TECHNICAL TRANSACTIONS 12/2019
CHEMISTRY

DOI: 10.4467/2353737XCT.19.126.11451
SUBMISSION OF THE FINAL VERSION: 1/12/2019

Wiesław Barabasz (rrbaraba@cyf-kr.edu.pl)
Anna Pikulicka
The East European State Higher School – Przemyśl, Institute of Technical Sciences
Zbigniew Wzorek orcid.org/0000-0001-9077-4699
Anna K. Nowak
Cracow University of Technology, Institute of Inorganic Chemistry and Technology, Department of Inorganic Technology and Environmental Biotechnology

Ecotoxicological aspects of the use of parabens in the production of cosmetics

Ekotoksykologiczne aspekty zastosowania parabenów w produkcji kosmetyków

Abstract
Parabens are synthetic preservatives that are used on a large scale in the cosmetics, pharmaceutical and food industries. Their task is primarily to prolong the shelf life of selected products – cosmetics, medicines or food – by maintaining their microbiological purity. Parabens protect products against deterioration and microorganisms, extending their durability by up to several months without interfering with their composition and operation. Parabens do not change the aroma, taste, density or other characteristics of cosmetic or food products. However parabens, which occur in most cosmetics with a creamy or liquid formula (face creams, body lotions, foundation, tonics, lipsticks, deodorants, perfumes), are becoming increasingly worse because of the prolonged list of side effects that they may cause. The presence of intact paraben esters in human body tissues has now been confirmed by independent measurements in human urine, and the ability of parabens to penetrate human skin intact without breakdown by esterases and to be absorbed systemically has been demonstrated through not only *in vitro* studies but also in vivo investigation using healthy human subjects.

Keywords: parabenes, toxicity, transformation, occurrence in environment

Streszczenie
Parabeny są syntetycznymi konserwantami, które wykorzystuje się na szeroką skalę w przemyśle kosmetycznym, farmaceutycznym i spożywczym. Ich zadaniem jest przede wszystkim przedłużanie trwałości wybranych produktów – kosmetyków, leków czy artykułów spożywczych – poprzez utrzymywanie ich czystości mikrobiologicznej. Parabeny chronią produkty przed zepsuciem i drobnoustrojami, przedłużając ich trwałość nawet o kilkanaście miesięcy i nie ingerując przy tym w ich skład oraz działanie. Parabeny nie zmieniają zapachu, smaku, gęstości oraz innych cech produktów kosmetycznych lub spożywczych. Parabeny, które występują w większości kosmetyków o kremowej lub płynnej formule (kremy do twarzy, balsamy do ciała, podkłady, toniki, pomadki, dezodoranty, perfumy) cieszą się jednak coraz gorszą sławą ze względu na wydłużającą się listę skutków ubocznych, które mogą powodować. Obecność estrów parabenów w tkankach ludzkiego ciała została potwierdzona przez niezależne pomiary w ludzkim moczu, a zdolność parabenów do penetracji nienaruszonej ludzkiej skóry bez rozpadu przez esterazy i do wchłaniania ogólnoustrojowego wykazano w badaniach nie tylko *in vitro,* ale także *in vivo* u zdrowych ludzi.

Słowa kluczowe: parabeny, toksyczność, przemiany, występowanie w środowisku

1. Ancient cosmetics

From the beginning of time, men and women have strived to increase their attractiveness in the eyes of the opposite sex. Primitive peoples were already revealing tendencies to beautify bodies through various types of treatments and decorations. In as early as 10,000 BC Egyptians used fragranced oils and ointments to clean themselves, soften their skin and mask body odours. Essential oils were vital in their belief: that "cleanliness is next to godliness". Hygiene was very important for primitive peoples. Trends have changed considerably. Archaeological excavations performed in Sumerian areas (southern Mesopotamia) resulted in the first body dyes and lipsticks being excavated in caves from the Ice Age – their origin dates back to around 3000 BC [1]. It can be said therefore that cosmetics have existed from time immemorial, and the very origin of the word is closely related to embellishment. The term comes from the Greek word *cosmeo*, meaning to adorn. The adjective *cosmeticos* defines the art of beautifying. One of the first fields of cosmetology that developed in ancient times was the production of perfumes [2]. Their were made from fragrant resin known as myrrh, and from selected species of shrubs and trees mainly from sandalwood. For the same purpose, flower petals, aromatic plant leaves and animal substances such as musk and ambergris were also used. For cosmetics, commonly used plants, known for their medicinal properties, were myrtle, various flowers, herbs and fruits and garlic and onions. They were not only intended to promote health, but also to improve mood and appearance. The first civilisations usually arose in warm climates, in which it was easy to get sunburns. Thus, there was a great need for soothing balms and various moisturising agents that soothed the skin irritated and dried by the sun and desert sand. Cosmetics in Ancient Egypt were based on two basic ingredients [3]. These were pigments of vegetable or mineral origin and oils (from almonds and the fruits of moringa plants) or ointments based on animal fat. To obtain the cosmetic, the minerals were first ground to a powder, and then on pads specially designed for the purpose were mixed together to obtain a paste, which was applied to the face, eyes or mouth. The green pigment was obtained from a mineral called malachite (copper ore) and black – was obtained from galena (lead sulphide), pyrolusite (manganese oxide) or coal [4, 5]. The mixture of powdered galena, soot and copper ore was called kohl. From ocher (a kind of clay) a yellow to brown pigment was obtained [6]. In addition to minerals, the Egyptians also used dried leaves of the shrub known as "defenseless lawsonia" pigment obtained from this plant is also a henna that is popular today. A wide range of plant ingredients was used, oils were made from olives, moringa tree nuts, safflower or castor oil. Interestingly, in today's pharmacies products made from the same ingredients can be bought. Moringa oil is recommended in softening and moisturising the skin and hair. It is also often used in massages. Safflower is used in the production of soaps. Castor oil, on the other hand, has even more applications, among others, we use it in the care of the skin and hair like the ancient Egyptians.

Another example of a cosmetic used both in Ancient Egypt and today is alabaster powder which is made of sodium carbonate and so-called salt of the north mixed with honey [6]. Specific components of alabaster powder are supposed to firm the muscles, and they also find application in masks that purify and reduce imperfections, as well as in treatments for firming around the neckline. The composition of today's creams also contains honey and milk to rejuvenate and nourish the skin. Bathing in goat milk was famoously initiated by Cleopatra VII herself [6]. In fact goat milk contains alpha hydrocarbons which smooth and elasticise the skin. We can encounter these compounds in today's creams. The Egyptians also used marigolds in creams, which they considered a rejuvenating herb. This belief is not without truth, because the extract of this plant has astringent properties – it smooths the surface of the epidermis and additionally has a bactericidal effect.

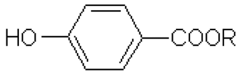
Ancient Egyptian cosmetics in some respects tower over contemporary products. The Egyptians used natural ingredients: – such as minerals, herbs and other plants [7]. For example, the base for the creation of perfumes was not alcohol, but fats: oils and resins. As a result of this, the perfumes of that time were characterised by a strong and long-lasting fragrance. By contrast, today's popular perfumes leave the scent of alcohol at first, after which the proper smell is released, but it is short-lived. The contemporary cosmetics industry, based on recipes of the ancient world, adds many other ingredients. Unfortunately, these additives can cause harmful effects. The health-adverse chemical compounds found in current cosmetics include phthalates, sodium lauryl sulfate and, in particular, parabens (parahydroxybensoates). The latter are by-products of crude oil and can be found in almost all cosmetics. They are designed to extend the shelf life of the product.

2. General characteristics of parabens

Cosmetics typicallyconsist of substances that are an excellent medium for microorganisms (bacteria and fungi), e.g. amino acids, peptides, protein hydrolysates, polysaccharides, plant extracts and vitamins. Cosmetics that have not been protected by a preservative quickly spoil, resulting in a change in the aroma and appearance of the product [8]. To prolong the durability of cosmetics and prevent the development of microorganisms, antimicrobial ingredients are added during production. Preservatives can be divided into those that inhibit the growth and development of microorganisms (fungistatic and bacteriostatic) and compounds that kill living microorganisms, through cell damage (bactericidal and fungicidal preservatives) [9]. Old and commonly used preservatives are derivatives of benzoic acid. Of particular importance in cosmetics are esters of parahydroxybenzoic acid (PHB), or 4-hydroxybenzoic acid, commonly referred to as parabens. Parabens primarily act fungistatically, that is, they stop the growth of fungi (mold), and to a lesser extent they affect bacteria. Apart from the paraben (e.g. methyl paraben), there is also another preservative that inhibits the growth of bacteria, e.g. phenoxyethanol [10]. The group of PHB preservatives also includes compounds with the names parasept, nipagin and aseptin [11]. The concentration of parabens in cosmetics ranges from 0.3 to 0.5% (in the EU to 0.4%). They are poor solubility in water with the lowest being benzyl para-hydroxybenzoate and methyl parahydroxybenzoate the highest of these esters. Parabens, although they are similar in structure to salicylic acid (2-hydroxybenzoic acid) and benzoic acid, have different toxicological and chemical properties.

