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Survey of parabens

Part of the LOUS-review

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Survey of parabensSurvey of parabens

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Preface

The Danish Environmental Protection Agency's List of Undesirable Substances (LOUS) is intended as a guide for enterprises. It indicates substances of specific concern due to the actual consumption in Denmark and for which the use should be reduced or eliminated completely. The first list was published in 1998 and updated versions have been published in 2000, 2004 and 2009. The latest version, LOUS 2009 (Danish EPA, 2011) includes 40 chemical substances and groups of substances which have either been classified as dangerous or identified as problematic due to other concerns. The criteria employed by the Danish EPA for inclusion of substances on the list include:

- Properties of concern according to the EU 'List of hazardous substances';
- Properties of concern identified using computer-based model calculations outlined in the Danish EPA's 'Advisory list for self-classification of dangerous substances' (the Self-classification list);
- PBT/vPvB substances as identified by the EU;
- Substances on the EU 'Priority list of substances for further evaluation of their role in endocrine disruption'

Furthermore a tonnage threshold has been used. Substances used in quantities exceeding 100 tons per year in Denmark and fulfilling any of the abovementioned criteria have been included in LOUS 2009. For substances which are the subject of special focus in Denmark, the tonnage threshold can however be different.

Over the period 2012-2015 all 40 substances and substance groups on LOUS will be surveyed. The surveys include collection of available information on the use and occurrence of the substances, internationally and in Denmark, information on environmental and health effects, on alternatives to the substances, on existing regulation, on monitoring and exposue and information regarding ongoing activities under REACH among others.

The Danish EPA will on the basis of the surveys assess the need for any further regulation, substitution/phase out, classification and labelling, improved waste management, development of new knowledge or increased dissemination of information.

This survey concerns 6 substances of the paraben group: methyl-, ethyl-, propyl-, butyl-, isopropyl- and isobutylparaben.

The reasons for including certain parabens (propyl- and butyl-) on LOUS are that the substances have special focus in Denmark because of their listing on EU's list of priorities substances due to their endocrine disrupting effects. Also, one of the substances, butylparaben, was identified on the previously Danish Advisory List for Self-Classification as N; R50/53 (chronic aquatic toxic). On the present CLP self-classification list propyl- and butylparaben are classified as acute aquatic toxic.

The project ”Survey of Parabens” was carried out from June till December 2012.

The project was carried out by DHI, Denmark.
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The project was financed by the Danish Environmental Protection Agency.
The report reflects the author’s views and opinions, but not necessarily the views of the Danish Environmental Protection Agency.

Summary and Conclusion

Parabens are esters of 4-hydroxybenzoic acid. They are used as preservatives in a wide range of products including those for children, such as cosmetics, pharmaceuticals, consumer products like pet care products, and in foods. They are used as single compounds and in combination to exert an antimicrobial effect. They were first used in pharmaceuticals in the 1920's, and since then have found wide application because of their antimicrobial efficacy.
Propyl- and butylparabens were included in LOUS due to their potential endocrine disrupting properties and their possible environmental effects.
Scarce information was received by the industry and authorities on total and application related use volumes in and outside EU. Based on existing and available data retrieved from the internet, in view of the general description of the substances, and especially in view of the numerous companies that have pre-registrated the substances under REACH, the use in various products and the overall amount of parabens appears to be substantial. World-wide the main use areas are cosmetic products, pharmaceuticals and food. Based on the data found in this survey, methyl- and propylparaben are the most widely used parabens with methylparaben showing the highest use volume. Data on use from the Nordic countries product registers indicate that the use of parabens has declined from 2006-2007, when the level peaked, until 2010. However, the use volume in 2010 was at the same level as in 1999.

In the European Union (EU), the use of parabens is regulated by various types of regulation depending on the use. Methylparaben is registered according to the European chemicals legislation REACH (Registration, Evaluation, Authorisation and Restriction of Chemical substances), while ethyl-, propyl-, butyl-, isopropyl- and isobutylparaben currently are only pre-registered under REACH.
In cosmetic products 4-hydroxybenzoic acid, its salt and esters (the parabens) are currently authorised as preservatives in cosmetic products under the Cosmetic Directive (76/768/EEC). The maximum concentration of use is 0.4% (as acid) for one ester and 0.8% (as acid) for a mixture of esters. These regulations are currently being discussed on the EU level due to an Opinion from the Scientific Committee on Consumer Safety (SCCS) from 2010. Based on the potential estrogenic effects of the parabens, this Opinion recommends lowering the limits for propyl- and butylparaben to a maximum total concentration of 0.19% (as esters) or 0.14 (as acid) (SCCS, 2010). The Opinion suggests maintaining the current concentration limit for methyl- and ethylparaben, while data on isopropyl- and isobutylparaben are too limited for evaluation. In 2011 the Danish government banned the use of some parabens in cosmetics intended for children up to three years of age. The banned compounds are propyl-, isopropyl-, butyl- and isobutylparabens.
In the EU, only methyl- and ethylparaben are allowed as food additive and only for specific applications (i.e., confectionery, surface treatment of dry meat products, cereal- or potato-based snacks and coated nuts). Previously propylparaben was also allowed, but because of its potential estrogenic effects the European Food Safety Authority (EFSA) was in 2006 not able to determine an ADI for propylparaben. Therefore, it is no longer allowed as a food additive in the EU. In the USA methyl- and propylparaben are regarded as GRAS (Generally Recognised As Safe) substances, and may thus be added directly to food at a level not exceeding 0.1%. In the USA parabens are used in a wide range of products.
In both the EU and the USA, the use of parabens in pharmaceuticals is allowed if it can be documented that they are of no harm to the consumer. However, as seen in the EU for the cosmetics, also the European Medicines Agency may possibly decide on a more strict regulation in the future as initiatives are on-going regarding the parabens.

For the environment, the assessment of fate and hazard for parabens indicated a low toxicity. This was despite the QSAR prediction on which the Advisory list for self-classification is based, identifying propyl- and butylparaben as acutely toxic to aquatic organisms. Only few data regarding the environmental toxicity of parabens were found. For the parabens, estimated risk ratios were calculated as MEC/PNEC (measured environmental concentrations/predicted no effect concentrations). The highest MEC/PNEC was (0.010) for propylparaben followed by butylparaben (max. of 0.0086) and methylparaben (max. of 0.0042). These estimated low risk ratios (<<1) thus indicate a low risk for environmental effects of parabens. Some studies have shown that parabens may have estrogenic effects in fish. However, the effects are seen at concentrations much higher (µg - mg) than actual environmental concentrations, as for instance in Spain and Japan (ng/L).

Human exposure to parabens occurs mainly through cosmetic products. An older USA estimation of exposure indicates that only 20% will be through food, making cosmetics the main exposure route for humans. Of the exposure through cosmetics, almost 100% will be dermal.

Concerns have been raised about the endocrine disrupting potential of parabens at high exposure levels. Some studies in young male rats have shown adverse effects on sperm production and testosterone levels following oral exposure to parabens, i.e. propyl- and butylparaben. However other studies with the same study design and of a more recent date did not confirm these finding even at very high doses. Both the studies with positive and negative findings on reproductive toxicity have shortcomings, which makes it difficult to assess and weigh the results. Parabens are known to be estrogenic *in vitro* and in uterotrophic assays *in vivo*, and estrogenicity appears to increase with side chain length. Therefore, methyl-, ethyl-, propyl- and butylparaben are on the EU list of potential endocrine disruptors in category 1. Isopropyl- and isobutylparaben are not on this EU list. Category 1 substances are substances for which endocrine disrupting activity has been documented in at least one study of a living organism and are given the highest priority for further studies.
This project reveals that the method for evaluating parabens for their endocrine disruption potential and their kinetics are still not agreed upon. In addition, discussions on the most relevant NOEL/NOAEL and the dermal absorption values have not yet come to a conclusion. Thus, considering the endocrine disrupting effects, a final risk assessment still awaits which NOEL/NOAEL to use and which dermal absorption fraction to use, and to further identify the overall exposure for children. Currently a new study concerning reproductive toxicity is being assessed by the SCCS. Only few studies are available on the combined exposure to several parabens from several products.

Alternatives to parabens could be preservatives that are approved for use in other areas. However, before changing preservatives on a large scale, the sensitising potential of many other preservatives must be borne in mind. Parabens themselves are rarely seen as sensitizers, although some of the parabens have been self-classified as skin- or respiratory sensitizers. Technologies totally reducing the need for preservation have not yet been marketed.

In conclusion, this survey has revealed that the most widely used parabens in EU are methyl- and propylparaben. The major use is in cosmetics. In the EU parabens are controlled in the REACH, cosmetics, pharmaceuticals and foods regulations. Stricter EU legislation is currently being considered for parabens in cosmetics and pharmaceuticals due to the substances' potential for endocrine disruption. In Denmark, a national band of 4 parabens was introduced in cosmetic products intended for children up to three years old in 2011. Propyl- and butylparaben and their isoforms are potential endocrine disrupters, and methyl-and ethylparaben potential weak endocrine disrupters. For the environment, the assessment of fate and hazard for parabens indicates a low toxicity. Alternatives could be other approved preservatives with a low toxicity profile or new technology totally reducing the need for chemical preservation. However, no concrete solutions are yet available.

Sammenfatning og konklusion

Parabener er estere af 4-hydroxybenzoesyre. De bruges som konserveringsmidler i en lang række produkter som kosmetik, lægemidler, forbrugerprodukter som plejeprodukter til kæledyr samt i fødevarer. De anvendes som enkeltstoffer og i kombination på grund af deres antimikrobielle effekt. De blev første gang brugt i lægemidler i 1920'erne, og siden da har de fundet bred anvendelse på grund af deres antimikrobielle effekt. Propyl-og butylparabener indgik i LOUS på grund af deres potentielle hormonforstyrrende egenskaber og mulige miljøeffekter.
Der blev indhentet oplysninger fra industri og myndigheder på anvendelsesrelaterede brugsmængder i og uden for EU, men kun modtaget få besvarelser. Baseret på eksisterende og tilgængelige data hentet fra internettet og i betragtning af den generelle beskrivelse af stofferne - navnlig i betragtning af de mange virksomheder, der har præregistreret stofferne under REACH, vurderes den samlede anvendelse af parabener i forskellige produkter at være væsentlig. På verdensplan er de vigtigste anvendelsesområder kosmetiske produkter, lægemidler og fødevarer. På baggrund af de data, der er fundet i denne undersøgelse, er methyl-og propylparaben de mest anvendte parabener med methylparaben som det stof, der anvendes i den største mængde. Data fra de nordiske landes produktregistre tyder på, at brugen af parabener er faldet fra 2006-2007, hvor niveauet toppede, til 2010. Dog var den anvendte mængde i 2010 på samme niveau som i 1999.

I Den Europæiske Union (EU) er brugen af parabener reguleret ved forskellige typer forordninger afhængigt af brugen. Methylparaben er registreret i henhold til den europæiske kemikalielovgivning REACH (Registration, Evaluation, Authorisation and Restriction of Chemical substances), mens ethyl-, propyl-, butyl-, isopropyl- og isobutylparaben i øjeblikket kun er præ-registreret under REACH.
4-Hydroxybenzoesyre, dens salte og estere (parabenerne) er tilladt som konserveringsmidler i kosmetiske produkter under kosmetikdirektivet (76/768/EØF). Den maksimalt tilladte koncentration er 0,4 % (som syre) for én ester og 0,8 % (som syre) for en blanding af estere. Disse regler bliver i øjeblikket drøftet på EU-plan på grund af en rapport fra 2010 udarbejdet af Den Videnskabelige Komité for Forbrugersikkerhed (VKF). Baseret på de potentielle østrogene effekter af parabener anbefaler VKF at sænke grænserne for propyl- og butylparaben til en maksimal tilladt koncentration på 0,19 % (som ester) eller 0,14 % (som syre) (VKF, 2010). VKF foreslår bibeholdelse af den nuværende tilladte koncentration for methyl- og ethylparaben, mens data for isopropyl- og isobutylparaben er for begrænset til en egentlig evaluering.
I 2011 forbød den danske regering anvendelsen af visse parabener i kosmetiske produkter beregnet til børn op til tre år. De forbudte forbindelser er propyl-, isopropyl-, butyl- og isobutylparaben.
I EU er kun methyl- og ethylparaben tilladt som tilsætningsstof til fødevarer og kun til særlige anvendelser (konfekture, overfladebehandling af tørrede kødprodukter, korn- eller kartoffel-baserede snacks samt overfladebehandlede nødder). Tidligere var propylparaben også tilladt, men på grund af dets potentielle østrogene effekter var den Europæiske Fødevaresikkerhedsmyndighed (EFSA) i 2006 ikke i stand til at bestemme en værdi for Acceptabelt Dagligt Indtag (ADI) for propylparaben. Derfor er stoffet ikke længere tilladt som tilsætningsstof i fødevarer i EU. I USA betragtes methyl- og propylparaben som GRAS (generelt anerkendte som sikre) stoffer og kan således tilsættes direkte til fødevarer i en koncentration, der ikke overstiger 0,1 %. I USA anvendes parabener i en lang række fødevareprodukter.

