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A Review of the Evaluation and Potential Genotoxicity of Sodium Benzoate and Potassium Benzoate as Food Preservatives in Health and Various Applications

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ABSTRACT: Food preservatives such as sodium benzoate (E211) and potassium benzoate (E212) are widely used to prolong the shelf life of various food products by inhibiting microbial growth. Despite their prevalent usage, concerns regarding their potential genotoxic effects necessitate a thorough evaluation of their safety. This review provides a comprehensive assessment of the genotoxic potential of sodium benzoate and potassium benzoate, synthesizing findings from in vitro, in vivo, and human studies.

Sodium benzoate, a sodium salt of benzoic acid, is primarily metabolized in the liver to hippuric acid, which is excreted in the urine. In vitro studies on sodium benzoate have shown mixed results, with some indicating DNA damage at high concentrations while others report no significant genotoxic effects. In vivo studies in animals have similarly provided conflicting evidence, with genotoxic effects observed at high doses but not at levels relevant to human consumption. Human studies are limited, but in vitro assessments using human cell lines have not conclusively demonstrated genotoxic effects at typical dietary exposure levels.

Potassium benzoate, the potassium salt of benzoic acid, shares a similar metabolic pathway with sodium benzoate. However, specific studies on the genotoxicity of potassium benzoate are less abundant. Preliminary in vitro studies have not indicated significant genotoxic effects at commonly used concentrations and limited in vivo animal studies suggest no significant genotoxic risk at doses relevant to human exposure. The absence of direct human studies on potassium benzoate necessitates reliance on extrapolations from sodium benzoate data, which are not entirely conclusive.

Regulatory authorities such as the FDA and EFSA have established acceptable daily intake (ADI) levels for both preservatives based on available toxicological data, considering them safe for use in food products within these limits. Potential genotoxic mechanisms may involve oxidative stress and the production of reactive oxygen species (ROS), but the evidence remains inconclusive and warrants further investigation.

High concentrations of sodium benzoate and potassium benzoate may pose genotoxic risks, their use in food products within the regulatory limits is considered safe. Continuous monitoring and research are essential to confirm these findings and ensure consumer safety considering long-term and cumulative exposure. This review underscores the importance of ongoing evaluation of food preservatives to maintain public health standards.

KEYWORDS: Sodium benzoate, Potassium benzoate, Food preservatives, Genotoxicity, Safety evaluation, In vitro studies, In vivo studies, Oxidative stress, Reactive oxygen species.

1 INTRODUCTION

Food preservatives play a critical role in the food industry by extending the shelf life of products and preventing microbial spoilage [1]. Among these preservatives, sodium benzoate (E211) and potassium benzoate (E212) are widely used due to their effectiveness in acidic environments. Sodium benzoate is a stable and water-soluble sodium salt of benzoic acid, which is used as a preservation agent for foods. It could inhibit the growth of fungus and bacteria [2].

Sodium benzoate, the sodium derivative of benzoic acid, and potassium benzoate, the potassium derivative of benzoic acid, are widely used in various items including mayonnaise, margarine, carbonated beverages, jams and jellies, sauces, tomato paste, soft drinks, fruit juices, and pickles.

[3], [4], [5]. It keeps products long-lasting for at least two years after purchase and is used at concentrations of less than 0.5% by volume. It can also be found in mouthwash, cream, and as a preservation agent in some medications [5].

Benzoic acid salts are quickly absorbed into the body after oral administration [6], and break down into hippuric acid [7]. The primary mechanism by which these benzoates exert their preservative effect is through the inhibition of microbial growth. Benzoic acid and its salts are known to interfere with the microbial cell membrane, disrupting cellular processes such as nutrient uptake and energy production [8]. This antimicrobial action is most effective in acidic environments, making these preservatives ideal for a variety of food products that have a low pH [4].

Sodium benzoate is considered safe, [9], [10], but scientists have shown that negative side effects happen when it's mixed with ascorbic acid (vitamin C) [11]. Their studies show that it turns into benzene, a chemical that may cause cancer. Benzene occurs naturally and results from human activities [5]. Despite their widespread use, there has been increasing concern over the safety of sodium benzoate and potassium benzoate, particularly regarding their potential genotoxic effects. Genotoxicity refers to the ability of a compound to damage genetic information in cells, which can lead to mutations and potentially contribute to cancer development [12]. The evaluation of genotoxicity is critical for assessing the long-term safety of food preservatives, especially given the chronic exposure of consumers to these substances.