The presence of parabens in cosmetics is a very controversial topic today. Although they have been thoroughly tested over the recent decades, and their use in production is fully legal, many people have mixed feelings about the impact of these compounds on the body. In 2007, parabens were included in the list of compounds that have a negative impact on the endocrine system. Some specialists also warn that they may cause allergic reactions. However some parabens also occur in nature; an example is methyl paraben which is present in blueberries. Many doctors and pharmacists also claim that the current acceptable dose of parabens in cosmetics is too low to harm anyone [12]. Parabens are a kind of ester and their main purpose is preservation. They fight the yeasts and bacteria that can develop in the cosmetic over time. Consequently – the parabens significantly extend the shelf life date of a given cream or mask. The durability of the cosmetic, and thus the selection of the right preservative is the most important element of cosmetic safety. Without preservatives, all water – based cosmetics would have a very short shelf life and in most cases would have to be stored in the refrigerator. Cosmetics must contain at least a small amount of preservative substance, because water is their main ingredient, and this is an ideal environment for the development of all kinds of microorganisms [13].

Parabens, i.e. esters of p-hydroxybenzoic acid and their analogues, are preservatives that have been used for several decades and are the most commonly used preservatives in cosmetic products. They are widely used not only in the cosmetics industry but also in the pharmaceutical and food industries. Additionally they are used in products intended for children's care and in cosmetics referred to as hypoallergenic. They are active antifungal and antibacterial; however, they are more active against Gram-positive than Gram-negative bacteria [14, 15]. In addition to their antimicrobial properties, they are also used in soaps as anti-perspiration agents and in shampoos as anti-dandruff substances. They are capable of percutaneous penetration. With regard to their penatrative ability, the parabens can be arranged in the following way: butylparaben> propylparaben> ethylparaben> methylparaben. There is a small risk of parabens accumulating in fatty tissues [16]. On the one hand, parabens protect cosmetics against microbial infections, on the other, – they are accused of causing disease. They are one of the most sensitising contact substances, although they are considered to be very weak allergens. Allergic reactions usually have a mild course, – they cause pruritus and erythema, but may also lead to the development of atopic dermatitis. Parabens have been shown to belong to a group of compounds with extremely low oestrogenic activity. Their potency is 1,000–1,000,000 times less than that of natural oestrogen. According to the Scientific Committee on Consumer Safety (SCCS) report [17], parabens used in acceptable concentrations are completely safe and have no toxic, carcinogenic, genotoxic or teratogenic effects. However, increasingly frequently voices are heard that they cause irritations and skin allergies, cancers and can even reduce fertility in men. It should be noted that in the EU Commission Regulation of 18 September 2014 [18], propylparaben and butylparaben and their isomers and salts have been banned in products for children under 3 years of age because of their potential effect on the endocrine system. Furthermore their concentration has been limited to 0.14% of the substance used alone or in a mixture. Similarly, in the EU Commission Regulation of 9 April 2013, due to the lack of studies confirming the safety of the use of isoparabens (isopropylparaben, isobutylparaben, pentylparaben, benzylparaben, phenylparaben), they have been banned in cosmetics. Parabens are solid bodies that resemble fine, odourless crystals. There are different groups of parabens:



R: CH_3 Methyl para-hydroxybenzoate

C_2H_5 Ethyl para-hydroxybenzoate

C_3H_7 Propyl para-hydroxybenzoate

$CH(CH_3)_2$ Isopropyl para-hydroxybenzoate

C_4H_9 Butyl para-hydroxybenzoate

Fig. 1. Different groups of parabens

The following parabens are used in cosmetics: methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, potassium methylparaben, potassium ethylparaben, potassium propylparaben, potassium butylparaben, sodium methylparaben, sodium ethylparaben, sodium propylparaben, sodium isopropylparaben, sodium butylparaben and sodium isobutylparaben [19].

Parabens are compounds that have no taste, smell or color. They do not change the characteristics of cosmetics or food, a result of which colour, aroma and density remain in their original form. The general characteristics of the parabens are shown in Table 1. Parabens differ from each other by the type of alkyl group, and hence their solubility in water and antimicrobial activity [20]. They are chemically stable lipophilic compounds, depending on the chain length their solubility in water is either weak or very weak (Table 2). Due to the fact that these preservatives are active only in the aqueous phase, it is necessary to add solubilising aids, such as propylene glycol, glycerol or ethanol. They exhibit antimicrobial activity over a wide pH range of 4–8. The antimicrobial activity of parabens can be reduced in the presence of some surfactants by the formation of hydrogen bonds or the incorporation of molecules into micelles. Parabens used on an industrial scale are usually synthetic compounds, however many of them, especially methylparaben and propylparaben, occur naturally in many commercial plants [21].

Table 1. Physicochemical Properties of Parabens*

Property	Methyl	Ethyl	Propyl	Butyl
1	2	3	4	5
Molecular weight	152.16	166.18	180.21	194.23
Melting point (T)	131 125–128	116–18 115–118	96.2–98 95–98	8–69 68–72
Boiling point (“C)	270–280	297–298	–	–

Table 1 (cont.)

1	2	3	4	5
Density	–	–	1.0630	–
Refractive index	1.5250	1.5050	1.5050	–
*max”’ in H_20	–	256 (1.5 x 1O^{-2})	256 (1.5 x 10^{-2})	256 (1.55 x 10^{-2})
PKa	8.17	8.22	8.35	8.37
Inorganic impurities**				
As	1 ppm	–	1 ppm	1 ppm
Pb	10 ppm	–	10 ppm	10 ppm
Ash	0.1%	0.1%	0.1%	0.1%
Residue on ignition* (%)	0.05	0.05	0.05	0.05
Loss on drying* (%)	0.5	0.5	0.5	0.5
Acidity* (mEq/750 mg)	0.02	0.02	0.02	0.02
Solubility				
Alcohol	vs	vs	s	s
Water	sl	sl	i	i
Ether	vs	vs	s	s
Acetone	vs	s	s	s
Benzene	sl	–	–	–
Carbon tetrachloride	sl	–	–	–
Glycerin	sl	sl	–	sl

**Maximum recommended; no information available on organic impurities.
vs = very soluble; s = soluble; sl = slightly soluble; i = insoluble.
*[106]

Table 2. Parabenes have limited solubility in H_2O

Property	Methylparaben sol. g/100 mg	Ethylparaben sol. g/100 mg	Propylparaben sol. g/100 mg	Butylparaben sol. g/100 mg
Water 18°C	0.16	0.08	0.023	0.005
Water 25°C	0.25	0.11	0.04	0.015
Water 80°C	3.2	0.86	0.45	0.15
Ethanol	22	25	26	110
Propylene, Glycol	1.7	0.5	0.4	0.3
Peanut Oil	0.5	1	1.4	5
Mineral Oil	0.01	0.025	0.03	0.1

In the cosmetics industry, parabens are used as kinds of preservative in products that are exposed to decay and are easily accessible to bacteria, as well as in products that should last for a long time after opening. These include:

- creams,
- lotions,
- oils,
- tonics,
- glosses,
- lipsticks,
- other wet cosmetics,
- powders and foundations and other cosmetics that are used for a long time,
- antiperspirants and perfumes.

As a result of the addition of parabens, the usefulness of products is extended by up to several months, – the products do not become covered with mould and are protected against other fungi and bacteria that are dangerous to health [22].

3. The mechanism of the action of parabens on microorganisms

The mechanism of the antibacterial action of parabens has not been fully explained. They are suspected to be inhibitors of the synthesis of DNA and RNA nucleic acids or to inhibit the enzymes necessary for the proper functioning of bacterial cells [23]. Parabens can also act by interfering with membrane transport processes. In addition, they can inhibit the influx of amino acids, such as alanine, serine, and phenylalanine, into the vesicles of bacterial cell membranes without altering glucose transport. It is also likely that they have antibacterial effects consisting in the denaturation of bacterial proteins, which increase in the acidic environment. All phenol derivatives work analogously [24, 25]. The mechanism of action of parabens is therefore multidirectional, and the minimum doses that inhibit the growth of selected microorganisms are presented in Tables 3–5.

