Al-Kitab Journal for Pure Sciences (2025); 9(1):68-90.
https://doi.org/10.32441/kjps.09.01.p5

Al-Kitab Journal for Pure Sciences
ISSN: 2617-1260 (print), 2617-8141(online)

https://isnra.net/index.php/kjps

A Review of Side Effects of Artificial Preservatives on the Human Health

Zahraa A. Hussein Al-Tameemi

Faculty of Medicine, Al-Iraqi University, Iraq

*Corresponding Author: Zahraaa-tameemi@aliraqia.edu.iq

Citation: Al-Tameemi ZAH. A Review of Side Effects of Artificial Preservatives on the Human Health. Al-Kitab J. Pure Sci. [Internet]. 2025 Jan. 9;9(01):68-90. DOI: https://doi.org/10.32441/kjps.09.01.p5.

Keywords: Food Preservation, Natural Preservatives, Chemical Preservatives, Nitrites and Nitrates, Sodium Benzoate, Cosmetics Preservatives, Paraben, Phenoxyethanol.

Article History

Received	03 Jun.	2024
Accepted	09 Aug.	2024
Available online	09 Jan.	2025

Abstract:

Food is necessary for all living humans to survive. Numerous nutrients, including proteins, lipids, carbs, vitamins, and minerals, are found in food. An organism consumes and breaks down these nutrients to create energy needed to support development and preserve regular bodily functions .

Food products can deteriorate due to microbiological, enzymatic, or chemical reactions to their surroundings. Preservatives extend the expiration of food and are also inserted into food goods to preserve quality; however, they may also have adverse side effects. Additionally, safety concerns are increasing as the need for cosmetics for teenagers and adults worldwide rises.

This review article's primary topic is the adverse effects of some specific preservatives commonly used in food and cosmetics, such as [sodium benzoate, parabens, and sulfites], to preserve or enhance their quality.

Keywords: Food preservation, Natural Preservatives, Chemical Preservatives, Nitrites and Nitrates, Sodium Benzoate, Cosmetics preservatives, Paraben, Phenoxyethanol.

الآثار الجانبية للمواد الحافظة الصناعية على صحة الإنسان

زهراء علي حسين التميمي

كلية الطب - الجامعة العراقية - العراق

Zahraaa-tameemi@aliraqia.edu.iq

الخلاصة:

الغذاء ضروري لجميع الكائنات الحية للبقاء على قيد الحياة. توجد العديد من العناصر الغذائية في الطعام، بما في ذلك البروتينات والدهون، والكربوهيدرات، والفيتامينات، والمعادن. يستهلك الكائن الحي هذه العناصر الغذائية ويكسرها لإنتاج الطاقة اللازمة لدعم النمو والحفاظ على وظائف الجسم المنتظمة.

يمكن أن تتدهور المنتجات الغذائية بسبب التفاعلات الميكروبيولوجية أو الأنزيمية أو الكيميائية مع البيئة المحيطة بها. تعمل المواد الحافظة على إطالة مدة صلاحية المواد الغذائية ويتم إدخالها أيضًا في السلع الغذائية للحفاظ على الجودة؛ ومع ذلك، قد يكون لها أيضًا آثار جانبية ضارة. بالإضافة إلى ذلك، مع تزايد الحاجة إلى مستحضرات التجميل للمراهقين والبالغين في جميع أنحاء العالم، تتزايد المخاوف المتعلقة بالسلامة.

الموضوع الرئيسي لمقالة المراجعة هذه هو الآثار الضارة لبعض المواد الحافظة المحددة المستخدمة بشكل شائع في الأغذية ومستحضرات التجميل، مثل [بنزوات الصوديوم، والبارابين، والكبريتات]، للحفاظ على جودتها أو تحسينها.

الكلمات المفتاحية: مواد حافظة غذائية، مواد حافظة طبيعية، مواد حافظة كيميائية، نتريت ونترات، بنزوات الصوديوم، ثاني أكسيد الكبريت، ميتابيسلفيت الصوديوم، مواد حافظة لمستحضرات التجميل، بارابين، فينوكسي إيثانول.

1. Introduction:

The functional use of a broad range of substances that prevent or slow down bacterial and enzymatic development in several products, such as meals, medications, and personal care items, is called "preservatives." These materials may be artificial or natural. Preservatives are essential in many kinds of stuff that people use daily because they help stop the growth of hazardous germs and keep products from spoiling or being contaminated [1]. Preservatives are added to prevent food from rotting due to germs, molds, fungus, and yeast. If preservatives are added, food can have a longer shelf life and stay fresher for longer. Additionally, food preservatives are employed to postpone rancidity and reduce or stop color, taste, or texture changes [2]. Preservatives are often used in medicine and pharmaceuticals to help prevent microbial contamination. Examples of these products include insulin, cough syrup, and acetaminophen. In other words, preservatives play a crucial role in our safety by inhibiting the growth of microorganisms, mainly bacteria, and fungi, that may cause disease or infection.

Preservatives are not just limited to food; they are also present in cosmetics and personal hygiene items. This versatile ingredient prevents contamination and the development of dangerous germs in items like toothpaste, sunscreen, lotions, and shampoos. Moreover, preservative-treated wood can be used in a wide range of construction projects, from raised flower beds to road signs [3].

1- Food Preservatives

Before the creation of preservatives, food was kept fresh and stored in vessels like clay jars. Food drying was a standard method of food preservation since most bacteria and fungi need moisture to thrive. Foods such as meat, fruits, and vegetables were frequently dried to preserve them. Salting is still used to protect various forms of meat, including fish and hams, as well as jams and jellies, which are high-sugar solutions [4-6].

1.2. Classification of Preservatives: Preservatives are classified into:

1.2.1 Natural Preservatives: Food preservatives come from Nature, such as Salt, Sugar, Vinegar, Spices, Honey, Edible Oil, etc. [7].

1.2.2. Chemical Preservatives: These food preservatives include benzoates, sorbates, nitrates and nitrates, potassium sulfate, glutamates, glycerides, and synthetic or semi-synthetic. There are three types of chemical preservatives: antimicrobial, antioxidant, and anti-enzymatic [8].

1.2.2.A: Antimicrobials: For instance, nitrites and nitrates stop food poisoning caused by bacteria in meat products [9]. Additionally, they can eradicate or stop the growth of mold, yeast, and bacteria. Sulfur dioxide prevents the deterioration of wine, beer, and fruits. Antifungal substances like benzoates and sorbates stop the growth of fungi and are used in cheese, pickles, jams, and salad dressings [10].

1.2.2.B: Antioxidants: These inhibit or halt the process of fats and oils in food, breaking down in the presence of air and leading to rancidity. There are three types of antioxidants:

(a) Synthetic Antioxidants: Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT).
(b) Reducing Agents: Ascorbic Acid
(c) Antioxidants Synergists: Sodium Edetate [11].

1.2.2.C: Anti-Enzymatic Preservatives: These inhibit the enzymatic processes that cause food items to ripen even after they are harvested. For example, erythorbic acid and citric acid avert the action of the enzyme phenology and cause the exposed surface of sliced fruits to turn brown [12]. Examples of these preservatives and their allowable quantities are provided in **Table 1**.

