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AN EFFECT OF FOOD ADDITIVES ON MICROBIOME

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Keywords: *food additives, sweeteners, microbiome, microbiota*

Abstract

The paper presents a review of available data about an effect of food additives on the human microbiome and lists the main physiological functions of the gut microbiome. The process of the human microbiome evolution is examined. The relationship between the emergence of a disease and the microbiome composition, as well as the main factors influencing the gut microbiome composition are described. The main food additives used today are listed, their key features are discussed and their structural formulas are given. The information about their effect on the human body through an influence on the microbiome composition is presented. The data on an effect of polysorbate 80, carboxymethylcellulose, sodium sulfite, nisin, potassium sorbate, sodium benzoate, sodium nitrate, essential oils, titanium dioxide and different sweeteners on the microbiome are analyzed. It is explained what microbial communities are suppressed and what communities gain advantages in multiplication when consumers eat food with one or another food additive. The consequences of alterations in the microbiome for the consumer's body are examined. Conclusions were made about the necessity of additional studies about an effect of food additives on the composition of the human microbiome.

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Introduction

A type and diversity of consumed food significantly affect the human microbiome composition. Changes in the food composition can lead to alterations in the metabolic pathways and immune processes in the consumer's body [1]. The human gastrointestinal tract is inhabited by various symbiotic microorganisms. They colonize mainly the colon; with that, a ratio of the microbiome cells to cells of the host organism is 1:1 [2]. It is believed that microbiota is in the mutually beneficial relationships with its host taking part in various metabolic and immune processes [3]. The complex microbial ecosystem is closely linked with the host health [3,4]. Alterations in the gut microbiome composition can be associated with metabolic disorders, inflammation and even with neurological diseases [5,6]. The microbiome composition alters along the gastrointestinal tract forming specific regional communities [7]. It is agreed today that the microbiome composition includes, at least, 1000 species [8]. With that, *Firmicutes* and *Bacteroidetes* are two predominant phyla representing Gram-positive and Gram-negative bacteria colonizing the mammalian gastrointestinal tract. They account for 90% of total bacterial counts in the intestine [9]. A ratio between the number of members of these two phyla can vary depending on the individual peculiarities of the host organism, but total proportions are similar in the majority of people [10]. Among other members, the human microbiome also includes *Fusobacteria*, *Verrucomicrobia, Actinobacteria, Proteobacteria* and several species of archaea [9]. Moreover, researchers emphasize the importance of the presence of *Bifidobacterium*, *Clostridium*, *Ruminococcus*, *Lactobacillus*, *Streptococcus*, *Bacteroides* and *Escherichia* [11]. It is believed that the diet that includes increased consumption of legumes, cereals, fruit and vegetables is beneficial for the consumer's body [12,13]. There is a trend towards an increasing presence of artificial sweeteners in our diet [14]. Nowadays, an effect of food additives on the consumer's body has been comprehensively studied. However, food additives can also affect the body indirectly by influencing the gut microbiome [4,15]. Experiments on animals show that food additives can have an adverse effect on the colon and cardiovascular system [1]. It was demonstrated that food emulsifiers such as polysorbates and carboxymethylcellulose can increase the intestine permeability, alter the microbiota composition, and facilitate penetration of Escherichia coli through epithelium [16].

In the Russian Federation, the use of food additives is regulated by Federal Laws № 29-FZ[1], № 52-FZ[2] and Technical Regulations of the Customs Union TR CU029/2012 "On the safety for food additives, flavorings and technological aids"[3]. The list of food additives permitted in Russia is approved by the Ministry of Health of the Russian Federation and the state control of their quality is performed by the Russian Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor).

[1] Federal Law No. 29-FZ on food quality and food safety. (In Russian)
[2] Federal Law No. 52-FZ on sanitary and epidemiological well-being of the population. (In Russian)
[3] TR CU029/2012 Technical Regulations of the Customs Union "On the safety for food additives, flavorings and technological aids" Retrieved from https://docs.cntd.ru/document/902359401. Accessed April 15, 2021. (In Russian)

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The available data on artificial sweeteners show disorders of the metabolic processes in rodents due to the disturbance in the microflora balance [17,18]. Therefore, it is important to study an effect of food additives on the gut microbiota composition [19]. Nowadays, there is limited knowledge about an effect of food additives on the human gut microbiota as available studies were carried out mainly on animal models [20].

