

# Parabens: what to tell our patients

## Editorial



A bill aiming to prohibit the use in France of certain chemicals considered endocrine disruptors was passed in early May 2011 after its first reading to the National Assembly. Among the compounds targeted are parabens, effective preservatives present in very many products in widespread use, including cosmetics.

For some years, parabens have given rise to various controversies which have been amplified in recent months by the media following the above bill. In consequence, dermatologists are increasingly questioned on the subject by patients. A recent survey of healthcare professionals showed that 50% of them considered that the increased concern of their patients relating to chemicals present in everyday life had become 'considerable'<sup>1</sup>. However, cosmetics, products that are extremely regulated in Europe, fulfill all the safety rules for consumer health.

In consequence, dermatologists should be among the first to reassure while giving information on the basis of the scientific data available. Alas, the sources of information frequently remain limited due to lack of time. The dermatologist, a professional specializing in the health of the skin, has the role of informing his/her patients which takes time and also asks clear and complete scientific information. For that reason, the Collège de Dermocosmétologie d'Unilever has decided to publish a special edition and thus offer you a **review of the knowledge of parabens** in order to give you all the relevant information on those substances and help you answer your patients' numerous questions.

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## The parabens

### Definition<sup>1</sup>

A paraben is an alkyl **PARA**hydroxy**BEN**zoate (cf. fig. 1). The various compounds in these series of esters differ in terms of the nature and length of their alkyl chain (R) in the para position on the benzene ring.

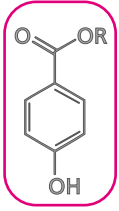


Figure 1 : General chemical structure of parabens (R = alkyl group).

The most widely used compounds of the paraben series are as follows:

- **methyl paraben** (R = -CH<sub>3</sub>; **E218**) and its sodium salt (**E219**);
- **ethyl paraben** (R = -CH<sub>2</sub>CH<sub>3</sub>; **E214**) and its sodium salt (**E215**);
- **propyl paraben** (R = -CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>; **E216**) and its sodium salt (**E217**);
- **butyl paraben** (R = -CH(CH<sub>2</sub>)<sub>2</sub>CH<sub>3</sub>).

### The natural parabens<sup>1-8</sup>

Generally synthetic, parabens, of which methyl paraben and propyl paraben in particular, occur naturally in a large number of foods such as blackberry, barley, strawberry, blackcurrant, vanilla, carrot, peach, white bean, grapefruit, onion and foods prepared from plants (grape juice, other juices, white wine, wine vinegar, etc.), yeast extracts and certain cheeses (cf. picture 1). Parabens are also found in products produced by bees (propolis, royal jelly, etc.). Parabens are also naturally present in the human body and more particularly in women as a precursor of coenzyme Q10 and may be synthesized by marine bacteria as a means of defense against other microorganisms.



Photo 1 : Foods naturally containing parabens.

### Use<sup>1,9-11</sup>

**'What products contain parabens?' Proposition of answer:** Parabens are present in a large number of products that we use daily: in thousands of cosmetics - makeup, shampoo, moisturizing creams, depilatory creams, shaving foams, cleansing gels, lubricants, toothpastes - and food products, including beverages - pastries, jam, etc. - and in hundreds of medicinal products.

Parabens are widely used in a large number of everyday products due to their excellent antifungal and antimicrobial properties. Their antimicrobial effect was first described by Sabalitschka in 1924 and they were first used as a preservative in 1930.

Generally speaking, parabens are very valuable molecules since they are colorless, odorless, tasteless, have no decolorizing power, are chemically stable, and are considered safe and effective over a large pH range (4.5 to 7.5) and temperature range. They nonetheless differ in terms of their activity spectrum. Their antibacterial potency, particularly with respect to Gram-positive bacteria, increases with the length of their alkyl chain. Nevertheless, due to the higher solubility of methyl and ethyl parabens in aqueous phases, those compounds are the most widely used since microbial attack mainly occurs in aqueous phases. The parabens are used alone or in combination to increase their activity and efficacy. For that reason, in formulations, parabens are used in combination ensuring protection of aqueous phases while limiting the necessary concentration of each molecule.