Several studies have investigated the genotoxic potential of sodium benzoate. In vitro studies, which involve testing on isolated cells in a controlled environment, have produced mixed results. Some studies have reported DNA damage and chromosomal aberrations at high concentrations of sodium benzoate, while others have found no significant genotoxic effects at doses relevant to human consumption. In vivo studies, conducted on living organisms, have similarly shown conflicting results [13]. Some animal studies suggest potential genotoxic effects at high doses [12], whereas others have not observed significant genotoxicity at lower doses [14].

Preliminary in vitro studies have generally do not indicate significant genotoxic effects at concentrations commonly used in food products. However, the scarcity of comprehensive in vivo and human studies on potassium benzoate necessitates caution and further investigation. Regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) have set acceptable daily intake (ADI) levels for these preservatives to ensure consumer safety [15], [16]. Given the potential health implications, it is crucial to continuously evaluate the safety of sodium benzoate and potassium benzoate. This review aims to provide a comprehensive assessment of the genotoxic potential of these preservatives, synthesizing findings from in vitro, in vivo, and human studies, and discussing the implications for regulatory policies and consumer health.

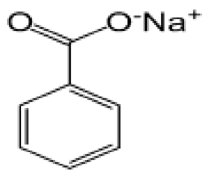
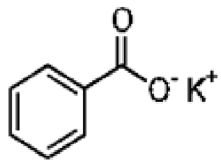
Sodium benzoate (E211) Molecular Formula: $C_7H_5NaO_2$ Molecular weight: 144.11	
Potassium benzoate (E212) Molecular Formula: $C_7H_5KO_2$ Molecular weight: 160.21	

Fig. 1. Chemical structures of sodium benzoate and potassium benzoate

Source: (Zengin et al., 2011) [13].

2 EVALUATION OF GENOTOXICITY IN SODIUM BENZOATE

Sodium benzoate's potential genotoxicity has been the subject of extensive scientific investigation, involving a variety of in vitro and in vivo studies. In vitro studies, which examine the effects of sodium benzoate on isolated cells, have yielded mixed results, a study by [17] found that high concentrations of sodium benzoate could induce DNA damage and chromosomal aberrations in cultured cells. These findings suggest that sodium benzoate may pose a genotoxic risk under certain conditions, particularly at high doses that exceed typical dietary exposure [2].

However, other in vitro studies, such as those conducted by [18], reported no significant genotoxic effects at concentrations relevant to human consumption. These conflicting results highlight the complexity of sodium benzoate's potential genotoxicity and underscore the need for further research to clarify its safety profile.

In vivo studies, which involve testing on living organisms, provide additional insights into the genotoxic potential of sodium benzoate. Animal studies have also produced varying results, with some indicating genotoxic effects at high doses and others showing no significant adverse effects. For example, [12] used the comet assay to test sodium benzoate on eight different mouse organs and found evidence of DNA damage at high doses. In contrast, [19] conducted a study using the Salmonella mutagenicity test and found no significant genotoxicity at doses that approximate human consumption levels. These discrepancies between studies could be due to differences in experimental design, dosing regimens, and the sensitivity of the assays used.

Human studies on the genotoxicity of sodium benzoate are limited, but the available data suggest that typical dietary exposures are unlikely to pose significant risks. Research involving human cell lines, as well as epidemiological studies, have generally not demonstrated conclusive genotoxic effects at the levels of sodium benzoate typically found in food products [18]. Regulatory bodies such as the FDA and EFSA have established acceptable daily intake (ADI) levels for sodium benzoate, considering these findings. The ADI for sodium benzoate is set at 5 mg/kg body weight per day by the [15], a level deemed safe based on current toxicological data. Consumption of SB beyond its ADI levels may produce toxic consequences in the exposed population. In a Swiss mouse model, it has been demonstrated that 4% levels of SB in diet result in death or growth depression within 5 weeks [20].

3 Evaluation Of Genotoxicity In Potassium Benzoate

The genotoxic potential of potassium benzoate has been less extensively studied than that of sodium benzoate, but the existing research suggests a similar safety profile. Preliminary in vitro studies have generally not shown significant genotoxic effects at concentrations typically used in food products. For instance, [13], found that potassium benzoate did not induce significant DNA damage in bacterial and mammalian cell cultures at doses relevant to human consumption. This suggests that potassium benzoate, like sodium benzoate, is unlikely to pose a genotoxic risk at the levels commonly used in the food industry.