Table 1: Maximum Possible Limits of Preservatives and Food Products That Can Be Used [13]

Preservatives	Class	Max Possible Limit	Products Where They Are Found
Sodium And Potassium Benzoate, Benzoic Acid	Antimicrobial	200ppm	Pickles, Margarine, Fruit Juices, Jams, Cheese, Baked Goods, Snacks
Methyl And Propyl Paraben	Antimicrobial	0.1%	Baked Goods, Beverages, Dressings, Relishes
Sorbic Acid, Sodium, Potassium and Calcium Sorbates	Antimicrobial	200ppm	Dairy Products, Bakery Goods, Sweets, Syrups, Fruit Juices, Jams, Jellies, Beverages
Sulfites And Sulfur Dioxide	Antimicrobial	200-300ppm	Dry Fruits and Fruits, Molasses, Fried or Frozen Potatoes, Shrimp and Lobster
Propionates	Antimicrobial	0.32%	Bakery Products, Cheese, Fruits

1.3. The Perfect Preservative Properties:

1. It ought not to cause irritation.
2. It ought not to be poisonous.
3. It must possess both chemical and physical stability.
4. The preservatives and other chemicals in the formulation should work well together.
5. It should have a broad range of action and function well as an antibacterial agent.
6. It must be strong enough to function as a preservative at low concentrations[13].

1.4. Dangers to Health Associated with Artificial Preservatives:

Although most artificial preservatives are thought to be harmless, a few have unfavorable and perhaps fatal adverse effects, like:

1.4.1. Nitrites and Nitrates: Meat and other perishable goods are frequently cured using nitrite and nitrate salts. In addition to helping to preserve food, they also impede the growth of potentially dangerous germs, such as Clostridium botulinum, the bacterium that causes the deadly botulism disease [9].

The component hemoglobin, which delivers oxygen from the blood to the body's tissues, attaches to nitrate and changes chemically to become methemoglobin, which reduces oxygen delivery to tissues and gives the skin its blue hue [14]. In adults, being subjected to greater levels of nitrates or nitrites (Figure 1) has been linked to a more significant risk of cancer; in children, some studies have suggested a rising risk of brain tumors, leukemia, and nasopharyngeal cancers [15-22]. Methemoglobinemia, or decreased hemoglobin oxygenation, has been linked to drinking water polluted with nitrate and nitrite. Because of the cyanotic (low oxygen) symptoms that arise from this reduced oxygenation of the blood, it is often referred to as the "blue baby syndrome [23].

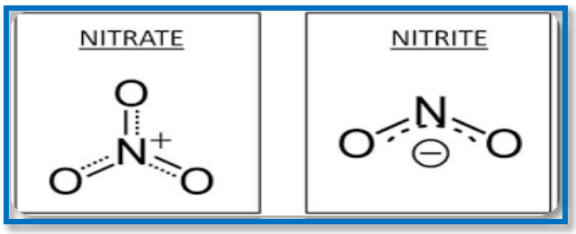

Figure 1: Nitrate and Nitrite structure [24]

Intrauterine development retardation was one of the additional health consequences that resulted from exposing a fetus to high amounts of nitrates in drinking water [25, 26], cardiac defects [27], and increased risk of nervous system defects. Research has also shown that children exposed to nitrates may be at risk for additional health problems, including a higher risk of childhood diabetes [28], recurrent respiratory tract infections, and diarrhea [29]. Brain tumors, leukemia, and nasopharyngeal cancers in children and young people have also been reported [19, 21] [30-34]. Additionally, another study found that drinking water containing nitrates might induce non-Hodgkin's lymphoma (NHL) because nitrate consumption results in the production of N-nitroso compounds, which are known to be carcinogenic after being absorbed in the stomach [35].

1.4.2. Sodium Benzoate: Sodium Benzoate is used in food to stop dangerous bacteria, yeasts, and molds from causing spoiling. Delaying or preventing alterations in food's color, flavor, PH, and texture also contributes to preserving freshness [36].

Sodium benzoate is a common preservative that enhances flavor and lengthens shelf life in various foods and beverages, including salad dressings, pickles, sauces, condiments, fruit juices, wines, and soft drinks. In laboratory animals, it has also been connected to cancer. It has been discovered that bottled tomato paste may be kept for up to 40 weeks without losing its quality, thanks to the widely used sodium benzoate (**Figure 2**). However, when mixed with vitamin C, it can produce the carcinogen benzene [37].

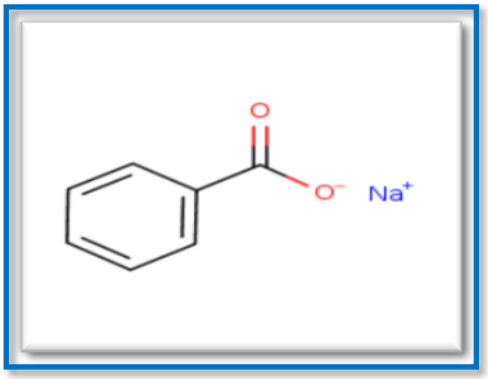

Figure (2): Sodium Benzoate structure[38]

Research has been done on how preservatives containing sodium benzoate affect the induction of micronuclei and chromosomal breakage. The lymphocyte cell line was treated with sodium benzoate at doses of 0.5,1.0,1.5, and 2.0 mg/mL for 24 and 48 hours, respectively. PCR, automated sequencing, conventional chromosome culture, and micronucleus tests were used to find micronucleus and chromosomal breaks. The findings demonstrated that, compared to the control group, micronucleus production was elevated at 24- and 48-hour incubation times at sodium benzoate doses of 1.0, 1.5, and 2.0 mg/mL ($P < 0.05$). Sodium benzoate doses of 2.0 mg/mL at 24- and 48-hour incubation times enhanced chromosomal break compared to the control group ($P < 0.05$). When micronuclei formed, and chromosomes broke in lymphocytes, sodium benzoate exhibited mutagenic and cytotoxic effects [39].

Short-lived exposure to sodium benzoate can disturb the eyes, skin, and respiratory system; however, repeated or sustained exposure can increase skin sensitivity [40]. High dosages can lead to alterations in gastrointestinal mucus production, ulcers, and the release of prostaglandin and histamine [41, 42]. Furthermore, research on soft drinks and fruit juices has shown that the presence of metal catalysts during the reaction between ascorbic acid and benzoic acid produces benzene [43].

Afshar et al. found that mice's fetal absorption rate was statistically significant at 280 and 560 mg sodium benzoate dosages. These doses also resulted in a decrease in the fetus's weight and crown-rump length in contrast to the control group [44, 45]. Sohrabi et al. conducted a study on mice in which they found that progesterone hormone at a dosage of 280 mg was lower than in the control group and that sodium benzoate at a concentration of 560 mg/kg decreased the weight of the ovaries and the hormones FSH and LH [46].

According to different research, mice's weight can be decreased by 200 mg/kg of sodium benzoate; however, the mice's separated serum included greater amounts of urea, uric acid, and creatinine. In a study involving rats and mice, Fujitani et al. located that at a concentration of 2.4%, the average weight of the rats decreased in comparison to the control group; at a concentration of 2.4% weight gain in the liver and kidney occurred in the rats, and at a concentration of 3%, the weight of the liver and kidney increased in comparison to the control group in the mice [47]. Eber Chukwu et al.'s study of sodium benzoate's effects in rats showed that it could reduce hemoglobin levels at all doses and the number of white blood cells at 60 and 120 mg/kg in comparison to the control group. As a result of this decline, the rats' WBCs are more vulnerable to infection [48]. Ibekwe et al.'s study on sodium benzoate's effects on rats showed that the drug might reduce hemoglobin at all doses and the number of white blood cells at 60 and 120 mg/kg in comparison to the control group. The rats' WBCs are more vulnerable

to infection due to this decline [49]. Yilmaz et al. examined how 200 and 500 µg/ml of benzoate sodium affected human cell lymphocytes. At 500µg/mL, benzoic acid lowered the mitotic index and raised the indices of chromosomal aberration (CA), sister chromatid exchanges (SCEs), and micronucleus (MN) [50]. Other studies have observed that sodium benzoate could alter the shape of lymphocytes and cause damage to the cell membrane when they examined lymph node cells taken from mice that were given varying amounts of the chemical compared to control cells. The negative effects of this chemical grow with higher concentrations and longer exposure time [51, 52].