**Absorption, metabolism, excretion.** Ingested parabens are readily absorbed from the gastrointestinal tract and rapidly hydrolyzed by liver and kidney esterases. Their metabolites do not accumulate in the body and their urinary excretion is fast (86% in 24 hours). In addition, it would seem that cutaneous barrier crossing is a function of the length of the alkyl chain. However, parabens

are frequently combined with surfactants in order to enhance their solubility in cosmetic products. The result is a decrease in penetration through the skin. The carboxyl esterases present in the skin and subcutaneous fat are responsible for paraben metabolism. It is to be noted that the carboxyl esterases present in subcutaneous fat are more active on short-chain parabens while those located in the keratinocytes are more active against long-chain parabens.

**Foods<sup>4,12</sup>.** Parabens are used worldwide, frequently as mixtures, as food additives, and have been so used for over 50 years. Parabens are thus present in cakes, sweetened beverages, creams and pastry, preserves, jellies, meats, table sweeteners, snacks, candies, preserved fruit and vegetables and syrups. The use of parabens as food additives is regulated by European directive 95/2/EC dated 20<sup>th</sup> February 1995. Only methyl and ethyl parabens and their salts are authorized in the European Union and are thus the only parabens to have been allocated food additive numbers (E214-215-218-219).

**Cosmetics<sup>4,13</sup>.** Methyl, ethyl, propyl and butyl parabens are the most widely used preservatives in a large number of cosmetic products irrespective of whether the product is to be rinsed off or not. They are mandatorily indicated in the labeling in the official statement of the composition of the cosmetic. Parabens are used in cosmetics because of their broad activity spectrum (bacteria, molds, yeasts, fungi), the absence of interaction with other substances contained in cosmetics, their chemical stability and their biodegradability. Thus, the parabens are accepted by all the international regulatory agencies because of their very good cutaneous tolerance and low toxicity. When most widely used at the start of the century, they were present worldwide in about 80% of hygiene and beauty products, all categories taken together. This is equivalent to over 13,200 formulations, 'hypoallergenic' formulations included.

**Medicines<sup>4,14-15</sup>.** In medicines, methyl and propyl parabens are the most widely used parabens in order to prevent microbial contamination and prevent the degradation of the active substances and hence loss of efficacy. Propyl paraben is one of the most effective active substances against mycoses. Methyl paraben is used as a plasticizer in certain medicinal products and added to local anesthetics to enhance antibacterial activity. The two preservatives are most frequently combined in order to widen the preservative spectrum and reduce their respective concentrations. In France, parabens are present in over 400 medicinal products, including disinfectant creams, cough syrups, nose and ear drops, ovules and suppositories, treatments for intestinal disorders, painkillers, antibiotics or the drugs used in cancer chemotherapy...

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## Parabens and cosmetics

### The cosmetic regulations: a guarantee of product safety<sup>10,16,17</sup>



While cosmetics do not require a marketing authorization, they must nonetheless fulfill certain regulatory requirements and are regularly controlled by the authorities. The cosmetic industries comply with the European Community directive 76/768/EEC dated 27<sup>th</sup> July 1976 and amended 7 times, which transfers all the marketing responsibilities to the organization putting the cosmetic on the market. It is to be noted that new European cosmetic regulations will be applicable from 2013. The

provisions regulate, in particular, the formulation of cosmetics and their labeling and require evaluation of product safety by the company in order to only market products devoid of risks for consumer health under normally foreseeable conditions of use. The documentation constituting the cosmetic product dossier may also be audited by the authorities. Once marketed, cosmetics are regularly controlled. The authorities responsible for the controls are the French Agency for the Safety of Health Products (AFSSAPS) and the Directorate General of Competition, Consumption and Fair Trading. In France, there is also a mandatory national system of cosmetovigilance for healthcare professionals which ensure the surveillance of the safety of cosmetic products throughout the product lifetime. Manufacturers are also required to indicate in the cosmetic dossier the adverse effects reported and to make them available on request in order to optimize consumer safety.