Table 3. Minimum Inhibitory Concentration of Parabens (%)**

Microorganism		MIC			
		MP*	**EP***	**PP***	**BP***
Molds	*Aspergillus niger* ATCC 10254	0.1	0.04	0.02	0.02
	Penicillium digitatum ATCC 10030	0.05	0.025	0.0063	0.0032
Yeasts	*Candida albicans* ATCC 10331	0.1	0.1	0.0125	0.0125
	Saccharomyces cerevisiae ATCC 9763	0.1	0.05	0.0125	0.0063
Bacteria	*Bacillus subtilis* ATCC 6633	0.2	0.1	0.025	0.0125
	Bacillus cereus var. mycoides ATCC 6462	0.2	0.1	0.0125	0.0063

*MP: Methylparaben, *EP: Ethylparaben, *PP: Propylparaben, *BP: Butylparaben, ** [105]

Table 4. Antimicrobial Effectiveness of Parabens [106]

Microorganisms species	Effective Concentration (% by Weight)			
	Methylparaben	**Ethylparaben**	**Propylparaben**	**Butylparaben**
Fungi				
Rhizopus nigricans	0.05	0.025–0.05	0.0125	0.0063
Trichoderma lignorum	0.025	0.0125	0.0125	0.0063
Chaetonium globosum	0.05	0.025	0.0063	0.0031
Candida albicans	0.1	0.1	0.0125–0.1	0.0125–0.1
Saccharomyces cerevisiae	0.1–0.23	0.05–0.1	0.01–0.0125	0.0063
S. pastorianus	0.1	0.05	0.0125	0.0063
Aspergillus flavus	0.04–0.125	0.03	0.06	0.02
A. niger	0.08–0.27	0.04–0.06	0.02–0.07	0.02
Penicillium digitatum	0.05	0.025	0.0063	0.0031
P. chrysoqenum	0.01	–	–	–
P. glaucum	0.04–0.1	0.03–0.15	0.15	0.02–0.15
P. expansum	–	–	–	0.02
Mucor mucedo	0.04–0.15	0.03–0.04	0.05–0.1	0.02
Torula *sp.*	0.125–0.15	0.025–0.1	0.05–0.1	–
Epidermophyton floccosum	0.025–0.1	–	0.01	0.01
Microsporum audovini	0.01–0.1	–	0.01	0.01
Trichophyton ferrugineum	0.025–0.1	–	0.01	0.01
T. mentagrophytes	>0.006	0.008	0.004	0.002
Hormodendrum compactum	0.025–0.1	–	0.01	0.01
Phialophora verrucosa	0.025	–	0.1	0.1
Geotrichum *sp.*	0.055	–	–	–
Monosporum apiospermum	0.1	–	0.1	0.01
Sporotrichum schenckii	0.05	–	0.01	0.01
Blastomyces dermatitidis	0.01–0.1	–	0.01–0.1	0.01
Cryptococcus neoformans	0.05–0.1	–	0.01	0.01
Haplosporangium parvum	0.025	–	–	–
Histoplasma capsufatum	0.1–0.025	–	0.01	0.01
Trichosporon beigelii	0.1	–	0.01	0.01
Piedraia hortai	0.1	–	0.01	0.01
Other fungi	–	0.1–0.025	–	–

Table 5. Antimicrobial Effectiveness of Parabens [106]

Microorganisms species	Effective Concentration (% by Weight)			
	Methylparaben	Ethylparaben	Propylparaben	Butylparaben
Bacteria				
Bacillus subtifis	0.12–0.25	0.1–0.2	0.025–0.2	0.0125
B. cereus	0.2	0.1	0.125	0.0063
B. coli	0.125–0.15	–	0.05–0.1	0.02
B. coagulans	0.15–0.35	–	0.05–0.07	–
B. megaterium	0.14	0.06	0.03	0.01
Staphylococcus aureus	0.16–0.4	0.065–0.15	0.04–0.15	0.0125–0.02
S. pyogenes	0.063	0.063	0.05	–
Sarcina lutea	0.25–0.4	0.25–0.1	0.25–0.05	0.0125
Klebsiella pneumoniae	0.1	0.05	0.025	0.0125
Escherichia coli	0.125–0.4	0.1–0.125	0.05–0.1	0.4
Salmonella typhosa	0.2	0.1	0.1	0.1
S. schottmulleri	0.2	0.1	0.05	0.1
S. typhimurium	–	–	0.02–0.025	–
Proteus vulgaris	0.2	0.1–0.15	0.05–0.15	0.05
Aerobacter aerogenes	0.125–0.24	0.1	0.05–0.1	0.4
Pseudomonas aeruginosa	0.1–0.4	0.2–0.4	0.2–0.8	0.8
P. fluorescens	0.15–0.4	0.2	0.05–0.2	0.4
Streptococcus hemolyticus	0.01	–	0.1	0.1
S. faecalis	–	0.13	0.04	0.012
Serratia marcescens	0.08	0.049	0.04	0.019
Achromobacter sp.	0.23–0.24	–	0.05–0.07	–
Arthrobacter simplex	0.36–0.38	–	0.07–0.09	–
Clostridium botulinurn	0.1–0.12	0.04	0.04	0.02
Corynebacterium acnes	–	–	1.0	–
Nocardia asteroides	0.025–0.1	–	0.1	0.01

4. Controversy about the use of parabens

If we consider that parabens are very well tested and penetrate the skin to a small extent, there is a growing number of people – experts from the medical community, members of ecological and pro-consumer organizations – who question the safety of these substances [26–28]. It is postulated that the most common parabens present in cosmetics are associated with the following issues:

- They cause skin irritations and allergies – parabens damage the bacterial flora, theymay affect the water management of the epidermis and contribute to the weakening of the lipid layer. Skin devoid of its natural protection, which protects it from the weather, is susceptible to severe allergic reactions. This is why it is sometimes said to be allergic to parabens. In addition, parabens can also cause redness, pruritus and urticaria. The more cosmetics with parabens you use, the greater the likelihood of skin problems. In particular, individuals who have delicate and sensitive skin prone to irritation should pay attention to this issue [29, 30].
- Producers of cosmetics, aware of the influence of parabens on skin condition, are using increasingly small amounts of these preservatives.
- They affect the functioning of the hormones – one theory states that parabens influence sex hormones and consequently reduce fertility in men.
- They can have carcinogenic effects. The paraben that has the strongest effect is butylparaben, it is blamed for triggering breast cancer.
- They should not be used by pregnant women – they may have a negative effect on foetal development [31, 32].

The use of parabens is constantly criticised by consumer protection organisations, the media and manufacturers of natural cosmetics. However, evidence has been put forward that all these fears are unfounded. The European Commission and its scientific advisory committees [33]. as well as the independent American evaluation committee, Cosmetic Ingredient Review (CIR) [34], have repeatedly confirmed that parabens do not pose a threat to health. According to these studies, all parabens absorbed by our bodies undergo rapid decomposition. Parabens are generally well tolerated. Like all substances, they can cause sensitisation in individual cases, but this happens less often than with other preservatives. According to the European Commission and the Polish Union of the Cosmetics Industry [35]: parabens used in cosmetics are safe. Similarly, the US Food and Drug Safety Agency (FDA) [36], has included methylparaben and propylparaben on the GRAS list (Generally Recognized as Safe) – i.e. as substances found safe for use in food [33].

When it comes to carcinogenic activity of PHB esters, the matter is controversial. It is known that parabens are lipophilic components (they have an affinity for fat), so they freely penetrate subcutaneous fat, including breasts, and can accumulate there [37]. There are test results confirming the accumulation of parabens in the mammary gland. To clarity, this is not a discovery, because it is hardly surprising. It is obvious that when we rub the lipophilic compounds into the skin every day, they will eventually penetrate the skin into the subcutaneous layer.

One of the most vocal acaedemics on the issue of the carcinogenic activity of PHB ester is Philippa Darbre [38], a senior lecturer in oncology and a researcher in biomolecular sciences at the University of Reading, in England. She specialises in the impact of oestrogen on breast cancer. In 2004, Darbre's team published a pivotal study that detected parabens in 18 out of 20 breast cancer biopsies. Her study did not prove parabens cause cancer, only that they were easily detected among cancerous cells. The study was criticised on the basis of paraben levels in normal tissue [39, 40].

The effect of parabens on oestrogen receptors exists. It is notpossible to discuss whether it is strong or weak, but it does occur and it is another factor used by a man who works oestrogens. In 2011, the Scientific Committee on Consumer Safety (SCCS) – an advisory body of the European Commission [33] to the safety of cosmetic ingredients – stated that methyl paraben and ethyl paraben are safe at the current maximum concentration of 0.4%, while for butyl paraben and propylparaben the maximum safe concentration should be reduced to 0.19%. With regard to the safety of the other parabens, the committee did not respond without having enough toxicological data. In May 2013, the SCCS re-examined the safety of butylparaben and propylparaben in cosmetics, in which it maintained its current position. The threat posed by parabens results from their enormous popularity. They are used in a wide range of cosmetics and personal hygiene products, which translates into a greater overall exposure to their potentially negative effects. According to FDA (Food and Drug Administration) data [36], the average daily exposure to parabens for a man weighing 60 kg is 76 mg, of which 50 mg comes from cosmetics. American data also indicates that women are more exposed to parabens than men.

Due to the prevelance of parabens and the fact that many sources constitute the average total exposure, the use of one cosmetic is not a serious threat from parabens. However, given that the amount of cosmetics used is often much higher, the potential side effect of parabens should be considered. The SCCS also draws attention to the use of parabens in cosmetics for infant skin care [33]. In the opinion of the SCCS in 2011, the use of parabens in cosmetics for children under 6 months of age is safe, with the exception of "under-nappy" cosmetics [41, 42]. This is associated with a greater risk of penetration of cosmetics ingredients, including parabens, through irritated or damaged skin in this area, as well as immature metabolism of newborns. An important aspect in favour of parabens is their poor penetration of the epidermal barrier – around 4–6%. At the same time, the parabens do not accumulate in the tissues. After crossing the epidermal barrier and entering the vascular bed, they are metabolised to p-hydroxybenzoic acid, which does not show oestrogenic effects.

Of course, scientific data that confirms parabens oestrogenic action cannot be ignored, on the other hand, it seems that parabens have also become the subject of negative PR. Evidence of the oestrogen action of parabens – for example, reduced male fertility. In addition, it should be noted that it is difficult to determine a specific alternative to parabens. Other preservatives, e.g. sorbic acid, essential oils, aldehyde have a number of limitations, such as, weak fungistatic activity, unacceptable odour, too high pH. In summary, parabens – according to the current state of knowledge – are effective and relatively safe preservatives and if used in accordance with the SCCS guidelines [35], do not pose a risk to their users. At the same time, the debate on them is not closed and perhaps further scientific data would lead to a possible review of opinions regarding the safety of parabens.

