SUBSPORT Specific Substances Alternatives Assessment – Parabens

March 2013

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1. Profiling parabens to be included in the Specific Section of the Case Story Database

1.1. Chemical identity

Paraben is a group of chemicals, hydroxybenzoate esters. There are a number of different parabens including:

CAS number	IUPAC name	INCI name	E number
99-76-3	Methyl-4-hydroxybenzoate	Methylparaben	E218
120-47-8	Ethyl-4-hydroxybenzoate	Ethylparaben	E214
94-13-3	Propyl-4-hydroxybenzoate	Propylparaben	
94-26-8	Butyl-4-hydroxybenzoate	Butylparaben	
6521-29-5	Pentyl-4-hydroxybenzoate	Pentylparaben	
1085-12-7	Heptyl-4-hydroxybenzoate	Heptylparaben	
1219-38-1	Octyl-4-hydroxybenzoate	Octylparaben	
4191-73-5	Isopropyl-4-hydroxybenzoate	Isopropylparaben	
4247-02-3	Isobutyl-4-hydroxybenzoate	Isobutylparaben	
94-18-8	Benzyl-4-hydroxybenzoate	Benzylparaben	
17696-62-7	Phenyl 4-hydroxybenzoate	Phenylparaben	

IUPAC: International Union of Pure and Applied Chemistry
INCI: International Nomenclature of Cosmetic Ingredients
E-number: number code for food additives that have been assessed within the European Union (by EFSA).

Parabens have a preservative function.

The focus of this report is on the four parabens:

- Methylparaben
- Ethylparaben
- Propylparaben
- Butylparaben

1.2. Hazard characteristics of parabens

Characterising parabens based on their inherent hazards is an essential component of conducting an alternatives assessment. This approach allows the reviewer to assess whether or not an alternative is indeed preferable from an environmental, health and safety perspective. The hazard properties are intrinsic to the chemical, which means that regardless of the way that a chemical is used, these characteristics do not change. The goal of the substitution processes is to advance inherently safer chemicals and products, consistent with the principles of green chemistry.

Sources that have been checked for hazard characterisation:

1. SUBSPORT Hazardous Substance Database according to SUBSPORT Screening Criteria, SDSC, including:
    a. CLP Regulation (CMR 1A or 1B)
    b. IARC (group 1, 2A or 2B carcinogens)
    c. CLP Regulation (Sensitiser: H317, H334)
    d. EC PBT Working Group
    e. OSPAR List of Substances of Possible Concern (PBT)
    f. EC Endocrine Disruptors Database
    g. SIN List (endocrine disruptors)
    h. Vela et al. (neurotoxins, cat 2-4)

2. The ESIS database for R and H phrases

3. TOXNET/HSDB (hazardous substances database)

For green house gases and ozone depleting substances:

4. Greenhouse gases- Kyoto protocol- Annex A, as presented in IPCC (intergovernmental panel on climate change)
5. Ozone Depleting Substances List (Montreal Protocol)

6. Additional sources have been checked for information, especially for endpoints where no information is available in the previous mentioned sources, and also for getting the most up-to-date information. These sources include:

- REACH registration dossiers
- Search for scientific studies using the search resources Google scholar PubMed.
- The endocrine disruption exchange list of potential endocrine disrupting substances:
- Ordinary google search

	Properties	Source of information
Physical Hazards		
Explosivity	no	REACH registration dossier for methylparaben
Flammability	no	REACH registration dossier for methylparaben
Oxidizing	no	REACH registration dossier for methylparaben
Other properties of reactivity	no	REACH registration dossier for methylparaben
Human Health Hazards		
Acute toxicity	Low to moderate toxicity seen from butylparaben in mice	TOXNET HSDB
Skin or eye corrosion / irritation	Suspected skin or sense organ toxicant A number of case reports of skin irritation and sensitisation	Scorecard TOXNET/HSDB
Chronic toxicity	No data	TOXNET/HSDB
Carcinogenicity	No evidence of direct carcinogenity, however a connection between parabens and breast cancer has been discussed following detection of parabens in breast cancer tissue.	TOXNET/HSDB Darbre et al. 2004

	Properties	Source of information
Mutagenicity	Changes in cell proliferation and DNA strand breaks in monkey kidney cell-line, DNA damage in hamster ovary cells have been reported and correlation between urinary levels of butylparaben and sperm DNA damage in humans	Martin *et al*. 2010; Tayama *et al.* 2008; Meeker et al. 2011.
Reproductive toxicity (including developmental toxicity)	Effects seen on human sperm. Mice exposed to butylparaben gave birth to fewer live pups.	Song et al. 1991, Meeker et al. 2011. Kang et al. 2002
Endocrine disruption	All four listed as EDCs Evidence of endocrine disruption in multiple studies both *in vivo* and *in vitro*. Estrogenic, antiandrogen, thyroid and progesterone effects. Estrogenicity increases with increased chain length. Also evidence of synergistic estrogen effects from exposure to low doses of several parabens.	EU COM database TEDX list Song *et al.* 1991; Routledge *et al*. 1998; Kang *et al*. 2002; Lemini *et al*. 2004; Gomez *et al*. 2005; Taxvig *et al*. 2008; Boberg *et al*. 2008; Yang et al.2012
Respiratory or skin sensitization	There are reports of specific cases of allergies towards parabens	Moward 2000; Shaw and deCatanzaro 2009
Neurotoxicity	No data	
Immune system toxicity	No data	
Systemic Toxicity	No data	
Toxic metabolites	Main metabolite parahydrobenzoic acid (PHBA) is an endocrine disruptor. Parabens are easily chlorinated, eg in tap water, the chlorinated forms have higher aquatic toxicity than the parent compound.	Boberg *et al*. 2010 Terasaki et al. 2009
Environmental Hazards		
Acute/chronic aquatic toxicity	Evidence of coral-bleaching (butylparaben) (laboratory studies). Endocrine disruption effects in fish (laboratory studies).	Danovaro *et al*. 2008; Brauch and Rand 2011; Yamamoto et al. 2011
Bioaccumulation	Bioackumulation factor (BCF) 6.4, 16, 44 and 110 for methyl-ethyl-propyl-and butylparaben respectively. Thus bioconcetration in aquatic organisms is moderate for propylparaben and high for butylparaben. One study showing bioaccumulation of parabens in amniotic fluid when mothers exposed (rat).	HSDB 2007 Frederiksen *et al.* 2008
Persistence	Readily biodegradable	REACH registration dossier for methylparaben
Greenhouse gas formation potential	Not listed	Kyoto protocol- Annex A

	Properties	Source of information
Ozone-depletion potential	Not listed	Ozone Depleting Substances List (Montreal Protocol)
Monitoring – has the substance been found in human or environmental samples?	Parabens have been found in rivers, and in effluents from sewage treatment plants. Also in indoor air and house dust *as* well as in human urine, breast milk and breast cancer tissue.	Peng *et al.* 2008; Jonkers *et al.* 2009; Rudel *et al.* 2003; Ye *et al.* 2006; Calafat *et al.* 2010; Schlumpf et al. 2010; Darbre *et al.* 2004, Barr et al. 2011, Ramirez et a. 2011