Interrelation between the gut microbiome composition and diseases

Disturbance of the balance in the gut microbiome composition is closely linked with the development of many human diseases, such as obesity, diabetes, cardiovascular and inflammatory pathologies [5]. It was shown that an increase in the number of *Streptococcus* and *Enterobacteriaceae* in the intestine is typical for the atherosclerotic cardiovascular diseases [21]. Also, the number of *Faecalibacterium prausnitzii* and *Lactobacillus* in patients with type 2 diabetes mellitus was significantly lower than in healthy individuals. The number of *Bifidobacterium* was significantly higher than in healthy individuals [22]. Probably, imbalance of the gut microbiota composition influences the cancer development [1]. For example, the increased number of *Bacteroides massiliensis* was observed in patients with prostate cancer, while the number of *Eubacterium rectale* and *Faecalibacterium prausnitzii* was lowered [23].

Metabolites of bacteria from the gut microbiome can be associated with human diseases. For example, arginine can be transformed into glutamate and then deaminated to gamma-aminobutyric acid, which as a neurotransmitter. Alterations in the expression of receptors of this neurotransmitter are linked to the development of anxiety and depression [24]. Another example is lysine, which can be metabolized with the formation of cadaverine, which increased level can be associated with ulcerative colitis [25,26]. However, it is necessary to note that in several cases, the above mentioned pathological mechanisms are a consequence of metabolic disorders.

Physiological functions of the gut microbiome and its effect on the human health

The gut microbiome affects the physiological processes in the human body mainly through microbial metabolism. Microorganisms in the gastrointestinal tract can break down complex carbohydrates, proteins and some fats [1]. They are also capable of producing various enzymes that take part in metabolism [27]. The microbiome produces many metabolites that can enter blood and act throughout the whole body. Short-chain fatty acids, alcohols, ammonia, fatty acids, amines, sulfur compounds, phenols, indoles, glycerol derivatives, carbon dioxide and hydrogen are among such metabolites [1,27]. For example, the physiological functions of short-chain fatty acids are extremely important as they affect functioning of the epithelial cells of the colon [28]. Also, microorganisms take part in catabolism of amino acids and lipids [1].

In addition to the influence on metabolism, the gut microbiome is also important for formation of the human immunity, especially for the development and regulation of the immune system as the body develops [3,4]. The gut microbiome interacts with the immune system sending "signals" that facilitate the differentiation of the immune cells and immunity development. Moreover, it influences the antibody production, T-cell differentiation and enhancement of the phagocytic function of macrophages [29]. The gut microbiome also facilitates maintenance of the integrity of the intestinal epithelial cells [1,30].

Thus, the gut microbiome contains a large diversity of different bacterial genomes and can produce a wide range of metabolites. These metabolites and components of bacterial cells are important for the host organism as they are associated with the physiological development and maintenance of the innate and adaptive immunity.

Factors influencing the gut microbiome composition

The diversity of the human gut microbiome is influenced by various factors such as intake of antibiotics, age, stress and climatic conditions [23]. Factors are divided into dietary and non-dietary [1]. As for non-dietary factors, age is one of the factors affecting the gut microbiota composition. For example, *Clostridium* and *Bacteroides* dominate in the gastrointestinal tract of elderly people, while the number of *Bifidobacteria* is reduced [31]. An effect of dietary factors on the microbiota has been widely studied [1–10]. It is shown that a diet rich in simple carbohydrates leads to multiplication of *Proteobacteria* and *Firmicutes,* while a diet rich in fats leads to a decrease in the intestinal microbial diversity. Food rich in animal protein and saturated fats promotes the development of *Actinobacteria* and *Bacteroidetes* in the intestine [32,33].

Therefore, changes in nutrition affect the gut microbiome diversity.

Evolution of the human gut microbiome

During the whole human life, the human gut mirobiome demonstrates continuous dynamic changes that are manifested in constant evolution and adaptation [34]. In the first month after birth, the gut microbiome diversity in infants is very low. By the sixth month, the composition and number of cells of the gut microbiota significantly increase due to an increase in the variety of consumed food [31]. With the cessation of breastfeeding, the nutrition structure changes and consumption of carbohydrates by microorganisms increases. More short-chain fatty acids and vitamins metabolized by microorganisms appear in food [34]. In the course of time, the gut microbiome dominated by *Bifidobacteria* in infants transforms into the gut microbiome of adults with domination of *Firmicutes* and *Bacteroides* [35]. At the age of 2.5–3 years, rapid increase

in the bacterial diversity is significantly retarded and the gut microbiome composition gradually achieves the adult condition by the age of 7–12 years [34].