5. The fate of parabens in the environment

In the last few years, cosmetics, as well as pharmaceuticals and many other products for personal care that do not fall within cosmetic regulation (disinfectants, insect repellents, dietary supplements), have raised significant concerns as one of the most important classes of emerging pollutants. This is as a result of them being continually released into the aquatic environment; their ecological and environmental impact is associated with large amounts being used and with the fact that sometimes they are environmentally persistent, bioactive, and potentially able to bioaccumulate [43–45].

Parabens have been fund in urban streams [46, 47] into which treated or untreated effluent from wasewater treatment plants flows. Consequently, these chemical compounds have been identified in rivers and drinking water sources. Parabens have been detected in soil from agricultural fields, possibly from irrigation or fertilisation practices [48]. Hause dust has also been found to contain parabens. Although commercially used parabens are of synthetic origin, some – parabens are produced by living organisms, especialty by plants and microbes, e.g., a marine bacterial strain belonging to the genus *Microbulibifer.* Plants such as blueberries, carrots, olives, strawberries and others produce parabens (mainly methylparaben) for its presumed antimicrobial activity. Overall, the concentration of parabenes within the environment are low with water concentrations of around 7 ng/L and effluent concentrations of up to 6 μg/L, soils concentration range from 0.5 to 8 ng/g while house dust contains up to 2,400 ng/g [49, 50].

Sewage treatment plants are not always effective in removing chemicals used as cosmetic ingredients, as shown, for example, with synthetic musks , perfluoroalkyls compounds, some organic UV-filters and microplastics. Another issue of concern is that some of these products can accumulate in sewage sludge [51]. Turning wastewater treatment and exist then in the environment because of the common practice of using sludge as a fertilizer on crops [52]. Cosmetics pose the most pressing ecological problems compared to pharmaceuticals because they are used in much larger quantities and throughout the course of life and being intended for external application, are not subjected to metabolic transformation; therefore they are introduced unaltered into the environment in large amounts during washing, showering and bathing [53]. Since relatively little is known about the fate and the toxicity of personal care products released into the environment, increasing attention is being placed on their occurrence, persistence, and potential threat to ecosystems and human health.

In 1996 the first analytical results of the occurrence of parabens in water were published. With parabens being considered as emerging contaminants, it is useful to review the knowledge acquired over the last decade regarding their occurrence, fate and behaviour in aquatic environments. Despite treatments that eliminate parabens relatively efficiently from wastewater, they are always present at low concentration levels in effluents of wastewater treatment plants. Although they are biodegradable, they are ubiquitous in surface water and sediments, due to the consumption of paraben-based products and their continuous introduction into the environment. Methylparaben and propylparaben predominate, reflecting the composition of paraben mixtures in common consumer products. As compounds containing phenolic hydroxyl groups, parabens can react readily with free chlorine, yielding halogenated by-products. Chlorinated parabens have been detected in wastewater, swimming pools and rivers, but not yet in drinking water [54]. These chlorinated by-products are more stable and persistent than the parent compounds and further studies are needed to improve knowledge regarding their toxicity.

Based on available use data, parabens are expected to be found in a range of household and commercial products available for use in Australia. Chemicals used in cosmetics and cleaning products are typically released in to sewers as a normal part of their use in domestic and industrial applications. Studies on the fate of parabens have indicated that their removal from influent is above 90% [20], with degradation and adsorption to sludge being major mechanisms of removal. Parabens may be released to the environment in treated effluent, while those removed by adsorption to sludge may be applied to land as biosolids. Thus, emissions of parabens to both environmental surface waters and soils are considered as part of this assessment.

6. Transformation of parabens

A biodegradation study conducted with river water as the inoculant found that benzylparaben had a half-life of 10–19 hours depending on temperature and origin of the river water inoculant [55]. In addition, biodegradation calculations for benzylparaben gave an ultimate biodegradation half-life of 14.1 days.

No biodegradation data was identified for the parabens with alkyl chain lengths of 7–12 carbons (long-chain parabens; heptyl-, octyl-, isooctyl- and lauryl-paraben). Calculated biodegradation rates for the long-chain parabens gave ultimate biodegradation half-lives of 9.5–10.4 days for the linear parabens and 20.1 days for the branched isooctylparaben.

Abiotic processes may also represent significant degradation pathways for the chemicals in this group. Yamamoto [56, 57] reported a photolysis half-life of less than one day for benzylparaben in water under natural light, with photolysis half-lives for butylparaben and isobutylparaben ranging from 14.6 to 24.2 days.

Parabens are stable in acidic conditions, but can undergo hydrolysis above pH 7. The methylparaben hydrolysis half-life at pH 8 is calculated to be 1260 days, and increases with longer ester alkyl chains. Therefore, abiotic hydrolysis is not expected to be a significant degradation pathway for parabens. Biotic or abiotic hydrolysis of the ester bond produces *p*HBA as a degradation product common to all parabens [58]. *p*HBA is a chemical that has been assessed at Tier I level under the IMAP framework and found to be of low concern to the environment [59, 60, 61].

A general scheme for the transformation of parabens in an ecological system is shown in Fig. 2.

Parabens readily undergo halogenation on the aromatic ring carbons *ortho* to the hydroxyl group to form several mono- and di-halogenated compounds [62]. These chemical derivatives can be formed in chlorinated waters such as drinking water, and during chlorine treatment in

STPs. They show slower biodegradation than the parent compounds; in a biodegradation study according to ISO 7827 using activated sludge as the inoculant, dichloromethylparaben (3,5-dichloro-4-hydroxybenzoic acid methyl ester, CAS RN 3337-59-5) had a half-life of 8.7 days, compared to 1.8 days for the parent chemical methylparaben [63, 64, 65]. In this study, 99% primary degradation of dichloromethylparaben was achieved after 16 days.

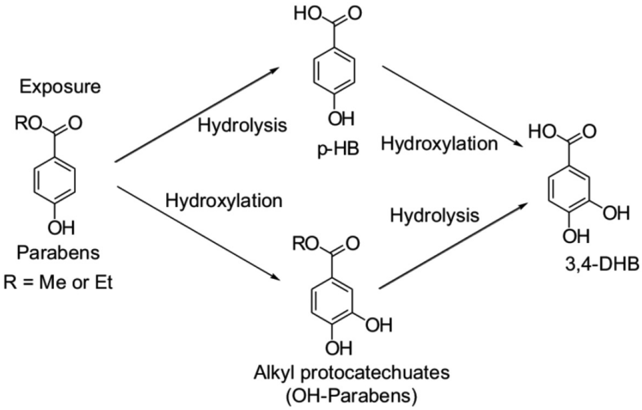


Fig. 2. Metabolic transformation of parabens in biological systems. DHB, 3,4-dihydroxybenzoic acid (source: [107])

7. Bioaccumulation

The short-chain parabens in this group and benzylparaben are not expected to bioaccumulate, while the long-chain parabens in this group have the potential to bioaccumulate [66].

Low octanol-water partition coefficient (K_{OW}) values for the short-chain parabens and benzylparaben do not exceed the domestic categorisation threshold for bioaccumulation hazards in aquatic organisms (log $K_{OW} \leq 4.2$). This indicates that there is a limited bioaccumulation potential for these chemicals .

There is evidence for the rapid metabolism of short-chain parabens in fish; a 10-day feeding study showed that less than 1% of the total ingested propylparaben was found in rainbow trout liver and muscle tissue after doses of 1830 mg kg^{-1} every second day [67]. Half-lives of 8.6 hours in liver and 1.5 hours in muscle tissue were derived. A similar study showed that less than 1% of the total butylparaben ingested at 51 mg kg^{-1} every second day over 12 days remained in rainbow trout liver tissue at the end of the experiment [68].

The long-chain parabens have measured or calculated K_{OW} values which exceed the domestic categorisation threshold for bioaccumulation hazards in aquatic organisms (log $K_{OW} > 4.2$). High octanol-water partition coefficients can indicate a high bioaccumulation potential, as the chemical may preferentially partition to lipid-rich tissues. This potential may be reduced by possible metabolism in biota, as seen for propyl- and butyl-paraben. Bioconcentration modelling for these compounds incorporating estimated rates of biotransformation in fish gave BCF values of 76 – 1,598 L/kg for heptyl-, octyl- and isooctyl-paraben, and 2,148 L/kg for laurylparaben .

A series of studies of parabens and their metabolites in biota found methylparaben and *p*HBA at high concentrations in many marine organisms [69, 70, 71]. A trophic magnification factor of 1.83 was calculated for methylparaben in one food web. It was noted that methylparaben could be formed from *p*HBA through biotransformation by gut microflora. The trophic magnification of methylparaben would, therefore, be partially reliant on the availability of a high concentration of *p*HBA, which can arise from ester hydrolysis of any paraben, or from natural sources. The highest methylparaben concentration was found in the liver of a bottlenose dolphin, at 865 ng/g wet weight.