There are an increasing number of scientific studies showing endocrine disruptive properties for parabens. Parabens can mimic the function of the female sex hormone oestrogen and disturb the function of the male sex hormone androgen. Adverse effects observed in animals include malformation of reproductive organs in pups born by exposed females and decreased sperm production in exposed males. In most studies propyl- and butylparaben show more negative effects than methyl- and ethylparaben. All of these four parabens have been categorised as Category 1 endocrine disrupters in the European Commission's database of potential endocrine disrupters. Category 1 lists substances for which there is evidence of endocrine disruption in animal studies (*in vivo* studies). Still there is a controversy regarding whether or not parabens are endocrine disrupters. Part of this controversy can be addressed to the fact that there are not yet any agreed definitions or criteria for endocrine disruptors on a regulatory level. When the Danish EPA evaluated the four parabens towards their suggested EDC criteria, they found all of the parabens to be endocrine disruptors. Butylparaben was considered as category 1 EDC and the others as category 2A.

Parabens are so widely used today that measurable levels can be found in most people's urine, blood or breast milk, for example. In two US studies propylparaben was found in more than 90 percent of the population (Calafat et al. 2010, Schlumpf et al. 2010). In a recent Norwegian study, the measured levels of parabens in frequent users of personal care products were higher than for any of the other environmental pollutants measured (Sandanger et al. 2011). Parabens are also spread in the aquatic environment, for example from swimmers using sunscreens, and from sewage treatment plants where they cannot always be removed from the incoming water (Jonkers et al 2009, Peng et al 2009). This vast exposure of the population and the environment causes concern, especially for individuals during sensitive stages of development, such as during foetal development, for young children and during puberty. As with other endocrine disruptive chemicals, effects may occur from low doses and may be delayed for years or decades after the exposure (UNEP and WHO 2013).

The most important route of exposure is expected to be from use of cosmetic products, but also through inhalation of dust containing parabens.

Isopropyl and isobutyl paraben are less studied than the other four, but available studied suggest that these are of concern (Koda et al. 2005, Vo et al. 2009).

2. Identification of functions and uses

2.1 Paraben uses

A key first step in identifying appropriate alternatives is to determine the functions, uses and processes associated with parabens, as potential feasible and safer alternatives are often differ particularly where a substance has numerous disparate applications.

Using the SPIN database, which is a database of substances in products in the Nordic countries, the above parabens have been registered to be used in the following types of products 2010:

- Cosmetics
- Non-agricultural pesticides and preservatives
- Cleaning/washing agent
- Pharmaceuticals
- Surface active ingredients
- Surface treatment
- Others

According to ESIS (European Chemical Substance Information System), ethylparaben and propylparaben are described as low production chemicals (LPV), produced in volumes between 10 and 1000 tonnes/year and producer/importer. Butylparaben is produced in less than 10 tonnes/year and producer/importer.

Of the parabens, only methylparaben has been registered according to REACH so far, in the tonnage band 1 000-10 000 tonnes per annum. Registered uses are:

- Manufacturing of substances
- Intermediate
- Manufacture of blends
- Manufacture of cosmetic products.

Registered producers are Clariant, Dr Knoell, SCAS Europe.

According to numbers from the Swedish Chemical Agency, KEMI, the number of products containing parabens in Sweden has doubled since the 1990:s. This statistic does not cover uses in personal care products, food or pharmaceuticals, which are out of the scope of KEMI.

Table 1. Uses of parabens reported in the SPIN (Substances in Preparations in Nordic Countries) database. Uses reported for 2010 with UCN codes to describe uses.

Use code	Function	Source of information
15. Cosmetics	Preservative	SPIN database for 2010
9. Cleaning/washing agents	Preservative	SPIN database for 2010
39. Non-agricultural pesticides and preservatives	Preservative	SPIN database for 2010
41. Pharmaceuticals	Preservative	SPIN database for 2010
50. Surface active agents	Preservative	SPIN database for 2010
61. Surface treatment	Preservative	SPIN database for 2010
55. Others	Preservative	SPIN database for 2010

Parabens are also used as preservatives in food, but this use is not covered by the SPIN database or REACH registration dossiers.

2.2 Prioritizing uses

For this report, alternatives for the following four uses will be identified and screened:

- **Cosmetics**
- **Food**
- **Cleaning products**
- **Pharmaceuticals**

For this report, the main focus will be use of parabens in cosmetics. There are two main reasons for this:

- There is currently an intensive debate on EU level on whether to restrict use of parabens in cosmetics or not, and Denmark has already done this on a national level.
- Several studies indicate that the most important route of exposure for parabens in humans is through cosmetic products.

3. Regulation of parabens

3.1.Cosmetic products

The EU Cosmetics Directive regulates parabens in cosmetics and personal care products with regard to human health concerns.

The safety of parabens in cosmetics and personal care products has been discussed at political level in the EU in recent years. As stated above, the four most commonly used parabens have been identified as endocrine disrupters in the European Commission database of possible endocrine disrupters. However the EU Cosmetics Directive currently allows parabens as long as the paraben concentration does not exceed 0.4 percent for an individual paraben or 0.8 percent when used as a mixture.

In 2009 the Danish National Food Institute published a risk assessment for parabens, demonstrating a potential risk, especially for small children, with the current use of the long-chained parabens. In March 2011 Denmark banned the use of propyl- and butylparaben as well as isopropyl and isobutylparaben in products intended for children under three years of age.

The European Commission has several times asked its Scientific Committee on Consumer Products (SCCP) for its opinion on potential risks with the current use of parabens. Taken together, the opinion statements from December 2010 and October 2011 suggest that the use of methylparaben and ethylparaben is safe, but recommend that the levels of propyl- and butylparaben should be lowered to 0.19 percent. For products intended for the “nappy area” for children under six months of age, SCCP states that it is not possible to exclude the risk of using butyl- and propylparaben. For other parabens, SCCP has stated that there was not enough data to make an assessment at the time. Currently (April 2013) there is a pending request from the European Commission for an updated opinion, this time with respect to new data on propyl- and butylparaben in all age groups including exposure from sunscreens for children under the age of three.

3.2. Food additives

In the EU food additives, including preservatives, must be authorised before they can be used in food. Once authorised, these substances are compiled on an EU list of permitted food additives, which also specifies their conditions of use. Food additives are identified using E-numbers.

Regulation (EC) No 1333/2008 of 16 December 2008 on food additives includes regulation of preservatives. It replaces the earlier directive 95/2/EC.