Acesulfame potassium

Acesulfame potassium is also known as acesulfame (E950). It is an acidic cyclic sulfonamide derivative, which is 200 times sweeter than sucrose (Figure 1). The acceptable daily intake of acesulfame is 15 mg/kg body weight/ day; 95% of this amount is fully excreted in urine after passing through the human digestive system [36]. A study of an effect of acesulfame potassium on the gut microbiota composition in mice showed that disorders of the metabolic pathways and intestinal microflora occurred after four weeks of its consumption. These disorders significantly differed depending on a gender. In male mice, the body weight significantly increased, the expression of the functional bacterial genes related to the carbohydrate and energy metabolism enhanced. In female mice, the body weight did not change significantly but several bacterial metabolites such as 2-oleoylglycerol, succinic acid and D-lactic acid were reduced. Moreover, the abundance of *Oxalobacteraceae*, *Clostridium*, *Lactobacillus* and *Ruminococcaceae* decreased, while the abundance of *Mucispirillum* increased [37].

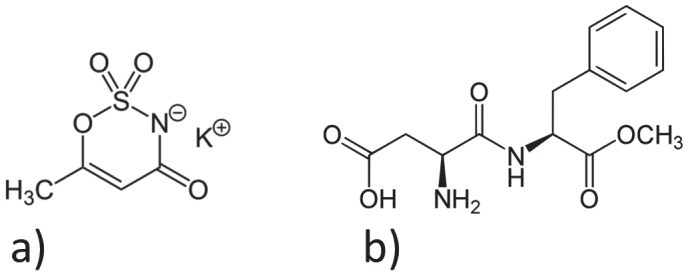

Figure 1. Structural formula of acesulfame potassium (a) and aspartame (b)

However, another study showed that acesulfame at doses equivalent to the human acceptable daily intake (ADI) did not significantly change the gut microbiome composition in mice. The abundance of *Clostridium IV, Clostridium IVXa*, *Bacteroides* and *Firmicutes* was the same in the experimental and control groups. [38]. Frankenfeld et al. [39] studied an effect of acesulfame potassium on the human gut flora. As a result, no significant differences were revealed between medians characterizing the number of bacteria in consumers and non-consumers of acesulfame. The ratio of *Bacteroidetes* to *Firmicutes* was also the same [1,39].

Aspartame

Aspartame (L-α-Aspartyl-L-phenylalanine methyl ester, E951) is 180 to 200 times sweeter than sucrose. Its acceptable daily intake (ADI) is 40 mg/kg body weight. The most part of aspartame is fully hydrolyzed in the intestine with formation of phenylalanine, methanol and aspartic acid [40]. Although many studies on aspartame safety for humans were carried out, little attention was given to an effect of aspartame intake on the human gut microbiome composition [1]. Palmnas et al. [41] reported about an effect of low aspartame doses (5–7 mg/kg body weight/ day) on metabolism and the gut microbiota in rats with and without diet induced obesity. For example, aspartame intake led to an increase in *Clostridium leptum* and *Enterobacteriaceae*, and an increase in the members of *Roseburia* was observed in rats with diet induced obesity. Compared to the control group, the gut microbiota composition in rats with obesity that consumed aspartame had the increased abundance of *Roseburia*, *Bifidobacterium*, *Clostridium leptum* and *Enterobacteriaceae*. Also, aspartame intake increased a level of circulated short-chain propionate and glucose, which may lead to hyperglycemia and insulin tolerance later on [1,41]. Suez et al. [38] analyzed an effect of aspartame on glucose metabolism and the gut microbiota. The glycemic response was significantly higher in the group consumed aspartame than in the control group ($p<0.001$). According to the authors' opinion, the revealed glucose tolerance can be associated with alterations in the gut microbiota composition, including a reduction of the abundance of *Clostridiales* and an increase in the abundance of *Bacteroides* [1,38].

Frankenfeld et al. [39] showed that although there was no significant difference in the ratio of *Bacteroidetes* to *Firmicutes* between the group consuming aspartame and the control group, the overall bacterial diversity differed between the groups. For example, aspartame intake was associated with an increase in *Actinobacteria*, *Deltaproteobacteria* and *Enterobacteriaceae* [1,39].

Saccharin

Saccharin (E954) is a derivative of naphthalene. It is about 240–300 times sweeter than sucrose and is one of the first artificial sweeteners used in various foods (Figure 2). It is slowly absorbed by the intestine and its acceptable daily intake is 5 mg/kg body weight/day, which is the lowest level among all artificial sweeteners [42].