Både i EU og USA er brugen af parabener i lægemidler tilladt, hvis det kan dokumenteres, at de ikke er til skade for forbrugeren. Men som det også ses i EU på kosmetikområdet, er Det Europæiske Lægemiddelagentur i drøftelser om en eventuelt strengere regulering i fremtiden, da der er initiativer i gang med hensyn til parabener.
Med hensyn til miljøet viser vurderingen af parabeners skæbne og fare en lav toksicitet. Dette til trods for at QSAR forudsigelser, som Miljøstyrelsens vejledende liste til selvklassificering er baseret på, angiver propyl- og butylparaben som akut toksiske for vandlevende dyr. Der blev kun fundet få data vedrørende parabeners økotoksicitet. For parabenerne blev en risikokoefficient beregnet som MEC/PNEC (målte miljø koncentrationer/forventede ingen-effekt-koncentrationer). Den højeste MEC/PNEC var (0,010) for propylparaben efterfulgt af butylparaben (maks. 0,0086) og methylparaben (maks. 0,0042). De beregnede lave risikokoefficienter (<< 1) indikerer således en lav risiko for miljømæssige effekter af parabener. Nogle undersøgelser har vist, at parabener kan have østrogene effekter på fisk. Dog ses virkningerne ved langt højere koncentrationer (ug - mg) end de faktisk målte miljø-koncentrationer, som for eksempel i Spanien og Japan (ng/L).

Human eksponering for parabener sker hovedsageligt gennem kosmetiske produkter. En ældre amerikansk eksponeringsvurdering viser, at kun 20 % af den samlede eksponering for parabener vil være gennem fødevarer, hvilket vil sige, at eksponering via kosmetik er hovedeksponeringsvejen for mennesker. Eksponeringen via kosmetik vil næsten udelukkende ske gennem huden.

Der er blevet udtrykt bekymring om parabeners potentielle hormonforstyrrende egenskaber ved høje eksponerings-niveauer. Nogle undersøgelser i unge hanrotter har vist skadelige virkninger på sædproduktionen og nedsatte testosteron-niveauer efter oral eksponering for parabener, dvs. propyl- og butylparaben. Men andre studier med samme undersøgelsesdesign og af nyere dato kunne ikke bekræfte disse fund selv ved meget høje doser. Både studierne med positive og negative resultater for reproduktionstoksicitet har mangler, hvilket gør det vanskeligt at vurdere resultaterne. Parabener vides at være østrogene *in vitro* og i uterotrofiske assays *in vivo*, og østrogeniciteten øges tilsyneladende med sidekædelængden. Derfor er methyl-, ethyl-, propyl- og butylparaben på EUs liste over potentielt hormonforstyrrende stoffer i kategori 1. Isopropyl- og isobutylparaben er ikke på denne EU-liste. Kategori 1 stoffer er stoffer, hvor den hormonforstyrrende effekt er dokumenteret i mindst én undersøgelse i en levende organisme. Kategori 1 stoffer har den højeste prioritet for yderligere undersøgelser.
Dette projekt viser, at metoden til vurdering af parabeners potentielle hormonforstyrrende effekter og kinetik stadig ikke er afklaret. Desuden er det endnu ikke konkluderet, hvilke NOEL/NOAEL samt dermale absorptionsværdier, der er de mest relevante til en endelig risikovurdering. Der mangler derfor endnu en afklaring af, hvilken NOEL/NOAEL og dermal absorptionsfraktion, der skal bruges ved en endelig risikovurdering baseret på stoffernes hormonforstyrrende potentiale samt yderligere at identificere den overordnede eksponering for børn. I øjeblikket bliver en ny undersøgelse om reproduktionstoksicitet vurderet af VKF. Der er kun få undersøgelser tilgængelige på kombineret eksponering for flere parabener fra flere produkter.

Alternativer til /parabener kan være konserveringsmidler, der er godkendt til brug på andre områder. Ved ændring af konserveringsmidler i stor skala skal det sensibiliserende potentiale af mange andre konserveringsmidler dog tages i betragtning. Parabener i sig selv ses sjældent at være sensibiliserende, selvom nogle af parabenerne er selvklassificeret som hud- eller luftvejssensibiliserende. Teknologier, der helt fjerner behovet for kemisk konservering, er endnu ikke blevet markedsført.

Sammenfattende har denne kortlægning vist, at de mest anvendte parabener i EU er methyl- og propylparaben. Den primære anvendelse er i kosmetik. I EU reguleres parabener i REACH, kosmetik-, lægemiddel- og fødevarelovgivningen. Strengere EU-lovgivning er i øjeblikket under overvejelse for parabener anvendt i kosmetik og lægemidler på grund af stoffernes potentielle

hormonforstyrrende effekt. I 2011 blev der i Danmark indført et nationalt forbud mod 4 parabener i kosmetiske produkter beregnet til børn op til tre år.
Propyl- og butylparaben og deres isoformer er potentielt hormonforstyrrende, og methyl- og ethylparaben er potentielt svagt hormonforstyrrende stoffer. Med hensyn til miljøet viser vurderingen af skæbne og fare, at parabener har en lav toksicitet. Alternativer til parabenerne kan være andre godkendte konserveringsmidler med en lav toksicitetsprofil eller ny teknologi, der reducerer behovet for kemisk konservering. Der er imidlertid ikke fundet nogen konkrete løsninger endnu.

1. Introduction

1.1 Survey background

Propyl- and butylparaben are included in LOUS due to their potential endocrine disrupting properties and their possible environmental effects. In this report, surveys of the use, legislation, exposure and environment and health properties of 6 parabens: methyl-, ethyl-, propyl-, butyl-, isopropyl- and isobutylparaben are made. The additional parabens compared to the ones included in LOUS were added to this survey as the parabens are often used in combination or alternatives to one another (see table 1). The survey is based on existing information only.

Parabens are a group of substances used as preservatives. Chemically they resemble benzoic acid, the preserving substance naturally present in lingon berries. They are highly effective in preventing the growth of fungi and bacteria and are used to preserve products and greatly extend their shelf life. Parabens have been used for decades as preservatives in the food, drug, personal care and cosmetic products.

1.2 Methods

1.2.1 Databases

For this survey the data from the Nordic SPIN database has been used. Information from web searches on the use and production of parabens was also reported.

1.2.2 Companies, authorities and other organisations contacted

Questionnaires were prepared for the industry, authorities and other organisations. For the industry part industrial companies were selected among those who have reported notifications to ECHA on all, several or one of the substances. They covered many different sectors, countries and were mainly larger industries but also some smaller. About 50 different European industrial companies have received a questionnaire. Additional 6 Chinese and Indian manufactures of parabens were contacted for information about manufacture volumes. Only two answers from one European company and one Indian manufacturer did return.

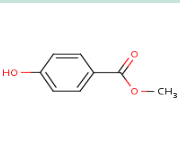
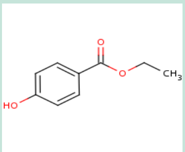
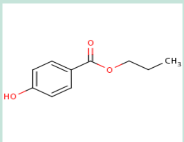
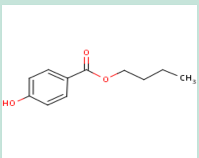
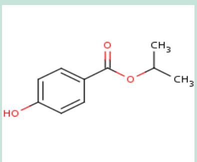
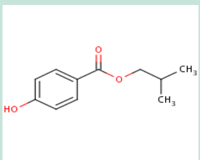
Among authorities, countries hosting companies selected above were prioritized. 11 countries received the questionnaire (Australian, Canada, Finland, France, Germany, Italy, Netherlands, Norway, Poland, Sweden and United Kingdom). Only one of them provided useful data. Two replied that they did not have additional data than what is available from REACH. Two replied that parabens are not substances of highest priority and therefore they have no data. One authority informed that they have not the resources to find available data based on the short deadline. Along with that some Danish industrial organizations, Danish EPA, the Danish Veterinary and Food Administration, the Danish Health and Medicines Authority and other contact persons have provided data to this present survey on parabens.

2. Identity of the substances

2.1 Name and other identifiers of the substances

Six different parabens are being evaluated in this report. The substances and their identity are presented in table 1.

TABLE 1
NAME AND OTHER IDENTIFIERS OF THREE OF THE SIX EVALUATED PARABEN SUBSTANCES (HSDB)

EC name:	**methyl 4-hydroxybenzoate**	**ethyl 4-hydroxybenzoate**	**propyl 4-hydroxybenzoate**
EC number:	202-785-7	204-399-4	202-307-7
CAS number:	99-76-3	120-47-8	94-13-3
Synonyms:	Methylparaben; Benzoic acid, p-hydroxy-, methyl ester; p-hydroxybenzoic methyl ester	Ethylparaben; Benzoic acid, p-hydroxy-, ethyl ester; p-hydroxybenzoic ethyl ester	Propylparaben; Benzoic acid, p-hydroxy-, propyl ester; p-hydroxybenzoic propyl ester
Molecular formula:	$C_8H_8O_3$	$C_9H_{10}O_3$	$C_{10}H_{12}O_3$
Molecular weight range:	152.15	166.17	180.20
Structure:			
EC name:	**butyl 4-hydroxybenzoate**	**isopropyl 4-hydroxybenzoate**	**isobutyl 4-hydroxybenzoate**
EC number:	202-318-7	224-069-3	224-208-8
CAS number:	94-26-8	4191-73-5	4247-02-3
Synonyms:	Butylparaben; Benzoic acid, p-hydroxy-, butyl ester; p-hydroxybenzoic butyl ester	Isopropylparaben; Benzoic acid, p-hydroxy-, isopropyl ester; p-hydroxybenzoic isopropyl ester	Isobutylparaben; Benzoic acid, p-hydroxy-, isobutyl ester; p-hydroxybenzoic isobutyl ester;
Molecular formula:	$C_{11}H_{14}O_3$	$C_{10}H_{12}O_3$	$C_{11}H_{14}O_3$
Molecular weight range:	194.23	180.20	194.23
Structure			

2.2 Physico-chemical properties

TABLE 2
PHYSICAL-CHEMICAL PROPERTIES FOR METHYL-4-HYDROXYBENZOATE AND ETHYL-4-HYDROXYBENZOATE (HSDB)

Property	Methyl-4-hydroxybenzoate	Ethyl-4-hydroxybenzoate	Ref. REACH, Annex, §
Physical state	Colourless crystals or white crystalline powder	Small, colorless crystals or white powder	VII, 7.1
Melting/freezing point	131°C	116 °C	VII, 7.2
Boiling point	270-280°C	297-298 °C	VII, 7.3
Relative density	No data found	No data found	VII, 7.4
Vapour pressure	2.37×10^{-4} mm Hg	9.29×10^{-5} mm Hg	VII, 7.5
Surface tension	No data found	No data found	VII, 7.6
Water solubility (mg/L)	2.50×10^{3} mg/L	8.85×10^{2} mg/L	VII, 7.7
Partition coefficient n-octanol/water (log value)	1.96	2.47	VII, 7.8
Stability in organic solvents and identity of relevant degradation products	No data found	No data found	XI, 7.15
Dissociation constant	pKa = 8.4	pKa = 8.34	XI, 7.16

TABLE 3
PHYSICAL-CHEMICAL PROPERTIES FOR PROPYL-4-HYDROXYBENZOATE AND BUTYL-4-HYDROXYBENZOATE (HSDB)

Property	Propyl-4-hydroxybenzoate	Butyl-4-hydroxybenzoate	Ref, REACH Annex, §
Physical state	White crystals	Small, colorless crystals or powder	VII, 7.1
Melting/freezing point	96-97 °C	68-69 °C	VII, 7.2
Boiling point	No data found	No data found	VII, 7.3
Relative density	1.063	No data	VII, 7.4
Vapour pressure	5.55 x 10-4 mm Hg	1.86 x 10-4 mm Hg	VII, 7.5
Surface tension	No data found	No data found	VII, 7.6
Water solubility (mg/L)	5.00×10^{2} mg/L	2.07×10^{2} mg/L	VII, 7.7
Partition coefficient n-octanol/water (log value)	3.04	3.57	VII, 7.8
Stability in organic solvents and identity of relevant degradation products	No data found	No data found	XI, 7.15
Dissociation constant	pKa = 7.91	pKa = 8.47	XI, 7.16

TABLE 4
PHYSICAL-CHEMICAL PROPERTIES FOR ISOPROPYL-4-HYDROXYBENZOATE AND ISOBUTYL-4-HYDROXYBENZOATE (CIR, 2008)

Property	Isopropyl-4-hydroxybenzoate	Isobutyl-4-hydroxybenzoate	REACH ref Annex, §
Physical state	No data found	No data found	VII, 7.1
Melting/freezing point	No data found	No data found	VII, 7.2
Boiling point	No data found	No data found	VII, 7.3
Relative density	No data found	No data found	VII, 7.4
Vapour pressure	No data found	No data found	VII, 7.5
Surface tension	No data found	No data found	VII, 7.6
Water solubility (mg/L)	No data found	No data found	VII, 7.7
Partition coefficient n-octanol/water (log value)	2.91	3.4	VII, 7.8
Stability in organic solvents and identity of relevant degradation products	No data found	No data found	XI, 7.15
Dissociation constant	No data found	No data found	XI, 7.16

3. Regulatory framework

Information on the regulatory framework that covers the use of parabens has been sought national in Denmark, in the EU and globally for the following areas:

- The European chemicals legislation REACH (Registration, Evaluation, Authorisation and Restriction of Chemical substances)
  - Harmonised classification
  - Self-classification
- Cosmetic legislation
- Food legislation
- Pharmaceuticals legislation
- Waste regulation

In addition, other national and European initiatives regarding the regulation of parabens are included in this chapter.