Following a scientific evaluation and opinion from 2004 (EFSA 2004) propylparaben is no longer allowed as a food preservative. Methylparaben and ethylparaben are however still allowed:

E 214: p-Hydroxibensoesyraetylester (Ethylparaben)
E 218: p-Hydroxibensoesyrametyl- ester (Methylparaben)

3.3. Cleaning products

Cleaning products are covered by the detergents directive (EG) no 648/2004. The intended use of the product rather than its specific content determines whether the product is a cleaning product. The directive states that added preservatives should be stated on the package.
The addition of preservatives to cleaning products has increased since more and more products are based on water instead of organic solvents, and thereby becomes more easily attacked by microorganisms. According to the product register of the Swedish chemicals agency (KEMI), isothiazoline compounds are the most commonly used preservatives. Benzoic acid derivates (including parabens) together with carbamates and phenolic compounds are increasingly used while alcohol and formaldehyde related compounds are decreasingly used as preservatives in different products including cleaning products (cosmetics, food and pharmaceuticals are excluded from this statistic).

3.4. Pharmaceuticals

Parabens are allowed in the EU for use in pharmaceuticals, but as for other preservatives, the use and concentration must be justified accordingly to risk. There is a current debate also within the pharmaceuticals sector, on the safety of using parabens as preservatives.

3.5 Consumer and NGO activities on parabens in cosmetic products

Consumer awareness regarding health concerns over parabens in cosmetic products has increased in recent years. Since the content of personal care and cosmetic products has to be clearly stated on packaging it is relatively easy for consumers to avoid products containing parabens and to ask for alternatives.

Environmental and consumer organisations recommend the avoidance of parabens, and a number of European and US consumer organisations have lately brought attention to endocrine disruptive chemicals in cosmetics and personal care products. Information for consumers can, for example, be found at www.safecosmetics.org and www.goodguide.com.

The Danish and Norwegian Consumer Councils, together with the Swiss organisation Federation Romande des Consommateurs, have specifically addressed 17 chemicals present on the European Commission's database of potential endocrine disrupters that are allowed and used in personal care products. Methyl-, ethyl, propyl- and butylparaben are among these 17 chemicals. Activities have included campaigns encouraging consumers to report all products containing any of these substances, listing companies that have or have not phased them out, as well as a smartphone app for quick identification of products containing these endocrine disrupters.

The SIN List contains substances that ChemSec has identified as *Substances of Very High Concern* based on the criteria established by the EU chemical regulation, REACH.

In May 2011 ChemSec added propyl- and butylparaben to the SIN List 2.0 to highlight the importance of including them on the REACH candidate list of Substances of Very High Concern, due to their endocrine disruptive properties. The inclusion on the SIN List was made after a scientific literature

review performed by the Endocrine Disrupting Exchange in the US, representing some of the world's leading scientists in the field. At the time there were not enough scientific studies to include methyl- and ethylparaben on the SIN List, however the available data suggests that these are also endocrine disruptive chemicals, and that they are similar to the long-chained parabens in both structure and properties.

4. Preliminary identification of alternatives

Parabens are used in the different applications as preservatives. Therefore there is a large overlap with regards to available alternatives for use in cosmetics, food, cleaning products and pharmaceuticals.

There are two main approaches to eliminating parabens for use as preservatives in products:

1. Changes in formulation, processes and packaging, so that no or significantly less preservatives are needed
2. Chemical solutions, using other preservatives than parabens

4.1 Use in cosmetic products

The available alternatives for use in cosmetic products are, for the EU, the preservatives listed in the cosmetics directive[1]. These alternatives are listed below for screening out regrettable substitutes. Non-chemical alternatives, such as packaging solutions, do not need to be listed in this directive.

4.2 Use as food preservatives

Food preservatives have E numbers ranging from E200-E297 and can be divided into the following groups: sorbates, benzoates, sulphites, phenols and formates, nitrates, acetates, lactates, proprionates and others. These alternatives are listed below for screening out regrettable substitutes.

4.3. Use as preservative in cleaning products

A larger number of preservatives are available for use in cleaning products. Therefore not all of them are screened in this study. Instead, a selection of substances made by Hahn et al. 2010 was used. They selected substances for further investigation based on available information on application quantity, range of applications and variety of products. Furthermore, the selected active substances should be stated as notified in the Second Review Regulation of the Biocidal Products Directive to guarantee that they will be on the market in future. These alternatives are listed below for screening out regrettable substitutes.

4.4 Use as preservative in pharmaceuticals

In an article from 2006 Peter Gilbert and David G Allison lists the agents most commonly used for preservation of pharmaceutical products.

5. Screening out regrettable substitutes

5.1 Possible chemical alternatives for use in cosmetic products

Table 1. Preservatives allowed in the EU for use in cosmetic products. There may be limits in percentages or in application set up in the directives that are not included in this table. Alternatives are checked against the hazardous Substance Database according to SUBSPORT Screening Criteria, SDSC and official classification according to CLP regulation has been investigated.

Chemical name	INCI name	CAS	SDSC	Additional comments
Salts of benzoic acid other than that listed under reference number 1 and esters of benzoic acid	*AMMONIUM BUTYL CALCIUM ETHYL ISOBUTYL ISOPROPYL MAGNESIUM MEA- METHYL PHENYL POTASSIUM PROPYL* - BENZOATE	1863-63-4 / 2090-05-3 / 582-25-2 / 553-70-8 / 4337-66-0 / 93-58-3 / 93-89-0 / 2315-68-6 / 136-60-7 / 1205-50-3 / 939-48-0 / 93-99-2	NO	
Benzoic acid and its sodium salt	BENZOIC ACID; SODIUM BENZOATE	65-85-0 / 532-32-1	NO	
Propionic acid and its salts	PROPIONIC ACID / AMMONIUM PROPIONATE / CALCIUM PROPIONATE / MAGNESIUM PROPIONATE / POTASSIUM PROPIONATE / SODIUM PROPIONATE	79-09-4 / 17496-08-1 / 4075-81-4 / 557-27-7 / 327-62-8 / 137-40-6	NO	H314
Salicylic acid (1) and its salts	SALICYLIC ACID / CALCIUM SALICYLATE / MAGNESIUM SALICYLATE / MEA-SALICYLATE / SODIUM SALICYLATE / POTASSIUM SALICYLATE / TEA-SALICYLATE	69-72-7 / 824-35-1 / 18917-89-0 / 59866-70-5 / 54-21-7 / 578-36-9 / 2174-16-5	NO	
Hexa-2,4-dienoic acid and its salts	SORBIC ACID / CALCIUM SORBATE / SODIUM SORBATE / POTASSIUM SORBATE	110-44-1 / 7492-55-9 / 7757-81-5 / 24634-61-5	NO	
Formaldehyde, paraformaldehyde	FORMALDEHYDE / PARAFORMALDEHYDE	50-00-0 / 30525-89-4	YES, IARC carcinogen and more	H351, H331, H311, H301, H314, H317
Biphenyl-2-ol, and its salts	OPHENYLPHENOL MEAOPHENYLPHENATE POTASSIUM O-PHENYLPHENATE SODIUM O-PHENYLPHENATE	90-43-7 132-27-4 13707-65-8 84145-04-0	YES, EU EDC cat 2	CLP H319, H335, H315, H400
Zink pyrithione	ZINC PYRITHIONE	13463-41-7	NO	Anti-dandruff. To be used accordingly.