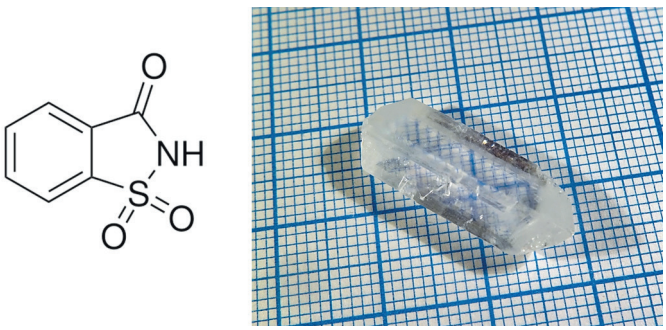

Figure 2. Structural formula of saccharin and a photo of its crystal grown in acetone

Suez et al. assessed an effect of saccharin on the blood glucose level and the gut microbiota composition in mice [38]. According to the authors' data, saccharin induced misbalance in the gut microbial community, including an increase in the abundance of *Clostridiales* and *Bacteroides* and a decrease in the abundance of lactobacilli and

Firmicutes. The same researchers reported that no disorders related to glucose tolerance were revealed in mice after saccharin consumption. However, transplantation of the gut microbiome from the *in vitro* cultures subjected to an exposure to saccharin to other mice led to impaired glucose homeostasis [38].

Sucralose

Sucralose (E955) is a chlorinated disaccharide. Its sweetening ability about 320–1000 times higher than that of sucrose (Figure 3). The acceptable daily intake is 15 mg/kg body weight/day. With that, the most part of ingested sucralose is excreted in faeces (65–95%) [36]. Uebanso et al. [43] reported that the number of *Clostridium IVXa* in faeces of mice given sucralose significantly reduced with an increase in the ratio of secondary/primary bile acids and a decrease in the level of luminal butyrate [43]. Bian et al. [44] studied an effect of sucralose on the gut microbiome in male mice. The gut microbiota composition altered significantly after sucralose intake during six months. After three months, the abundance of *Ruminococcus* increased and that of *Bacillales, Peptostreptococcaceae*, *Staphylococcus* and *Anaerostipes* decreased. After six months, an increase in the abundance of *Christensenellaceae*, *Clostridiaceae*, *Akkermansia*, *Roseburia* and *Turicibacter*, and a decrease in the abundance of *Erysipelotrichaceae*, *Dehalobacterium*, and *Streptococcus* were observed [44].

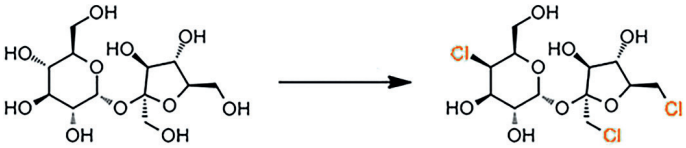

Figure 3. A simplified scheme of sucralose production from saccharose as a result of the five-stage reaction

Sodium cyclamate

Sodium cyclamate (E952) is used as a sweetener in more than 50 countries, and its sweetness is 30–40 times higher than that of sucrose (Figure 4).

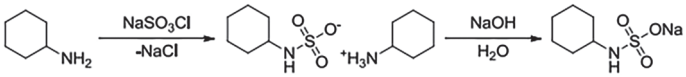

Figure 4. A scheme of sodium cyclamate production

However, the U. S. Food and Drug Administration (FDA) removed sodium cyclamate from the list of substances generally recognized as safe ("GRAS") in 1969 and fully prohibited it in 1970 [42]. It was found that sodium cyclamate can be metabolized to toxic cyclohexylamine under the action of the gut microbiota [1]. For example, the animal experiments showed that bladder cancer was found in rats fed with a mixture of cyclamate and saccharin [45]. However, correctness of these studies was subjected to question and the safety of sodium cyclamate was revised. In 1982, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established the acceptable daily intake of 11 mg/kg body weight/day for sodium cyclamate [1]. In the USA, the use of this substance is still prohibited. Subsequently, an effect of sodium cyclamate on the monkey gut microbiota was studied. Compared to the control group, total counts of coliforms and the presence of the microbial population including *Bifidobacterium*, *Clostridium*, *Enterobacteriaceae*, *Veillonella* and *Bacteroidaceae* did not have significant differences [46].

Neotame

Neotame (E961) is an artificial sweetener produced by reductive alkylation of aspartame. It is often used in combination with other sweeteners in sauces, fermented dairy drinks, lemon tea and soft drinks [1]. Although the structural formulas of neotame and aspartame are similar, neotame has higher sweetness, which is 7000–13000 times higher than that of sucrose (Figure 5).

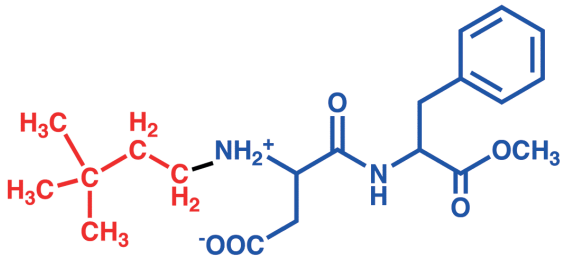

Figure 5. Structural formula of neotame. The blue color shows aspartame as part of neotame; this part of the molecule is responsible for sweet taste formation in this substance [49]

Both the FDA and European Food Safety Authority (EFSA) approved the use of neotame; with that, its acceptable daily intake (ADI) is 2 mg/kg body weight/day [47]. Neotame is quickly metabolized and is not accumulated in the body. Half of the consumed neotame does not enter blood and is excreted in faeces, while another half is excreted in urine as deesterified neotame. Up to now, there have been no reports about its toxicity for mice and other experimental animals [36].