3.1 Classification

3.1.1 Harmonised classification in the EU

None of the six parabens are assigned a *harmonised* classification and labelling code according to the classification and Labelling of Products (CLP) regulation: Regulation (EC) No 1272/2008 (Annex VI, part 3, Table 3.1).

3.1.2 Self-classifications in the EU

In the classification and labelling (C&L) inventory (database) notifiers have reported classifications for parabens (ECHA, 2012). In table 5 the spectrum of different classifications, reported as of November 17 2012, are shown.

TABEL 5
THE (CLP) SELF-CLASSIFICATION NOTIFIED BY MOST MANUFACTURERS AND IMPORTERS ACCORDING TO ECHA 'CLASSIFICATION AND LABELLING (C&L) INVENTORY'

Substance	No. of notifiers (total)	Classification		No. of notifiers reporting a specific classification
		Hazard Class and Category Code	Hazard Statement Code	
Methyl-4-hydroxybenzoate	1908	Skin Irrit.2 Eye Irrit.2 STOT SE3	H315 H319 H335	47%
		Not classified		43%
		Aquatic Chronic 3 Muta.2 Resp. Sens.1	H412 H341 H334	Fewer than 10%

Substance	No. of notifiers (total)	Classification		No. of notifiers reporting a specific classification
		Hazard Class and Category Code	Hazard Statement Code	
Ethyl-4-hydroxybenzoate	767	Not classified		46%
		Asp.tox.3 Skin Irrit.2 Skin Sens.1 Eye Irrit.2	H304 H315 H317 H319	38%
		STOT SE 3 Acute Tox. 4 Resp. Sens.1	H335 H302 H334	Fewer than 16%
Propyl-4-hydroxybenzoate	1566	Skin Irrit.2 Eye Irrit.2 STOT SE 3	H315 H319 H335	55%
		Not classified		29%
		Eye Dam.1 Aquatic Acute 1 Skin Sens.1	H318 H400 H317	Fewer than 16%
Butyl-4-hydroxybenzoate	633	Skin Irrit.2 Eye Irrit.2 STOT SE 3	H315 H319 H335	50%
		Not classified		40%
		Eye Dam.1 Aquatic Chronic.4	H318 H413	Fewer than 10%
Isopropyl-4-hydroxybenzoate	67	Eye Irrit.2	H319	43%
		Acute tox.4 Eye Dam.1	H302 H318	34%
		Not classified		16%
isobutyl-4-hydroxybenzoate	262	Not classified		85%
		Eye Dam.1	H318	11%
		Aquatic Acute 1	H400	2%

H302; Harmful if swallowed
H304; May be fatal if swallowed and enters airways
H315; Causes skin irritation
H317; May cause an allergic skin reaction
H318; Causes serious eye damage
H319; Causes serious eye irritation
H334; May cause allergy or asthma symptoms or breathing difficulties if inhaled
H335; May cause respiratory irritation
H341; Suspected of causing genetic defects
H400; Very toxic to aquatic life
H412; Harmful to aquatic life with long lasting effects
H413; May cause long lasting harmful effects to aquatic life

As can be seen in table 5 the substances are typically self-classified for local irritation in relation to skin, eyes and the respiratory tract and for respiratory or skin sensitisation.

3.2 The European chemical legislation; REACH

The parabens are regulated within the EU. Methylparaben are registered according to the European chemical legislation REACH, while ethyl-, propyl-, butyl-, isopropyl- and isobutylparaben are currently only pre-registered by numerous notifiers. For methylparaben the registrant has reported long-term DNEL values for both dermal and oral exposure of 1.04 mg/ kg bw/day and for inhalation a long-term DNEL value of 3.62 mg/m^3 in relation to the general population.

3.3 Other regulations

Parabens are used in a broad spectrum of products not regulated under REACH. Other pieces of legislation by which parabens are regulated are presented below.

3.3.1 Cosmetics

Some parabens are restricted both in and outside EU. As the only member state in the EU, Denmark has introduced a ban at national level. For the use of parabens as preservative in cosmetics the restrictions are the following:

In the EU:

4-Hydroxybenzoic acid, its salt and esters (parabens) are currently authorised in Annex VI, entry 12 of the Cosmetic Directive (76/768/EEC) at a maximum use concentration of 0.4% (as acid) for one ester and 0.8% (as acid) for a mixture of esters.

National regulation in Denmark:

In 2011, the Danish government banned the use of some parabens (propyl-, isopropyl-, butyl- and isobutylparabens) in cosmetic products intended for children up to three years old as a precautionary measure, as children might be especially vulnerable to endocrine disrupting effects (BEK no. 166 24/02/2011).

In the USA:

All six selected parabens are allowed in cosmetics without any concentration limit in the USA (FDA, 2012a). The Cosmetic Ingredient Review (CIR) reviewed the safety of methylparaben, propylparaben, and butylparaben in 1984 and concluded they were safe for use in cosmetic products at levels up to 25%. Typically parabens are used at levels ranging from 0.01 to 0.3%. In 2005 this evaluation was reviewed again. However, after considering the margins of safety for exposure of women and infants, CIR determined that there was no need to change its original conclusion that parabens are safe for use in cosmetics. The FDA is aware of the possible estrogenic effects of some parabens, but believes that at the present time there is no reason for consumers to be concerned about the use of cosmetics containing parabens. However, the FDA will continue to evaluate new data in this area (FDA, 2007).

3.3.2 Food

In the EU:

Two of the selected parabens may be used as preservative in food:

- Ethylparaben, E 214, its sodium salt E 215
- Methylparaben, E 218, its sodium salt E 219.

The two parabens are allowed in confectionery (excluding chocolate) in amounts up to 300 mg parabens/kg. Methyl- and ethylparaben are also allowed as surface treatment of dried meat products, cereal- or potato-based snacks and coated nuts (maximum 300 mg/kg) (Regulation (EU) No. 1129/2011).

On July 13th 2004 the European Food Safety Authority (EFSA) established a group ADI of 0 - 10 mg/kg body weight for the sum of methyl and ethyl p-hydroxybenzoic acid esters and their sodium salts. EFSA considered that propylparaben should not be included in this group ADI because propylparaben, contrary to methyl- and ethylparaben, had effects on sex hormones and the male reproductive organs in juvenile rats. Therefore, due to lack of a clear no observed adverse effect level (NOAEL), EFSA was unable to recommend an ADI for propylparaben. It was necessary to withdraw E 216 propyl p-hydroxybenzoate and E 217 sodium propyl p-hydroxybenzoate from Regulation (EU) No. 1129/2011.

In the USA:
Methyl- and propylparaben added directly to human food are affirmed as generally recognized as safe (GRAS) (FDA, 2012b), and are GRAS for use at a level not exceeding 0.1% in accordance with good manufacturing or feeding practice (FDA, 2012c).
This conclusion was based on the following information: Upon consumption of parabens in amounts greatly exceeding those current in the normal diet in the USA population, there are no short-term toxicological consequences in the rat, rabbit, cat, dog, or man and no long-term toxicological consequences in rats. In addition, there is no evidence that consumption of the parabens as food ingredient has had an adverse effect on man in the 40 years they have been so used in the US. In the light of these observations, the Select Committee concluded: There is no evidence in the available information on the two parabens methyl and propyl p-hydroxybenzoic acid that demonstrates a hazard to the public when the substances are used at levels that are now current or that might reasonably be expected in future (FDA, 2012d).

Other countries:
Several other countries, including Canada, Japan, and the Philippines have also approved the use of parabens as antimicrobial food additives (Soni *et al*, 2002).

3.3.3 Pharmaceutical use

In the EU:
Parabens as preservatives are allowed in pharmaceuticals in the EU, but as for other preservatives, the use and concentration must be justified accordingly to risk (EMEA, 2006). In addition, the pharmaceutical legal and regulatory context and the evaluation process all imply that similar principles of risk assessment are applied both to excipients and to active substances where appropriate. However, excipients have only an indirect benefit for the patient, as part of a medicinal product. Therefore, any risk identified for an excipient, and in particular a CMR substance, would be acceptable only on certain conditions. These are either that this excipient cannot be substituted by a safer alternative available or that the toxicological effects of the excipient in animal models are considered not relevant for humans (e.g. species-specific or very large safety ratio), or that the overall benefit of the product outweighs the risk posed by the excipient (EMA, 2009).

In the US:
Parabens are permitted in pharmaceutical products. Preservatives are considered inactive ingredients and must meet the requirements specified in the Code of Federal Regulations Title 21, §330.1 (FDA, 2012e). Accordingly, the preservatives must be a suitable ingredient that is safe and does not interfere with effectiveness of the medicinal product.

3.4 Waste water and solid waste regulations

No data were found on this topic.

3.5 Regulatory and risk management initiatives

In the EU there are initiatives to strengthen the regulation of some parabens when they are used as preservatives in cosmetics. In a review of the most up-to-date scientific information, the Scientific Committee on Consumer Safety (SCCS) confirmed that for the smaller parabens (methyl-and ethylparaben), the current concentration limit is considered safe (SCCS, 2010). For propyl- and butylparaben, the SCCS recommends lowering the limit to a maximum total concentration of 0.19% (as ester) or 0.14% (as acid) for each of the substances (SCCS, 2010). For other, less used, parabens (isopropyl-, isobutylparabens), only a very limited amount of information is available, and the potential risk could not be evaluated (SCCS, 2010).
Also for use in pharmaceutical products, initiatives are being considered to adjust the acceptable levels of methyl- and propylparaben in oral medicinal products. At the moment a "Reflection paper on the presence of parabens in human medicinal products" is being prepared.

Methyl-, ethyl-, propyl- and butylparaben are on the EU list of potential endocrine disruptors which are to be studied further for endocrine-disrupting properties (EU, 2012). They are entered as category 1 substances, which are substances for which endocrine activity have been documented in at least one study of a living organism. These substances are given the highest priority for further studies. Furthermore, propyl- and butylparaben were both added to the SIN list (Substitute It Now) at the latest update of the database (SIN list 2.0). The SIN project is an NGO-driven European project to speed up the transition to a toxic-free world with the purpose to identify substances of very high concern according to REACH criteria. Propyl- and butylparaben are considered to belong to this category solely due to their potential endocrine disrupting properties.

3.5.1 Danish Advisory List for Self-Classification

Parabens are found in the Danish Advisory list for CLP self-classification of dangerous substances', which is based on QSAR predictions (Danish EPA, 2010). The self-classifications for the parabens are shown in table 6.

TABLE 6
CLP SELF-CLASSIFICATION ACCORDING TO THE DANISH 'ADVISORY LIST FOR CLP SELF-CLASSIFICATION OF DANGEROUS SUBSTANCES'

Substance	CAS No.	Classification Health*/	Classification Environment*
Methyl-4-hydroxybenzoate	99-76-3	Muta2	-
Ethyl-4-hydroxybenzoate	120-47-8	Muta2	Acute1
Propyl-4-hydroxybenzoate	94-13-3	-	Acute1
Butyl-4-hydroxybenzoate	94-26-8	-	Acute1
Isopropyl-4-hydroxybenzoate	4191-73-5	SkinSens1	-
isobutyl-4-hydroxybenzoate	4247-02-3	-	Acute1

* - : not listed
Muta2: mutagenic category 2
Acute1: Aquatic acute toxicity category 1
SkinSens1: Skin sensitizer category 1

3.6 Conclusion

Due to the endocrine disrupting potential of some of the parabens, the substances are restricted both in the EU, elsewhere in the world, and a national ban was implemented in Denmark in 2011.

In the European Union (EU), the use of parabens is regulated by various types of regulation depending on the use. Methylparaben is registered according to the European chemicals legislation REACH (Registration, Evaluation, Authorisation and Restriction of Chemical substances), while ethyl-, propyl-, butyl-, isopropyl- and isobutylparaben currently are only pre-registered under REACH.