8. Predicted environmental concentration (PEC)

In the absence of comprehensive reported Australian environmental monitoring data, standard exposure modelling for the release of chemicals to surface waters in STP effluents was used to calculate riverine environmental concentrations, assuming annual introduction volumes of 100 tones [59]. The calculated riverine PECs from this analysis are 7.88 micrograms per litre (μg/L) for methyl- and ethylparaben, 7.27 μg/L for propylparaben, 6.66 μg/L for butyl- and benzylparaben, and 4.85 μg/L for heptyl-, octyl- and isooctylparaben.

These calculated values are reasonably consistent with available domestic monitoring data for short-chain parabens. A study focusing on the concentrations of the short-chain parabens in urban water and storm water drainage systems in the Sydney metropolitan area took seventy-two water samples from a variety of sources across different land use areas [72]. Methylparaben was detected at an average concentration of 5.41 μg/L and a highest observed concentration of 13.78 μg/L. Ethylparaben was detected at an average and highest concentration of 13.86 and 305.55 μg/L respectively – propylparaben at an average and highest concentration of 2.97 and 8.29 μg/L respectively – butylparaben at an average and highest concentration of 4.36 and 8.47 μg/L respectively. The study also sampled STP effluent, finding the highest concentrations of methyl-, ethyl-, propyl- and butyl-paraben to be 12.28, 4.95, 3.15 and 4.82 μg/L, respectively.

The highest observed concentration of each paraben were from diverse water sources, covering both river water and storm water samples from both industrial and residential land use areas. The sample containing ethylparaben at 305.55 μg/L was taken from the Duck River, downstream from an industrial area which includes a waste transfer station [73].

Based on this domestic monitoring data, and for the purposes of this assessment, the PECs for methyl-, ethyl-, propyl- and butyl-paraben are determined to be 13.78, 305.55, 8.29 and 8.47 μg/L, respectively.

It is noted that these measured concentrations for parabens are somewhat higher than results from international monitoring studies [72]. Methyl- and propylparaben are the most commonly detected parabens, and occurat higher concentrations than other parabens due to their combined use in cosmetics [74]. In effluent from a Spanish STP, methyl- and propylparaben were found at maximum concentrations of 50 and 21 ng/L respectively, with lower maximum concentrations of ethyl- and butylparaben [64]. Two studies on parabens in Japanese rivers found methyl- and propylparaben at maximum concentrations of 525 and 181 ng/L respectively [14], and at 676 and 207 ng/L respectively [75]. These maximum concentrations are all significantly lower than the mean values of parabens measured in Sydney surface waters and Sydney STP effluent [72].

Long-chain parabens are very rarely detected in international monitoring studies, and at much lower concentrations than short-chain parabens. Heptyl- and octylparaben were detected in urban surface water samples in Beijing at maximum concentrations of 2.94 and 4.89 ng/L respectively [76]. In the same study, methylparaben was detected at a maximum concentration of 920 ng/L. Heptyl- and benzylparaben were found in influent waters of a STP in the Albany area in New York at maximum concentrations of 0.31 and 0.27 ng/L respectively [77], indicating low emissions to waste waters. Benzylparaben was found at a maximum concentration of 3.93 ng/L in urban surface waters in Beijing, and two further studies concluded that benzylparaben was present below the limit of detection in STP effluent samples [64, 78, 79].

It would not be appropriate to predict the Australian environmental concentrations of heptyl-, octyl- or benzylparaben based on this international monitoring data, given the disparity between the measured domestic and international concentrations of the short--chain parabens. Therefore, the PECs for heptyl-, octyl- and isooctylparaben are taken to be 4.85 μg/L, and 6.66 μg/L for benzylparaben, based on calculations using the default introduction volume and the SimpleTreat model.

Chlorinated transformation products of parabens have been detected in wastewater treatment plant waters. At an STP in Beijing, 3,5-dichloromethylparaben and 3,5-dichloroethylparaben (3,5-dichloro-4-hydroxy benzoic acid ethyl ester, CAS RN 17302-82-8) were detected in effluent water after secondary treatment at mean concentrations of 13.6 and 19.8 ng/L respectively. These concentrations were higher than the effluent concentrations of their respective non-chlorinated parent parabens [77, 78]. In a second study, the average total chlorinated paraben concentration in river water was found to be 50.1 ng/L, while the average total paraben concentration was 44.3 ng/L [79, 80]. One study investigated chlorinated parabens in river water in Shizuoka City, Japan, as combined concentrations from suspended solid and dissolved phases [81]. Dichloromethylparaben was found in one sample at 6.1 ng/L, while dichloropropylparaben (3,5-dichloro-4-hydroxy benzoic acid propyl ester, CAS RN 101003-80-9) was found at up to 28 ng/L.

9. Effects on Aquatic Life

The chemicals in this group range from slightly to highly toxic in aquatic organisms [82, 83]. The measured median lethal concentration (LC50) and median effective concentration (EC50), as well as the no observed effect concentration (NOEC) and the lowest observed effect concentration (LOEC) values for model organisms across three trophic levels for methylparaben (MeP), ethylparaben (EtP), propylparaben (PrP), butylparaben (BuP), benzylparaben (BzP), heptylparaben (HeP), and octylparaben (OcP) have been reported [75, 84, 85].

Calculated data for long-chain parabens indicates higher levels of toxicity than for short-chain parabens. This trend is consistent with previous studies, which demonstrated that the toxicity of parabens is proportional to their lipophilicity [75]. This indicates that the acute toxicity of parabens is likely to occur through the non-specific disruption of the cell membrane function [86]. Calculated and measured toxicity values for the short-chain parabens were fairly consistent – therefore the calculated ecotoxicity endpoints for the long-chain parabens appears to be reliable. Reliable values for acute ecotoxicity endpoints for laurylparaben cannot be calculated.

Data for the branched isomers in this group have not been presented. However, acute ecotoxicity endpoint values for isopropylparaben and isobutylparaben have been published [55, 56, 75, 84]. The calculated acute ecotoxicity values of octyl- and isooctylparaben are very similar. These values indicate that the acute toxicity of the branched isomers is expected to be similar to or less than that of straight chain isomers:

A study investigated the comparative acute invertebrate toxicities of parabens and their chlorinated transformation products according to OECD TG 202 [87]. The dichlorinated transformation products of methyl-, ethyl- and propylparaben all showed increased acute toxicity compared to their parent parabens.

Chlorination increases the acute toxicity of the parabens with comparative EC50 values of 62 mg/L for methylparaben and 16 mg/L for dichloromethylparaben, 32 mg/L for ethylparaben and 13 mg/L for dichloroethylparaben, and 23 mg/L for propylparaben and 8.3 mg/L for dichloropropylparaben. This trend is consistent with the trend of increasing toxicity with increased lipophilicity of these chemicals, as the chlorinated parabens are more lipophilic than their parent paraben. These increases in acute toxicity may be a cause for concern when considered in the context of the increased persistence of the chlorinated parabens.

A study investigated the comparative chronic toxicity of parabens and their chlorinated transformation products in the invertebrate *C. dubia* [86, 87]. In contrast with the comparative study of acute toxicity, the chronic toxicity of chlorinated parabens was lower than that of their parent compounds.

10. Endocrine Activity

Parabens are considered to have oestrogenic activity, though at much lower potency than naturally produced oestrogens [59]. The estrogenic effect of parabens in fish has been investigated in a number of studies. Oestrogenic activity in fish can be measured by blood vitellogenin levels, a known biomarker for exposure to environmental estrogens [88]. Propyl-, butyl- and benzylparaben have all been shown to increase the average blood vitellogenin concentration in studies conducted with rainbow trout and medaka, but at concentrations well above what is expected to be found in the environment [55, 67–88].

The oestrogenic effect of chlorinated paraben transformation products was investigated in a yeast assay incorporating the medaka oestrogen receptor gene [86]. Chlorinated parabens were found to generally have lower ability to activate the receptor than their parent parabens.

Pharmaceuticals, the ingredients of personal care products and cosmetics and detergents are products commonly used in everyday life, and routinely find their way into sewage system [89]. Because they are usually difficult to biodegrade, there is a serious risk of accumulation and the occurrence of irreversible changes in nature. These products are harmful because they have a long disintegration time and they show the ability to bioaccumulate in living organisms, as a result of which they easily enter the trophic chain. The environmental effects and health effects of these preparations have been extensively researched [90], and the most important include: abnormal hormone levels, masculinisation of feminisations of males, and consequently reduced fertility [91, 92, 93, 94, 95] Studies comparing the similarity of the structure of compounds with the alkylhydroxybenzo group to alkylphenols of known oestrogenic compounds have confirmed that the parabens are oestrogens [96, 97, 98, 99]. The more spatial alkyl group enhances the lipophilic hydrophobic character, and also affects a more efficient association with oestrogen receptors. The longer the chain, the higher the estrogenic activity. Parabens are placed on the European list of priority compounds in category 1. As substances with proven effects on the endocrine system. Oestrogen tests have shown that parabens have lower estrogenic potency than 17β-estradiol. Studies have shown that benzylparaben has the highest oestrogenic potency of all parabens. It has been demonstrated that benzylparaben (YES test, EC50 = 0.351 mg•dm-3) has similar estrogenicity to Bisphenol A (YES test, EC50 = 0.342 mg•dm-3) [100, 101]. As a result of estrogenic activity, benzylparaben is suspected of participating in the development of breast cancer. Toxicity and oestrogenicity studies have shown that benzylparaben is the most harmful of all parabens [100]. Benzyl-barane also has a high acute toxicity against *Vibrio fischeri,* green algae – *Pseudokirchneriella subcapitata,* as well as *Daphnia magna* and against the Japanese median *Oryzias latipes* (Table 4) [84].