Chi et al. [48] studied an effect of neotame on the gut microbiota in male mice. After four-week neotame consumption, a significant increase in *Bacteroidetes* and a significant decrease in *Firmicutes* were observed in the neotame-treated mice. Total microbial counts were significantly lower in the neotame-treated mice than in the control group [48].

Emulsifiers and their effect on the gut microbiome

Emulsifiers are substances having the surface activity that are capable of creating stable emulsions when mixing with other substances. They help improving the food structure and taste, extend product shelf life [1,50]. Some emulsifiers are present in food as a natural component, for example, surface active protein casein, while others are synthesized artificially, for example, substances such as carboxymethylcellulose and polysorbate 80. Over the last years, there has been a trend towards an increasing number of studies showing that food emulsifiers can af-

fect the gut microbiome, cause intestinal inflammation and facilitate the development of the metabolic syndrome [1,50,51].

Carboxymethylcellulose

Carboxymethylcellulose (CMC, E466) is an amorphous colorless substance, a weak acid. According to the classifier of food additives, it is assigned to the class of stabilizers; it imparts shape and viscosity to a product. Carboxymethylcellulose is a cellulose derivative obtained from cellulose upon its treatment with chloroacetic acid and alkali. It can be seen from the presented chemical structures (Figure 6) that carboxymethylcellulose has the higher water solubility than the initial raw materials due to the presence of the polar carboxymethyl group; however, the polymer structure remains to be unchanged. The chemical, food and pharmaceutical industries use the carboxymethylcellulose sodium salt (croscarmellose, E468), which aqueous solutions are viscous and have pseudoplasticity. The CMC sodium salt is an amorphous colorless substance with a molecular mass $(30–25)*10^3$, browning temperature 227 °C, carbonization temperature 252 °C. It is soluble in water, aqueous alkaline solutions, NH_3, NaCl and solvents for cellulose; it is not soluble in organic solvents, mineral oils. When solving in water, the CMC sodium salt forms viscous transparent solutions.

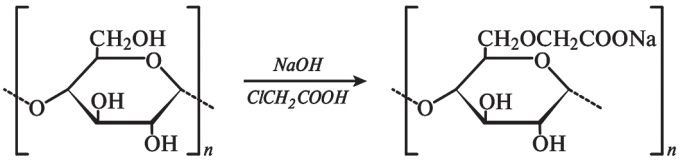

Figure 6. A scheme for production of the carboxymethylcellulose sodium salt

Toxicological studies showed that mice and rats treated with CMC did not have any significant side effects over 100 weeks [52]. Carboxymethylcellulose is a polysaccharide, which is hard to hydrolyze and digest by the enzymes of the human gastrointestinal tract; therefore, its fermentation usually depends on the gut microbiota [1]. Carboxymethylcellulose can be fermented by the gut microflora into short-chain organic acids, such as lactic acid, succinic acid, formic acid, acetic acid, butyric acid and propionic acid. Swidsinski et al. [53] studied an effect of CMC on mice with deactivated IL-10 gene (IL-10 gene suppresses production of all pro-inflammatory cytokines). Bacterial overgrowth was observed in CMC-treated mice. The bacterial concentration in the ileum was higher than 10^8 CFU/ml (colony forming units/ ml). It was found that leucocytes migrated into the intestinal lumen in four out of seven CMC-treated mice. CMC intake caused a reduction in *Eubacterium rectale* in the ileum and jejunum, and also increased *Bacteroides*. The authors assumed that CMC intake can lead to the bacterial overgrowth and cause inflammation of the intestine in susceptible mice [1,53].

Viennois et al. [54] studied an effect of CMC on intestinal inflammation and alterations of the mouse gut microbiota composition in colorectal cancer development. After CMC intake for 13 weeks, the mouse gut microbiome composition altered: the abundance of *Proteobacteria* and *Firmicutes* significantly decreased and the abundance of *Bacteroidetes* increased. With that, the levels of the marker of intestinal inflammation (lipocalin 2) were elevated. Several groups took part in the study and the frequency of tumor development also increased in a group treated only with CMC compared to the control group. The authors concluded that CMC intake promoted carcinogenic processes [1,54].