Chemical name	INCI name	CAS	SDSC	Additional comments
Inorganic sulphites and hydrogensulphites	SODIUM SULFITE / AMMONIUM BISULFITE / AMMONIUM SULFITE / POTASSIUM SULFITE / POTASSIUM HYDROGEN SULFITE / SODIUM BISULFITE / SODIUM METABISULFITE / POTASSIUM METABISULFITE	7757-83-7 / 10192-30-0 / 10196-04-0 / 10117-38-1 / 7773-03-7 / 7631-90-5 / 7681-57-4 / 16731-55-8	NO	
Chlorobutanol	CHLOROBUTANOL	57-15-8	NO	
3-Acetyl-6-methylpyran-2,4(3H)-dione and its salts	DEHYDROACETIC ACID / SODIUM DEHYDROACETATE	520-45-6 / 4418-26-2 / 16807-48-0	NO	H302
Formic acid and its sodium salt	FORMIC ACID / SODIUM FORMATE	64-18-6 / 141-53-7	NO	
3,3'-Dibromo-4,4'-hexamethylenedioxydibenzamidine and its salts (including isethionate)	DIBROMOHEXAMIDINE ISETHIONATE	93856-83-8	NO	
Thiomersal	THIMEROSAL	54-64-8	NO	Mercury compound
Phenylmercuric salts (including borate)	PHENYL MERCURIC ACETATE / PHENYL MERCURIC BENZOATE	62-38-4 / 94-43-9	NO	Mercury compound
Undec-10-enoic acid and its salts	UNDECYLENIC ACID / POTASSIUM UNDECYLENATE / SODIUM UNDECYLENATE / CALCIUM UNDECYLENATE / MEA-UNDECYLENATE / TEA-UNDECYLENATE	112-38-9 / 6159-41-7 / 3398-33-2 / 1322-14-1 / 84471-25-0 / 56532-40-2	NO	
5-Pyrimidinamine, 1,3-bis(2-ethylhexyl)hexahydro-5-methyl-	HEXETIDINE	141-94-6	NO	
5-Bromo-5-nitro-1,3-dioxane	5-BROMO-5-NITRO-1,3-DIOXANE	30007-47-7	NO	Formaldehyde donor
Bronopol	2-BROMO-2-NITROPROPANE-1,3-DIOL	52-51-7	NO	H312,H302,H335,H315,H318,H400
2,4-Dichlorobenzyl alcohol	DICHLOROBENZYL ALCOHOL	1777-82-8	NO	
1-(4-Chlorophenyl)-3-(3,4-dichlorophenyl)urea	TRICLOCARBAN	101-20-2	YES PBT OSPAR Possible concern	
Chlorocresol	P-CHLORO-M-CRESOL	59-50-7	YES EU EDC database	H312,H302,H318, H317,H400
5-Chloro-2-(2,4-dichlorophenoxy)phenol	TRICLOSAN	3380-34-5	YES SIN List	H319, H315, H400, H410

Chemical name	INCI name	CAS	SDSC	Additional comments
Chloroxylenol	CHLOROXYLENOL	88-04-0 / 1321-23-9	YES sensitizer	H302, H319, H315, H317
N,N''-Methylenebis[N'-[3-(hydroxymethyl)-2,5-dioxoimidazolidin-4-yl]urea]	IMIDAZOLIDINYL UREA	NO		Formaldehyde donor
Poly(methylene), .alpha.,.omega.-bis[[[(aminoiminomethyl)amino]iminomethyl]amino]-, dihydrochloride	POLYAMINOPROPYL BIGUANIDE	70170-61-5 / 28757-47-3 / 133029-32-0		Cationic (incompatible with anionic surfactants).
2-Phenoxyethanol	PHENOXYETHANOL	122-99-6	NO	H302, H319
Methenamine	METHENAMINE	100-97-0	YES sensitizer	H228, H317
Methenamine 3-chloroallylochloride	QUATERNIUM-15	4080-31-3	NO	Formaldehyde donor
1-(4-Chlorophenoxy)-1-(imidazol-1-yl)-3,3-dimethylbutan-2-one	CLIMBAZOLE	38083-17-9	NO	
1,3-Bis(hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione	DMDM HYDANTOIN	6440-58-0	NO	Formaldehyde donor
Benzyl alcohol	BENZYL ALCOHOL	100-51-6	NO	H332, H302
1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2 pyridon and its monoethanolamine salt	1-HYDROXY-4-METHYL-6-(2,4,4-TRIMETHYLPENTYL)-2 PYRIDON, PIROCTONE OLAMINE	50650-76-5 / 68890-66-4	NO	
2,2'-Methylenebis(6-bromo-4-chlorophenol)	BROMOCHLOROPHENE	15435-29-7	NO	
4-Isopropyl-m-cresol	O-CYMEN-5-OL	3228-02-2	NO	
Mixture of 5-Chloro-2-methyl-isothiazol-3(2H)-one and 2-Methylisothiazol-3(2H)-one with magnesium chloride and	METHYLCHLOROISOTHIAZOLINONE AND METHYLISOTHIAZOLINONE	55965-84-9 / 26172-55-4 / 2682-20-4	YES sensitizer	H311, H331, H301, H314, H317, H400, H410

Chemical name	INCI name	CAS	SDSC	Additional comments
magnesium nitrate				
2-Benzyl-4-chlorophenol	CHLOROPHENE	120-32-1	NO	
2-Chloroacetamide	CHLOROACETAMIDE	79-07-2	YES sensitizer	H316f, H301, H317
N,N'-bis(4-chlorophenyl)-3,12-diimino-2,4,11,13-tetraazatetradecanediamidine and its digluconate, diacetate and dihydrochloride	CHLORHEXIDINE / CHLORHEXIDINE DIACETATE / CHLORHEXIDINE DIGLUCONATE / CHLORHEXIDINE DIHYDROCHLORIDE	55-56-1 / 56-95-1 / 18472-51-0 / 3697-42-5	NO	
1-Phenoxypropan-2-ol	PHENOXYISOPROPANOL	770-35-4	NO	
Alkyl (C12-C22) trimethyl ammonium bromide and chloride	BEHENTRIMONIUM CHLORIDE / CETRIMONIUM BROMIDE / CETRIMONIUM CHLORIDE / LAURTRIMONIUM BROMIDE / LAURTRIMONIUM CHLORIDE / STEARTRIMONIUM BROMIDE / STEARTRIMONIUM CHLORIDE	17301-53-0 / 57-09-0 / 112-02-7 / 1119-94-4 / 112-00-5 / 1120-02-1 / 112-03-8	NO	
4,4-Dimethyl-1,3-oxazolidine	DIMETHYL OXAZOLIDINE	51200-87-4	NO	
N-(Hydroxymethyl)-N-(dihydroxymethyl-1,3-dioxo-2,5-imidazolidinyl-4)-N'-(hydroxymethyl) urea	DIAZOLIDINYL UREA	78491-02-8	NO	Formaldehyde donor
Benzenecarboximidamide, 4,4'-(1,6-hexanediylbis(oxy))bis-, and its salts (including isothionate and p-hydroxybenzoate)	HEXAMIDINE / HEXAMIDINE DIISETHIONATE / HEXAMIDINE DIPARABEN / HEXAMIDINE PARABEN	3811-75-4 / 659-40-5 / 93841-83-9 / -	NO	
Glutaraldehyde (Pentane-1,5-dial)	GLUTARAL	111-30-8	YES sensitizer	H331, H301, H314, H334, H317, H400
5-Ethyl-3,7-dioxa-1-azabicyclo[3.3.0] octane	7-ETHYLBICYCLOOXAZOLIDINE	7747-35-5	NO	

