. The chemical structure is present in Figure 1.

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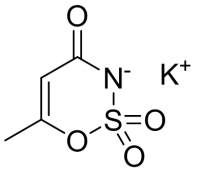


Figure 1. Chemical structure of ACK

ACK is quickly absorbed and excreted in its original chemical structure in the body without being metabolized or stored. But it can eventually degrade to acetoacetamide when expired. Acetoacetamide is toxic at high doses. 1% acetoacetamide in the diet for 3 months will cause tumor growth in the thyroid gland according to the animal experiments [2].

The presence of methylene chloride, a known carcinogenic chemical, as a potential impurity in ACK can be attributed to its utilization as a solvent during the initial manufacturing process [3]. Expose to methylene chloride leads to dizziness, nausea and even cause death and increase the risk of suffering from cancer [4, 5].

3. HEALTH IMPLICATIONS OF ACK

Recent studies have revealed potential health implications associated with ACK consumption, thereby creating a questionable risk-benefit ambiguity about this widely accepted sugar substitute. Of particular interest are the metabolic disruptions that might lead to cardiovascular complexities. There are mounting concerns on its effects on neurological health, with some findings indicating some degree of neurotoxicity. Intriguingly, increasing evidence suggests a possible interplay between ACK consumption and Endocrine health. The artificial sweetener has been reported to potentially contribute to disruptions in insulin regulation and glucose homeostasis, thereby possibly leading to the development of metabolic syndrome and Type 2 diabetes.

Further, the gastrointestinal tolerance to ACK and its impact on gut microbiota has been the subject of recent investigations, given its propensity to resist degradation in the digestive tract. Although ACK is deemed as safe within the stipulated Acceptable Daily Intake (ADI) levels, concrete evidence on the impact of chronic and sub-chronic exposure still remains indeterminate. Accordingly, this section, in the context of existing research, offers an overview of pertinent health implications associated with ACK consumption, discussing its hypothesized influences on cardiovascular, neurological, endocrine, and gastrointestinal health.

3.1. Cardiovascular Health

The effect of ACK on cardiovascular health has been a subject of considerable contention. Research points to associations between the ingestion of artificially sweetened beverages and certain cardiovascular risk factors. An observational study conducted by Nettleton et al. that included 5011 individuals in the Multi-Ethnic Study of Atherosclerosis cohort, revealed a correlation between diet soda consumption (a common source of NNS including ACK) and a 36% greater relative risk of incident metabolic syndrome as compared to individuals who did not consume diet soda. Specifically, diet soda intake was linked to increased waist circumference and fasting hyperglycemia, parameters that independently contribute to cardiovascular morbidity [6].

A large scale prospective NutriNet-Santé cohort study by Debras et al. that included 10388 participants indicates that total artificial sweetener (including ACK) intake was associated with increased risk of cardiovascular diseases and particularly cerebrovascular disease. Specifically, ACK associated with the risk increasing of coronary heart disease [7].

However, it is critical to note the divergences in outcomes across multiple types of studies conducted on this topic. Randomized control trials (RCTs) produce conflicting results. For example, in the

Choose Healthy Options Consciously Everyday trial, adults were divided into two groups based on their beverage intake - one group consumed artificial beverages while the other group consumed water. Findings revealed that both groups decreased intakes of several dietary elements potentially detrimental for cardiovascular health, including total daily energy, carbohydrates, fat, protein, saturated fat, total sugar, added sugars, and other carbohydrates. Importantly, the artificial beverage group demonstrated decreased consumption of caloric sweeteners (CS) and desserts more significantly than the water group [8].

A meta-analysis by Miller and Perez, which encompassed 15 RCTs and nine prospective cohort studies, investigated the connections between body weight and composition and low-calorie sweeteners (including ACK). Analysis of RCTs signified that substituting sugar with low-calorie sweeteners resulted in a modest weight reduction, along with a decrease in BMI, fat mass, and waist circumference, all of which could confer cardiovascular protection [9].

Subsequently, it is discernible that the correlation between ACK use and cardiovascular health is nuanced. This underlines the need for further, more extensive studies to ascertain the implications of ACK on cardiovascular health.

3.2. Neurological Health

Research studies have delved into the effect of ACK on cognitive functions. Studies postulate that acute exposures to ACK could lead to decreases in intracellular ATP production. This decline is potentially detrimental to the viability and protection activity of neuronal cells. Furthermore, chronic ingestion of ACK in mice has demonstrated potentials to impair learning and memory functions, specifically functions that can be localized to the hippocampus [10]. Transfer the ACK dosage in experimental mice to the equivalent human dosage, the experimental doses go beyond 1.2 to 1.9 times the estimated human ADI. It indicates that excessive ingestion of ACK is associated with the increasing of neurological risks.