1.4.3. Sulfites, Sulfur Dioxide, and Sodium Metabisulfite: Broad-spectrum antimicrobials that inhibit bacteria, yeasts, and molds include sulfites and sulfating agents, including sulfur dioxide (SO2), sodium and potassium sulfite, metabisulphite, and bisulfites (**Figure 3**). It is specifically used to stop malolactic fermentation during wine production. Sulfites are preservatives for food and drink goods to avoid oxidation and bacterial growth. Sulfites are also applied to keep fruits and vegetables that are canned, dried, frozen, and frozen from browning enzymatically and nonenzymatically [53].

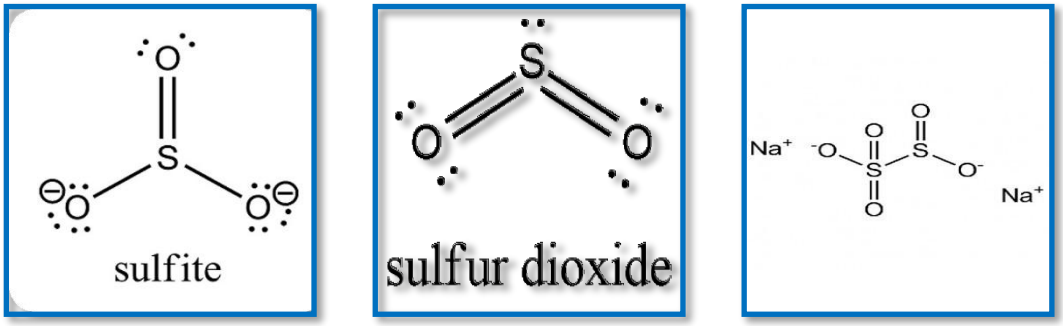

Figure 3: Structures of Sulfite, Sulfur dioxide, and Sodium metabisulfite [54]

The following goods are permitted to include SO2, sulfite, and metabisulfite according to the Codex General Standard for Food Additives: Fruit products, fresh, frozen, fermented, canned, and dried fruit; and dried vegetables; starches; precooked pasta; fish and some shellfish products; sugar products; herbs and spices; vinegar varieties; mustards; sauces; cider, wines; flavored water drinks; distilled spirituous drinks with a minimum 15% alcohol content; and snacks. Depending on the product, the maximum concentration allowed might vary from 15 to 1000 ppm [55].

Although sulfite additions are widely used because they seem harmless, reports of negative responses to sulfite exposure started to surface in the 1970s [56, 57]. Most reports, however, described the induction of bronchoconstriction in asthmatic patients. These comprised inducing anaphylactic responses and various symptoms, including flushing, dermatitis, urticaria,

diarrhea, hypotension, and stomach discomfort [58, 59]. Some people get mild to extremely severe asthmatic symptoms when exposed to sulfite, whereas, for some people, these responses can be fatal [60].

Til et al. investigated the sulfite toxicity in recently weaned Wistar rats. Six groups, each with 20 males and 20 females, were created from the 120 males and 120 females. For up to two years and three generations, the groups were kept on the stock diet that included 0.0 (control), 0.125, 0.25, 0.5, 1.0, or 2.0% sodium metabisulphite. In two generations of rats, a 2% sulfite level somewhat slowed their development, but not significantly. There was blood in the stools for the groups that received 1% or more sulfite. Pathological analysis showed that the three generations had hyperplastic alterations in the epithelial and foregut with 2% and 1% sulfite levels, respectively. A series of brief experiments involving 10 male and 10 female rats were conducted on high sulfite levels (0–8%) for 10–56 days. Growth depression and substantial food intake and efficiency decreases were seen in diets containing 6% sulfite. At 2% and above, anemia was seen. Levels of 4% and above were associated with increased splenic weight. The presence of blood in the stool and alterations in the shape of the stomach were the most sensitive indicators of sulfite injury in the current investigations [59].

The same research group investigated the sub-chronic and chronic oral toxicity of sodium metabisulphite. Twenty pigs, twenty females, and twenty males were fed diets containing 0.0, 0.125, 0.25, 0.5, 1.0, or 2.0% Na2S2O5. Fourteen males and fourteen females from each group were slain after fifteen weeks. For 48 weeks, the six male and six female survivors in each group were fed identical meals. The average amounts of sulfite that remained in the different experimental diets after the pigs ate them were determined to be 0.06, 0.16, 0.35, 0.83, and 1.72%, respectively. The liver, kidneys, heart, and spleen showed a substantial rise in organ-to-body weight ratios when fed at dietary levels of 1.72% after 15 and 48 weeks and only at dietary levels of 0.83% after 48 weeks. The study determined that 0.35% Na2S2O5 in the pigs' diet for 48 weeks was the no-effect threshold [61]. More recently, Kadi et al. assessed the sub-chronic toxicity of sodium metabisulphite on 24 female Wistar rats that were split into four groups and given different amounts of sodium metabisulphite (0.0, 0.25, 1, and 4%) in their drinking water for 90 days. The 1% and 4% Na2S2O5 injections significantly affected body weight, food intake, and water consumption. Biochemical markers such as calcium, urea, creatinine, uric acid, and transaminases increased, but immunoglobulin levels decreased. Hematology showed leukocytosis and a reduction in hemoglobin and red blood cells. They concluded that sub-chronic Na2S2O5 1% and 4% ingestion in Wistar rats appeared to affect the immunological function and biochemical, hematological, and physiological parameters [62].

1.5 Can Food Preservatives Cause Hormone Disturbances in People and Encourage Obesity?

According to a new study published in Nature Communications, Cedars-Sinai researchers developed a unique platform and process for assessing the effects of chemicals known as endocrine disruptors on humans. The preservatives under investigation in this study are commonly accessible in modern society. Some products, such as cookware and carpeting, contain a polymer called perfluorooctanoic acid (PFOA); paints contain a compound called tributyltin (TBT), which can contaminate water and accumulate in seafood; and breakfast cereals and other foods often contain an antioxidant called butylhydroxytoluene (BHT) to preserve nutrients and prevent fats from going rancid. In mice genetically predisposed to the condition, these alterations resulted in aberrant immune systems that led to chronic colitis. It is exceedingly tough to shed weight due to obesity since this process slows down metabolism and depletes the liver of energy. The mice developed weight gain and insulin resistance prediabetes when they were subjected to the same quantity of propionate as humans normally ingest on a long-term basis [63]. The research aimed to design human subject studies to test its hypothesis. The researchers used tissues that generate hormones from human stem cells to reveal how long-term use of these compounds can hinder the signals the digestive system delivers to the brain, signaling when a person feels "full" after eating. People eat more when this signaling system isn't working correctly, which leads to weight gain. It was found that each of these preservatives harmed hormones that connected the gut with the brain. When all three chemicals were evaluated together, there was a significant amount of combined stress, with BHT having some of the most potent negative impacts. While other scientists have appeared, these compounds can hold up hormone systems in laboratory animals. This is the first research to document how preservative-containing compounds may block hormones essential for gut-to-brain transmission and avoid obesity in humans using human pluripotent stem cells and tissues. Used the stem cells to grow human epithelial tissue, which lines the intestines, as well as neuronal tissues of the hypothalamus area of the brain, which controls metabolism and hunger. Then, tissues were exposed to BHT, PFOA, and TBT alone and in combination, and the researchers watched to see how the cells responded. They found that the chemicals disrupt the networks that allow signaling hormones to stay structurally intact and be transported outside of cells, rendering them ineffective. Mitochondria were also damaged by the poisons. Because the "young" cells that suffered the chemical harm were still in the early stages of development, the findings suggest that a hormone system breakdown might affect the unborn child as well as the pregnant woman [64].