Preservatives are extremely rigorously regulated in Europe : the European regulations provide a positive list (Appendix V) of authorized preservatives with their maximum admissible concentration, limitations and requirements, conditions of use and any warnings to be indicated on the labeling. The list is regularly reviewed as a function of scientific progress by the Scientific Committee on Consumer Safety (SCCS) responsible for advising the European Commission on scientific matters.

The use of parabens in cosmetics, on which abundant toxicological literature is available, is regulated in France by article R.5263-3 of the Code of Public Health relating to the marketing and labeling of authorized substances and/or substances subject to restrictions entering in the composition of cosmetics. The use of parabens in cosmetics is authorized by the European directive up to a total concentration of 0.8%. The maximum concentration of each ester is restricted to 0.4% for methyl paraben and ethyl paraben and 0.19% for butyl and propyl parabens. The levels were confirmed by the SCCS on 10<sup>th</sup> October 2011.

## Role and nature of the preservatives in cosmetics<sup>18,19</sup>

The preservatives are series of molecules whose role is to protect the health and safety of consumers. They are only used when they are essential to prevent any risk of bacteriological contamination during product or raw material manufacture and during product use by the consumer. Preservative use thus enables limitation, slowing or arrest of the growth of bacteria, yeasts and molds while protecting the product and the consumer. Without bacteriostatic and fungistatic preservatives, cosmetics could become a prolific nest for microorganisms and would rapidly become unusable or even dangerous; the products might be contaminated by bacteria which could subsequently be transmitted to the user and thus potentially cause infection.

The parabens are not the only preservatives used today in cosmetics. A recent Swedish study showed that the preservatives most frequently used in shampoos, conditioners, liquid soaps and wipes were as follows: methylparaben (41%), phenoxyethanol (39%), sodium benzoate (34%), propylparaben (25%) and methylchloroisothiazolinone (MCI) / methylisothiazolinone (MI) (22%).

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**‘What are parabens for?’ Proposition of answer:** Due to their antibacterial and antifungal properties, parabens are used as preservatives in order to prevent the contamination of the products in which they are present by bacteria, yeasts and molds... during manufacture and in order to protect the consumer’s health and ensure his/her safety.

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## Is there a link between health risks and use of cosmetics containing parabens<sup>1,4,6,9,20-22</sup>

The use of parabens has always been regulated and the regulations regularly updated to take into account the questions raised by studies reviewing parabens. Nonetheless, their use is controversial because of their ability to activate estrogen receptors, inducing a potential action on the development of the sex organs and fertility and on estrogen-dependent tumors (breast, prostate, testicles). The polemic with regard to preservatives began in 2004 following publication of a British study suggesting a potential link between the use of cosmetics containing parabens and the emergence of breast cancer. Considered highly controversial by the scientific community, the study led to an in-depth review of the toxicity of parabens at the request of the European agencies. The review was based on numerous toxicokinetic and toxicological studies conducted using the various exposure routes, including the cutaneous and oral routes, in rats, rabbits, dogs and human. At the end of 2005, the AFSSAPS reported the results of the review: the pursuit of the use of methyl, ethyl, propyl and butyl parabens in cosmetics was recommended since their safety profiles were excellent and the compounds were endowed with very good antimicrobial efficacy. They would in fact be difficult to replace.