Chemical name	INCI name	CAS	SDSC	Additional comments
3-(p-Chlorophenoxy)-propane-1,2-diol	CHLORPHENESIN	104-29-0	NO	
Sodium hydroxymethylamino acetate	SODIUM HYDROXYMETHYLGLYCINATE	70161-44-3	NO	
Silver chloride deposited on titanium dioxide	SILVER CHLORIDE	7783-90-6	NO	
Benzenemethanaminium, N,N-dimethyl-N-[2-[2-[4-(1,1,3,3,-tetramethylbutyl)phenoxy]ethoxy]ethyl]-, chloride	BENZETHONIUM CHLORIDE	121-54-0	NO	
Benzalkonium chloride, bromide and saccharinate	BENZALKONIUM CHLORIDE / BENZALKONIUM BROMIDE / BENZALKONIUM SACCHARINATE	8001-54-5/ 63449-41-2 / 91080-29-4 / 68989-01-5 / 68424-85-1 / 68391-01-5 / 61789-71-7 / 85409-22-9	NO	H312, H302, H314, H400
Methanol, (phenylmethoxy)-	BENZYLHEMIFORMAL	14548-60-8	NO	Formaldehyde donor
3-Iodo-2-propynylbutylcarbamate	IODOPROPYNYL BUTYLCARBAMATE	55406-53-6	NO	

Using the above information, the following alternatives to parabens in cosmetic products are screened out as regrettable substitutes:

- **Formaldehyde, parabenformaldehyde**
- **Ophenylphenol, meaophenylphenate, potassium o-phenylphenate, sodium o-phenylphenate**
- **Triclocarban**
- **P-chloro-m-cresol**
- **Triclosan**
- **Chloroxylenol**
- **Imidazolidinyl urea**
- **Methenamine**
- **Quartenium-15**
- **DMDM Hydantoin**
- **Methylchloroisothiazolinone and methylisothiazolinone**
- **Chloroacetamide**
- **Dizolidinyl urea**
- **Glutaral**
- **Benzylhemiformal**

5.1.2 Other available alternatives for cosmetic products

It is possible to produce personal care products without preservatives – if these are produced under clean conditions and can be contained in packaging that allows no transfer of microorganisms from the user to the product. Such alternative packaging solutions are available on the market and used by several companies.

5.1.3 Prioritizing alternatives for cosmetic products for in-depth assessment

Of the alternatives screened above, many substances pass the initial screening criteria. In these report the following alternatives, commonly used, will be subject to in-depth-assessment.

When discussing with manufacturers and when looking at cosmetic ingredients lists- the following substances were selected for further evaluation:

- Phenoxyethanol CAS 122-99-6, IUPAC name 1-hydroxy-2phenoxyethane
- Sorbic acid CAS 110-44-1
- Benzoic cid CAS 65-85-0

In addition packaging solutions will be discussed

5.2. Identification and screening of alternatives for food

Table 2. Preservatives allowed in the EU for use as food additives. There may be limits in percentages or in application set up in the directive that are not included in this table. Alternatives are checked against the hazardous Substance Database according to SUBSPORT Screening Criteria, SDSC and official classification according to CLP regulation has been investigated. (E-number: number code for food additives that have been assessed within the European Union (by EFSA).)

Chemical	E-number	CAS number	SDSC	Additional comments
Sorbic acid	E200	110-44-1	NO	Also on the cosmetics list
Potassium sorbate	E202	24634-61-5	NO	Also on the cosmetics list
Calcium sorbate	E203	7492-55-9	NO	Also on the cosmetics list
Benzoic acid	E210	65-85-0	NO	Also on the cosmetics list
Sodium benzoate	E211	532-32-1	NO	Also on the cosmetics list
Potassium benzoate	E212	582-25-2	NO	Also on the cosmetics list
Calcium benzoate	E213	2090-05-3	NO	Also on the cosmetics list
Sulphur dioxide	E220	7446-09-5	NO	
Sodium sulfite	E221	7757-83-7	NO	Also on the cosmetics list
Sodium bisulfite	E222	7631-90-5	NO	Also on the cosmetics list
Sodium disulfite	EE223	7681-57-4	NO	Also on the cosmetics list

Chemical	E-number	CAS number	SDSC	Additional comments
Potassium dislufite	E224	16731-55-8	NO	Also on the cosmetics list
Calcium sulfite	E226	10257-55-3	NO	
Calcium bisulfite	E227	13780-03-5	NO	
Potassium bisulfite	E228	7773-03-7	NO	
Ortophenylphenol	E231	90-43-7	Yes EU EDC cat2	CLP H319, H335, H314, H317 Also on the cosmetics list
Potassium orto phenylphenol	E232	13707-65-8	NO	Properties should be similar as above Also on the cosmetics list
Nisin	E234	1414-45-5	NO	
Natamycin	E235	7681-93-8	NO	
Hexamethylenteramine	E239	100-97-0	YES, CLP sensitizer	H317, H334 Not approved in USA, Australia or new Zeeland
Dimethylcarbonate	E242	616-38-6	NO	H225
Potassim nitrite	E249	7758-09-0	NO	
Sodium nitrite	E250	7632-00-0	NO	
Sodium nitrate	E251	7631-99-4	NO	
Potassium nitrate	E252	7757-79-1	NO	
Acetic acid	E260	64-19-7	NO	H226, H314
Potassium acetate	E261	127-08-2	NO	
Sodium acetate	E262	127-09-3	NO	
Calcium acetate	E263	62-54-4	NO	
Lactic acid	E270	50-21-5	NO	H315, H318
Propionic acid	E280	79-09-4	NO	H314
Sodium propionate	E281	137-40-6	NO	
Calcium propionate	E282	4075-81-4	NO	
Potassium Proprionate	E283	327-62-8	NO	
Boric acid	E284	10043-35-3	YES, CMR, EDC	H360FD
Borax	E285	1303-96-4	YES, CMR	H360FD Banned in the US
Carbon dioxide	E290	124-38-9	NO	
Malic acid	E296	6915-15-7	NO	
Fumaric acid	E297	110-17-8	NO	H319

5.3 Identification and screening of alternatives for cleaning products.

Table 3. A selection of substances used as preservatives in household products. The selection has been based on a selection made by Hahn et al. 2010. They selected substances for further investigation based on available information on application quantity, range of applications and variety of products. Furthermore, the selected active substances should be stated as notified in the Second Review Regulation of the Biocidal Products Directive to guarantee that they will be on the market in future. Alternatives are checked against the hazardous Substance Database according to SUBSPORT Screening Criteria, SDSC and official classification according to CLP regulation has been investigated.