In vivo studies on potassium benzoate are more limited, but the available data do not indicate significant genotoxic risks. Animal studies, although fewer in number, have generally reported no significant genotoxic effects at doses relevant to human consumption. This is consistent with the findings for sodium benzoate and supports the notion that benzoate salts are generally safe when used within regulatory limits. However, the paucity of comprehensive in vivo studies on potassium benzoate highlights the need for further research to confirm its safety profile.

Human studies specifically addressing the genotoxicity of potassium benzoate are scarce. As a result, regulatory assessments often rely on extrapolations from data on sodium benzoate, due to their similar chemical structures and metabolic pathways. The EFSA and FDA have also established ADI levels for potassium benzoate, ensuring its safe use in food products. The EFSA's re-evaluation of benzoic acid and its salts, including potassium benzoate, reaffirmed the safety of these preservatives at established ADI levels [15].

4 Comparative Analysis And Risk Assessment

Both sodium benzoate and potassium benzoate are approved by major food safety authorities, which have established acceptable daily intake levels based on extensive toxicological evaluations. These ADI levels are designed to protect consumers from potential adverse effects, including genotoxicity, by ensuring that the preservatives are used within safe limits. The potential mechanisms of genotoxicity for both preservatives may involve oxidative stress and the production of reactive oxygen species (ROS), but the evidence for such mechanisms is not definitive and requires further investigation [10].

Current consensus indicates that sodium benzoate and potassium benzoate are safe for use in food products within the established regulatory limits High concentrations of these preservatives may pose genotoxic risks, but such levels are unlikely to be encountered through normal dietary intake. Continuous monitoring and research are essential to confirm these findings and ensure consumer safety, particularly considering long-term and cumulative exposure. This review underscores the importance of ongoing evaluation and research to maintain public health standards and ensure the safety of food preservatives. [6], [15].

5 Synergistic Effects With Other Preservatives

Sodium benzoate and potassium benzoate often exhibit synergistic effects when used in combination with other preservatives, such as sorbic acid or sulfur dioxide [21]. This combination can enhance the overall antimicrobial efficacy, allowing for lower concentrations of each preservative while maintaining effective microbial control. This synergism can also help in reducing the potential for resistance development in microorganisms.

Table 1. The mechanisms of action, chemical interactions, stability, and regulatory considerations for sodium benzoate and potassium benzoate as food preservatives

Aspect	Sodium Benzoate	Potassium Benzoate
Chemical Formula	$NaC_7H_5O_2$	$KC_7H_5O_2$
pH Dependency	Effective in acidic conditions (pH < 4.5)	Effective in acidic conditions (pH < 4.5)
Active Form	Benzoic acid	Benzoic acid
Intracellular Acidification	Disrupts intracellular pH balance by penetrating microbial cell membranes and dissociating into benzoic acid, inhibiting enzyme activity and metabolic processes	Same as sodium benzoate
Enzyme Inhibition	Interferes with enzymes involved in glycolysis and other metabolic pathways, hindering energy production	Same as sodium benzoate
Membrane Integrity	Increases membrane fluidity, disrupting membrane integrity and permeability, causing leakage of cellular contents	Same as sodium benzoate
Inhibition of Yeast Cells	Affects proton gradient across mitochondrial membrane, impairing ATP synthesis	Same as sodium benzoate
Inhibition of Mold Spores	Inhibits spore germination and mycelial growth by disrupting cellular homeostasis and energy production	Same as sodium benzoate
Stability in Food Matrices	Stable in various food matrices; influenced by pH, temperature, and food components	Same as sodium benzoate
Interaction with Food Components	High protein or fat content can reduce availability of benzoic acid; presence of certain ions and additives can affect activity	Same as sodium benzoate
Regulated Usage Limits	Maximum allowable concentrations established by regulatory agencies (FDA, EFSA)	Same as sodium benzoate
Potential Health Risks	Genotoxicity, allergic reactions, oxidative stress, inflammatory responses	Same as sodium benzoate
Monitoring and Research	Continuous monitoring and research on safety, potential genotoxic effects, and safer alternatives	Same as sodium benzoate

6 Adverse Effects Of Sodium Benzoate And Potassium Benzoate Preservatives

Sodium benzoate (E211) and potassium benzoate (E212) are widely used food preservatives due to their effective antimicrobial properties. While generally regarded as safe within regulatory limits, these preservatives have been associated with several adverse effects. This section reviews the documented adverse effects of sodium benzoate and potassium benzoate, supported by scientific studies and regulatory reports.