In addition, the European Food Safety Agency (EFSA) defined an Acceptable Daily Intake (ADI) for methyl and ethyl parabens and their salts: 10 mg/kg on the basis of the No Observed Adverse Effect Level (NOAEL) of 1000 mg/kg of body weight/day for each compound in the long-term toxicity studies and studies of

sex hormones and male reproductive organs in young rats. These values are to be compared with the total daily exposure (food, cosmetics and medicines taken together) estimated to be 76 mg/day, i.e. 1.26 mg/kg/day for a subject of body weight 60 kg. This value is markedly below the ADI cited above and thus in favor of consumer safety.

On 10<sup>th</sup> October 2011, after review, the SCCS rendered its opinion public and again confirmed that parabens are devoid of health risk, in particular in children. Given the safety margins adopted, the SCCS estimated that methyl, ethyl, propyl and butyl parabens were not associated with safety issues, irrespective of user age. However, as a precaution, the SCCS recommended prohibition of paraben use in non-rinsed cosmetic products for the nappy area of children under six months of age.

**Parabens and irritant and sensitizing effects<sup>1,4,9,10,17,23-28</sup>.** The parabens, at the concentrations at which they are used in cosmetics, are considered to be practically devoid of irritant and sensitizing potential under normal conditions of use on healthy skin. With regard to the irritation reactions due to these compounds, the number of cases reported is very low compared to the wide use of paraben. In addition, delayed skin allergy cases have been reported but a *contrario* the sensitized subjects may nonetheless continue to use and tolerate cosmetic products containing parabens when applied to other body areas where the skin is healthy and intact. The phenomenon, named the ‘paraben paradox’ was evidenced by Fisher in 1973. It should nonetheless be noted that the prevalence of paraben allergy, which mainly occurs when the skin has been damaged, is very low compared to that of the other preservatives used in cosmetics.

**Parabens & the endocrine disruptor effect<sup>1,4,6,9,14,22,29-34</sup>.** Endocrine disruptors are organic compounds that may act on hormone equilibria by mimicking the action of natural hormones (estrogens, testosterone) and by interfering with the synthesis, storage, secretion, transport and elimination or action of these hormones. *In vitro* and *in vivo* studies have shown that parabens have an estrogenic effect. Their potential to activate estrogen receptors is, however, markedly less than that of estradiol-17 $\beta$ , the main natural estrogen: from 100,000- to 10 million-fold weaker depending on the length of the alkyl chain and the gene expression, that results, is different. Thus, on the basis of the daily exposures cited above, it seems improbable that parabens constitute a risk in terms of estrogenic activity. Moreover, no estrogenic activity has been detected *in vivo* for methyl, ethyl or propyl parabens during uterotrophic studies with oral and subcutaneous administration of high doses to mice and rats. After reviewing all the studies, the EFSA stated that the metabolite common to the parabens, para-hydroxybenzoic acid, was non-estrogenic. In addition, para-hydroxybenzoic acid has been shown to be devoid of toxicity. With regard to the evaluation of the effects of parabens on male reproductive function, the *in vivo* studies concur in finding no effect of either of the two short-chain molecules (methyl and ethyl parabens) on the male sex hormones or reproductive organs. For long-chain parabens (propyl and butyl parabens), the results of the *in vivo* studies are contradictory. Certain authors consider that the fast metabolism of those compounds by esterases and their lesser percutaneous penetration compared to short-chain parabens may constitute an explanation of their safety *in vivo*. An ongoing AFSSAPS study seems to show the safety of propyl paraben in juvenile rats.