Chemical	CAS number	SDSC	Additional comments
Alkyl dimethyl benzyl ammonium chlorides (QAC)	68391-01-5	NO	
Triclosan	3380-34-5	YES EDC	
Formaldehyde	50-00-0	YES, Carcinogen, toxic, aquatox, sensitizing	H351, H331, H311, H301, H314, H315
Benzoic acid	200-618-2	NO	
mixture of 5-chloro-2-methyl-2H-isothiazolin-3-one and 2-methyl-2H-isothiazolin-3-one (CMI/MI)	55965-84-9	YES, acute tox, aquatox, sensitizer	H331, H311, H331, H314, H317, H400 H410
1,2-Benzisothiazolin-3-one	2634-33-5	YES, acute tox, aqautox, sensitizing	H301, H315, H318, H317, H400
Bronopol	52-51-7	NO	
2-Phenoxyethanol	122-99-6	NO	
Chloroacetamide	79-07-2	YES, CMR sensitizing	H361f***, H301, H317

5.4. Identification and screening of alternatives for pharmaceuticals

Table 4. A selection of substances used as preservatives in pharmaceuticals. The identification of "agents most commonly used for preservation of pharmaceuticals" comes from an article by Gilbert and Allison from 2006. Alternatives are checked against the hazardous Substance Database according to SUBSPORT Screening Criteria, SDSC and official classification according to CLP regulation has been investigated.

Name	CAS	SDSC	Additional comments
Benzoic acid	65-85-0	No	Also for cosmetics
Sorbic acid	110-44-1	No	Also for cosmetics
Ethanol	64-17-5	Yes, but only for beverages	flammable
Isopropyl alcohol	67-63-0	no	H225, H319, H336
Bronopol	52-51-7	no	Also for cosmetics H312, H302, H335, H315, H318, H400
Formaldehyde	50-00-0	Yes, IARC carcinogen and more	Also for cosmetics H351, H331, H311, H301, H314, H317
Glutaraldehyde	111-30-8	Yes, sensitizer	Also for cosmetics H331, H301, H314, H334, H317, H400
Chlorhexidine	55-56-1	no	Also for cosmetics
Polyhexamethylene biguanide	28757-47-3	no	
Hypochlorite	14380-61-1	no	
Povidone-iodine	25655-41-8	no	
Cloroform	67-66-3	Yes, IARC carcinogen	H351, H302, H373, H315

Name	CAS	SDSC	Additional comments
Chlorocresol	59-50-7	Yes, EU EDC database	Also for cosmetics H312, H302, H318, H317, H400
Cetrimide	57-09-0	No	Also for cosmetics
Benzaolkonium chloride	8001-54-5	no	Also for cosmetics H312, H302, H314, H400

6. Characterizing alternatives for cosmetic products

6.1 Technical aspects of substitution of parabens

6.1.1.Why are preservatives used?

Preservatives are used to prevent the growth of microorganisms. Microbial contamination of personal care products is unwanted and could, in addition to spoiling the odour or appearance of the product, spread infections to the user. A major source of contamination of products is in fact the user, since bacteria and fungi are always present on the skin.

The amount and type of preservatives needed to prevent this depends on the type of product, the package and the shelf life of the product. According to the EU Cosmetics Directive a product should have a shelf life of at least 30 months and a period of safe use after opening should be stated on the packaging. The Cosmetics Directive also lists all preservatives that are allowed for use in cosmetics in Europe.

The need for preservation is also dependent on the product itself, for example the water activity and the pH decide how easily microorganisms can grow in the product. It may be necessary to preserve not only the final product, but also the raw materials used in production. The need for preservation is also dependent on the conditions during manufacturing. If the product is not contaminated during production, preservation only needs to cover the use phase.

It is possible to produce personal care products without preservatives – if these are produced under clean conditions and can be contained in packaging that allows no transfer of microorganisms from the user to the product.

The Rapid Alert System for non-food consumer products in the EU (RAPEX) notifies every week the member states on dangerous products sold in the EU. A study published in 2008 investigated the number of recalled microbiological contaminated cosmetics products in the RAPEX database from 2005 to until week 17 in 2008. A total of 173 cosmetic products were recalled in the period (Lundov et al. 2008).

6.1.2.Recognised barriers for a swift substitution of parabens

For many years parabens have been the most common preservative in cosmetic products. The popularity is due to the fact that parabens are inexpensive, they are efficient to a wide range of microorganisms, the function in a variety of formulations and they have not been associated with e.g. skin irritation or allergies. In spite of the latest scientific development, parabens are still by many cosmetic producers regarded as the best available option for preservation.

In order to be able to protect the product against the large variety of microorganisms that may contaminate the product during the use by the consumer, it is often necessary to combine two or more preservatives with complementary spectrum (e.g. an antibacterial plus an antifungal). Cosmetic products are therefore protected from the growth of diverse microorganisms via associations or combinations of preservatives.

Preservative systems must also be adapted to the different types of cosmetic products and be compatible with the other raw materials used in the products (e.g UV filters, pigments, active ingredients). In order to replace parabens, new specific associations must be developed and/or formulas redesigned.

In addition, many raw materials are protected from microbiological contamination with parabens. Therefore it is also necessary to develop solutions along the supply chain to replace parabens.

6.1.3.Factors to consider for preservation of cosmetic products

The most suitable preservative for a products will also depend on the following factors:

- pH: organic acids are potential substitutes but active only in a specific pH range. However blends with other substances may increase this span.
- Water content: the more available water in the product, the easier for microorganisms to grow, and the more preservatives might be needed.
- Packaging and product type: the design of the package and how the product is use determines the need for preservation. E.g open jars may require better preservation than tubes.

Increasingly popular are also “preservative boosters” – formulations not labelled as preservatives, but added to enhance preservation.

Another approach can be found in “nature cosmetics”. Here preservation is often said to be due to careful balance between the different ingredients, or from “natural preservatives”. However also for nature cosmetics the cosmetic directive is valid and no other preservative than the ones stated in the directive can be used.

7. Hazard characteristics of alternatives

The hazard characterisations of the alternatives are performed according to the same methodology as described for the hazard characterisation of parabens.

7.1 Phenoxyethanol

Phenoxyethanol is a glycol used as a preservative in cosmetics and personal care products and also in e.g cleaning products, paints and pharmaceuticals. In addition it is used in aquaculture as a fish anaesthetic. It is allowed in cosmetic products up to 1,0%. The substance is also used as a fragrance ingredient.