In cosmetic products 4-hydroxybenzoic acid, its salt and esters (the parabens) are currently authorised as preservatives in cosmetic products at a maximum concentration of use is 0.4% (as acid) for one ester and 0.8% (as acid) for a mixture of esters. The limits are currently being discussed on the EU level due to an Opinion from the Scientific Committee on Consumer Safety (SCCS) from 2010. Based on the potential estrogenic effects of the parabens, this Opinion recommends lowering the limits of propyl- and butylparaben to a maximum total concentration of 0.19% (as ester) or 0.14 (as acid) (SCCS, 2010). The Opinion suggests maintaining the current concentration limit for methyl- and ethylparaben, while data on isopropyl- and isobutylparaben are too limited for evaluation.

In 2011 the Danish government banned the use of some parabens in cosmetics intended for children up to three years of age. The banned compounds are propyl-, isopropyl-, butyl- and isobutylparabens.

In the EU, only methyl- and ethylparaben are allowed as food additive and only for specific applications (i.e., confectionery, surface treatment of dry meat products, cereal- or potato-based snacks and coated nuts). Previously propylparaben was also allowed, but because of its potential estrogenic effects the European Food Safety Authority (EFSA) was in 2006 not able to determine an ADI for propylparaben. Therefore, it is no longer allowed as a food additive in the EU. In the USA methyl- and propylparaben are regarded as GRAS (Generally Recognised As Safe) substances, and may thus be added directly to food at a level not exceeding 0.1%. In the USA parabens are used in a wide range of products.

In both the EU and the USA, the use of parabens in pharmaceuticals is allowed if it can be documented that they are of no harm to the consumer. However, as seen in the EU for the cosmetics, also the European Medicines Agency may possibly decide on a more strict regulation in the future as initiatives are on-going regarding the parabens.

4. Manufacture, import, export and use

The literature indicates that parabens are primarily used as preservatives in cosmetics, food and pharmaceuticals. However, other products like cleaning agents, biocidal products and pet care products may also contain parabens.

4.1 Manufacturing

4.1.1 Manufacturing sites

Several manufacturing sites are found in Europe, USA and Asia. Based on searches on the internet it was established that a lot of manufactures are located in India and China. Several of them have been contacted during this survey, but none of them wanted to participate in the survey.

4.1.2 Manufacturing volumes

Based on the large amount of companies pre-registration the substances in the EU it can be deduced that the manufacture and import of the substances is substantial. It has not been possible to collect/find a total amount of manufacturing volume for each of the parabens even though the information has been looked for at many places and several companies has been asked for data.

Information on production and/or use of parabens in the USA was identified from the USA Non-confidential Inventory Update Reporting production Volume information (Table 7). This is however only documenting the production/use from 1986 to 2002 and is therefore regarded as data of lower value.

TABLE 7
THE PRODUCTION OF PARABENS IN USA (THE PRODUCTION VALUES ARE SHOWN IN TONNES PER YEAR)

Year	Methyl-	Ethyl-	Propyl-	Butyl-	Isopropyl	Isobutyl
1986	250 – 500	5 – 250	5– 250	5 – 250	-	-
1990	500 – 5000	5 – 250	250 – 500	5 - 250	-	-
1994	500 – 5000	-	250 – 500	5 - 250	-	-
1998	250 – 500	-	5 – 250	-	-	-
2002	5 - 250	5 - 250	5 – 250	-	-	-

“-“: No information given (USA Non-confidential Inventory Update Reporting production Volume information)

Even though based on old data, the data indicates that the parabens produced in largest amounts have been methyl-,and propylparaben, but in 2002 the level of methyl-, ethyl- and propylparaben is the same. No information was available on the iso-compounds. There appears to be decrease in consumption in 2002. However, more recent data are lacking.

4.2 Import and export volumes

Parabens are produced all over the world, and many companies import parabens from manufacturers in Asia and US.
Non-confidential data collected during the survey was received from the Danish and Finnish EPAs product registers and shown in table 8 and 9. This information shows that methylparaben is the substance imported the most in Denmark and in Finland. In Denmark, the use volume of propylparaben is the second highest.

TABLE 8
INFORMATION OF USE VOLUMES FROM THE DANISH PRODUCT REGISTERS (2011), DATA IS SHOWN AS TON PER YEAR

Substance	Use Volume
Methylparaben	0.689
Ethylparaben	0.042
Propylparaben	0.393
Butylparaben	0.005
Iso-propylparaben	-
Iso-butylparaben	0.004

TABLE 9
INFORMATION OF IMPORT VOLUMES FROM THE FINNISH PRODUCT REGISTER FROM 2011.. DATA ARE SHOWN AS TON PER YEAR

Substance	Manufacture (tonnes)	Imports Tonnes / Origin		Relevant year(s)
Methylparaben	0	1.8	N/A	2011
Ethylparaben	0	0.2	N/A	2011
Propylparaben	0	0.2	N/A	2011
Butylparaben	0	N/A	N/A	2011
Iso-propylparaben	0	0	N/A	2011
Iso-butylparaben	0	N/A	N/A	2011

N/A: Not available

4.3 Information on use

Parabens has been used for several decades mainly as preservative in cosmetics covered by the Council Directive 76/768/EEC, but is also used as preservative in pharmaceuticals, food, pet care products, biocides etc.

4.3.1 Use volumes

From the Nordic SPIN database ("Substances in Preparations in the Nordic Countries") information of use volumes has been retrieved. The SPIN database is the result of a common Nordic initiative to gather non-confidential, summarized information from the Nordic product registers on the common use of chemical substances in different types of products and industrial areas. All the data are summarized and no references can be made to specific concentrations of any given substance in any kind of product. The Nordic product registers are among the most comprehensive product registers in the world with regard to completeness of information and the number of registered products and substances. Of the Nordic product registers, the Danish and Swedish product registers contain information on the largest numbers of products and the highest proportion of products on the market. In Sweden, the declaration requirements are based on the customs tariff codes, so that as a general rule, they apply to all chemical products (substances and preparations). The Swedish register therefore contains more products than those that are classified as dangerous according to EU legislation. In Norway, declaration is mandatory for all products to which the Regulations relating to the classification, labelling, etc. of dangerous chemicals (the Chemical Labelling Regulations) apply, including consumer products. These regulations implement EU directives on the classification, labelling, etc. of chemicals in Norwegian legislation.

The requirements for declaration to the Finnish and Danish product registers are also based on these directives (in Denmark, declaration is limited to dangerous products for professional use), but there are additional extensive national rules for notification. In Finland these additional requirements for example apply to chemicals that cause danger although they are not classified, and in Denmark they apply to chemicals that cause danger although they are not classified and solvents, pesticides and biocides.

All four countries exempt products that come under legislation on foodstuffs and medicinal products from mandatory declaration. Additionally, it is important to note that the use categories in the database do not include all potential uses of the parabens; e.g. the duty to declare products to the product registers does not apply to cosmetic products, and therefore these use volumes do not cover the total use volume of the parabens. However, the figures can give a rough estimate, especially of the use trends.

In figure 1, 3, 5 and 7 the total amount of parabens in combination with the number of products containing the substances are illustrated.

4.3.1.1 Methylparaben

The total use volume of methylparaben registered in Sweden, Denmark, Finland and Norway from the period from 1999 to 2010 (data indirectly retrieved from the Nordic SPIN database) is shown in Figure 1. The total use volume and the number of products containing methylparaben for each separate country are shown in Figure 2. It is observed in figure 1 that the use volume of methylparaben increased from 1999 until 2005-2006 (peaking at about 60 ton) and then has decreased until 2010. The level in 2010 is at the same level as seen in 2002. At the same time the number of preparations containing methylparaben (figure 2) has remained on almost the same level indicating that the preparations contains a lower concentration of methylparaben in 2010 than in 2005-2006.

FIGURE 1 THE TOTAL AMOUNT OF METHYLPARABEN REGISTERED IN SWEDEN, DENMARK, FINLAND AND NORWAY (DATA INDIRECTLY RETRIEVED FROM THE NORDIC SPIN DATABASE)

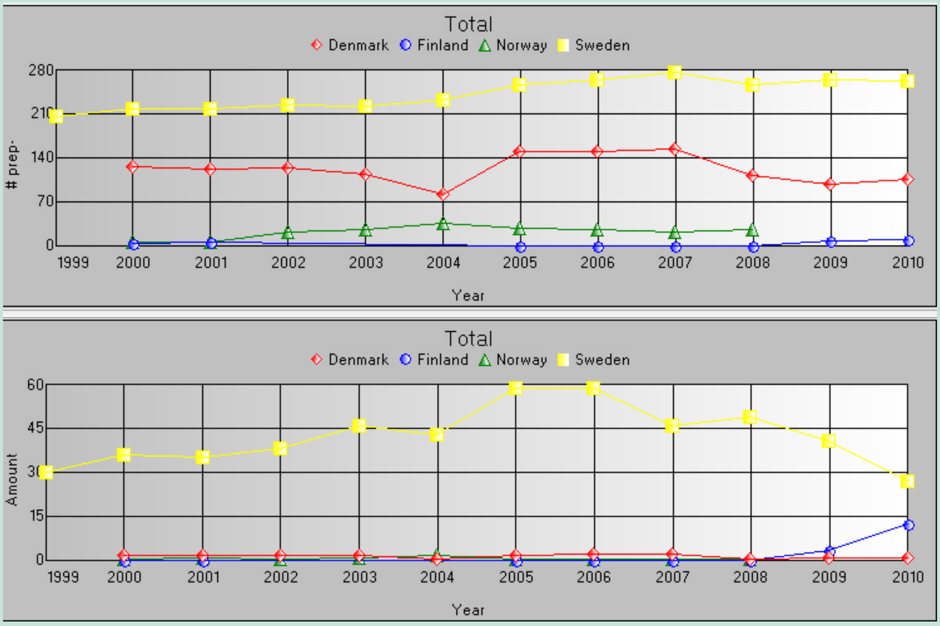


FIGURE 2 THE TOTAL USE OF METHYLPARABEN AND THE NUMBER OF PRODUCTS. THE DATA COVERS A PERIODE FROM 1999 TO 2010 FOR SWEDEN, DENMARK, FINLAND AND NORWAY SEPERATELY (DATA RETRIEVED FROM THE SPIN DATABASE)

4.3.1.2 Ethylparaben

The total use volume of ethylparaben registered in Sweden, Denmark, Finland and Norway from the period from 1999 to 2010 (data indirectly retrieved from the Nordic SPIN database) is shown in Figure 3. The total use volume and the number of products containing ethylparaben for each separate country are shown in Figure 4. It is observed in figure 3 that the use volume of ethylparaben is varying from year to year from 1 tonnes in 2004 to a peak of 4.5 tonnes in 2007 and in 2010 being at a low level compared to 2007. At the same time the number of products containing ethylparaben (figure 4) has remained on almost the same level indicating that the products contains a lower concentration of methylparaben in 2010 than in 2007.

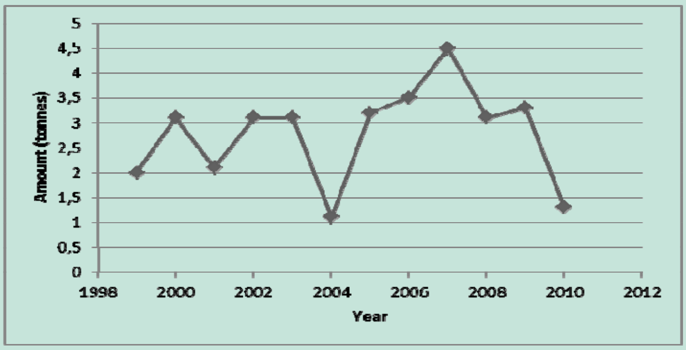


FIGURE 3 THE TOTAL AMOUNT OF ETHYLPARABEN REGISTERED IN SWEDEN, DENMARK, FINLAND AND NORWAY (DATA INDIRECTLY RETRIEVED FROM THE NORDIC SPIN DATABASE)