7 Potential Adverse Effects

1. Genotoxicity: In Vitro Findings, some studies have reported genotoxic effects of sodium benzoate at high concentrations. [17], found DNA damage and chromosomal aberrations in cultured mammalian cells exposed to high doses of sodium benzoate. However, these concentrations are much higher than typical dietary exposures while in Vivo Findings, [12] Sasaki reported DNA damage in mice at high doses of sodium benzoate, raising concerns about potential genotoxic risks at extreme exposures. Nonetheless, other studies have found no significant genotoxic effects at doses relevant to human consumption [19], [22].
2. Hyperactivity and Behavioral Changes in Children: [23]. McCann and his group conducted a study that linked the consumption of sodium benzoate and certain artificial food colorings with increased hyperactivity in children. The study suggested that some children might be sensitive to these additives, resulting in behavioral changes [18].
3. Allergic Reactions and Sensitivity: Sodium benzoate can cause allergic reactions in sensitive individuals. These reactions may include symptoms such as skin rashes, itching, and asthma exacerbations [24]. Potassium benzoate is chemically like sodium benzoate and may induce similar allergic reactions, though specific studies are less prevalent.
4. Potential Carcinogenicity: There are concerns about the formation of benzene, a known carcinogen, when sodium benzoate is combined with ascorbic acid (vitamin C) in beverages. Benzene formation is more likely under certain conditions such as heat and light exposure [11] [22]. While regulatory agencies have set limits to minimize this risk, the potential for benzene formation remains a concern.
5. Metabolic Acidosis: High doses of sodium benzoate have been associated with metabolic acidosis, a condition where there is too much acid in the body fluids. This adverse effect has been primarily observed in clinical settings where sodium benzoate is used as a therapeutic agent for treating urea cycle disorders [25].

8 Benefits Of Sodium Benzoate And Potassium Benzoate Preservatives

1. Antimicrobial Properties: Sodium benzoate and potassium benzoate are effective antimicrobial agents, inhibiting the growth of bacteria, yeast, and fungi. Their primary mechanism of action involves lowering the internal pH of microbial cells, thereby inhibiting their growth and reproduction. Sodium Benzoate is effective against a wide range of microorganisms, particularly in acidic foods with a pH below 4.5 [3]. and Potassium Benzoate is like sodium benzoate, it is effective in acidic environments and provides an alternative for low-sodium diets.
2. Preservation of Food Quality: By preventing microbial growth, these preservatives help maintain the quality and safety of food products, extending their shelf life. This reduces food waste and ensures that food remains safe for consumption over a longer period. It extended Shelf Life, helps in maintaining the taste, texture, and nutritional value of foods by preventing spoilage. Also, it keeps consistency in Product Quality, ensuring that consumers receive products with consistent quality and safety.
3. Versatility: Both preservatives are widely used in various food and beverage products, including soft drinks, fruit juices, syrups, jams, salad dressings, and pickles. Sodium Benzoate is commonly used in acidic foods like salad dressings, carbonated drinks, jams, and fruit juices and Potassium Benzoate is often used in similar products as sodium benzoate but preferred in formulations where low sodium content is desired.
4. In terms of Cost-Effectiveness: Sodium benzoate and potassium benzoate are cost-effective solutions for food preservation, providing reliable antimicrobial effects at relatively low concentrations. The economic benefits are that they are affordable for food manufacturers, contributing to lower production costs while ensuring food safety and efficiency, which is effective at low concentrations, which also minimizes the amount needed for preservation and reduces potential health risks.

Sodium benzoate and potassium benzoate are stable under various food processing conditions, including heat and acidity, making them suitable for a wide range of food products. Remain effective during the processing and storage of food products and can be easily incorporated into food production processes without significant alterations to manufacturing protocols.

Both preservatives are approved by major food safety regulatory bodies such as the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA), which have established acceptable daily intake levels based on comprehensive safety assessments.