An effect of CMC on the gut microbial diversity was also studied with the use of *in vitro* models. For example, Chassaing et al. [55] studied an effect of CMC on the intestinal ecosystem using an artificial model that simulated the intestinal mucosa (M-Shime). The M-Shime model is an *in vitro* model consisting of several glass vessels with regulated pH, which simulate the stomach, small intestine and different parts of the colon. For better simulation of the human intestinal tract covered with mucus, the "mucous environment" was created in M-Shime using mucins, which allowed studying various microbiota types [55,56]. During simulation of the colon microflora treated with 1% of CMC in M-Shime for 13 days, *Bacteroidaceae* decreased, while *Enterobacteriaceae* and *Proteobacteria* increased. It was found that CMC treatment increased the flagellin gene expression. When microbiota treated with 1% of CMC was transplanted to C57BL/6 $Rag^{-/-}$ mice without microflora, alterations in the gut microbiota composition similar to those in the artificial system M-Shime were observed [55,56].

However, it is still necessary to study how CMC is related to alterations in the gut microbiota composition and the development of intestinal inflammation. One of the possible pathogenic mechanisms can be a damage of the intestinal mucosa by CMC, which can lead to mucosal inflammation [53]. Another potential mechanism can consist in CMC-induced increase in flagellin production, which, in turn, enhances the bacterial ability to penetrate into the mucus layer, and thereby, facilitates the overgrowth of gut bacteria and alters functional characteristics of the gut microbiota [50]. However, it is still necessary to investigate to what extent the above described pathogenic mechanisms can be extrapolated from artificial systems to the human body.

Polysorbate 80

In the USSR, polysorbates were synthesized for the first time in the All-Union Scientific Research Institute of Organic Intermediates and Dyes in 1958. Polysorbate 80 (Tween 80, P80, E433) is obtained by co-polymerization of sorbitol and its dehydrated monooleate with ethylene oxide. It is often used in the food industry as an emulsifier, solvent and stabilizer (Figure 7).

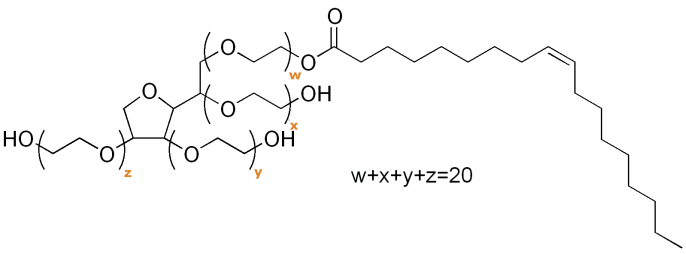

Figure 7. Structural formula of polysorbate 80

It can be seen from the presented formula that the polysorbate molecule actually consists of two parts: hydrophilic (left) and containing a long hydrophobic "tail" (right). Such structure from the hydrophilic and hydrophobic parts is typical for many emulsifiers. For polysorbate 80, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established the acceptable daily intake of 25 mg/kg body weight/day. Similar to carboxymethylcellulose (CMC), polysorbate 80 showed weak assimilation in the gastrointestinal tract and most part of it is excreted in faeces; however, it is known that it can increase serum levels of lipopolysaccharide *in vivo*, facilitate microbial invasion and lead to alterations in the gut microbiota composition [6]. Chassaing et al. [51] studied an effect of 1% polysorbate 80 solution on the gut microbiota, colitis development and metabolic syndrome in C57BL/6 mice and two lines of genetically modified mice (IL10 $^{-/-}$ and TLR5 $^{-/-}$). The 12-week study showed that intake of polysorbate 80 did not have a significant effect on the mouse microbial community; however, it was found that polysorbate 80 reduced the thickness of the intestinal mucosa, facilitated the contact between bacteria and epithelial cells and did cause changes in the gut microflora. Polysorbate 80 also led to an increase in the intestinal permeability and increased levels of lipopolysaccharide and flagellin. In addition, these authors studied effects depended on the amount of polysorbate 80. Mice treated with 0.1% solution of polysorbate 80 had low indicators of inflammation and obesity; while mice treated with 0.5% solution of polysorbate 80 showed mild hypoglycemia [1,51].