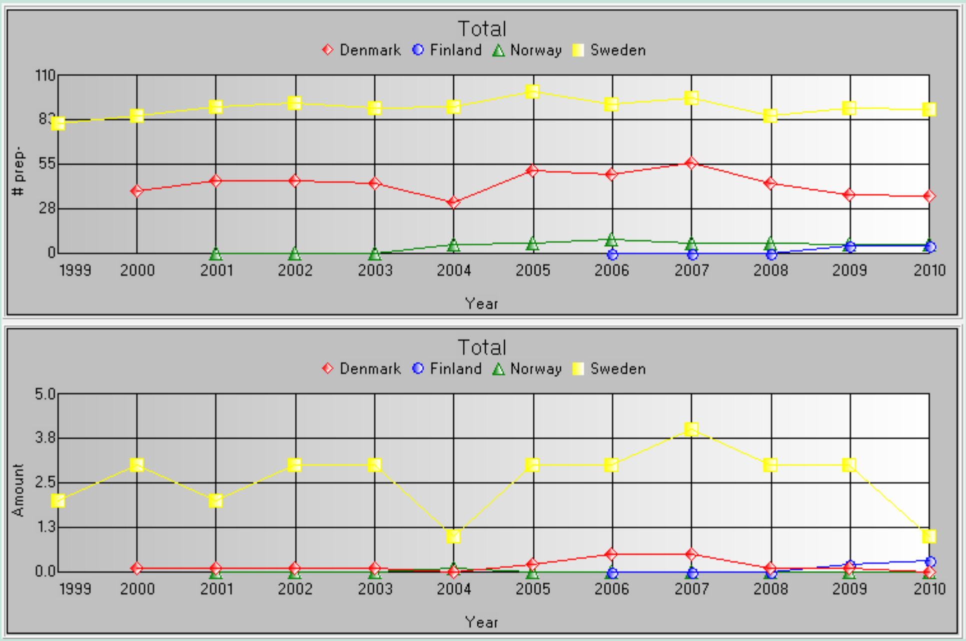


FIGURE 4 THE TOTAL USE OF ETHYLPARABEN AND THE NUMBER OF PRODUCTS. THE DATA COVERS A PERIODE FROM 1999 TO 2010 FOR SWEDEN, DENMARK, FINLAND AND NORWAY SEPERATELY (DATA RETRIEVED FROM THE SPIN DATABASE)

4.3.1.3 Propylparaben

The total use volume of propylparaben registered in Sweden, Denmark, Finland and Norway from the period from 1999 to 2010 (data indirectly retrieved from the Nordic SPIN database) is shown in Figure 5. The total use volume and the number of products containing propylparaben for each separate country are shown in Figure 6. As for methylparaben, it is observed in figure 5 that the use volume of propylparaben increased from 1999 until 2005-2006 (peaking at about 32 ton) and then has decreased until 2010. The level in 2010 is at the same level as seen in 1999. At the same time the number of products containing propylparaben (figure 6) has remained on almost the same level or only a slight decrease. This could indicate a lower mean concentration of propylparaben in the products 2010 compared to the concentration in 2005-2006.

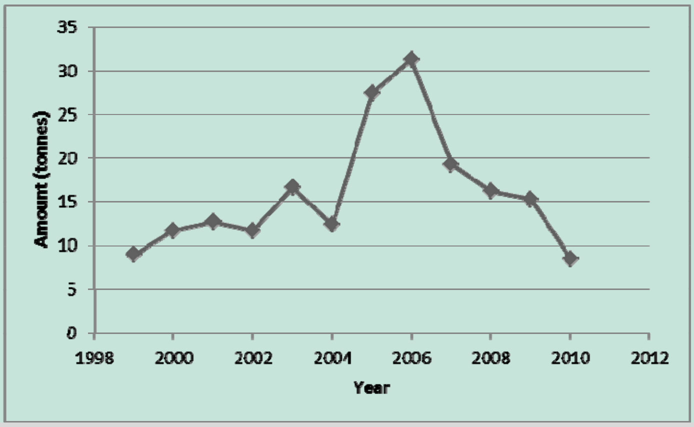


FIGURE 5 THE TOTAL AMOUNT OF PROPYLPARABEN REGISTERED IN SWEDEN, DENMARK, FINLAND AND NORWAY (DATA INDIRECTLY RETRIEVED FROM THE NORDIC SPIN DATABASE)

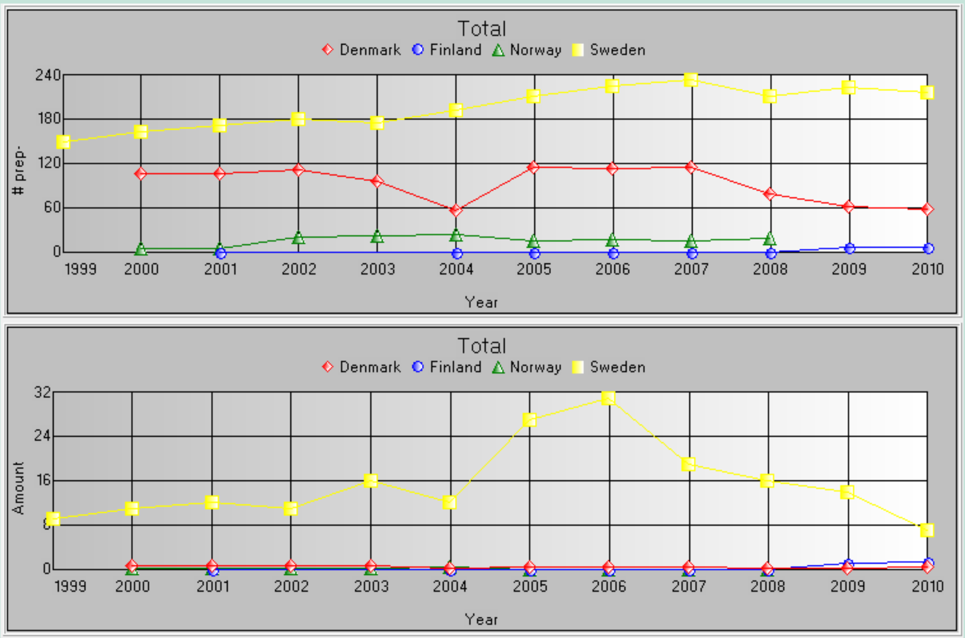


FIGURE 6 THE TOTAL USE OF PROPYLPARABEN AND THE NUMBER OF PRODUCTS. THE DATA COVERS A PERIODE FROM 1999 TO 2010 FOR SWEDEN, DENMARK, FINLAND AND NORWAY SEPERATELY (DATA RETRIEVED FROM THE SPIN DATABASE)

4.3.1.4 Butylparaben

The total use volume of butylparaben registered in Sweden, Denmark, Finland and Norway from the period from 1999 to 2010 (data indirectly retrieved from the Nordic SPIN database) is shown in Figure 7. The total use volume and the number of products containing butylparaben for each separate country are shown in Figure 8. The use volume data for butylparaben has a slight peculiar course (figure 7). The use volume is almost constant from 1999 to 2008 (about 1.1 ton), whereas the volume decrease until "0" in 2009. However, at the same time the number of products containing butylparaben (figure 8) does not decline to 0 at 2009! In Sweden and Denmark there are still several products in 2009 and 2010 although the volume is registered as "0" in this period. This could be due to error in the data retrieved from the SPIN database.

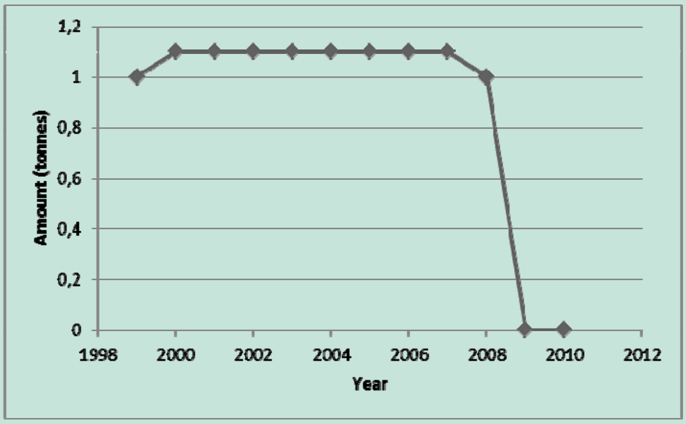


FIGURE 7 THE TOTAL AMOUNT OF BUTYLPARABEN REGISTERED IN SWEDEN, DENMARK, FINLAND AND NORWAY (DATA INDIRECTLY RETRIEVED FROM THE NORDIC SPIN DATABASE)

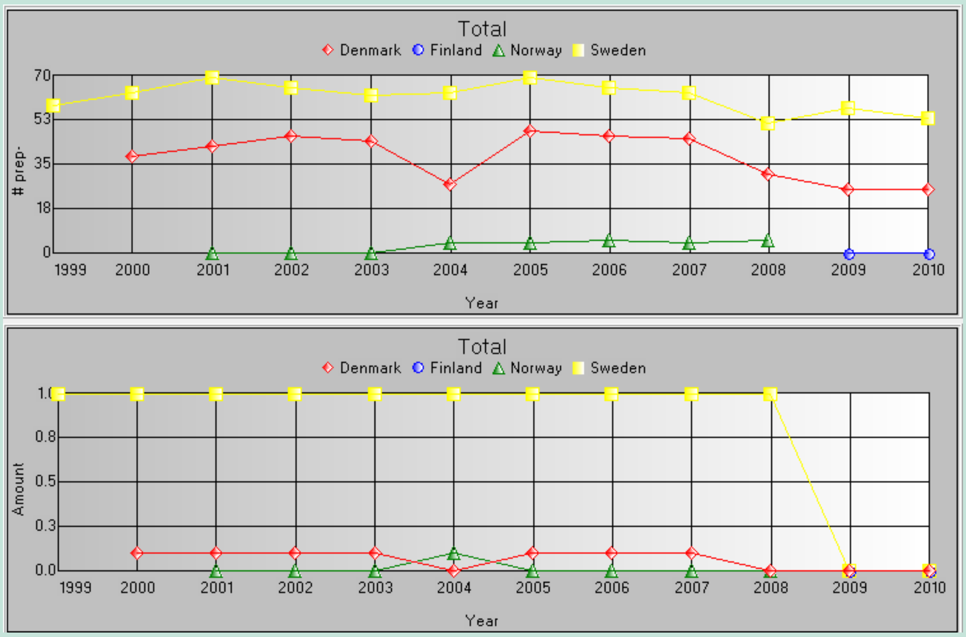


FIGURE 8 THE TOTAL USE OF BUTYLPARABEN AND THE NUMBER OF PRODUCTS. THE DATA COVERS A PERIODE FROM 1999 TO 2010 FOR SWEDEN, DENMARK, FINLAND AND NORWAY SEPERATELY (DATA RETRIEVED FROM THE SPIN DATABASE)

4.3.1.5 Isopropylparaben and isobutylparaben

No data is available in the Nordic SPIN database. No data on use volumes found other places, but several papers and links on the internet suggests that the use volume of isopropyl- and isobutyl paraben are limited within EU (SCCS, 2011).

4.3.2 Use in cosmetics

Parabens are widely used as preservatives in cosmetics worldwide. The substances are present in a large variety of products including products for children. The products include face, body and hand creams, lotions and moisturizers; eye makeup products; foundation and other makeup products; night creams and lotions; cleansing products; hair conditioners; bubble baths; shampoos; mud packs; underarm deodorants and skin lighteners (Soni *et al*, 2002). Methyl paraben and propyl paraben are the most commonly used preservatives in cosmetics. Rather old data from 1984 indicates that parabens are found in all types of cosmetic formulations and have a use in over 13,200 formulations (Soni *et al*, 2002). Parabens have excellent chemical stability in relation to pH (effective between pH 4.5 and 7.5) and temperature and formulate well because they have no perceptible odour or taste, are practically neutral, do not produce discoloration, and do not cause hardening or "muddying" (Soni *et al*, 2002).

The Danish Association of Danish Cosmetics, Toiletries, Soap and Detergent Industries did a survey in 2010 asking their members regarding the use of parabens in children products. The survey showed that, whit a few temporary exceptions, propyl- and butylparaben were no longer used in cosmetic products for children under three years of age (SPT, 2010).

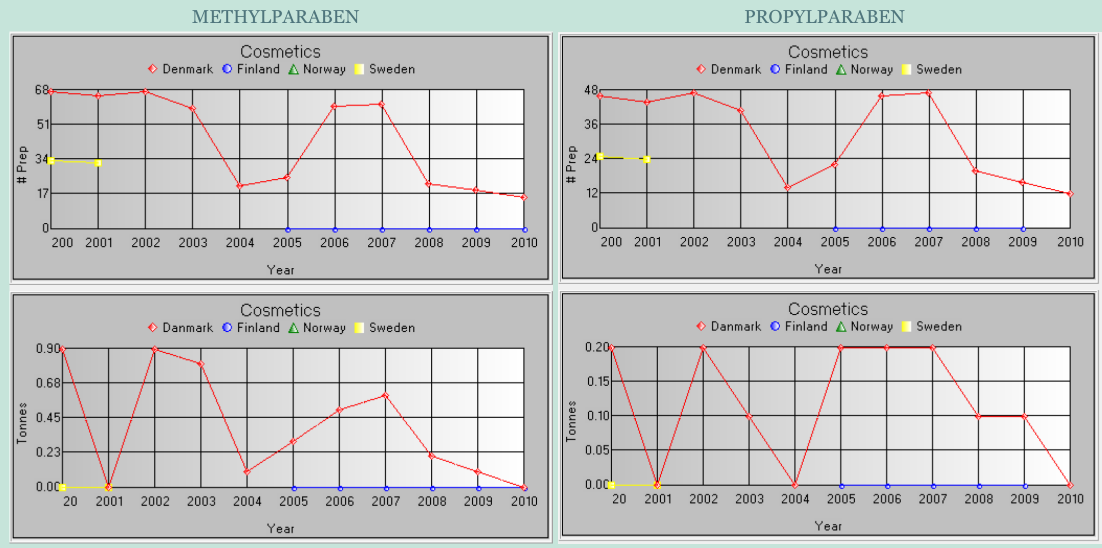


FIGURE 9 THE USE OF METHYLPARABEN AND PROPYLPARABEN IN COSMETICS BASED ON AMOUNT (TONNES) AND NUMBER OF PRODUCTS. THE DATA IS RETRIVED FROM THE NORDIC SPIN DATABASE. THERE IS NO DUTY TO DECLARE COSMETIC PRODUCTS TO THE PRODUCT REGISTERS

Data from the Nordic SPIN database illustrates an incomplete picture of the use of methyl- and propylparaben in cosmetics in the Nordic countries. It is important to note that the duty to declare products to the product registers does not apply to cosmetic products, and therefore these use volumes do not cover the total use volume of parabens in cosmetics, but may give a rough estimate. The use of the other 4 parabens are low compared to methyl- and propylparaben and therefore not included in the figure. Figure 9 shows that the data in the Nordic SPIN database regarding the use of parabens in cosmetic may not show the full picture. In 2010 only 12 products containing propylparaben are registered in Denmark even though that consumer projects prepared by the

Danish EPA has shown that several products like sunscreen products and body lotions on the Danish market contain parabens (etc. Tønnig *et al*, 2009; Andersen *et al*, 2012).