However, take ACK at a recommended daily dosage, but prolonged usage may potentially lead to detrimental neurological consequences. Experiments conducted by Wu et al. have provided compelling evidence, both in humans and animals, suggesting that the consumption of low-dose ACK (approximately 1–4% ADI) is associated with an increased risk of early puberty in girls [11].

3.3. Endocrine Health

A focus of endocrine research has been on the role of artificial sweeteners, including ACK, in glucose homeostasis. Several studies have dwelt on the potential role of ACK in influencing insulin secretion and glycemic control. The possibility that ACK may influence the body's insulin reactions and glucose metabolism could have a profound effect on endocrine health, particularly in regard to diabetes and metabolic syndrome.

In laboratory settings, specifically in studies conducted on Sprague-Dawley rats, certain trials have indicated potential alterations in insulin regulation following the consumption of ACK.

The diabetogenic potential, which is essentially the proclivity of a substance to induce diabetes, has been measured for ACK alongside two other common artificial sweeteners: aspartame and sucralose. To establish the comparative diabetogenic effects, ADI doses of these artificial sweeteners were converted into equivalent animal doses and administered to experimental rats over a period of 13 weeks in a stepwise ascending order. Of the three artificial sweeteners, sucralose induced a comparatively less drastic increase, as corroborated by histology reports. In comparison, ACK and aspartame registered more pronounced diabetogenic effects. Hence, while the diabetogenic effect is evident across all the tested artificial sweeteners at higher dosage levels, sucralose may potentially pose lesser health risks compared to aspartame and ACK [12].

Otherwise, ACK may cause allergy. A case study was conducted to investigate allergic reactions to sulfur-containing compounds, including ACK. The participants were administered products with varying doses of ACK - high, low, or none. The group receiving the high dose of ACK exhibited a significant allergic reaction, while the low dose group showed a reduced allergic response and the no ACK group did not exhibit any allergic reaction. Experimental findings have demonstrated that ACK can act as an allergen. It is hypothesized that the presence of sulfites and nitrogen-containing ring structure in ACK contributes to its allergenic properties [13].

3.4. Gastrointestinal Health

In the gastrointestinal (GI) tract, the role of NNS such as ACK has been a subject of critical research attention. Most importantly, their synergistic role with glucose in the upregulation and insertion of small intestine transporters, facilitating glucose absorption, poses significant health concerns. Research evidence shows that upon incubation with glucose, ACK promotes an increase in glucose uptake in the enterocytes by 20-30%. This process is GLUT2-dependent and provides insight into the potential for postprandial hyperglycemia, particularly among type 2 diabetics, who may have an overexpression of these transporters at baseline [14].

Further, it has been found that ACK, along with other NNS, may influence gut hormone secretion, particularly GLP-1, which plays a crucial role in glucose homeostasis. However, this change in secretion pattern differs between ACK and other sweeteners such as sucralose and saccharin [15].

Recent studies indicate a molecular-scale interaction between ACK and the gut microbiota, with responses varying among individuals. Intake of noncaloric artificial sweeteners, including ACK, has been linked to alterations in the gut microbiota, which inherently leads to dysbiosis and metabolic abnormalities. Such anomalies encompass augmented body weight and waist-to-hip ratio, elevated fasting blood glucose levels, response to glucose tolerance test, as well as heightened serum alanine aminotransferase concentrations [16-19].

The influence of the metabolism of E.coli of ACK, aspartame and sucralose were investigated. E.coli is one of the most important gut microbes that play a crucial role for maintaining human health. The experiment result shows that ACK induce the growth of E.coli K-12. Although all three sweeteners significantly altered the expressions of multiple key enzymes that regulate important metabolic pathways, it was observed that ACK induced the most pronounced changes in this aspect. Consistent with the gene expression pattern, E. coli treated with acesulfame potassium exhibited the greatest deviation in their metabolite profiles compared to untreated cells [20].

3.5. ACK’s Genotoxic Impacts

Interestingly, results from an Ames mutagenic assay featuring aspartame, ACK, and sucralose have produced negative results, suggesting that these artificial sweeteners, including ACK, may not produce mutagenic effects when consumed within ADI doses [21].