Table 6. Toxicity of benzylparaben [100; 75]

	Daphnia magna	***Vibrio fischeri***	***Pseudokirchneriella subcapitata***	***Oryzias latipes***	**YES test**
EC50 mg/dm-3	30 (48 h)	0,11 (15 min.)	1,2 (72 h	0,73 (LC50, 96 h)	0,351

In sewage flowing out of the treatment plant, benzylparaben was detected at a concentration of 0.01–0.26 μg•dm-3 in Spain and Canada, while in Sweden it wasat a concentration of 1 μg•dm-3 [55]. However, many times the concentration of this xenoestrogen was below the detection threshold [56]. Studies confirm that even in such low concentrations xenoestrogens may interfere with the work of internal endocrine organs [55, 56]. The extensive and ever--growing body of scientific evidence confirms the harmfulness of chemical compounds, such as benzylparaben for species living in the natural environment. There is a justified fear that these chemicals contribute to an increase in the number of ailments associated with the immune, nervous and, above all, reproductive systems [102, 103, 104].

11. Conclusion

The number of emerging contaminants released in the environment as a consequence of human activity is increasing day by day and reflects the growing consumption of a wide range of products, including cosmetics and personal care products. Chemical compounds that comprise cosmetics formulations number in the several thousands, and the annual production and consumption of personal care products exceeds thousands of tons. The hazard of the continuous release of these huge amounts of chemicals into waters should not be underestimated. The environmental fate of these products is largely unknown, and, if in some cases they are removed in wastewater treatment plants, in other cases, they can escape conventional treatment processes, persist in the environment at unexpected levels, undergo bioaccumulation, and even react with other pollutants to form new unpredictable contaminants. Banning the products responsible for these problems is an impracticable option, except in particular circumstances (for instance, the use of sunscreen is banned in some marine ecoparks in Mexico). Addressing this issue realistically requires different approaches and strategies. To some extent, our increased awareness of the pollution potential of these products is the result of advanced technologies of analytical chemistry. Therefore, the development of improved extraction and analytical methods would allow a more comprehensive and accurate evaluation of environmental pollutants in complex matrices. Further studies on the acute and chronic toxicity of these contaminants should be conducted to allow a more precise assessment of their actual ecological and health risk. Finally, information displayed on packaging concerning the environmental impact of cosmetics could encourage consumers to employ a more responsible and informed use of these products.

It should be noted that EU cosmetics legislation (Regulation 1223/2009/EC) is the most advanced system of legal requirements for cosmetic products in the world. Each cosmetic product and all ingredients contained in the product are subjected to a detailed toxicological and dermatological assessment before being placing on the market. The assessment takes into account who might use the product (e.g. a child, a pregnant woman, a person with sensitive skin), how often they might use it (several times a day, once a week) and how the product will be used. Substances for which the safety is questionable are subject to additional toxicological evaluation by the Scientific Committee on Safety of Cosmetics – an independent advisory team of the European Commission consisting of toxicologists, allergists, epidemiologists and experts in the field of risk assessment. Based on the recommendations of the committee, in justified cases, the European Commission may decide to ban or restrict the use of a given substance in cosmetic products. Cosmetic products legally placed on the European Union market, including Poland, do not contain toxic substances for which their presence in cosmetics could endanger the health or safety of users.

Generally parabens are the most commonly used preservatives. They are relatively active against a broad spectrum of microorganisms. The methyl ester is most effective against bacteria and moulds while the ethyl, propyl and butyl esters are more active against yeast and moulds. Parabens are more effective against gram negative than gram positive organisms.

Parabens are commonly used as antimicrobial preservatives in household products, cosmetics, pharmaceuticals, and food and beverage processing, and are environmental compounds with oestrogenic activity.

References

[1] Bardiès-Fronty I., Bimbenet-Privat M., Walter P., *Le bain et le miroir. Soins du corps et cosmétiques de l'Antiquité á la Renaissance*, Gallimard, Paris 2009.

[2] Leblanc C., Shimy M.A.H., Goyon J.-C., *Parfums, onguents et cosmétiques dans l'Égypte ancienne: actes des rencontres pluri disciplinaires tenues au Conseil National de la Culture*, Le Caire, 27–29 avril 2002, Centre français de culture et de coopération du Caire, Cairo 2003.

[3] Walter P. et all, *Making make-up in Ancient Egypt*, Nature 397/1999, 483.

[4] Diamandopoulos A., Kolonas L., Grapsa-Kotrosou M., *Use of lead cosmetics in Bronze-Age Greece*, Lancet 344/1994, 754.

[5] Stos-Gale Z.A., Gale N.H., *Sources of galena, lead and silver in Predynastic Egypt*, Rev. d'Archéométrie 5/1981, 285.

[6] Lucas A., *Cosmetics, perfumes and incense in ancient Egypt*, J. Egypt Archaeol. 16/1930, 41.

[7] Welcomme E., Walter P., van Elslande E., Tsoucaris G., *Investigation of white pigments used as make-up during the Greco-Romans period*, Appl. Phys. A83/2006, 551.

[8] Pawlik K., Duda-Grychtoł K., *Niebezpieczne kosmetyki – prawda czy fałszywy pogląd*, Pol. J. Cosmet. 16(3)/2013, 200.

[9] Cashman A.L., Warshaw E. M., *Parabens: a review of epidemiology, structure, allergenicity, and hormonal properties*, Dermatitis. 16/2005, 57.

[10] Song C., Lin J., Huang X., Wu Y., Liu J., Wu C., *Effect of butyl paraben on the development and microbial composition of periphyton*, Ecotoxicology 25 (2)/2016, 342.

[11] Soni M.G., Taylor S.L., Greenberg N.A., Burdock G.A., *Evaluation of the health aspects of methyl paraben: a review of the published literature*, Food and Chemical Toxicology 40/2002, 1335.

[12] Bojarowicz H., Wnuk M., Buciński A., *Efektywność i bezpieczeństwo stosowania parabenów*, Problemy Higieny i Epidemiologii 93/2012, 647.

[13] Świerkot J., Duda-Grychtoł K., Klasik-Ciszewska S., *Parabeny jako przykład niebezpiecznych konserwantów*, Med. Rodz. 20 (3)/2017, 222.

[14] Kimura K., Kameda Y., Yamamoto H., Nakada N., Tamura I., Miyazaki M., Masunaga S., *Occurrence of preservatives and antimicrobials in Japanese rivers*, Chemosphere 107/2014, 393.

[15] Siegert W., *Microbiological quality management for the production of cosmetics and toiletries*, Cosmetic Science Technology 189/2005.

[16] Cross S.E., Roberts M.S., *The effect of occlusion on epidermal penetration of parabens from a commercial allergy test ointment, acetone and ethanol vehicles*, J Invest Dermatol 115/2000, 914.

[17] COMMISSION REGULATION (EU) No 1004/2014 of 18 September 2014 amending Annex V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products.
[18] COMMISSION REGULATION (EU) No 344/2013 of 4 April 2013 amending Annexes II, III, V and VI to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products.
[19] Golden R., Gandy J., Vollmer G., *A review of the endocrine activity of parabens and implications for potential risks to human health*, Critical Reviews in Toxicology, 35/2005, 435.
[20] Haman C., Dauchy X., Rosin C., Munoz J-F., *Occurrence, fate and behavior of parabens in aquatic environments: A review*, Water Research 68/2015, 1.
[21] Błędzka D., Gromadzińska J., Wąsowicz W., *Parabens. From environmental studies to human health*, Environ. Int. 67/2014, 27.
[22] Roden K., *Preservatives in personal care products*, Microbiology Australia 9/2010, 195.
[23] Doron S., Friedman M., Falach M., Sadovnic E., Zvia H., *Antibacterial effect of parabens against planktonic and biofilm Streptococcus sobrinus*, Int J Antimicrob Agents 18/2001, 575.
[24] Johnson T.A., Sims G.K., Ellsworth T.R., Ballance A.R., *Effects of moisture and sorption on bioavailability of p-hydroxybenzoic acid to* Arthrobacter *sp. in soil*, Microbiol Resources 153/1999, 349.
[25] Terasaki M., Makino M., Tatarazako N., *Acute toxicity of parabens and their chlorinated by-products with Daphnia magna and Vibrio fischeri bioassays*, J Appl Toxicol 29(3)/2009, 242.
[26] Alexiades-Armenakas M., *Parabens toxicity to skin and other organs*, J Drugs Dermatol 7 (1)/2008, 77.
[27] Bojarowicz H., Wojciechowska M., Gocki J., *Substancje konserwujące stosowane w kosmetykach oraz ich działania niepożądane*, Problemy Higieny i Epidemiologii 89/2008, 30.
[28] Dhanirama D., Gronow J., Voulvoulis N., *Cosmetics as a potential source of environmental contamination in the UK*, Environ. Technol. 33(14)/2012, 1597.
[29] Pedersen S., Marra F., Nicoli S., Santi P., *In vitro skin permeation and retention of parabens from cosmetic formulations*, Int J Cosm. Sci. 29/2007, 361.
[30] Soni M.G., Burdock G.A., Taylor S.L., Greenberg N.A., *Safety assessment of propyl paraben: a review of the published literature*, Food Chem. Toxicol. 39/2001, 513.
[31] Rudel R.A., Perovich L.J., *Endocrine disrupting chemicals in indoor and outdoor air*, Atmos. Environ. 43/2009, 170.
[32] Sánchez-Quiles D., Tovar-Sánchez A., *Are sunscreens a new environmental risk associated with coastal tourism?*, Environ. Int. 83/2015, 158.
[33] SCCP/1348/10, Scientific Committee on Consumer Safety, OPINION ON Parabens, COLIPA n° P82, Revision 22 March 2011.
[34] CIR – Safety Assessment of Parabens as Used in Cosmetics, Report for Panel Review, February 23, 2018.
[35] Polish Union of Cosmetics Industry response to the public consultation on the draft Commission Regulation (EU) No 1223/2009 amending Annexes II, III and V to

Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products.
[36] FDA (CFR) CITE: 21 CFR 184.1490, Chapter I – Food and Drug Administration Department of Health and Human Services, Subchapter B – Food for Human Consumption, Part 184 – Direct Food Substances Affirmed as Generally Recognized as SAFE, Subpart B – Listing of Specific Substances Affirmed as GRAS, Sec. 1840. 1490 Methylparaben. Title 21, Volume 31, April 1, 2018.
[37] Okubo T., Yokoyama Y., Kano K., Kano I., *ER-dependent estrogenic activity of parabens assessed by proliferation of human breast cancer MCF-7 cells and expression of ERalpha and PR*, Food Chem. Toxicol. 39/2001, 1225.
[38] Darbre P.D., *Environmental oestrogens, cosmetics and breast cancer*, Best Pract. Res. Clin. Endocrinol. Metab. 20/2006, 121.
[39] Darbre P., Harvey P., *Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks*, J Appl Toxicol 28/2008, 561.
[40] Darbre P., Charles A.K., *Environmental Oestrogens and Breast Cancer: Evidence for Combined Involvement of Dietary, Household and Cosmetic Xenoestrogens*, Anticancer Res. 30/2010, 815.
[41] Calafat A., Weuve J., Ye X., Hauser R., *Exposure to Bisphenol A and Other Phenols in Neonatal Intensive Care Unit Premature Infants*, Environ. Health Perspect. 117/2009, 639.
[42] Calafat A., Ye X., Wong L.Y., Bishop A.M., Needham L.L., *Urinary Concentrations of Four Parabens in the US Population: NHANES 2005–2006*, Environ. Health Perspect. 118/2010, 679.
[43] Brausch J.M., Rand G.M., *A review of personal care products in the aquatic environment: Environmental concentrations and toxicity*, Chemosphere 82/2011, 1518.
[44] Carballa M., Omil F., Lema J.M., Lompart M., García-Jares C., Rodríguez I., Gómez M., Ternes T., *Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant*, Water Res. 38/2004, 2918.
[45] Chunyang L., Sunggyu L., Hyo-Bang M., Yamashita N., Kannan K., *Parabens in Sediment and Sewage Sludge from the United States, Japan, and Korea: Spatial Distribution and Temporal Trends*, Environ. Sci. Technol. 47(19)/2013, 10895.
[46] Díaz-Cruz M.S., García-Galán M.J., Guerra P., Jelic A., Postigo C., Eljarrat E., Farré M., López de Alda M.J., Petrovic M., Barceló D., *Analysis of selected emerging contaminants in sewage sludge*, Trends Anal. Chem. 28/2009, 1263.
[47] Zgoła-Grześkowiak A., Jeszka-Skowron M., Czarczyńska-Goślińska B., Grześkowiak T., *Determination of parabens in Polish river and lake water as a function of season*, Analytical Letters 49 (11)/2016, 1734.
[48] Jiang J.-J., Lee C.-L., Fang M.-D., *Emerging organic contaminants in coastal waters: anthropogenic impact,environmental release and ecological risk*, Mar. Pollut. Bull. 85/2014, 391.
[49] Kolpin D.W., Skopec M., Meyer M.T., Furlong E.T., Zaugg S.D., *Urban contamination of pharmaceuticals and other organic wastewater contaminants to streams during differing flow conditions*, Sci. Total Environ. 328/2004, 119.

[50] Kucińska M., Murias M., *Kosmetyki jako źródło narażenia na ksenoestrogeny*, Prz. Lek. 70 (8)/2013, 647.
[51] Ternes T.A., Joss A., Siegrist H., *Scrutinizing pharmaceuticals and personal care products in wastewater treatment*, Environ. Sci. Technol. 38/2004, 392.
[52] Ferreira A.M., Möder M., Laespada M.E., *Stir bar sorptive extraction of parabens, triclosan and methyl triclosan from soil, sediment and sludge with in situ derivatization and determination by gas chromatography-mass spectrometry*, J. Chromatogr. 1218/2011, 3837.
[53] Zhang X., *Fate and Transport of Fragrance Materials in Principal Environmental Sinks*, Chemosphere 93 (6)/2013, 857.
[54] Tarasaki M., Makino M., *Determination of chlorinated by-products of parabens in swimming pool water*, Inter. J. Environ. Anal. Chemistry 88 (13)/2008, 911.
[55] Yamamoto H., Watanabe M., Hirata Y., Nakamura Y., Nakamura Y., Kitani C., Sekizawa J., Uchida M., Nakamura H., Kagami Y., Koshio M., Hirai N., Tatarazako N., *Preliminary Ecological Risk Assessment of Butylparaben and Benzylparaben-1. Removal Efficiency in Wastewater Treatment, Acute/Chronic Toxicity for Aquatic Organisms, and Effects on Medaka Gene Expression*, Environmental Sciences 14/2007a, 73.
[56] Yamamoto H., Watanabe M., Katsuki S., Nakamura Y., Moriguchi S., Nakamura Y., Sekizawa J., *Preliminary Ecological Risk Assessment of Butylparaben and Benzylparaben-2. Fate and Partitioning in Aquatic Environments*, Environmental Sciences 14/2007, 97.
[57] Tay K.S., Rahman N.A., Abas M.R.B., *Ozonation of parabens in aqueous solution: Kinetics and mechanism of degradation*, Chemosphere 81/2010, 1446.
[58] Valkova N., Lépine F., Valeanu L., Dupont M., Labrie L., Bisaillon J.-G., Beaudet R., Shareck F., Villemur R., *Hydrolysis of 4-Hydroxybenzoic Acid Esters (Parabens) and Their Aerobic Transformation into Phenol by the Resistant Enterobacter cloacae Strain EM*, Appl. Environ. Microbiol. 67 (6)/2001, 2404.
[59] NICNAS. Inventory Multi-tiered Assessment and Prioritisation (IMAP) Framework. National Industrial Chemicals Notification and Assessment Scheme, Sydney, Australia. 2013.
[60] NICNAS. IMAP Human Health Tier I Assessment for Parabens. National Industrial Chemicals Notification and Assessment Scheme, Sydney, Australia. 2016.
[61] NICNAS. IMAP Human Health Tier II Assessment for Parabens. National Industrial Chemicals Notification and Assessment Scheme, Sydney, Australia. 2017.
[62] Canosa P., Rodríguez I., Rubí E., Negreira N., Cela R., *Formation of halogenated by-products of parabens in chlorinated water*, Anal. Chim. Acta 575 (1)/2006, 106.
[63] González-Mariño I., Quintana J.B., Rodriguez I., Cela A.R., *Simultaneous determination of parabens, triclosan and triclocarban in water by liquid chromatography/electrospray ionisation tandem mass spectrometry*, Rapid Commun. Mass Spectrom. 23/2009, 1756.
[64] González-Mariño I., Quintana J.B., Rodríguez I., Cela A.R., *Evaluation of the occurrence and biodegradation of parabens and halogenated by-products in wastewater by accurate-mass liquid chromatography-quadrupole-time-of-flight-mass spectrometry* (LC-QTOF-MS), Water Res. 45 (20)/2011, 6770.