2. Cosmetics preservatives

Many people use lotions on their bodies and skin almost every day. The skin creams are sometimes contained in little pots. We apply the cream with our fingers and don't always wash our hands before applying the cream to our skin. As a result, bacteria from the hands enter the cream pots. The creams frequently contain loads of water and are kept in warm bathrooms, which creates ideal circumstances for the bacteria's fast microbial development within the pots. For this reason, extra precautions need to be taken to prevent the cream from being damaged. Nearly all body lotions and skin creams contain preservatives. Without preservatives, bacteria would grow and multiply in the cream, eventually leading to skin issues or even dermatitis [65]. Because makeup products are nutrient-rich environments that promote the growth of microorganisms, this impacts the effectiveness of the preservatives [66].

2.1 Stages of preservation

To supply cosmetic goods with adequate defense against microbiological pollution, the industry offers:

2.1.1. Primary Preservation Strategy: GMPs must be rigorously followed when manufacturing cosmetics. Cosmetics must be prepared in an absolutely aseptic manner to prevent microbiological contamination. Ways to lower the risk of contamination are water handling, microbiological domination of raw materials, tools disinfection, and staff qualification [67, 68].

2.1.2. Secondary Preservation Strategy: In order to maintain the firm of cosmetics throughout storage, transportation, and use, three fundamental methods have been utilized: physical, chemical, and physicochemical preservation [69].

2.1.2.A. Secondary Preservation in Physical Terms: In order to maintain the firmness of cosmetics throughout storage, transportation, and use, three fundamental methods have been utilized: physical, chemical, and physicochemical preservation [69]. Primary packaging is used to accomplish this sort of preservation in situations when a physical barrier is present to avoid microbiological contamination [70]. The packaging can offer two layers of protection: one versus pollution during use and another opposed to contamination building up in the apportionment chain [71].

2.1.2.B. Physicochemical Secondary Preservation

• Water Activity. • Emulsion Form. • pH Control [72].

2.1.2.C. Chemical Secondary Preservation

• Synthetic Chemical Preservatives.

• Natural Chemical Preservatives.

• Multifunctional Ingredients [73].

The following is a list of preservative chemicals and their applications:

Table (2) Preservative cosmetics detected in the previous study [74-85]

Preservative detected	Products
2-phenoxyethanol 4-hydroxybenzoic acid Benzalkonium chloride Benzothiazolinone Benzoic acid Benzyl alcohol Benzyl paraben Bronopol Butylated hydroxy anisole Butylated hydroxy toluene Butyl paraben Cetrimonium chloride Chlorhexidinedigluconate Chlorhexidine dihydrochloride Chloroacetamide Chlorphenesin Dehydroacetic acid Dimethylol dimethyl hydantoin Ethyl benzoate Ethylparaben Formaldehyde Formalin Formic acid Glutaral Imidazolidinyl urea Iodopropynylbutylcarbamate Glutaral Imidazolidinyl urea Iodopropynylbutylcarbamate Isobutylparaben Kathon CG Methamine Methyl chloroisothiazolinone Methyldibromoglutaronitrile Methylisothiazolinone Methyloldimethylhydantoin Methylparaben	Aftershave balms Anti-stretch marks cream Bath gel Body care product Body milk Cosmetics Creams Deodorant Eye drop Face cream Hair conditioners Hand creams / gel Hand soaps Hygiene wash Lanoline cream Lipsticks Liquid formulations Liquid soaps Lotions Makeup Moisturizing creams Multi-purpose cleaners Oil-based lotions Ointments Products for babies Shampoos Shower gel Skin cream Skin milk Sun-related cosmetics Toiletries Washing-up liquids Water-based lotions Wet tissues

2.2 Hazardous Ingredients in Cosmetics:

Cosmetics with a high water content are susceptible to microbiological contamination, which might change the product's composition or pose a health risk to the consumer. Pathogenic bacteria frequently reside in contaminated cosmetics. To avoid contamination in bacteria like (Staphylococcus aureus and Pseudomonas aeruginosa), manufacturers insert preservers into cosmetic products [85]. Colorless, odorless, water-soluble, nonpoisonous, non-allergic, non-irritating, influential across a broad pH range, and able to inhibit the growth of bacteria and fungus—these qualities make the preservatives excellent for cosmetics [86]. As of right now, no preservative meets all these requirements. Among the most widely used cosmetic

preservatives in the last 20 years are parabens (methyl, propyl, butyl, and ethyl paraben), formaldehyde, formaldehyde releasers, and methylchloroisothiazolinone /methylisothiazolinone (MCI/MI) [87, 88]. Numerous recent investigations have determined that preservatives are the most prevalent allergens in cosmetic contact [89, 90].

Three primary categories may be used to classify them: UV light absorbers, antioxidants, and antimicrobials. Additional classifications of antimicrobial agents include formaldehyde-releasers, non-formaldehyde-releasing preservatives, and formaldehyde preservatives. Quaternium-15, 2-bromo-2-nitropropane-diol, imidazolidinyl urea, diazolidinyl urea, and DMDM hydantoin are examples of formaldehyde-releasing preservatives (FRP). Preservatives that don't release formaldehyde include parabens, methyl dibromo glutaronitrile-phenoxyethanol (MDBGN-PE), methyl chloroisothiazolinone-methylisothiazolinone (MCI-MI), and iodopropynyl butylcarbamate. Anyone with a formaldehyde allergy may also have an allergy to any of the FRPs [91].

Human meibomian gland epithelial cells (HMGECs) have recently been found to be particularly sensitive to the cosmetic preservative formaldehyde and benzalkonium chloride. At doses permitted for human consumption, exposure to these substances causes cellular atrophy and death in a matter of hours. We propose that additional cosmetic preservatives may potentially have detrimental effects on HMGECs and that these effects are not exclusive to them. Parabens, phenoxyethanol, and chlorphenesin are among these substances; studies have shown that they irritate the eyes and are harmful to the kidney, liver, and corneal and conjunctival epithelial cells[92]. This hypothesis was investigated to examine the effects of phenoxyethanol, chlorphenesin, and parabens on the morphology, signaling, survival, proliferation, and lipid expression of immortalized (I) HMGECs. These cells were cultured in either proliferating or differentiating conditions for up to five days, with varying concentrations of methylparaben, ethylparaben, phenoxyethanol, and chlorphenesin. The IHMGECs' capacity to transmit signals, their quantity, appearance, neutral lipid content, and lysosome buildup were observed. The results show that after being exposed to these preservatives for 30 minutes, IHMGECs' Akt pathway activity significantly decreased. This dose-dependent activity is seen at concentrations comparable to chlorphenesin and lower than all other doses approved for human use. Furthermore, cellular atrophy and mortality occur when the IHMGECs are exposed for a whole day to concentrations of methylparaben, ethylparaben, phenoxyethanol, and chlorphenesin that are close to or equivalent to the recommended human dose. No preservative did not increase IHMGEC proliferation at any of the tested doses. Of special note, because the cells did not make it through the treatment, it was impossible to assess the impact of these

preservatives, at doses almost equivalent to those permitted for humans, on IHMGEC differentiation. In conclusion, the findings validate the theory and demonstrate the toxicity of methylparaben, ethylparaben, phenoxyethanol, and chlorphenesin [93].