Singh et al. [57] studied an effect of polysorbate 80 on the mouse gut microflora and development of the intestinal inflammation and liver dysfunction [57]. Compared to the control group, the number of Gram-positive bacteria significantly increased in mice consumed polysorbate 80, which, according to the authors' opinion, promoted the development of non-alcoholic fatty liver disease due to an influence of the gut microflora on the enterohepatic circulation of bile acids. It was found that the abundance of *Bacteroides* decreased and the abundance of *Salmonella*, *Helicobacter*, *Clostridium* increased. With that, *Campylobacter jejuni*, *Salmonella* spp. and *Helicobacter* spp. are associated with the development of inflammation. Mice treated with polysorbate 80 showed the shortened colon, damage of epithelial cells, reduction in the faecal level of short chain fatty acids, such as butyrate, propionate and acetate, as well as a significant decrease in expression of proteoglycan mucin-2. Mice in a group received polysorbate 80 also demonstrated an increased level of the lipocalin-2 content in colon and faeces, an increase in intestinal permeability and in the flagellin content. These markers are associated with chronic intestinal inflammation. Also, intake of polysorbate 80 increased expression in the liver of alkaline phosphatase by 40%, alanine aminotransferase and aspartate aminotransferase by 50%. Moreover, lipid droplets and steatosis related to the increased activity of liver enzymes were observed in the liver, which indicated liver damage [1,57].

Viennois et al. [54] studied an effect of polysorbate 80 on microbiota and intestinal inflammation in mice. In their study, *Proteobacteria* and *Firmicutes* significantly decreased and *Bacteroidetes* increased in mice received polysorbate 80 [1,54].

Although both polysorbate 80 and CMC increase expression of pro-inflammatory flagellin, an increase induced by polysorbate 80 occurs more slowly than that induced by CMC. Compared to CMC, which promotes the overgrowth of bacteria in mice and, therefore, affects the development of inflammation, polysorbate 80 increases bacterial translocation through mucosa [58].

Therefore, both CMC and polysorbate 80 can affect microbiota in mice, increase its ability to penetrate the mucus layer, influence the signal pathways of cell proliferation and apoptosis, and lead to intestinal inflammation and disorder of metabolic homeostasis [1]. However, it is necessary to further investigate how these results obtained mainly on rodents can be extrapolated to humans.

Sodium sulfite

Sodium sulfite (E221) is a sodium salt of sulfurous acid and is used in foods to inhibit the microbial growth and stabilize color. In 1974, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) established the acceptable daily intake of 0.7 mg/kg body weight for sodium sulfite. Sodium sulfite is readily soluble in water and is a strong reducer; therefore, it is quickly oxidized in the air. Irwin et al. [59] studied an effect of sodium sulfite in different concentrations on four bacterial species residing in the intestine: *Streptococcus salivarius, Lactobacillus casei, Lactobacillus rhamnosus* and *Lactobacillus plantarum*. Although the used media were suitable for the growth of all four species and the exposure time was short, sodium sulfite exerted the bacteriostatic and bactericidal effects against all four tested species at a concentration lower than the acceptable daily intake. Therefore, up to now, there are no data about an effect of sodium sulfite on the microbiome of the human gut, which is an environment more complex than those in *in vitro* experiments.

Nisin

Due to the high antibacterial activity, especially against Gram-positive bacteria, nisin (E234) is the only bacteriocin approved by JECFA as a food preserving agent.

Its acceptable daily intake is 2 mg/kg body weight/day. Lauková et al. [60] used rabbits to study changes in the gut microbiota after continuous nisin intake for 28 days. They observed a significant reduction in pseudomonads, clostridiae, coliforms and coagulase-positive staphylococci. Ronan et al. [61] studied an effect of nisin in two different matrices (starch dough and starch gel) on the mouse intestinal microbiota. They found that the relative abundance of *Bifidobacterium*, and Gram-positive bacteria belonged to the *Clostridium* cluster XIVa was significantly lower in two groups fed with a diet containing nisin than in the control group [61]. However, it is necessary to study further how these alterations in the microbial community can affect human health.

Potassium sorbate, sodium benzoate and sodium nitrite

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established that the acceptable daily intake for sodium benzoate (E211), sodium nitrite (E250) and potassium sorbate (E202) is 5, 0.07 and 25 mg/kg body weight, respectively [1]. Hrncirova et al. [62] determined in the *in vitro* experiments an effect of combinations of sodium benzoate, potassium sorbate and sodium nitrite on bacteria isolated from human faeces. It was found that microflora was very sensitive to the antimicrobial food additives. *Bacteroides coprocola* was most sensitive. This microorganism is associated with Crohn's disease and ulcerative colitis. *Clostridium tyrobutyricum* was also sensitive to sodium nitrite. *Lactobacillus paracasei* and *Bifidobacterium longum* were most sensitive to sodium benzoate. These microorganisms can enhance antitumor immunity *in vivo*. *Enterococcus faecalis* was also sensitive to sodium benzoate, while *Escherichia coli* was most sensitive to potassium sorbate [62]. In another study, Hrncirova et al. [63] used mice colonized with the human gut microbiome to investigate an effect of food preserving agents on the gut microbiota. In their investigation, the second generation of mice, similar to the first one, received sodium benzoate (4.8 mg/kg body weight/day), sodium nitrite (0.36 mg/kg body weight/day) and potassium sorbate (19 mg/kg body weight/day). Wild-type and Nod2-deficient C57BL/6 mice were included in this study. The experiment revealed a reduction of the overall microbial diversity, a decrease in *Clostridiales* and an increase in *Proteobacteria*. The authors noted that Nod2-deficient mice were particularly susceptible to gut microbiota disruption. They also noted that an impact of preserving additives on the human gut microbiota can cause dysbiosis even at low doses [1,62,63].