9 Implications Of Sodium Benzoate And Potassium Benzoate On Vulnerable People

Hyperactivity and Behavioral Issues: There is evidence linking sodium benzoate with hyperactivity and behavioral changes in children, particularly when combined with certain artificial food colorings. The study by [18] highlighted an increase in hyperactive behavior in children consuming these additives. This suggests that children, especially those with attention deficit hyperactivity disorder (ADHD), may be more susceptible to adverse behavioral effects from these preservatives. Due to these findings, some regulatory bodies have recommended caution in the use of these preservatives in products targeted at children.

Allergic Reactions: Individuals with Allergies or Sensitivities, Sodium benzoate can cause allergic reactions in sensitive individuals, manifesting as skin rashes, itching, and asthma exacerbations [26]. These reactions can be more pronounced in individuals with pre-existing conditions like asthma or chronic urticaria. There is a Cross-Sensitivity reaction between PB and SB. Potassium benzoate, due to its structural similarity to sodium benzoate, may induce similar allergic responses, although specific studies are less prevalent.

Asthma Exacerbation: Sodium benzoate has been shown to potentially exacerbate asthma symptoms in sensitive individuals. A study by Cardet and his group [27], indicates that food preservatives, including sodium benzoate, can trigger asthmatic responses in susceptible individuals. Asthmatic patients may need to avoid foods containing these preservatives to prevent exacerbations and manage their condition effectively.

Individuals with Metabolic Disorder is also known as Metabolic Acidosis: High doses of sodium benzoate, used therapeutically in medical settings to treat urea cycle disorders, have been associated with metabolic acidosis. While dietary levels are much lower, individuals with metabolic disorders might be at a higher risk if exposed to higher than recommended levels. It is crucial for individuals with metabolic disorders to monitor and manage their intake of sodium benzoate to avoid potential complications [21].

Increased Sensitivity for Elderly Population: The elderly may have increased sensitivity to food additives due to age-related changes in metabolism and organ function. While there is limited specific research on the elderly population and benzoates, their overall susceptibility to adverse effects from various food additives might be higher. Considering the elderly often consume multiple medications and may have comorbid conditions, the cumulative exposure to sodium and potassium benzoates from various dietary sources needs careful consideration.SB could improve cognitive performance by boosting ovarian to follicle-stimulating hormone proportions in later-phase dementia women [28], and it also improved treatment adherence in late-life depression patients [29].

Pregnant and Breastfeeding Women: There is limited data on the effects of sodium benzoate and potassium benzoate during pregnancy and breastfeeding. However, due to the potential for transfer to the fetus or infant, it is advisable for pregnant and breastfeeding women to minimize exposure to these preservatives. Given the precautionary principle, reducing the intake of foods containing these preservatives during pregnancy and breastfeeding could be beneficial in avoiding any unknown risks.

10 Further Studies Of Sodium Benzoate And Potassium Benzoate

Alternative Preservatives: Research is actively pursuing natural alternatives to synthetic preservatives like sodium benzoate and potassium benzoate, with a focus on plant-based extracts and other natural compounds. Further studies are necessary to investigate the long-term effects of these preservatives on human health, especially regarding potential genotoxicity and their impact on the gut microbiome. Additionally, the development of more advanced analytical techniques to detect and quantify these preservatives in various matrices is essential for ensuring better regulatory compliance and safety assessments.

Environmental Impact: It is crucial to investigate the environmental impact of these preservatives, particularly their biodegradability and potential effects on ecosystems, to ensure their sustainable use. Sodium benzoate and potassium benzoate play a crucial role in preserving food, pharmaceuticals, and personal care products, contributing significantly to health and industry. Ongoing research and regulatory oversight are essential to ensure their continued safe use and to explore potential alternatives for future applications.

11 Conclusion

Sodium benzoate and potassium benzoate offer several benefits as food preservatives, including effective antimicrobial properties, preservation of food quality, versatility in application, cost-effectiveness, regulatory approval, and compatibility with food processing. These advantages make them valuable tools in the food industry, helping to ensure the safety, quality, and longevity of various food products. While sodium benzoate and potassium benzoate are generally considered safe within regulatory limits, certain vulnerable groups such as children, individuals with allergies or asthma, those with metabolic disorders, the elderly, and pregnant or breastfeeding women may experience adverse effects.

It is essential to consider these potential implications when consuming foods containing these preservatives. Regulatory agencies and healthcare providers should continue to monitor and provide guidance to protect these vulnerable populations.