Frequently, cosmetic goods like mascara, eye shadow, eyeliner, and makeup remover usually include preservatives (like Benzalkonium chloride BAK and formaldehyde-releasing preservatives FA) to stop microorganisms from growing [94]. These preservatives were conjectured to harm the ocular surface and adnexal cells at quantities (FA = 0.74 mg/ml; BAK = 1 mg/ml) authorized for consumer usage. Thus, the effects of BAK and FA on the morphology, survival, proliferation, and signaling capacity of corneal (iHCECs), conjunctival (iHConjECs), and meibomian gland (iHMGECs) were investigated. For a maximum of seven days, iHMGECs, iHCECs, and iHConjECs were grown in various BAK (5 µg/ml to 0.005 µg/ml) or FA (1 mg/ml to 1 µg/ml) concentrations under basal, increasing, or differentiating conditions. Was used modest BAK concentrations since was discovered that 0.5 mg/ml and 50 µg/ml BAK eliminated iHMGECs in just one day after a 15-minute treatment. The three cell types were subjected to studies of AKT signaling, lysosome accumulation (LysoTracker), and cell appearance, number, and neutral lipid content (LipidTox) [95]. Results showed that iHMGECs, iHCECs, and iHConjECs undergo dose-dependent alterations in their morphology, survival, proliferation, and AKT signaling. After five days of exposure, several measured doses caused poor adherence, reduced proliferation, and cell death. Furthermore, AKT phosphorylation after 15 (FA) or 30 (BAK) minutes of treatment demonstrated that cellular signaling was decreased in a dose-dependent way in all three cell types, irrespective of whether the cells had been grown in proliferating or differentiating conditions. The findings support the research's hypothesis, demonstrating that cosmetic preservatives BAK and FA have several negative effects on the ocular surface and adnexal cells [96].

2.3 The most prevalent preservatives' adverse effects on cosmetic items:

2.3.1 Paraben: Various cosmetic products use parabens (**Figure 4**) as preservatives, including (deodorants, scrubs, shampoos, eye makeup, and lotions), food items, and pharmaceutical items that the general public is exposed to [97].

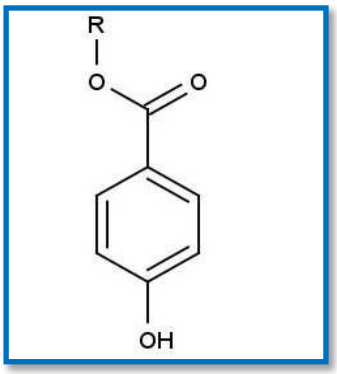

Figure 4: Structure of Paraben [98]

Thin-layer chromatography may be used to extract parabens from human breast tissue and identify them, according to preliminary research. Through more thorough research, the mean amounts of each paraben were found and measured in samples of 20 human breast cancers using tandem mass spectrometry and high-pressure liquid chromatography. The average paraben concentration in 20 human breast tumors was (20.6 ± 4.2 ng g−1) tissue. Upon comparing the different parabens, it was found that methylparaben exhibited the most significant degree of presence (mean value of 12.8 ± 2.2 ng g−1 tissue), accounting for 62% of the total parabens taken back during the extraction processes. Investigations showed that parabens are present in a sound form in the breast of humans, which should theoretically pave the way for the acquisition of more thorough data regarding paraben body loads and, in particular, whether or not these burdens change between normal tissues and malignancy [99]. The water solubility of parabens diminishes as the ester chain length increases, and they have a high oil/water partition coefficient. Consequently, if any parabens can enter the human body unharmed, they may be able to accumulate in biological tissues' fatty components similarly to other lipophilic [100, 101].

Although the majority of research has shown that parabens do not induce mutations, certain reports have shown that they can cause chromosomal abnormalities, especially when polychlorinated biphenyls are present. Additionally, rats who receive methylparaben subcutaneously have been shown to develop mammary adenocarcinomas [102]. Research has demonstrated that parabens can cause mitochondrial malfunction and impede lysosomal enzyme secretion, hence impairing cellular function [103].

2.3.2 Phenoxyethanol: Cosmetic items include Phenoxyethanol (**Figure 5**) as a preservative (it can be found in makeup products and skin, body, and hair care products for adults, baby wipes, baby lotions, fragrances, hair removal waxes, hand sanitizer, and ultrasound gel) and also as a stabilizer in perfumes and soaps [104].

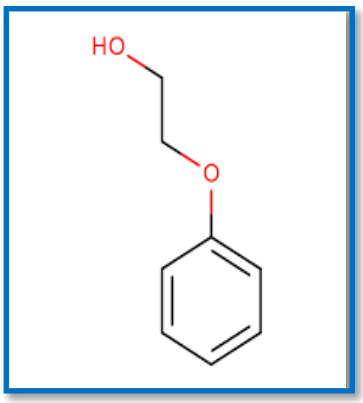

Figure (5): Phenoxyethanol structure [105]

Phenoxyethanol exposure has been connected to a variety of allergic responses, including anaphylaxis, eczema, and hives. Another typical adverse response to products containing one percent or more phenoxyethanol on the skin is eczema. Only the application area reacts, and eczema goes away if the irritating substance is avoided [106]. According to research in 2015, the most common side effect of Doppler ultrasonography gel was skin irritation, yet there were also sporadic instances of potentially fatal responses called anaphylaxis. Doppler ultrasonography gel containing mixtures of phenoxyethanol and parabens may cause more severe allergy responses than phenoxyethanol alone [107]. Effects on the infant's acute nervous system: The FDA warned customers in 2008 not to buy Mommy's Bliss Nipple Cream. Breastfeeding infants had vomiting and diarrhea due to phenoxyethanol, a substance present in the cream that depressed their central nervous system. Reduced hunger, trouble awakening the baby, limp extremities, and skin color changes are all signs of a depressed neurological system [108].

3. Conclusion:

The primary purpose of preservatives in food and cosmetics is their antibacterial effectiveness. However, the food and cosmetics industries must worry about these compounds' toxicity. Therefore, it is essential to keep looking for safe and valuable preservatives. Because of their toxicity, laws restrict or even forbid using the most vital preservatives. They also demand that food and cosmetic items be free of contamination.

Consequently, food and cosmetics producers seek innovative preservation techniques to get around legal restrictions while presenting a safer product regarding toxicological and microbiological aspects. However, a preservative's range of action is limited based on the microorganisms and the target species, which incentivizes producers to combine different preservative forms.

4. References

[1] G. Evans, B. de Challemaison, and D. N. Cox, "Consumers' ratings of the natural and unnatural qualities of foods," Appetite, vol. 54, no. 3, pp. 557-563, 2010.

[2] Z. Ashagrie and D. Abate, "Improvement of injera shelf life through the use of chemical preservatives," African journal of food, agriculture, nutrition and development, vol. 12, no. 5, pp. 6409-6423, 2012.

[3] H. K. HN, A. K. Jha, K. K. Taneja, K. Kabra, and H. M. Sadiq, "A study on consumer awareness, safety perceptions & practices about food preservatives and flavoring agents used in packed/canned foods from South India," National Journal of community medicine, vol. 4, no. 03, pp. 402-406, 2013.

[4] C. Kulkarni, A. Deshpande, and S. More, "Assessment of microbial contamination in commercial herbal oral medicinal liquids," Int J Pharm Res Dev, vol. 2, no. 9, pp. 191-193, 2010.

[5] A. P. Fraise, J.-Y. Maillard, and S. Sattar, Russell, Hugo and Ayliffe's principles and practice of disinfection, preservation and sterilization. John Wiley & Sons, 2012.

[6] P. K. Kumari, S. Akhila, Y. S. Rao, and B. R. Devi, "Alternative to artificial preservatives," Syst. Rev. Pharm, vol. 10, pp. 99-102, 2019.

[7] J. S. Anjali Langeh*, Anju Bhat, Julie D. Bandral, Seerat Gupta and Skarma Choton, " Role of Preservatives in Preservation of Fruits and Vegetables: A review," Chemical Science Review and Letters, vol. Volume 12(48):217-221, 2023.

[8] A. Deshpande and B. Deshpande, "Food additives and preservation: A review," Indian Journal of Sciences and Research, vol. 13, pp. 219-225, 2017.