4.3.3 Use in food

Parabens have been added to food for more than 50 years and over the years, the use of parabens has steadily increased to include many more food categories in USA (Soni *et al*, 2005), while in EU the regulation regarding the use of parabens in food seems considerably stricter.
In USA parabens are employed in several foods including processed vegetables, baked goods, fats and oils, seasonings, sugar substitutes, coffee extracts, fruit juices, pickles, sauces, soft drinks and frozen dairy products at concentrations of between 450 and 2000 ppm (Soni *et al*, 2005), while in Europe their use is restricted to confectionery (excluding chocolate) in amounts up to 300 mg parabens/kg and as surface treatment of dry meat products, cereal- or potato-based snacks and coated nuts (maximum 300 mg/kg) (Directive 2006/52/EC). In 2006 it was necessary to withdraw the use of E216 propyl p-hydroxybenzoate and E217 sodium propyl p-hydroxybenzoate. (JECFA, 2006). Propylparaben could not be included in the group ADI because of effects on sex hormones and the male reproductive organs in juvenile rats.

4.3.4 Use in pharmaceuticals

Parabens have a long history of use in drug products. They were first employed as preservatives in pharmaceutical products in the mid-1920's (Sabalitschka, 1930). Parabens have been incorporated as preservatives in a variety of drug formulations. Combinations of parabens are more active than individual parabens (Boehm and Maddox, 1972). Among the parabens, propyl paraben is one of the most effective fungistats used in pharmaceutical products. A variety of drug formulations including suppositories, anesthetics, pills, syrups, weight gaining solutions, injectable solutions and contraceptives are known to contain parabens as preservatives (Soni *et al*, 2005).

In Denmark the main products preserved with parabens are oral mixtures/suspensions and injection fluids and in minor product numbers creme formulations. It is primarily methyl- and propylparaben that is used (personally contact to the Danish Health and Medicines Authority).

4.3.5 Use in other products

Parabens may be used as preservative in a broad range of products other than the three main uses in cosmetics, food and pharmaceuticals.

According to information from the American homepage "household products database (U.S. Department of Health & Human Services) parabens are also used in pet care products. The Nordic SPIN database also shows small use in the category 'paints, laquers, and varnishes', 'surface treatments, and 'anti-static agents'.

4.3.5.1 Cleaning/washing agents

Based on data from the SPIN database parabens (especially methyl- and propylparaben) are used as preservative in cleaning products, washing products and dish washing products (machines). In 2010 around 1 tonnes of methylparaben was used in these kind of products in Sweden, while less were used in the other Nordic countries, and it seems like the amount used in these products are declining. The same trend is seen for propylparaben with a lower total amount (figure 10). However, the number of products is not declining indicating the use of no or other substances as preservation instead of paraben.

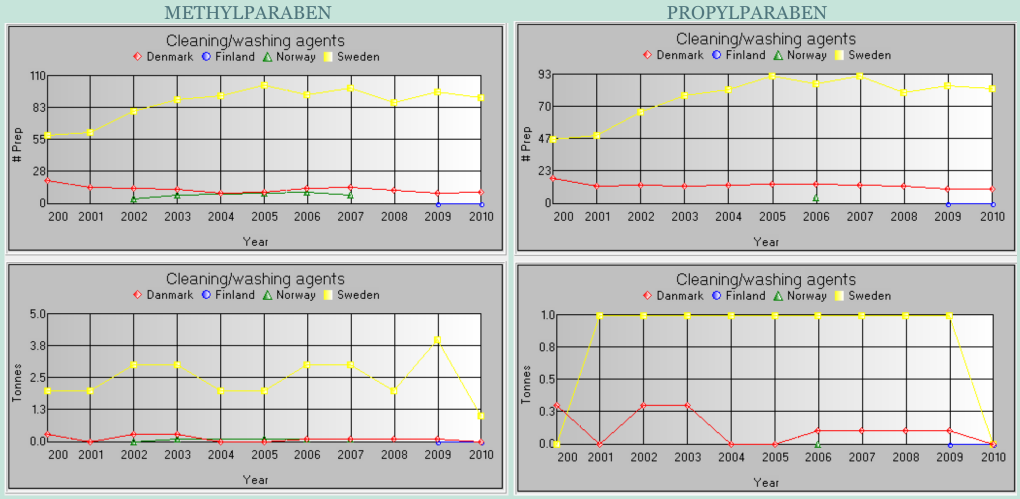


FIGURE 10 METHYLPARABEN AND PROPYLPARABEN USED IN CLEANING/WASHING AGENTS (NUMBER OF PRODUCTS AND TOTAL AMOUNTS IN TONNES) ILLUSTRATED FOR SWEDEN, FINLAND, NORWAY AND DENMARK

4.3.5.2 Non-agricultural pesticides and preservatives (Biocides/in-can preservatives)

According to data from the SPIN database (especially methyl- and propylparaben) used in non-agricultural pesticides and preservatives. In 2010 around 27 tonnes of methylparaben was used in these kinds of products in Sweden. Going into further details for this category the primary amount is used as in-can preservatives. However, none of the 6 parabens are notified under the Biocides Directive (98/8/EC), and therefore, they are not allowed to be used as in can preservatives. The data from the SPIN database should therefore be investigated further to clarify, whether they may be due to erroneous filing

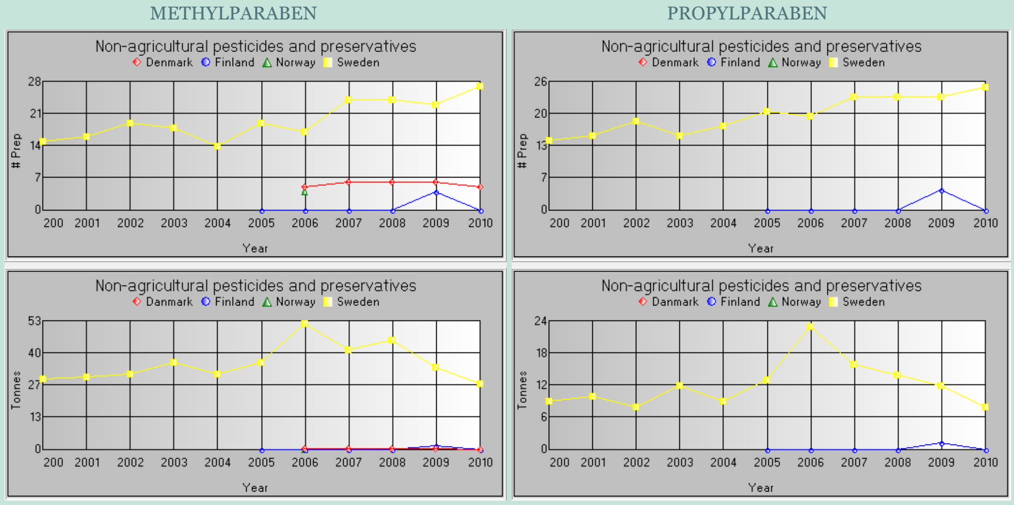


FIGURE 11 METHYLPARABEN AND PROPYLPARABEN USED IN NON-AGRICULTURAL PESTICIDES AND PRESERVATION (NUMBER OF PRODUCTS AND TOTAL AMOUNTS IN TONNES) ILLUSTRATED FOR SWEDEN, FINLAND, NORWAY AND DENMARK

4.3.6 Estimated trends in use

The information found regarding the trend in production and/or use of parabens indicates that the volume of use is decreasing. The data is mainly based on data from the Nordic SPIN database with information from 1999 to 2010 (figure 1-8) and from the USA Non-confidential Inventory Update Reporting production Volume information (table 10). However, the USA data is based on rather old data from 1986 to 2002.
One could assume that the use would shift from use of longer chain parabens to short chain parabens based on the massive press and discussions regarding especially propyl- and butylparaben. However, the data identified shows, that there has been a decrease in use volumes for both short- and long chain parabens. It has not been possible to identify 2011 and 2012 data, which could confirm the decreasing trend seen from 2007 to 2010.

On the homepage of the Swedish Chemicals Agency (KemI) information on the trend in use was retrieved (Figure 12). As cosmetic products and food are not included in KemI´s Product Register it is not possible to find out whether use in cosmetics and food increases. On the other hand it is possible to see that an increasing number of other chemical products, e.g. dish washing products, are preserved with parabens. However, it seems that the volume (in tonnes) is increasing from the beginning of the 90's until the use volume is peaking in 2005-2006 and then declining from 2006 until 2010 for the products included in the products register. The level in 2010 is on the same level as in 1999.

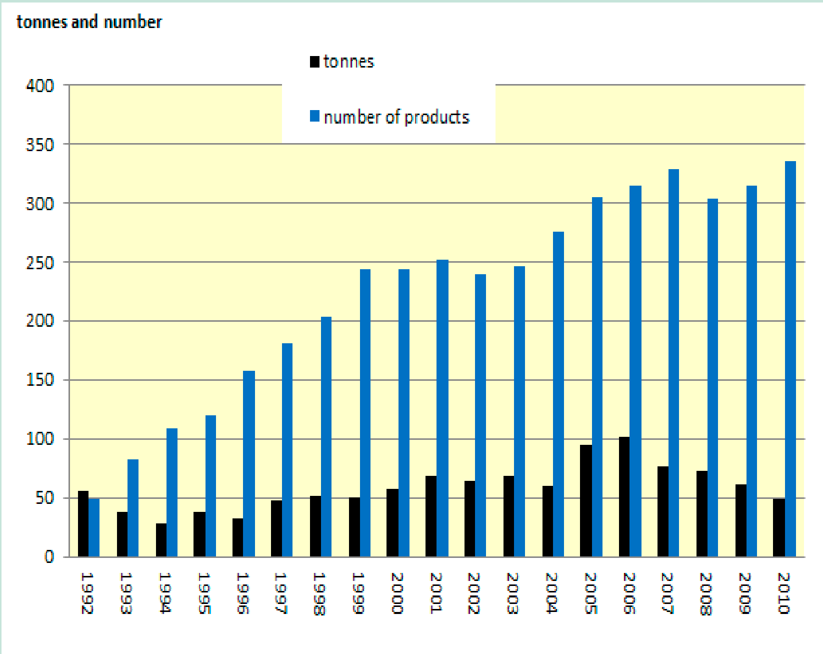


FIGURE 12 TURNOVER OF PARABENS IN CHEMICAL PRODUCTS EXCLUDING COSMETICS AND FOOD (SOURCE: PRODUCTS REGISTER, SWEDISH CHEMICALS AGENCY, KEMI)

4.4 Conclusions

Scarce information was received by the industry and authorities on total and application related use volumes in and outside EU. Based on existing and available data retrieved from the internet, in view of the general description of the substances, and especially in view of the numerous companies that have pre-registrated the substances under REACH, the use in various products and the overall amount of parabens appears to be substantial. World-wide the main use areas are cosmetic products, pharmaceuticals and food. Based on the data found in this survey, methyl- and propylparaben are the most widely used parabens with methylparaben showing the highest use volume. Data on use from the Nordic countries product registers indicate that the use of parabens has declined from 2006-2007, when the level peaked, until 2010. However, the use volume in 2010 was at the same level as in 1999.

5. Information on exposure

5.1 Occupational exposure

Exposure may occur at manufacturing sites and production sites of cosmetics and other consumer or chemical products containing parabens. Occupational exposure to parabens may occur through inhalational exposure or through dermal contact, the latter generally being stated as the major exposure route for the worker. Normally, oral exposure is not considered a significant route of exposure in working situations.