References

[1] del Olmo, A., Calzada, J., & Nuñez, M. (2015). Benzoic acid and its derivatives as naturally occurring compounds in foods and as additives: Uses, exposure, and controversy. *Critical Reviews in Food Science and Nutrition, 57* (14), 3084–3103. https://doi.org/10.1080/10408398.2015.1087964.

[2] Olofinnade, A. T., Onaolapo, A. Y., Onaolapo, O. J., & Olowe, O. A. (2021). The potential toxicity of food-added sodium benzoate in mice is concentration-dependent. *Toxicology Research, 10* (3), 561–569. https://doi.org/10.1093/toxres/tfab024.

[3] Chipley, J. R. (2020). Sodium Benzoate and Benzoic Acid. *Antimicrobials in Food,* 41–88. https://doi.org/10.1201/9780429058196-3.

[4] Han, J. (2020, March 30). *What Is Sodium Benzoate (E211) In Food & Why Are People Afraid It with Vitamin C?* Foodadditives.net. https://foodadditives.net/preservatives/sodium-benzoate/#Uses.

[5] Seed, S. (2024, January 8). *What to Know about Sodium Benzoate*. WebMD. https://www.webmd.com/diet/what-to-know-about-sodium-benzoate.

[6] European Food Safety Authority. (2016). Scientific Opinion on the re-evaluation of benzoic acid (E 210), sodium benzoate (E 211), potassium benzoate (E 212) and calcium benzoate (E 213) as food additives. *EFSA Journal, 14* (3). https://doi.org/10.2903/j.efsa.2016.4433.

[7] European Chemicals Agency (ECHA). (2018). *Homepage - ECHA*. Europa.eu. https://echa.europa.eu/

[8] Food Additives. (2020, March 7). *What Is Potassium Benzoate (E212) In Food? Uses, Safety, Side Effects*. FOODADDITIVES. https://foodadditives.net/preservatives/potassium-benzoate/.

[9] Walczak-Nowicka, Ł. J., & Herbet, M. (2022). Sodium Benzoate—Harmfulness and Potential Use in Therapies for Disorders Related to the Nervous System: A Review. *Nutrients, 14* (7), 1497. https://doi.org/10.3390/nu14071497.

[10] FDA. (2024, March 22). *CFR - Code of Federal Regulations Title 21*. https://www.accessdata.fda.gov/scripts/cdrh/Cfdocs/cfCFR/CFRSearch.cfm?fr=184.1733.

[11] Centre for science in the public interest. (2022, February 4). *Sodium benzoate (Benzoic acid).* Center for Science in the Public Interest. https://www.cspinet.org/article/sodium-benzoate-benzoic-acid.

[12] Sasaki, Y. F., Kawaguchi, S., Kamaya, A., Ohshita, M., Kabasawa, K., Iwama, K., Taniguchi, K., & Tsuda, S. (2002). The comet assay with 8 mouse organs: results with 39 currently used food additives. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 519* (1-2), 103–119.
https://doi.org/10.1016/s1383-5718 (02) 00128-6.

[13] Zengin, N., Yüzbaşıoğlu, D., Ünal, F., Yılmaz, S., & Aksoy, H. (2011). The evaluation of the genotoxicity of two food preservatives: Sodium benzoate and potassium benzoate. *Food and Chemical Toxicology, 49* (4), 763–769.
https://doi.org/10.1016/j.fct.2010.11.040

[14] Nohmi, T. (2018). Thresholds of Genotoxic and Non-Genotoxic Carcinogens. *Toxicological Research, 34* (4), 281–290.
https://doi.org/10.5487/tr.2018.34.4.281

[15] Scientific Opinion on the re-evaluation of benzoic acid (E 210), sodium benzoate (E 211), potassium benzoate (E 212) and calcium benzoate (E 213) as food additives (2016); Published: 31 March 2016 Adopted: 8 March 2016
https://www.efsa.europa.eu/en/efsajournal/pub/4433.

[16] Shahmohammadi, M., Javadi, M., & Nassiri-Asl, M. (2016). An overview on the effects of sodium benzoate as a preservative in food products. *Biotechnology and Health Sciences, 3* (3), 7-11.

[17] De Flora et al. (1999) found DNA damage and chromosomal aberrations in cultured mammalian cells exposed to high doses of sodium benzoate. However, these concentrations are much higher than typical dietary exposures.