[65] Nelly V., Francois L., Loredana V., Maryse D., Louisette L., Jean-Guy B., Rejean B., Francois S., Richard V., *Hydrolysis of 4- Hydroxybenzoic Acid Esters (Parabens) and Their Aerobic Transformation into Phenol by the Resistant Enterobacter cloacae Strain EM*, Appl. Environ. Microbiol. 67/2001, 2404.
[66] Gao Y., Ji Y., Li G., An T., *Theoretical investigation on the kinetics and mechanisms of hydroxyl radical-induced transformation of parabens and its consequences for toxicity: Influence of alkyl-chain length*, Water Res. 91/2016, 77.
[67] Bjerregaard P., Andersen D., Pedersen K., Pedersen S., Korsgaard B., *Estrogenic effect of propylparaben (propylhydroxybenzoate) in rainbow trout Onchorhunchus mykiss after exposure via food and water*, Comp. Biochem. Physiol. C Toxicol. Pharmacol. 136 (4)/2003, 309.
[68] Alslev B., Korsgaard B., Bjerregaard P., *Estrogenicity of butylparaben in rainbow trout Oncorhynchus mykiss exposed via food and water*, Aquat Toxicol 72 (4)/2005, 295.
[69] Xue J., Sasaki N., Elangovan M., Diamond G., Kannan K., *Elevated Accumulation of Parabens and their Metabolites in Marine Mammals from the United States Coastal Waters*, Environ. Sci. Technol 49 (20)/2015, 12071.
[70] Xue J., Kannan K., *Accumulation profiles of parabens and their metabolites in fish, black bear, and birds, including bald eagles and albatrosses*, Environ. Int. 94/2016, 546.
[71] Xue X., Xue J., Liu W., Adams D.H., Kannan K., *Trophic Magnification of Parabens and Their Metabolites in a Subtropical Marine Food Web*, Environ. Sci. Technol. 51 (2)/2017, 780.
[72] Evans W.A., Davies P.J., Mcrae C., *The occurrence of methyl, ethyl, propyl, and butyl parabens in the urban rivers and stormwaters of Sydney, Australia*, Environ. Sci-Wat. Res. 2 (4)/2016, 733.
[73] Vos J.G., Dybing E., Greim H.A., Ladefoged O., Lambre C., Tarazona J.V., Brandt I., Vethaak A.D., *Health effects of endocrine disrupting chemicals on wildlife, with special reference to the European situation*, Crit. Rev. Toxicol. 30 (1)/2000, 71.
[74] Guo Y., Kannan K., *A Survey of Phthalates and Parabens in Personal Care Products from the United States and Its Implications for Human Exposure*, Environ. Sci. Technol. 47/2013, 14442.
[75] Yamamoto H., Tamura I., Hirata T., Kato J., Kagota K., Katsuki S., Yamamoto A., Kagami Y., Tatarazako N., *Aquatic toxicity and ecological risk assessment of seven parabens: Individual and additive approach*, Sci. Total Environ. 410–411/2011, 102.
[76] Li W., Gao L., Shi Y., Wang Y., Liu J., Cai Y., *Spatial distribution, temporal variation and risks of parabens and their chlorinated derivatives in urban surface water in Beijing, China*, Sci. Total Environ. 539/2016, 262.
[77] Wang W., Kannan K., *Fate of Parabens and Their Metabolites in Two Wastewater Treatment Plants in New York State, United States*, Environ. Sci. Technol. 50 (3)/2016, 1174.
[78] Li W., Shi Y., Gao L., Liu J., Cai Y., *Occurrence, fate and risk assessment of parabens and their chlorinated derivatives in an advanced wastewater treatment plant*, J. Hazard. Mater. 300/2015, 29.
[79] Li W., Shi Y., Gao L., Liu J., Cai Y., *Occurrence and human exposure of parabens and their chlorinated derivatives in swimming pools*, Environ. Sci. Pollut. Res. Int. 22 (22)/2015, 17987.

[80] Liu J.-L., Wong M.-H., *Pharmaceuticals and personal care products (PPCPs): A review on environment al contamination in China*, Environ. Int. 59/2013, 208.
[81] Terasaki M., Takemura Y., Makino M., *Paraben-chlorinated derivatives in river waters*, Environ. Chem. Lett. 10 (4)/2012, 401.
[82] Jonkers N., Kohler H.-P.E., Dammshäuser A., Giger W., *Mass flows of endocrine disruptors in the Glatt River during varying weather conditions*, Environ. Pollut. 157/2009, 714.
[83] Kamaya Y., Fukaya Y., Suzuki K., *Acute toxicity of benzoic acids to the crustacean Daphnia magna*, Chemosphere 59/2005, 255.
[84] Dobbins L.L., Usenki S., Brian R., Brooks B.W., *Probabilistic Ecological Hazard Assessment of Parabens using Daphnia magna and Pimephales promelas*, Environ. Toxicol. Chem. 28 (12)/2009, 2744.
[85] Madsen T., Boyd H.B., Nylén D., Pedersen A.R., Petersen G.I. Simonsen F., *Environmental and Health Assessment of Substances in Household Detergents and Cosmetic Detergent Products*, Danish Environmental Protection Agency, Copenhagen 2001.
[86] Terasaki M., Kamata R., Shiraishi F.,Makino M., *Evaluation of estrogenic activity of parabens and their chlorinated derivatives by using the yeast two-hybrid assay and the enzyme-linked immunosorbent assay*, Environ. Toxicol. Chem. 28 (1)/2009, 204.
[87] Terasaki M., Abe R., Makino M., Tatarazako N., *Chronic toxicity of parabens and their chlorinated by-products in Ceriodaphnia dubia*, Environ. Toxicol. 30 (6)/2015, 664.
[88] Pedersen K.L., Pedersen S.N., Christiansen L.B., Korsgaard B., Bjerregaard P., *The Preservatives Ethyl-, Propyl- and Butylparaben are Oestrogenic in an in vivo Fish Assay*, Pharmacol. Toxicol. 86/2000, 110.
[89] Aziza I.H.H., Ingrid B., Khémary U., Aghleb B., Gonzalez C., *Estrogenic activity and parabens occurrence in three Tunisian wastewater treatment plants*, Eur. J. Water Qual. 42/2011, 91.
[90] Orlando E.F., Guillette L.J. Jr, *Sexual dimorphic responses in wildlife exposed to endocrine disrupting chemicals*, Environ. Res. 104/2007, 163.
[91] Barr L., Metaxas G., Harbach C.A., Savoy L.A., Darbre P.D., *Measurement of paraben concentrations in human breast tissue at serial locations across the breast from axilla to sternum*, J. Appl. Toxicol. 32/2012, 465.
[92] Bayülken D.G., Tüylü B.A., Sinan H., Sivas H., *Investigation of genotoxic effects of paraben in cultured human lymphocytes*, Drug Chem Toxicol 1/2017, 34.
[93] Kawaguchi M., Irie K., Morohoshi K., Watanabe G., Taya K., Morita M., Kondo Y., Imai H., Himi T., *Maternal isobutyl-paraben exposure alters anxiety and passive avoidance test performance in adult male rats*, Neurosci. Res. 65/2009, 136.
[94] Kawaguchi M., Morohoshi K., Masuda J., Watanabe G., Morita M., Imai H., Taya K., Himi T., *Maternal Isobutyl-Paraben Exposure decreases the Plasma Corticosterone Level in Dams and Sensitivity to Estrogen in Female Offspring Rats*, J Vet Med Sci 71/2009, 1027.
[95] Kawaguchi M., Morohoshi K., Imai H., Morita M., Kato N., Himi T., *Maternal Exposure to Isobutyl-Paraben Impairs Social Recognition in Adult Female Rats*, Exp. Anim. 59/2010, 631.
[96] Oishi S., *Effects of butyl paraben on the male reproductive system in rats*, Toxicol Ind Health 17/2001, 31.

[97] Oishi S., *Effects of propyl paraben on the male reproductive system*, Food Chem. Toxicol. 40/2002, 1807.
[98] Oishi S., *Effects of butyl paraben on the male reproductive system in mice*, Arch Toxicol. 76 (7)/2002, 423.
[99] Oishi S., *Lack of spermatotoxic effects of methyl and ethyl esters of p-hydroxybenzoic acid in rats*, Food Chem. Toxicol. 42 (11)/2004, 1845.
[100] Bazin I., Gadal A., Touraud E., Roig B., *Hydroxy Benzoate Preservatives (Parabens) in the Environment: Data for Environmental Toxicity Assessment*, Environ. Pollut. 16/2010, 24.
[101] Beck I.C., Bruhn R., Gandrass J., *Analysis of estrogenic activity in coastal surface waters of the Baltic Sea using the yeast estrogen screen*, Chemosphere 63/2006, 1870.
[102] Harvey P.W., Darbre P., *Endocrine disrupters and human health: Could oestrogenic chemicals in body care cosmetics adversely affect breast cancer incidence in women? A review of evidence and call for further research*, J Appl Toxicol 24/2004, 167.
[103] Meekerj D., Yang T., Ye X., Calafat A.M., Hauser R., *Urinary Concentrations of Parabens and Serum Hormone Levels, Semen Quality Parameters, and Sperm DNA Damage*, Environ. Health Perspect. 119/2011, 252.
[104] Nakagawa Y., Moldéus P., *Mechanism of p-Hydroxybenzoate Ester-induced Mitochondrial Dysfunction and Cytotoxicity in Isolated Rat Hepatocytes*, Biochem. Pharmacol. 55/1998, 1907.
[105] Aalto T.R., Firman M.C., Rigler N.E., *p-Hydroxybenzoic acid esters as preservatives*, J.Am. Pharm. Assoc. Sci. Ed. 42/1953, 449.
[106] Journal of The American College of Toxicology, Vol. 3, No. 5, 1984, Mary Ann Liebert, Inc., Publishers.
[107] Rajendiran Karthikraj, Kurunthachalam Kannan, Human Biomonitoring of Select Ingredients in Cosmetics, [in:] Amparo Salvador, Alberto Chisvert (eds.), *Analysis of Cosmetic Products*, 2nd Edition, Chapter: 15, Elsevier, 387–434.

If you want to quote this article, its proper bibliographic entry is as follow: Barabasz W., Pikulicka A., Wzorek Z., Nowak A.K., *Ecotoxicological aspects of the use of parabens in the production of cosmetics*, Technical Transactions, Vol. 12/2019, pp. 99–124.