[9] M. Govari and A. Pexara, "Nitrates and Nitrites in meat products," Journal of the Hellenic veterinary medical society, vol. 66, no. 3, pp. 127-140, 2015.

[10] S. Dey and B. H. Nagababu, "Applications of food color and bio-preservatives in the food and its effect on the human health," Food Chemistry Advances, vol. 1, p. 100019, 2022.

[11] S. Dwivedi, P. Prajapati, N. Vyas, S. Malviya, and A. Kharia, "A review on food preservation: methods, harmful effects and better alternatives," Asian J. Pharm. Pharmacol, vol. 3, no. 6, pp. 193-199, 2017.

[12] Z. M. Sharif, F. Mustapha, J. Jai, and N. Zaki, "Review on methods for preservation and natural preservatives for extending the food longevity," Chemical Engineering Research Bulletin, vol. 19, 2017.

[13] R. Gupta and R. K. Yadav, "Impact of chemical food preservatives on human health," Palarch's Journal Of Archaeology Of Egypt/Egyptology, vol. 18, no. 15, pp. 811-818, 2021.

[14] L. Knobeloch, B. Salna, A. Hogan, J. Postle, and H. Anderson, "Blue babies and nitrate-contaminated well water," Environmental health perspectives, vol. 108, no. 7, pp. 675-678, 2000.

[15] J. Sanchez-Echaniz, J. Benito-Fernández, and S. Mintegui-Raso, "Methemoglobinemia and consumption of vegetables in infants," Pediatrics, vol. 107, no. 5, pp. 1024-1028, 2001.

[16] L. B. Dusdieker, J. P. Getchell, T. M. Liarakos, W. J. Hausler, and C. I. Dungy, "Nitrate in baby foods: adding to the nitrate mosaic," Archives of pediatrics & adolescent medicine, vol. 148, no. 5, pp. 490-494, 1994.

[17] W. S. Fisher, L. E. Jackson, G. W. Suter, and P. Bertram, "Indicators for human and ecological risk assessment: a US Environmental Protection Agency perspective," Human and Ecological Risk Assessment: An International Journal, vol. 7, no. 5, pp. 961-970, 2001.

[18] D. Douer, S. Preston-Martin, E. Chang, P. W. Nichols, K. J. Watkins, and A. M. Levine, "High frequency of acute promyelocytic leukemia among Latinos with acute myeloid leukemia [see comments]," 1996.

[19] M. H. Ward et al., "Dietary exposure to nitrite and nitrosamines and risk of nasopharyngeal carcinoma in Taiwan," International journal of cancer, vol. 86, no. 5, pp. 603-609, 2000.

[20] J. M. Pogoda and S. Preston-Martin, "Maternal cured meat consumption during pregnancy and risk of paediatric brain tumour in offspring: potentially harmful levels of intake," Public health nutrition, vol. 4, no. 2, pp. 183-189, 2001.

[21] S. Sarasua and D. A. Savitz, "Cured and broiled meat consumption in relation to childhood cancer: Denver, Colorado (United States)," Cancer Causes & Control, vol. 5, pp. 141-148, 1994.

[22] M. McCredie, P. Maisonneuve, and P. Boyle, "Antenatal risk factors for malignant brain tumours in New South Wales children," International journal of cancer, vol. 56, no. 1, pp. 6-10, 1994.

[23] A. Shamsuddina, S. Ismailb, S. Shamc, and E. Abidind, "Nitrate in groundwater and excretion of nitrate and nitrosamines in urine: a review," Int J Sci Basic Appl Res, vol. 15, no. 2, pp. 176-91, 2014.

[24] W. Laue, M. Thiemann, E. Scheibler, and K. W. Wiegand, "Nitrates and nitrites," Ullmann's Encyclopedia of Industrial Chemistry, 2000.

[25] J. Bukowski, G. Somers, and J. Bryanton, "Agricultural contamination of groundwater as a possible risk factor for growth restriction or prematurity," Journal of occupational and environmental medicine, vol. 43, no. 4, pp. 377-383, 2001.

[26] L. A. Croen, K. Todoroff, and G. M. Shaw, "Maternal exposure to nitrate from drinking water and diet and risk for neural tube defects," American Journal of epidemiology, vol. 153, no. 4, pp. 325-331, 2001.

[27] M. I. Cedergren, A. J. Selbing, O. Löfman, and B. A. Källen, "Chlorination byproducts and nitrate in drinking water and risk for congenital cardiac defects," Environmental research, vol. 89, no. 2, pp. 124-130, 2002.

[28] S. Virtanen et al., "Nitrate and nitrite intake and the risk for type 1 diabetes in Finnish children," Diabetic Medicine, vol. 11, no. 7, pp. 656-662, 1994.

[29] S. K. Gupta et al., "Recurrent diarrhea in children living in areas with high levels of nitrate in drinking water," Archives of Environmental Health: An International Journal, vol. 56, no. 4, pp. 369-373, 2001.

[30] S. S. Nielsen, B. A. Mueller, S. Preston-Martin, F. M. Farin, E. A. Holly, and R. McKean-Cowdin, "Childhood brain tumors and maternal cured meat consumption in pregnancy: differential effect by glutathione S-transferases," Cancer epidemiology, biomarkers & prevention, vol. 20, no. 11, pp. 2413-2419, 2011.

[31] M. Xiong, Y. Zhang, X. Li, and C. Ma, "Effects of dietary Chinese cured meat on lipid metabolism in rats," Food chemistry, vol. 107, no. 1, pp. 60-67, 2008.

[32] M. McCredie, P. Maisonneuve, and P. Boyle, "Perinatal and early postnatal risk factors for malignant brain tumours in New South Wales children," International journal of cancer, vol. 56, no. 1, pp. 11-15, 1994.

[33] J. S. P.J Clemmensen, N. Brix, T. Sigsgaard, L.T.Stayner,H. A. Kolstad, and C. H. Ramlau-Hansen,, "Prenatal Exposure to Nitrate in Drinking Water and Adverse Health Outcomes in the Ofspring: a Review of Current Epidemiological Research," Current Environmental Health Reports, vol. 10:250–263, 16 July 2023.

[34] S. S. N. B.A.Mueller, S. Preston-Martin, E.A.Holly, S.Cordier, G. Filippini, ... & N.W.Choi, , " "Household water source and the risk of childhood brain tumours: results of the SEARCH International Brain Tumor Study"," International journal of epidemiology,, vol. 33(6), 1209-1216., 2004.

[35] M. H. Ward, S. D MARK, K. P. Cantor, D. D WEISENBURGER, and A. Correa-Villasenor, "Non-Hodgkin's lymphoma and nitrate in drinking water," Journal of Epidemiology & Community Health, vol. 54, no. 10, pp. 772-773, 2000.

[36] B. G. Linke, T. A. Casagrande, and L. A. Cardoso, "Food additives and their health effects: A review on preservative sodium benzoate," African Journal of Biotechnology, vol. 17, no. 10, pp. 306-310, 2018.

[37] C. Xu et al., "Investigation of benzoic acid and sorbic acid in snack foods in Jilin province, China," International journal of food properties, vol. 22, no. 1, pp. 670-677, 2019.

[38] M. Mostafavi, "In-line/on-line measuring techniques in the solution crystallization processes," 2015.

[39] M. Pongsavee, "Effect of sodium benzoate preservative on micronucleus induction, chromosome break, and Ala40Thr superoxide dismutase gene mutation in lymphocytes," BioMed research international, vol. 2015, 2015.

[40] M. Shahmohammadi, M. Javadi, and M. Nassiri-Asl, "An overview on the effects of sodium benzoate as a preservative in food products," Biotechnology and Health Sciences, vol. 3, no. 3, pp. 7-11, 2016.