**Parabens and breast cancer<sup>1,4,6,21,30,31,35,36</sup>.** Given the major role played by estrogens in the development of a number of cases of breast cancer, some authors have raised the question of the potential role of paraben use in cosmetics, particularly when applied to the axillae (deodorants and antiperspirants), in the increasing incidence of the disease. The results of the study by Darbre *et al.* in 2004, which showed traces of parabens in a small number of tissue samples from female breast tumors, have been widely reviewed and criticized by the scientific community due to a certain number of methodological biases: low number of subjects, absence of control tissues, no patient histories - possible intake of cancer medications containing parabens, histology of the tumor not specified - presence of blank samples contaminated by parabens, paraben metabolism and excretion rate not taken into account, potential contamination. To date, no causal relationship has been demonstrated. Darbre *et al.*, who incriminated the parabens present in antiperspirants, did not provide any explanation as to the systemic or non-systemic origin of the parabens and were unable to conclude with respect to a potential correlation between paraben presence and tumor formation. The higher frequency of tumors of the superolateral quadrant of the breast, closer to the area where antiperspirants are applied, may simply be related to the larger quantity of breast tissue present in that quadrant. Moreover, there were not more cases of breast cancer among women using antiperspirants than among those who did not use them. Lastly, almost all (> 98%) of the deodorants/antiperspirants in the most widely

used forms - sprays, beads and sticks - do not contain parabens since they do not require preservation due to their intrinsic antibacterial properties (presence of alcohol or antibacterial antiperspirant active substances).

**Parabens and mutagenicity and carcinogenicity**<sup>1,4,22,31</sup>. Various general toxicity studies (acute, subacute and chronic) conducted *in vitro* and *in vivo* have generated concordant results showing the absence of toxic, mutagenic, genotoxic or teratogenic effects of parabens. In addition, various carcinogenicity studies in rodents are available and none has evidenced any carcinogenic potential of parabens (bladder, liver, kidneys, heart, lungs, spleen, pancreas, hematopoietic system, soft tissues). This may be explained by the fact that parabens are rapidly metabolized in the body and excreted, and therefore do not accumulate.

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**‘Is it dangerous for my health to use cosmetics containing parabens?’ Proposition of answer:** The studies conducted to date have not evidenced any health risk related to the use of parabens in cosmetics. On the contrary, the SCCS has reviewed the studies and concluded that we can continue to use parabens in cosmetics without any health risk. Parabens have been used for many years without risk and are among the best tolerated preservatives at the present time.

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## What does the statement ‘preservative-free’ or ‘paraben-free’ mean?<sup>6,18,28</sup>

Parabens have been used for more than 80 years as preservatives. Their cutaneous tolerance is optimal, their toxicity is relatively low and they are rapidly hydrolyzed in the body making them substances recognized to be safe for user health. In general, in the absence of preservatives, cosmetics may be stored for less time and have to be stored under more demanding conditions: cosmetics without preservatives would have to be stored in the refrigerator and discarded after a few days. Nonetheless, because of numerous rumors circulating about parabens, numerous cosmetic products are currently marketed with statements such as ‘preservative-free’ or ‘paraben-free’.

Consumers have become fearful of ingredients, in particular preservatives and, above all, parabens. The statement ‘paraben-free’ has thus become a sales argument reassuring worried consumers. Products thus labeled do not contain parabens. This can be checked by reading the product labeling. ‘Paraben-free’ does not, however, mean that there are no preservatives but that the product is probably preserved with another system since it is not possible to market products which may be contaminated or become contaminated and thus potentially dangerous.

It should be noted, however, that certain product categories do not require preservatives and may therefore be labeled ‘preservative-free’. It is possible to avoid preservatives under certain conditions: for example, solid products, heat-treated products, single-use packagings, or acne products containing antibacterials, and creams with a very low pH such as anti-wrinkle creams containing fruit acids. Similarly, when a product has a high alcohol or essential oil content, the addition of a preservative is not necessary, but problems of odor or poor tolerance may emerge. Other preservation processes are under study such as decreasing water content, since water promotes bacterial and mold proliferation. There are also airless tubes in which the cream is packaged in a bag that contracts as the cream is used so as not to aspirate inside microbes. Lastly, the ‘preservative-free’ statement may also indicate that the product contains substances that are active against microorganisms but are not included on the official list of preservatives.

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In any event, with or without parabens, and with or without other preservatives, cosmetics are products that are safe for the consumer’s health and guaranteed by the strictest regulations in the world, the European regulations.

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