5.2 Consumer exposure

Exposure to parabens from consumer products can arise from the substances themselves, products or articles containing the substance. As described in earlier chapters, parabens are widely used in cosmetic products, pharmaceuticals and in food and thus human exposure to parabens is expected to be widespread.

A literature search has been performed identifying papers on exposure to parabens. Several biomonitoring studies describe that parabens are found in urine from pregnant Japanese women and in Spanish and American women. Urinary excretion of free and total (free plus conjugated) forms of methyl-, ethyl-, propyl- and butylparabens and their metabolite p-hydroxybenzoic acid were measured for 111 pregnant Japanese women. Frequent detection of parabens and their metabolite indicated that exposure takes place daily for pregnant Japanese women. The order of total concentrations of the 4 parabens were methyl- > propyl- > ethyl- > butylparaben, which concurs with the results of studies in the USA (Calafat *et al*, 2010) and Spain (Casas *et al*, 2011). This indicates a similar usage in personal care products and/or foods in these countries and in Japan (Sayaka *et al*, 2012), and confirms the pattern shown in chapter 4.2 that methyl- and propylparaben are the mostly used parabens.
A study in Norway including 332 individuals found elevated levels of native paraben in plasma from the general population. Methylparaben was the paraben found in highest amounts (median level of 9.4 ng/ml) and was detected in 63% of the samples. Propylparaben was detected in 29% of the samples in a median concentration of less than 2 ng/ml. The authors found a strong and significant association between the observed plasma levels of parabens with the use of skin care products (Sandanger *et al*, 2011).
Depending of the nature of the products and its use different exposure routes may be relevant. The different exposure routes are described for relevant product groups and exposure is estimated based on literature information.

5.2.1 Cosmetics

The main exposure route from cosmetics is dermal. The USA Cosmetic Ingredient Expert Panel estimated that skin metabolism of parabens is likely to result in as little as 1% of un-metabolized parabens being available for absorption into the body (CIR, 2008), whereas the SCCS estimated that 3.7% of intact propylparaben or butylparaben may be absorbed intact through the skin (SCCS, 2011). The issue regarding the amount of intact parabens absorbed though intact human skin is still at discussion with new studies being performed (Frederiksen, 2011; Aubert *et al*, 2012). Aubert *et al,* 2012) argue that dermal absorptions of 14.5% (for methylparaben) to 27.1% (for butylparaben) measured in rat studies would project a human systemic exposure ranging from 0.5% to 9% taking into account the high permeability of rat skin compared to human skin. Furthermore, they argue that topical use of parabens does not produce a significant systemic exposure to the parent compounds, but to a metabolite, i.e. para-hydroxybenzoic acid (PHBA).

Several approaches have been made to estimate the exposure for parabens from cosmetics:

- The SCCS has estimated an external aggregate exposure from cosmetic product of 69.6 mg/person/day, equal to 1.16 mg/kg bw/day (SCCS/1348/10). This is derived from an estimated total use of cosmetic products of 17.4 g/person/day and a maximum concentration of 0.4%. Using a dermal absorption of 3.7 % this leads to a systemic exposure of 0.043 mg/kg bw/day.

- An adult human systemic dose of 1.18 mg/kg bw/day of multiple parabens (based on 50% absorption through skin) and an infant systemic dose of 0.336 mg/kg bw/day (also based on 50% absorption through skin) was estimated by CIR from the use of average daily cosmetics of 17.76 gram of products per day for adults and 378 mg of products for infants (CIR, 2008).

- In a project funded by the Danish EPA "Exposure of pregnant consumers to suspected endocrine disruptors" an estimated systemic exposure of 0.089 mg/kg bw/day for each single paraben as a worst-case exposure was found for propyl-, butyl- and isobutylparabens (Andersen *et al*, 2012). This was estimated based on a scenario, where the cosmetic product contained maximum 0.1% (as acid) propyl-, butyl- or isobutylparaben.

- Cumulative exposure was estimated to 1.3 mg/kg bw/day based on refined aggregate exposure estimates in Cowan-Ellsberry and Robison, 2009. Of this, 0.79, 0.34, and 0.0016 mg/kg bw/day was methyl-, propyl- and butylparaben, respectively.

5.2.2 Food

In the EU, the allowed content of methyl- and ethylparaben in food are maximum 300 mg paraben/kg food (in total as methyl-or/and ethylparaben). EFSA has established a full-group ADI of 10 mg/kg bw for the sum of methyl and ethyl parabens and their sodium salts (Regulation (EU) No. 1129/2011).
In the US, some estimations of paraben exposure from food have been done. Two exposure estimates for methyl- and propylparaben, the two parabens that are used most extensively in food in the USA, have been done. The first approach was to use the disappearance data on the amount of these parabens used each year. These data would estimate that an average person consumes as much as 0.001 mg/kg/day of methylparaben in food and 0.013 mg/kg/day of propylparaben in food assuming a body weight of 60 kg. The second approach uses Flavor Extract Manufacturer's Association (FEMA) estimates of Possible Average Daily Intake which employs the usual use levels in products and mean consumption values for the various foods. The estimated exposure via food using this approach is 0.004 mg/kg/day for both methyl- and propylparaben assuming a body weight of 60 kg. It is important to note that these exposure estimates are based on USA data, were the regulation of parabens in food are less strictly compared to the EU and that the estimations are based on rather old use volume data from the 80's. However, the estimation may give an impression of the level of exposure.

The Danish Veterinary and Food Administration perform yearly control analyses of different kind of foods for their content of parabens (See table 10).

TABLE 10
YEARLY CONTROL ANALYSES OF DIFFERENT KIND OF FOODS

Year	Methyl- and Ethylparaben	Propylparaben
2007	76 samples (fish pate, takeaway dishes, spices, sauces)	75 samples (fish pate, takeaway dishes, spices, sauces, pizza filling, cakes, and marzipan)
2008	3 samples (fish pate, fish cake)	3 samples (fish pate, fish cake)
2009	2 samples (chocolate, potato chips)	2 samples (chocolate, potato chips)
2010	37 samples: (chocolate, potato chips, cakes, marinades, sauce, sausage, fish cakes, marzipan)	3 samples: (tomato sauce, pesto, olive oil)
2011	4 samples: (olive oil, pesto, tomato sauce)	4 samples: (olive oil, pesto, tomato sauce)
2012	45 samples: (chocolate)	45 samples: (chocolate)

None of the analysed samples in table 10 contained methyl-, ethyl- or propylparaben.

In the project “Exposure of pregnant consumers to suspected endocrine disruptors “funded by the Danish EPA the exposure to parabens from food were also included: However, the exposure to parabens (propyl-, butyl- and isobutylparaben) from food was estimated to be negligible (Andersen *et al*, 2012).

5.2.3 Pharmaceuticals

Exposure to parabens in pharmaceuticals may be via the oral, dermal, intravenously or inhalation route depending on the pharmaceutical products intended use. Data to estimate the exposure is available for Denmark (data received from the Danish Health and Medicines Authority). However, it will be an extensive work to calculate the exposure, which is out of range of this project.

5.3 Human exposure via the environment

Human exposure via the environment is considered as being minor. However, new studies indicate that exposure may take place via indoor dust. In a study, 158 indoor dust samples from the US, China, Korea, and Japan were collected and the concentrations of six parabens and their common hydrolysis product, 4-hydroxybenzoic acid (4-HB) were determined. All of the target compounds were found in dust samples from four countries. Concentrations of sum of six parabens in dust were on the order of several hundred to several thousands of nanogram per gram. Methyl- and propylparaben were the predominant compounds found in dust samples. Methylparaben accounted for 42–73% of the total paraben concentrations, with mean concentrations ranging from 226 to 1670 ng/g. Propylparaben accounted for 12–46% of the total paraben concentrations, with mean concentration range of 123–761 ng/g. On the basis of the measured concentrations of target chemicals, an estimated daily intake (EDI) via dust ingestion was assessed. The EDIs of parabens via dust ingestion were 5–10 times higher in children than in adults. Among the four countries studied, the EDIs of parabens (5.4 ng/kg bw/day) through dust ingestion were the highest for children in Korea and Japan. This is explained by the use of cosmetics in the four countries as the consumption of cosmetics and skin care products by Korean and Japanese women was similar, which was five times higher than that reported for American women, and 50 times higher than that reported for Chinese women (Wang *et al*, 2012).

5.4 Conclusions

Human exposure to parabens is mainly through cosmetic products. An older USA estimation of exposure indicates that only 20% will be through food, making cosmetics the main exposure route for humans. Of the exposure through cosmetics, almost 100% will be dermal. The health risk from exposure to parabens in cosmetics has long been, and still is, the object of much discussion.

6. Environmental hazard and fate assessment

6.1 Monitoring

The use of parabens as a preservative in food, cosmetics, pharmaceuticals and other chemical products (cleaning agents e.g.) may result in its release to the environment through various waste streams. Most ingredients in cosmetic products may eventually end up in the aquatic environment through sewage treatment systems, either directly when they are used (e.g. soaps, toothpastes, shampoos, hair dyes) or after use (wash-off during showering) (e.g. make-up, deodorants, hair-styling products, perfumes). Some products/ingredients may also be released directly into the environment (both the aquatic environment and air) upon use (e.g. sunscreen lotions, hair-styling products, creams). In a study from Spain results showed the presence of methyl- and propylparaben in sewage sludge at low ng/ g levels. The occurrence of parabens in sewage sludge was studied analysing samples collected in three wastewater treatment plants during a period of four years. Methylparaben and propylparaben were detected in three wastewater treatment plants throughout the study and while methylparaben levels remained rather constant (5.1 to 26.2 ng/g dry weight) an increase in the concentration of propylparaben was observed (levels up to 44.1 ng/g dry weight). The study demonstrates that parabens can be found in sewage sludge from wastewater treatment plants, although at low concentrations (ng/g levels) (Albero *et al*, 2012/in press). In Tokushima and Osaka, in a Japanese study they found aquatic concentrations of seven parabens in urban streams highly affected by treated or untreated domestic sewage. The detected highest concentrations were 670, 207, and 163 ng/l for methyl-, propyl- and butylparaben, respectively (Yamamoto *et al*, 2011).

6.2 Fate assessment

6.2.1 Air

If parabens are released to air, their estimated vapour pressure indicates that they will exist mainly as a vapour in the atmosphere. They will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 10 - 15 days (HSDB, 2007). However, no data on parabens measured in air were found.

6.2.2 Soil

If parabens are released to soil, they are expected to have from low to high mobility based upon their estimated Koc ranging from 119 – 2100.
All parabens may readily biodegrade in the environment based on the biodegradation data of methylparaben, which degraded 100% after 6 days using the Zahn-Wellens test which suggests that biodegradation may be an important environmental fate process (HSDB, 2007).

6.2.3 Water

If released into water, methyl- and ethylparaben are not expected to adsorb to suspended solids and sediment based upon the estimated log Koc (see Table 2). Propyl- and butylparaben, however, are expected to adsorb to suspended solids and sediment based upon the estimated log Koc of 3.04 - 3.57 (see Table 3) (HSDB, 2007). No data is available for isopropyl- and isobutylparaben.
Based on the estimated Henry's Law constant values for parabens ($6.4\ 10^{-4}$ – $8.5\ 10^{-9}$ atm m^3/mol) volatilization from water surfaces is not expected to be an important fate process. An estimated

bioconcentration factor (BCF) of 6.4 and 16 for methyl- and ethylparaben respectively suggests that the potential for bioconcentration in aquatic organisms is low for these two substances. An estimated BCF of 44 for propylparaben suggests that the potential for bioconcentration in aquatic organisms is moderate, while an estimated BCF of 110 for butylparaben suggests the potential for bioconcentration in aquatic organisms is high. Hydrolysis is not expected to be an important environmental fate process (HSDB, 2007).

6.3 Environmental hazard

The Advisory list for self-classification (table 6) indicates a potential acute aquatic toxicity of propyl- and butylparaben based on QSAR predictions. However, butylparaben was previously self-classified as chronic aquatic toxic based on the QSAR calculations available at the time the LOUS list was established. Results from acute and chronic toxicity studies in algae, daphnia and fish are shown in figure 13.

Results of acute toxicity tests for seven parabens using medaka, *Daphnia magna*, and green alagae.