In line with these considerations, while the consumption of ACK at ADI doses may not directly contribute to genetic material alteration, it is suggested that overconsumption or prolonged consumption may have indirect genotoxic impacts through metabolic disturbances. The standard plate-incorporation assay was conducted using three sweeteners in Salmonella typhimurium TA 97a and TA 100 strains. The results show that sweeteners induced DNA strand breaks especially ACK [21]. Therefore, it would be prudent for consumers, especially those that belong to vulnerable groups, to maintain a cautious approach towards the consumption of ACK, ensuring that its intake stays within the ADI limits.

3.6. Cancer risk of ACK

Over the decades, the issue regarding the cancer risk of ACK (ACK) has sparked a myriad of debates among scientific communities. The potential of ACK to induce carcinogenic risks remains one of the health concerns. It is evident that continuous exposure to these sweeteners could potentially impose significant health risk of cancer over a certain period. Consumers with a higher total artificial sweetener intake had a higher risk of cancer, with ACK in particular showing a higher association with cancer [22, 23].

In a study conducted by Zopun et al., it was discovered that human gastric wall tumor cells (HGT-1) possess a fully functional sweet taste receptor T1R3, which can be activated by ACK. Subsequent experimental findings demonstrated that the activation of ACK can modulate the behavior of gastric wall tumor cells, including enhancing cell proliferation, migration, and invasion. This discovery highlights the potential impact of long-term high consumption of ACK on the functionality of gastric wall tumor cells [24].

4. CONCLUSION

ACK's status as a NNS has resulted in its wide incorporation into thousands of beverages and food products. The reason for these vast incorporations, particularly by the food and beverage industry, is its ability to act as a high intensity sweetener, with sweetness levels significantly surpassing those of sucrose. The utilization of NNS like ACK has seen a global increment, majorly owing to its attributes as a low-calorie, low-carbohydrate substitute. The beneficial effects of ACK on human health are proven. Switching to ACK-added foods from regular foods with sugar can assist in weight loss and blood sugar control [9; 25, 26].

However, the potential health implications of ACK, alongside other NNS, present a challenge that cannot be overlooked. Intaking ACK may increase the risk of suffering cardiovascular diseases, Gastrointestinal diseases, cancers and passive neurological effects. Studies have highlighted the diabetogenic potential of ACK when consumed at higher doses, causing statistical changes in fasting blood glucose, glycated haemoglobin, total cholesterol, triglyceride, LDL, and VLDL levels. One must acknowledge these insights, particularly considering the significant use of ACK and potential roles it may play in the onset of Type 2 diabetes, obesity, and metabolic syndrome.

Overall, while ACK is seemingly a safer option in comparison to traditional high-calorie sugars, caution must be exercised in its usage due to the potential health implications at higher consumption levels. Further research is required to comprehensively understand the health-related risks and effects associated with ACK consumption. It is particularly important to explore the molecular mechanism underlying ACK-induced changes in human health. Moreover, consumer awareness and understanding need to be improved to mitigate the adverse effects due to over-consumption.

5. PROSPECT FOR FUTURE RESEARCH

Despite the compelling evidence provided in this review, several gaps remain, underscoring the need for future research in understanding the comprehensive effects of ACK on human health. Firstly, although ACK, along with other artificial sweeteners such as aspartame and sucralose, has been implicated in diabetic potential at elevated dose levels, our understanding of the specific biochemical pathways and molecular mechanisms involved is still in a nascent stage. Further studies are critical to shed light on these mechanisms and to clarify the direct or indirect effect of these artificial sweeteners on diabetes progression.

Secondly, while our review indicates that ACK does not exhibit mutagenic potential, the studies conducted so far primarily focused on the Ames test using Salmonella typhimurium strains TA 97

and TA1535, which may not fully represent the wide range of human cellular responses. Wider breadth in the test models employed, including other genetic assays and in vivo experiments, may provide a more comprehensive picture of the mutagenic or carcinogenic potential posed by ACK.

Moreover, it is worth noting that the safety studies conducted have generally been under the threshold of the ADI dose. There is, however, considerable public concern and uncertainty around the long-term effects of the consumption of artificial sweeteners, potentially even below the ADI levels. Expanding the scope of future research to include longer-term studies, potentially over several years, will be crucial to ascertain the safety profile of the compounds under investigation, thereby addressing these concerns.

Finally, all current studies assess the effects of artificial sweeteners in isolation. Future research should investigate the impact of combined intake of these substances, as is common in many modern diets, thus more accurately reflecting real world consumption patterns. This will provide novel insights into their cumulative and potentially synergistic effects on human health, leading to more targeted and effective public health intervention strategies.

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