[41] S. Sambu, U. Hemaram, R. Murugan, and A. A. Alsofi, "Toxicological and teratogenic effect of various food additives: An updated review," BioMed Research International, vol. 2022, 2022.

[42] W. Schaubschläger, W.-M. Becker, U. Schade, P. Zabel, and M. Schlaak, "Release of mediators from human gastric mucosa and blood in adverse reactions to benzoate," International Archives of Allergy and Immunology, vol. 96, no. 2, pp. 97-101, 1991.

[43] K.-J. Jang, C. Cha, and K.-G. Lee, "Analysis and reduction of benzene in various beverages such as vitamin drinks and cranberry juice," LWT, vol. 115, p. 108444, 2019.

[44] M. Afshar, S. Moallem, T. M. HASANZADEH, M. Shahsavan, F. Sukhtanloo, and F. Salehi, "Effect of long term consumption of sodium benzoat before and during pregnancy on growth indexes of fetal balb/c mice," 2012.

[45] N. A. Alwan, A. M. Kudayer, and E. A. Al-Masoudi, "The Toxic Effect of Oral Gavaged of Sodium Benzoate (SB) on Adult Male Rabbits," Malaysian Journal of Medicine & Health Sciences, vol. 18, 2022.

[46] D. Sohrabi, M. Rahnama, A. M. SHAMS, and F. Fakheri, "The effects of sodium benzoate (c6h5coona) on ovaries and its hormones and gonadotropins on female balb/c mice," 2007.

[47] S. Khan, K. B. Dar, S. A. Ganie, and M. N. Ali, "Toxicological impact of sodium benzoate on inflammatory cytokines, oxidative stress and biochemical markers in male Wistar rats," Drug and Chemical Toxicology, vol. 45, no. 3, pp. 1345-1354, 2022.

[48] M. Afshar, M. Taheri, S. Moallem, M. Golalipour, and M. Shahsavan, "Fetal malformations due to long term consumption of Sodium Benzoate in pregnant balb/c mice," AJPT, vol. 2, pp. 1-7, 2014.

[49] S. E. Ibekwe, A. A. Uwakwe, and M. O. Monanu, "Effect of oral intake of sodium benzoate on some haematological parameters of wistar albino rats," Sci. Res. Essays, vol. 2, pp. 006-009, 2007.

[50] S. Yılmaz, F. Ünal, and D. Yüzbaşıoğlu, "The in vitro genotoxicity of benzoic acid in human peripheral blood lymphocytes," Cytotechnology, vol. 60, pp. 55-61, 2009.

[51] M. Hu, J. Wang, J. Cai, Y. Wu, and X. Wang, "Analysis of sodium benzoate biotoxicity using atomic force microscope," Chinese Journal of Biotechnology, vol. 24, no. 8, pp. 1428-1432, 2008.

[52] S. Mamur, D. Yüzbaşıoğlu, F. Ünal, and H. Aksoy, "Genotoxicity of food preservative sodium sorbate in human lymphocytes in vitro," Cytotechnology, vol. 64, pp. 553-562, 2012.

[53] H. Vally and N. L. Misso, "Adverse reactions to the sulphite additives," Gastroenterology and hepatology from bed to bench, vol. 5, no. 1, p. 16, 2012.

[54] E. P. o. F. Additives et al., "Follow-up of the re-evaluation of sulfur dioxide (E 220), sodium sulfite (E 221), sodium bisulfite (E 222), sodium metabisulfite (E 223), potassium metabisulfite (E 224), calcium sulfite (E 226), calcium bisulfite (E 227) and potassium bisulfite (E 228)," EFSA Journal, vol. 20, no. 11, p. e07594, 2022.

[55] E. Mani-López, E. Palou, and A. López-Malo, "Preservatives: classifications and analysis," 2016.

[56] Kochen, "Sulfur dioxide, a respiratory tract irritant, even if ingested," Pediatrics, vol. 52, no. 1, pp. 145-146, 1973.

[57] S. L. Taylor, R. K. Bush, and J. A. Nordlee, "Sulfites," Food Allergy: Adverse Reactions to Foods and Food Additives, pp. 361-374, 2013.

[58] A. F. Gunnison, D. W. Jacobsen, and H. J. Schwartz, "Sulfite hypersensitivity. A critical review," CRC critical reviews in toxicology, vol. 17, no. 3, pp. 185-214, 1987.

[59] M. R. Lester, "Sulfite sensitivity: significance in human health," Journal of the American College of Nutrition, vol. 14, no. 3, pp. 229-232, 1995.

[60] D. Peroni and A. Boner, "Sulfite sensitivity," Clinical & Experimental Allergy, vol. 25, no. 8, pp. 680-681, 1995.

[61] H. Til, V. Feron, and A. De Groot, "The toxicity of sulphite. I. Long-term feeding and multigeneration studies in rats," Food and Cosmetics Toxicology, vol. 10, no. 3, pp. 291-310, 1972.

[62] F. Z. El Kadi, A. I. Bénali, M. Bénali, and S. Belbraouet, "Effect of sodium metabisulphite on blood metabolic status of wistar rats," Food and Nutrition Sciences, vol. 2014, 2014.

[63] H. A. Paula Neto, P. Ausina, L. S. Gomez, J. G. Leandro, P. Zancan, and M. Sola-Penna, "Effects of food additives on immune cells as contributors to body weight gain and immune-mediated metabolic dysregulation," Frontiers in immunology, vol. 8, p. 253755, 2017.

[64] C.-S. M. Center., ""How food preservatives may disrupt human hormones and promote obesity: Innovative stem-cell testing system demonstrates potential for evaluating health effects of chemicals used in everyday life."," ScienceDaily,, 9 August 2017.

[65] N. Halla et al., "Cosmetics preservation: a review on present strategies," Molecules, vol. 23, no. 7, p. 1571, 2018.

[66] E. Neza and M. Centini, "Microbiologically contaminated and over-preserved cosmetic products according Rapex 2008–2014," Cosmetics, vol. 3, no. 1, p. 3, 2016.

[67] E. Guzmán and A. Lucia, "Essential oils and their individual components in cosmetic products," Cosmetics, vol. 8, no. 4, p. 114, 2021.

[68] S. Papageorgiou, A. Varvaresou, E. Tsirivas, and C. Demetzos, "Abstracts: New alternatives to cosmetics preservation," International Journal of Cosmetic Science, vol. 32, no. 5, pp. 395-395, 2010.

[69] S. H. Jeong, "A Review of safety evaluations of cosmetic preservatives," Kor J Aesthet Cosmetol, vol. 11, no. 5, pp. 827-833, 2013.

[70] A. Herman, "Antimicrobial ingredients as preservative booster and components of self-preserving cosmetic products," Current microbiology, vol. 76, no. 6, pp. 744-754, 2019.

[71] S. Roy, S. Majumder, A. Deb, and L. Choudhury, "Microbial contamination of cosmetics and the pharmaceutical products, and their preservation strategies: A comprehensive review," Novel Research in Microbiology Journal, vol. 7, no. 5, pp. 2116-2137, 2023.

[72] S. Martínez and J. Carballo, "Physicochemical, sensory and nutritional properties of foods affected by processing and storage," vol. 10, ed: MDPI, 2021, p. 2970.

[73] G. Alvarez-Rivera, M. Llompart, M. Lores, and C. Garcia–Jares, "Preservatives in cosmetics: Regulatory aspects and analytical methods," in Analysis of cosmetic products: Elsevier, 2018, pp. 175-224.

[74] Yazar, S. Johnsson, M. L. Lind, A. Boman, and C. Liden, "Preservatives and fragrances in selected consumer-available cosmetics and detergents," Contact Dermatitis, vol. 64, no. 5, pp. 265-272, 2011.