Titanium dioxide

Food-grade titanium dioxide (E171) is used as a colorant in many food products [43]. With that, 17–36% of titanium dioxide particles in food products have the nano size (<100 nm) [64]. JECFA did not establish an acceptable daily intake level for titanium dioxide in foods due to the absence of toxicity [1]. However, the studies on animals showed that titanium dioxide nanoparticles can affect the gut microbiota composition, which raises concerns about the potential health risks associated with oral exposure to titanium dioxide nanoparticles [1,65].

Essential oils

Essential oils are volatile oil-like compounds with typical strong odor and taste. They are insoluble in water, mainly colorless or slightly colored liquids. The majority of essential oils consist of light fractions; therefore, they are quickly evaporated and do not leave "fatty" stains on paper. Essential oils are complex mixtures of terpenes, terpenoides and other aromatic and aliphatic compounds extracted with organic solvents or by distillation from various spices and herbs [66]. Essential oils are widely used as flavoring agents, but they also have the antibacterial activity (Figure 8). Thapa [67] studied 21 essential oils and found that 19 of them possessed the antimicrobial activity against, at least, one of the following microorganisms: *Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Klebsiella pneumonia, Bacillus subtilis* and *Staphylococcus aureus* [1,67].

It is known that essential oils can be added to feed for shrimps, broiler chickens, ducks and other animals [60,68,69]. Some essential oils are added into food as preserving agents and antioxidants, for example, thyme oil, cinnamon oil and clove oil [1].

Bento et al. [70] noted that the blend of cinnamon and thyme oils had a beneficial effect on the gut microbiome of monogastric animals and inhibited the growth of pathogens and opportunistic pathogens, for example, *Salmonella spp.* and *Escherichia coli* [70].

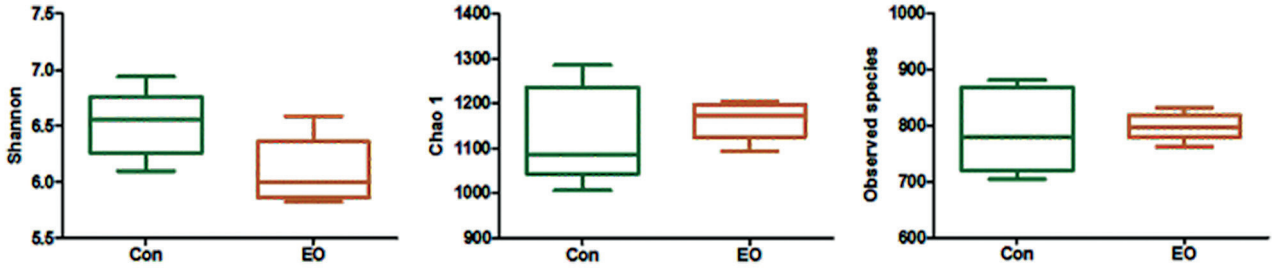

Figure 8. An effect of essential oils on colon microflora diversity in piglets
The values of Shannon and Chao1 indices, as well as the total counts of the studied bacterial species are given.
Con: the control group; EO: the experimental group [71].

Conclusion

In several cases, food additives exert a pronounced physiological effect. Theoretically, their influence on the body can have various features due to multiple classes of substances used as food additives and their subsequent metabolic transformation. With that, in case of a direct effect on the body, an action of food additives is well studied; however, it is studied insufficiently in case of indirect impact with participation of microbiome. Many studies demonstrate an importance of microbiome for the healthy functioning of the consumer's body. For example, it is known that the gut microbial composition affect immunity formation and production of different physiologically active substances.

As microbiome is an assembly of microorganisms, a researcher studying even one substance entering the body can encounter many metabolic pathways, in which various bacteria take part transforming the initial food additive into other substances. It is necessary to note that in several cases, genes responsible for encoding one or another metabolic enzyme can be on extra-chromosomal elements (for example, plasmids), which possibly would make prediction of metabolic pathways more difficult. Therefore, researchers can face a problem of explaining an effect on the human body of many minor metabolites even in investigation of one food additive. In this situation, machine learning can be used to process such volumes of data.

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