There is a controversy regarding phenoxyethanol, also among environmental groups. In the US and in France the substance is heavily debated and questioned, while NGOs in e.g. Denmark (Forbrugerrådet) and Sweden (Sweden Society for Nature Conservation) regard this as a safe preservative.

A French study from the agency ANSM from 2012 concludes that for children under three, there could be risks from use of phenoxyethanol in personal care products. The US Food and Drug Administration (FDA) concludes that the substance can depress the central nervous system and cause vomiting and diarrhea.

The major safety concern regarding the substance are some studies showing neurotoxic effects, and it is also a classified eye irritant. In addition there are reports of cases of the substance causing allergy.

Many claim that the use of phenoxyethanol has increased following the debate on parabens. Some manufacturers claim that phenoxyethanol has a strong smell that could be problematic in some formulations. Otherwise it is regarded as a cost-effective and efficient preservative.

This substance is also used as a solvent in inks and paints, and exposure to vapours of the substance can be an occupational problem, since it has irritant properties.

	Properties	Source of information
PHENOXYETHANOL CAS 122-99-6		
Physical Hazards		
Explosivity	conclusive but not sufficient for classification	REACH registration dossier
Flammability	conclusive but not sufficient for classification	REACH registration dossier
Oxidizing	conclusive but not sufficient for classification	REACH registration dossier
Other properties of reactivity	No data	
Human Health Hazards		
Acute toxicity	H302 Harmful if swallowed	CLP
Highly toxic		
Skin or eye corrosion / irritation	H319 Causes serious eye irritation	CLP TOXNET/HSDB: case reports of allergy and exzema.
Carcinogenicity	Data lacking	REACH registration dossier
Mutagenicity	Conclusive but not sufficient for classification	REACH registration dossier
Reproductive toxicity (including developmental toxicity)	Significant reproductive and developmental toxicity	TOXNET/HSDB: national toxicology program studies 2002
Endocrine disruption	Not listed	EU com EDC database, TEDX database
Respiratory or skin sensitization	There are case reports of skin irritation and sensitization.	TOXNET/HSDB
Neurotoxicity	Cytotoxic to neurons in vitro Can depress central nervous system, leading to vomiting and diarrhea	TOXNET/HSDB Regulska et al. 2010 FDA 2008
Immune system toxicity	Data lacking	
Systemic Toxicity		
Toxic metabolites	In the body the substance is oxidized to phenoxyacetic acid, which may also contribute to the irritant properties of the substance.	TOXNET/HSDB

Environmental hazards		
Acute/chronic aquatic toxicity	Effects in fish are quite well studied since this agent is used in aquaculture. A recent risk assessment suggests that levels found in nature does not pose a risk to aquatic organisms	Tamura et al. 2012.
Bioaccumulation	Not PBT/vPvB Estimated BCF 1.5	REACH registration dossier TOXNET/HBCD
Persistence	Not PBT/vPvB	REACH registration dossier
Greenhouse gas formation potential	Not listed	Kyoto protocol- Annex A
Ozone-depletion potential	Not listed	Ozone Depleting Substances List (Montreal Protocol)
Monitoring – has the substance been found in human or environmental samples?	Detected in workers, urine samples	REACH registration dosser: Göen et al. 2001

7.2 Sorbic acid

Sorbic acid is an unsaturated fatty acid. Sorbic acid, together with is salts, is used as a preservative in food and cosmetics. The substance is naturally occurring and often regarded as safe. In cosmetics the maximum allowed concentration is 0.6%.

As for other organic acids used as preservatives in cosmetic products, these can only be used at an acidic pH of the product (pKa 4.8). In addition the water solubility is low (0.25%). This may limit the number of products that can be preserved with sorbic acid.

Potassium sorbate is a salt of sorbic acid. This is more water-soluble than sorbic acid, although the preservative effect comes from its disassociation into sorbic acid.

However, the substance can be an irritant for skin, and also for the respiratory tract.

SORBIC ACID CAS 110-44-1		
Physical Hazards		
Explosivity	Conclusive but not sufficient for classification	REACH registration dossier
Flammability	Conclusive but not sufficient for classification	REACH registration dossier
Oxidizing	Conclusive but not sufficient for classification	REACH registration dossier
Other properties of reactivity		
Human Health Hazards		
Acute toxicity	Conclusive but not sufficient for classification	REACH registration dossier
Skin or eye corrosion / irritation	There are reports of irritation, especially skin irritation from the substance Skin and eye irritant	TOXNET Clayton et al. 1993 Walker 1990 REACH registration dossier

Carcinogenicity	Conclusive but not sufficient for classification	REACH registration dossier
Mutagenicity	Conclusive but not sufficient for classification	REACH registration dossier
Reproductive toxicity (including developmental toxicity)	Conclusive but not sufficient for classification	REACH registration dossier
Endocrine disruption	Not listed	EU COM EDC database, TEDX list
Respiratory or skin sensitization	There are case reports of contact allergy after using the substance May cause respiratory irritation	TOXNET Marks et al. 1992 REACH registration dossier
Neurotoxicity	Data lacking	
Immune system toxicity	Data lacking	
Systemic Toxicity		
Toxic metabolites	No, metabolised as fatty acids, finally to carbon dioxide and water	TOXNET/HSDB
Environmental hazards		
Acute/chronic aquatic toxicity	Conclusive but not sufficient for classification	REACH registration dossier
Bioaccumulation	Conclusive but not sufficient for classification Low potential for bioconcentration based on BCF 6.0	REACH registration dossier
Persistence	Conclusive but not sufficient for classification	REACH registration dossier
Greenhouse gas formation potential	Not listed	Kyoto protocol- Annex A
Ozone-depletion potential	Not listed	Ozone Depleting Substances List (Montreal Protocol)
Monitoring – has the substance been found in human or environmental samples?	The substance is naturally occurring therefore difficult to know the sources of measured benzoic acid from biomonitoring.	

7.3 Benzoic acid

Benzoic acid is a natural occurring preservative. Benzoic acid is allowed in cosmetic products, with limitations between 0,5 and 2,5% depending on the type of product. 0,5% for leave-on products amd 2,5% for rinse-off products.

Benzoic acid has been self-classified in its REACH registration dossier as eye corrosive and respiratory irritant from exposure to benzoic acid dust.

As for sorbic acid, a limitation for use is that benzoic acid is only active at an acidic pH and that it has low water solubility. Soidum benzoate is the sodium salt of benzoic acid and can be used in water based products were it dissociates into benzoic acid.

Benzoic acid is on the TEDX list of potential endocrine disrupters, refererring to one study from 1995 in sheep, with effects on insulin and glucagon. It is also classified in the REACH registration dossier as an eye corrosive. There are also reports of skin irritation and/or sensitization.