[75] A. Jain, S. Soni, and K. K. Verma, "Determination of parabens in cosmetics by liquid-phase microextractions and high-performance liquid chromatography–diode array detection," Journal of Liquid Chromatography & Related Technologies, vol. 38, no. 1, pp. 82-91, 2015.

[76] Y.-f. Liu, J.-l. Zhang, X.-f. Nie, P. Zhang, X.-q. Yan, and K.-f. Fu, "Simultaneous determination of 11 preservatives in cosmetics and pharmaceuticals by matrix solid-phase dispersion coupled with gas chromatography," Acta Chromatographica, vol. 32, no. 3, pp. 203-209, 2020.

[77] A. Flyvholm, "Preservatives in registered chemical products," Contact dermatitis, vol. 53, no. 1, pp. 27-32, 2005.

[78] J. Q. Huang, C. C. Hu, and T. C. Chiu, "Determination of seven preservatives in cosmetic products by micellar electrokinetic chromatography," International journal of cosmetic science, vol. 35, no. 4, pp. 346-353, 2013.

[79] Memon, M. I. Bhanger, and M. Khuhawer, "Determination of preservatives in cosmetics and food samples by micellar liquid chromatography," Journal of separation science, vol. 28, no. 7, pp. 635-638, 2005.

[80] J. F. Schwensen, U. F. Friis, T. Menné, M.-A. Flyvholm, and J. D. Johansen, "Contact allergy to preservatives in patients with occupational contact dermatitis and exposure analysis of preservatives in registered chemical products for occupational use," International archives of occupational and environmental health, vol. 90, pp. 319-333, 2017.

[81] A. Othman, L. Norton, A. S. Finny, and S. Andreescu, "Easy-to-use and inexpensive sensors for assessing the quality and traceability of cosmetic antioxidants," Talanta, vol. 208, p. 120473, 2020.

[82] Tanaka et al., "Rapid Determination of Preservatives in Cosmetics Using a Core–Shell Column," Journal of Chromatographic Science, vol. 61, no. 7, pp. 637-643, 2023.

[83] D. Tahiraj, "Dermatoses Due to Cleaning and Cosmetic Products," ANGLISTICUM. Journal of the Association-Institute for English Language and American Studies, vol. 4, no. 6, pp. 78-83, 2015.

[84] L. Sanchez-Prado, G. Alvarez-Rivera, J. P. Lamas, M. Lores, C. Garcia-Jares, and M. Llompart, "Analysis of multi-class preservatives in leave-on and rinse-off cosmetics by matrix solid-phase dispersion," Analytical and bioanalytical chemistry, vol. 401, pp. 3293-3304, 2011.

[85] A. L. Byrd, Y. Belkaid, and J. A. Segre, "The human skin microbiome," Nature Reviews Microbiology, vol. 16, no. 3, pp. 143-155, 2018.

[86] Poddębniak and U. Kalinowska-Lis, "A Survey of Preservatives Used in Cosmetic Products," Applied Sciences, vol. 14, no. 4, p. 1581, 2024.

[87] H. Y. Sherry, A. Sood, and J. S. Taylor, "Patch testing for methylisothiazolinone and methylchloroisothiazolinone-methylisothiazolinone contact allergy," JAMA dermatology, vol. 152, no. 1, pp. 67-72, 2016.

[88] A. K. Nowak, E. Jabłońska, and W. Ratajczak-Wrona, "Controversy around parabens: Alternative strategies for preservative use in cosmetics and personal care products," Environmental research, vol. 198, p. 110488, 2021.

[89] E. M. Warshaw et al., "Importance of supplemental patch testing beyond a screening series for patients with dermatitis: the North American Contact Dermatitis group experience," JAMA dermatology, vol. 157, no. 12, pp. 1456-1465, 2021.

[90] E. M. Warshaw et al., "Contact dermatitis associated with hair care products: a retrospective analysis of the North American Contact Dermatitis Group Data, 2001–2016," Dermatitis, vol. 33, no. 1, pp. 91-102, 2022.

[91] M. J. Zirwas, "Contact dermatitis to cosmetics," Clinical Reviews in Allergy & Immunology, vol. 56, pp. 119-128, 2019.

[92] R. F. Althulthi, R. M. Moman, A. A. Ghalbun, and M. R. Alsagher, "Evaluation of Bacteriological Quality and Preservatives Efficacy of Cosmetics," Sch Acad J Biosci, vol. 12, pp. 442-451, 2023.

[93] J. Wang, Y. Liu, W. R. Kam, Y. Li, and D. A. Sullivan, "Toxicity of the cosmetic preservatives parabens, phenoxyethanol and chlorphenesin on human meibomian gland epithelial cells," Experimental eye research, vol. 196, p. 108057, 2020.

[94] X. Chen, D. A. Sullivan, A. G. Sullivan, W. R. Kam, and Y. Liu, "Toxicity of cosmetic preservatives on human ocular surface and adnexal cells," Experimental Eye Research, vol. 170, pp. 188-197, 2018.

[95] G. Song, G. Ouyang, and S. Bao, "The activation of Akt/PKB signaling pathway and cell survival," Journal of cellular and molecular medicine, vol. 9, no. 1, pp. 59-71, 2005.

[96] M. Bilal and H. M. Iqbal, "An insight into toxicity and human-health-related adverse consequences of cosmeceuticals—a review," Science of the total environment, vol. 670, pp. 555-568, 2019.

[97] A. Esrafili, Y. Yamini, M. Ghambarian, and M. Moradi, "Analysis of paraben preservatives in cosmetic samples: comparison of three different dynamic hollow fiber liquid-phase microextraction methods," Chromatographia, vol. 77, pp. 317-327, 2014.

[98] E. Jungman, "Development of a percutaneous penetration predictive model with chromatographic and spectroscopic tools," Université Paris Sud-Paris XI, 2012.

[99] M. G. Kirchhof and G. C. de Gannes, "The health controversies of parabens," Skin Therapy Lett, vol. 18, no. 2, pp. 5-7, 2013.

[100] F. A. Andersen, "Final amended report on the safety assessment of methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzylparaben as used in cosmetic products," Int J Toxicol, vol. 27, no. Suppl 4, pp. 1-82, 2008.

[101] J. Lincho, R. C. Martins, and J. Gomes, "Paraben compounds—part I: an overview of their characteristics, detection, and impacts," Applied Sciences, vol. 11, no. 5, p. 2307, 2021.

[102] S. Siddique, C. Kubwabo, and S. A. Harris, "A review of the role of emerging environmental contaminants in the development of breast cancer in women," Emerging Contaminants, vol. 2, no. 4, pp. 204-219, 2016.

[103] D. Güzel Bayülken and B. Ayaz Tüylü, "In vitro genotoxic and cytotoxic effects of some paraben esters on human peripheral lymphocytes," Drug and Chemical Toxicology, vol. 42, no. 4, pp. 386-393, 2019.

[104] K. Shivaram, "Disproportionate chemical exposure: How the marketing and production of beauty products in the United States impose health burdens on women," Intersect: The Stanford Journal of Science, Technology, and Society, vol. 12, no. 3, 2019.

[105] L. E. Wineski and A. W. English, "Phenoxyethanol as a nontoxic preservative in the dissection laboratory," Cells Tissues Organs, vol. 136, no. 2, pp. 155-158, 1989.

[106] S. Bohn and A. Bircher, "Phenoxyethanol-induced urticaria," Allergy, vol. 56, no. 9, 2001.

[107] F. Chasset et al., "Contact dermatitis due to ultrasound gel: A case report and published work review," The Journal of Dermatology, vol. 43, no. 3, pp. 318-320, 2016.

[108] A. Panico et al., "Skin safety and health prevention: an overview of chemicals in cosmetic products," Journal of preventive medicine and hygiene, vol. 60, no. 1, p. E50, 2019.