[18] McCann D, Barrett A, Cooper A, Crumpler D, Dalen L, Grimshaw K, Kitchin E, Lok K, Porteous L, Prince E, Sonuga-Barke E, Warner JO, Stevenson J. Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. Lancet. 2007 Nov 3; 370 (9598): 1560-7. doi: 10.1016/S0140-6736 (07) 61306-3. Erratum in: Lancet. 2007 Nov 3; 370 (9598): 1542. PMID: 17825405.

[19] Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., & Kristien Mortelmans. (1992). Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. *Environmental and Molecular Mutagenesis, 19* (S21), 2–141.
https://doi.org/10.1002/em.2850190603.

[20] Yadav, A., Kumar, A., Das, M., & Tripathi, A. (2016). Sodium benzoate, a food preservative, affects the functional and activation status of splenocytes at non cytotoxic dose. *Food and Chemical Toxicology, 88,* 40–47.
https://doi.org/10.1016/j.fct.2015.12.016

[21] Lennerz, B. S., Vafai, S. B., Delaney, N. F., Clish, C. B., Deik, A. A., Pierce, K. A., Ludwig, D. S., & Mootha, V. K. (2015). Effects of sodium benzoate, a widely used food preservative, on glucose homeostasis and metabolic profiles in humans. *Molecular Genetics and Metabolism, 114* (1), 73–79.
https://doi.org/10.1016/j.ymgme.2014.11.010

[22] Phillips, D. H., & Arlt, V. M. (2009). Genotoxicity: damage to DNA and its consequences. *EXS, 99,* 87–110.
https://doi.org/10.1007/978-3-7643-8336-7_4.

[23] McDougal, E., Gracie, H., Oldridge, J., Stewart, T. M., Booth, J. N., & Rhodes, S. M. (2021). Relationships between cognition and literacy in children with attention-deficit/hyperactivity disorder: A systematic review and meta-analysis. *British Journal of Developmental Psychology, 40* (1), 130–150.
https://doi.org/10.1111/bjdp.12395.

[24] More, D. (2022, September 9). *9 Food Additives That May Cause an Adverse Reaction*. Verywell Health.
https://www.verywellhealth.com/allergy-to-food-additives-and-preservatives-82899.

[25] MedicineNet. (2023, March 15). *Sodium Benzoate/Sodium Phenylacetate: Uses, Side Effects*. MedicineNet.
https://www.medicinenet.com/sodium_benzoate_sodium_phenylacetate/article.htm

[26] Blouin, M., Han, Y., Burch, J., Farand, J., Mellon, C., Gaudreault, M., Wrona, M., Jean-François Lévesque, Denis, D., Mathieu, M.-C., Stocco, R., Vigneault, E., Therien, A., Clark, P., Rowland, S., Xu, D., O'Neill, G., Ducharme, Y., & Friesen, R. (2010). The Discovery of 4- {1- [({2,5-Dimethyl-4- [4- (trifluoromethyl) benzyl] -3-thienyl} carbonyl) amino] cyclopropyl} benzoic Acid (MK-2894), A Potent and Selective Prostaglandin E_2 Subtype 4 Receptor Antagonist. *Journal of Medicinal Chemistry, 53* (5), 2227–2238.
https://doi.org/10.1021/jm901771h.

[27] Cardet, J. C., White, A. A., Barrett, N. A., Feldweg, A. M., Wickner, P. G., Savage, J., Bhattacharyya, N., & Laidlaw, T. M. (2014). Alcohol-induced Respiratory Symptoms Are Common in Patients with Aspirin Exacerbated Respiratory Disease. *The Journal of Allergy and Clinical Immunology: In Practice, 2* (2), 208-213.e2.
https://doi.org/10.1016/j.jaip.2013.12.003

[28] Lin, C.-H., Chen, P.-K., Wang, S.-H., & Lane, H.-Y. (2021). Effect of Sodium Benzoate on Cognitive Function Among Patients with Behavioral and Psychological Symptoms of Dementia. *JAMA Network Open, 4* (4), e216156.
https://doi.org/10.1001/jamanetworkopen.2021.6156.

[29] Lin, C.-H., Wang, S.-H., & Lane, H.-Y. (2022). Effects of Sodium Benzoate, a D-Amino Acid Oxidase Inhibitor, on Perceived Stress and Cognitive Function Among Patients with Late-Life Depression: A Randomized, Double-Blind, Sertraline- and Placebo-Controlled Trial. *International Journal of Neuropsychopharmacology, 25* (7), 545–555.
https://doi.org/10.1093/ijnp/pyac006.