BENZOIC ACID 65-85-0		
Physical Hazards		
Explosivity	Conclusive but not sufficient for classification	REACH registration dossier
Flammability	Data lacking	REACH registration dossier
Oxidizing	Data lacking	REACH registration dossier
Other properties of reactivity	No data	
Human Health Hazards		
Acute toxicity		
Highly toxic	Conclusive but not sufficient for classification	REACH registration dossier
Skin or eye corrosion / irritation	Corrosive, can cause serious eye damage	REACH registration dossier
Carcinogenicity	Not classifiable as to human carcinogenicity	USEPA 2006
Mutagenicity	Conclusive but not sufficient for classification	REACH registration dossier
Reproductive toxicity (including developmental toxicity)	Conclusive but not sufficient for classification	REACH registration dossier
Endocrine disruption	On TEDX list of potential EDCs	Mineo et al. 1995.
Respiratory or skin sensitization	May cause respiratory irritation, mildly irritating to mucous membranes, several case reports of allergy and asthma following exposure	TOXNET/HSDB
Neurotoxicity	Data lacking	
Immune system toxicity	Data lacking	
Systemic Toxicity		
Toxic metabolites	No, common metabolite is hippuric acid	TOXNET/HSDB
Environmental hazards		
Acute/chronic aquatic toxicity	Conclusive but not sufficient for classification	REACH registration dossier
Bioaccumulation	Conclusive but not sufficient for classification Reported BCF values suggests that bioconcentration in aquatic organisms is low	REACH registration dossier
Persistence	Conclusive but not sufficient for classification	REACH registration dossier
Greenhouse gas formation potential	Not listed	Kyoto protocol- Annex A
Ozone-depletion potential	Not listed	Ozone Depleting Substances List (Montreal Protocol)

Monitoring – has the substance been found in human or environmental samples?	There are evidence of workers being exposed to emissions from primers and paints. The substance is naturally occurring and released e.g. when burning wood, therefore difficult to know the sources of measured benzoic acid from biomonitoring.	TOXNET/HSDB

7.4 Packaging solutions

Single-use packaging could be one way to avoid preservatives, but this solution has other environmental disadvantages, since it is very material-intensive. There are however a number of multidose-solutions available, and as demand for preservative-free products increase, also these solutions are developed and diversified.

There are several multidose-packaging solutions on the market, some of them described below:

One example is Sterisol AB a Swedish company producing skin care products mainly for professional use but lately also for consumers. The manufacturing facility is highly automated and operates under strict cleanroom conditions. Together with an air- and bacteria-tight packaging that does not allow any contamination from the user to the product, there is no need to use any preservatives in the products. This packaging solution is used for Sterisols own product, but the technology is quite well described and could serve as inspiration also for others. An advantage is also that the package weight is low to minimise waste and transportation.

Packaging solutions for preservative-free products are also provided by MWV. This is a pump designed mainly for medical products that protects the products from contamination. The packages have a pump system that filters or blocks the returning air, and an actuator that prevents bacterial ingress into the dispenser. The company says they are expanding the range of preservative-free pumps to meet consumer demands for preservative-free formulations, and that their solutions are suitable for dermal and topical products.

Salient Asia Pacific also produces a range of airless dispensers that allows producers to produce preservative-free products. These are available for different volumes and types of products.

Another solution comes from Aptar. They have solutions both for pharmaceuticals and cosmetic products. The series for cosmetic products is called Irresistible.

8. Comparing alternatives

	Phenoxyethanol	Sorbic acid	Benzoic acid	Packaging solution, example Sterisol
Health aspects	PROS: Well-investigated and tested. CONS: Harmful if swallowed, causes eye irritation and is a potential neurotoxic according to some sources	PROS: Well-investigated and tested. CONS: Can be a skin irritant	PROS: Well-investigated and tested. CONS: Can cause eye damage, may cause respiratory irritation.	PROS: No preservatives are used, and thus the side-effects of such are eliminated. CONS:
Environmental aspect	PROS: Not identified as a PBT substance CONS:	PROS: Occurring naturally and relatively easily degraded to carbon dioxide and water CONS:	PROS: Occurring naturally, not a PBT substance CONS:	PROS: Does not require more packaging materials than for other products CONS:
Performance aspects	PROS: works well in many formulations, not pH dependent CONS: Strong smell	PROS: Well established CONS: pKa 4,8, active only at acidic pH, low water solubility	PROS: Well established CONS: pKa 4,8, active only at acidic pH, low water solubility	PROS: CONS : Might not be a possible solution for all types of products
Cost aspects	PROS: The substance is widely available and widely used CONS: All re-formulation is costly initially	PROS: The substance is widely available and widely used CONS: All re-formulation is costly initially	PROS: The substance is widely available and widely used CONS: All re-formulation is costly initially	PROS: Formulation may be easier without needing to take preservatives into account. CONS: Requires manufacturing under clean-room conditions

9. Summary and conclusion

Parabens are preservatives that have been used widely for a long time, especially in cosmetic products. Parabens have historically been regarded as safe, especially since there are not many reports on skin irritation or sensitization. However, an increasing amount of evidence shows that parabens have endocrine disruptive effects. Considering the vast exposure, especially of humans, the safety of parabens is now extensively discussed in Europe.

This study considered the aspects of paraben substitution and identifies available alternatives for four uses: cosmetics, food, cleaning products and pharmaceuticals. The focus is however on cosmetics.

Different aspects relating to preservation of cosmetics are being discussed, and it can be concluded that preservation of cosmetics is a challenging task. Preservatives are most often used in combination to assure a wide activity spectra towards different types of microorganisms. It is almost never possible with a simple substance-to-substance substitution of parabens, but rather a need to reformulate the entire product using a new preservation system.

When screening substances that are allowed in the EU for preservation of cosmetics against the hazardous Substance Database according to SUBSPORT Screening Criteria (SDSC), many alternatives passes these criteria.

In this reports the following substances that passed the criteria were further assessed:
Phenoxyethanol
Sorbic acid
Benzoic acid

Phenoxyethanol is a preservative that is being debated; limited evidence of neurotoxic effects has decreased the popularity of the substance. The two acids do not show much toxic properties, but the fact that they may be irritants, may be a problem for use in cosmetics. Also, acids can be used as preservatives only for products with an acidic pH. In view of other options, the organic acids can still be seen as a relatively safe option.

There is an increasing demand for and availability of specialised packages and solutions that allows formulation of preservative-free cosmetic products. This is a very promising future perspective, however it may be difficult to find suitable packages for every type of cosmetic products.

10. References

This report is mainly built on publically available information, with references to sources of information below. However, especially regarding some of the information on technical aspects of preservation, the information in this report has been compiled after series of discussions with a number of relevant companies, however for confidentiality reasons these companies are not mentioned in this report.

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Aptar packaging solution: http://www.aptar.com/pharma/consumer-health-care-division/news/press-releases/aptar-pharma-increases-capacities-in-preservative-free-systems-to-meet-demand
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FDA opinion on phenoxyethanol: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm049301.htm

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