	Algae (72 h-EC_{50})		Daphnia (48 h-EC_{50})		Fish (96 h-LC_{50})	
	Our results	Literature	Our results	Literature	Our results	Literature
Methyl-paraben	80,000 (ND[b])	91,000[a]	34,000 (30,000–39,000)	11,200[a] 41,100[c] 62,000[e]	63,000 (50,000–93,000)	<160,000[d]
Ethyl-paraben	52,000 (ND[b])	18,000[a]	7400 (6200–8900)	24,600[d] 20,000–50,000[a] 32,000[e]	14,000 (10,000–19,000)	34,300[d]
n-propyl-paraben	36,000 (ND[b])	15,000[a]	2000 (770–2900)	18,700[d] 15,400[a] 23,000[e]	4900 (3600–6700)	9700[d]
i-propyl-paraben	48,000 (33,000–69,000)		3500 (3100–4200)	12,300[d] 30,000[e] 8500[d]	4500 (3100–6800)	17,500[d]
n-butyl-paraben	9500[f]	.	1900[b] (1700–2600)	9200[e] 5300[d]	3100[b] (2500–8200)	4200[d]
i-butyl-paraben	4000[f]		3300[f]	9800[e] 7600[d]	4600[f]	6900[d]
Benzyl-paraben	1200[f]		2100[f]	6600[e] 4000[d]	730[f]	3300[d]

Unit: μg l^{-1}
Range of 95% confidence level was determined and presented within the parentheses for the acute data.
[a] From Madsen et al. (2001).
[b] Not determined due to the high jump in inhibition ratio.
[c] From Kamaya et al. (2005).
[d] From Dobbins et al. (2009).
[e] From Terasaki et al. (2008).
[f] From Yamamoto et al. (2007a).

Results of chronic toxicity tests, medaka vitellogenin assay, and DNA microarray analysis for the seven parabens.

	Algae	Daphnia		Fish			
	Our results (72 h-NOEC)	Our results (21 d-NOEC)	Literature (10 d- LOEC growth/reproduction)	Our results (14 d-NOEC VTG)	Literature (LOEC VTG)	Our results (14 d-LOEC microarray)	Literature (7 d-LOEC growth)
Methyl-paraben	21,000	2400	1500[a]	160		<10	25,000[a]
Ethyl-paraben	18,000	[1600]	2300[a]	[80]			17,000[a]
n-propyl-paraben	7400	[1100]	400[a]	[40]			2500[a]
i-propyl-paraben	11,000	[1200]	2000[a]	[50]	<9200[b]		9000[a]
n-butyl-paraben	800[c]	*800*[c]	300[a]	30[c]	210[d] 134[e]		1000[a]
i-butyl-paraben	600[c]	*640*[c]	200[a]	*20*[c]			3500[a]
Benzyl-paraben	520[c]	*840*[c]	100[a]	*20*[c]		*<4.0*[c]	1700[a]

Unit: μg l^{-1} Predicted values are presented within the parenthesis; Nominal values are italicized.
[a] From Dobbins et al. (2009).
[b] From Inui et al. (2003).
[c] From Yamamoto et al. (2007a).
[d] From Alslev et al. (2005).
[e] From Bjerregaard et al. (2008).

FIGURE 13 RESULTS (μG/L) FROM ACUTE AND CHRONIC TOXICITY STUDIES IN ALGAE, DAPHNIA AND FISH FOR 7 DIFFERENT PARABENS (TABLES COPIED FROM YAMAMOTO *ET AL*, 2011).

The data shows, that none of the tested parabens would be classified as acute or chronic toxic for aquatic animals. The acute toxicity of methyl-, ethyl- and propylparaben in the study by Yamamoto *et al* (2011) is comparable to previous studies by Madsen *et al.* (2001) and Dobbins *et al.* (2009). Yamamoto *et al* (2011) measured environmental concentrations (MECs) of seven parabens in

Tokushima (maximum 676 ng/l) and Osaka (maximum 199 ng/l) and divided them by the predicted no effect concentrations (PNECs). The risk ratio (MEC/PNEC) was determined for individual parabens. The MEC/PNEC was highest for propylparaben (0.010) followed by butylparaben (max. of 0.0086) and methylparaben (max. of 0.0042). The sum of the MEC/PNEC for seven parabens was 0.0049 (Yamamoto *et al*, 2011).
It has been shown, that the longer chain parabens may have potential estrogenic effects on fish as they induce the production of vitellogenin in rainbow trout after intraperitoneal injection at doses of 100-300 mg/kg and/or after exposure in water containing propylparaben at a concentration of 225 µg/L (Petersen *et al*, 2000), (Bjerregaard *et al*, 2003).

6.4 Conclusion

For the environment, the assessment of fate and hazard for parabens indicated a low toxicity. This was despite the QSAR prediction on which the Advisory list for self-classification is based, identifying propyl- and butylparaben as acute toxic to aquatic animals. Only few data regarding the environmental toxicity of parabens were found. For the parabens, estimated risk ratios were calculated as MEC/PNEC (measured environmental concentrations/predicted no effect concentrations). The highest MEC/PNEC was (0.010) for propylparaben followed by butylparaben (max. of 0.0086) and methylparaben (max. of 0.0042). These estimated low risk ratios (<<1) thus indicate a low risk for environmental effects of parabens. Some studies have shown that parabens may have estrogenic effects in fish. However, the effects are seen at concentrations much higher (µg - mg) than actual environmental concentrations, as for instance in Spain and Japan (ng/L).

7. Human health hazard assessment

Acute, subchronic, and chronic studies in rodents generally indicate that parabens have a low toxicological potential. In individuals with normal skin, parabens are for the most part non-irritating and non-sensitizing. However, application of products containing parabens to damaged or broken skin has resulted in sensitization. Genotoxicity testing of parabens in a variety of *in vitro* and *in vivo* studies primarily gave negative results. The paraben structure is not indicative of carcinogenic potential, and experimental studies support these observations (Elder, 1984; Soni *et al*, 2005).

In 1984 the Cosmetic Ingredient Review (CIR) looked into the safety of methylparaben, propylparaben, and butylparaben and concluded they were safe for use in cosmetic products at levels up to 25%. Typically parabens are used at levels ranging from 0.01 to 0.3% (Elder, 1984). The CIR is an industry-sponsored organization that reviews the safety of cosmetic ingredients and publishes its results in open, peer-reviewed literature. In 2005, the CIR decided to re-open the safety assessment for parabens and requested exposure estimates and a risk assessment for cosmetic uses. In December 2005, the authors concluded that a high margin of safety exists for human exposure to parabens despite reports of numerous endocrine-related effects of these chemicals. This high safety margin was illustrated by an adult human dose of 1.2 mg/kg bw/day of multiple parabens and an infant dose of 0.3 mg/kg bw/day when comparing with a no-observed adverse effect level (NOAEL) of 1000 mg/kg bw/day for all parabens. The NOAEL was established by CIR based on the most statistically, powerful and well-conducted study of the effects of butylparaben on the male reproductive system, although adverse effects of butyl-, isobutyl-, propyl-, ethyl-, and methylparaben at doses below 1000 mg/kg bw/day were reported by CIR.

Subsequently, the European Scientific Committee on Consumer Safety reviewed the parabens (SCCS)[1]. The first SCCS Opinion (SCCP, 2005a) was performed in 2005 and addressed issues about parabens and breast cancer from use of underarm cosmetics. The Opinion concluded that with the current knowledge there is no evidence of a demonstrable risk for the development of breast cancer caused by the use of underarm cosmetics.
Another Opinion (SCCP, 2005b) was published in 2005. This Opinion was an extensive evaluation of the safety of parabens. This Opinion concluded that the maximum authorised concentration of 0.4% (as acid) for one ester and 0.8% (as acid) for a mixture of esters should be maintained for methyl- and ethylparaben. SCCS also concluded that data for propyl-, isopropyl-, butyl- and isobutylparaben were insufficient. An acceptable daily intake (ADI) of 10 mg/kg bw/day which was determined for methyl- and ethylparaben by the European Food Safety Authority (EFSA) is mentioned in the SCCS Opinion. The safety of those two parabens was considered well documented. The SCCS did not find data sufficient for an assessment of the other parabens, and the EFSA was also not able to determine an ADI for those parabens. The SCCS requested reproductive and developmental toxicity studies and *in vitro* studies on percutaneous absorption on propyl-, isopropyl-, butyl- and isobutylparaben.

[1] Until February 2009 the Committee was called the European Scientific Committee on Consumer Products (SCCP)

Based on this request additional data was submitted to the SCCS, who made an evaluation of these and published a new Opinion in 2006 (SCCP, 2006). SCCS concluded that there were still too many shortcomings in data to change or modify the conclusions from the 2005 Opinion (SCCP, 2005b). Based on this conclusion a hearing took place in which industry defended their submission. The result of this hearing and a few new publications were discussed in a new Opinion from 2008 (SCCP, 2008). The conclusions remained the same; data were not sufficient to perform a safety assessment of the long chained parabens, and industry was again encouraged to submit additional data on reproductive toxicity and kinetics.
In 2010 the SCCS performed a safety assessment based on available data, even though it was stated that those were not sufficient. A conservative NOEL of 2 mg/kg bw/day was chosen from a study with butylparaben (Fisher, 1999) and the dermal absorption was set to 3.7%. The resulting margin of safety pointed to unsafe use if the current concentration limits were used. Lowering the maximum limit for propyl- and butylparaben to 0.14% (as acid) or 0.19% (as ester) would result in a margin of safety of 100, which is considered to be adequate. The conclusion was therefore that methyl- and ethylparaben are safe in the currently allowed concentrations whereas propyl- and butylparaben are safe in a lower concentration. The isoforms of propyl- and butylparaben could not be assessed based on existing data (SCCS, 2010).

In March 2011 Denmark issued a ban against propyl- and butylparaben in cosmetic products for children under the age of 3 years. As a result of this, the SCCS made a clarification to its Opinion from 2010 (SCCS, 2010) in October 2011 (SCCS, 2011). The conclusion in the 2011 Opinion was that relevant human data on the metabolism of parabens are still lacking, and that these data are required in order to reduce uncertainties in the assessment (SCCS, 2011). However, the SCCS also concluded that for the time being there is no safety concern for children by using general cosmetics that contain parabens, with the specific exception of products for the nappy area (SCCS, 2011).

In March 2012 a new study on the reproductive toxicity of propylparaben was presented to the Working Group on Cosmetic Products (SCCS, 2012). The new study has a similar study design as two former studies and does not demonstrate any reproductive effects on rats. The study has not been published. Thus, this new study will result in an update of the 2010 and 2011 Opinions on propyl- and butylparaben. In addition, the new Opinion will take into account information on exposure to sunscreens, especially for children below three years of age.

7.1 Absorption, metabolism, and excretion

7.1.1 Absorption

Overall, parabens are well absorbed after oral and subcutaneous administration (Aubert *et al*, 2012). It has also been argued that parabens are quickly and nearly completely hydrolysed into para-hydroxybenzoic acid (PHBA) after dermal application to human skin, so the systemic absorption of the parent compound is very low (Soni *et al*, 2005). However, other studies indicate that the biotransformation of the different parabens into PHBA is not as efficient as claimed (Ye *et al*, 2006; Janjua *et al*, 2007). The available *in vitro* dermal absorption studies are considered of poor scientific quality by SCCS (2011), and the results of biomonitoring studies show the presence of unmetabolised parabens in the plasma of human volunteers (Janjura *et al*, 2007; Sandanger *et al*, 2011).
According to SCCS (2010), data for the conversion from rat to human dermal absorption are still lacking, especially for the absorption and metabolism of the parent compound in the skin.
As long as properly conducted dermal absorption and/or toxicokinetic studies in humans are not available, the SCCS has established dermal absorption of parabens to be 3.7%. This value is derived from the results of three *in vitro* dermal absorption studies (Fasano, 2004a, b; Fasano, 2005). The value is based on a worst-case assumption for the dermal absorption of butylparaben, and it derives from the mean dermal absorption of 37% measured in split-thickness skin (Fasano, 2004b), using a

correction factor of 10 to account for skin metabolism as seen in the full thickness skin experiments (Fasano, 2004b, 2005).

7.1.2 Metabolism and Excretion

Parabens are excreted in urine as the metabolite PHBA or as conjugates of the parent compound with either glycine, glucuronide or sulphate. Data indicates that parabens are not accumulated in the body, and serum concentrations of parabens quickly decline and remain low (Boberg *et al*, 2010). Total levels of metabolites and parent compounds excreted in urine of orally and dermally exposed rats and rabbits are high, indicating that parabens and/or their metabolites are taken up in considerable amounts but rapidly metabolized and excreted (Boberg *et al*, 2010).

7.2 Estrogenic potential

Concern has been raised about the endocrine disrupting potential of parabens at high exposure levels. Studies in young male rats have shown adverse effects on sperm production and testosterone levels following oral exposure to parabens with longer side chains, i.e. butyl- and propylparaben (Oishi, 2001 and 2002). However studies with a similar design and of a more recent date do not confirm these findings (Hoberman, 2008). Parabens are known to be estrogenic *in vitro* and in uterotrophic assays *in vivo*, and estrogenicity appears to increase with side chain length (SCCS, 2011; Boberg *et al*, 2010).
However, there also seems to be a controversy about the endocrine disrupting potential of parabens. The USA FDA finds that at the present time there is no reason for consumers to be concerned about the use of cosmetics containing parabens. Although parabens can act similarly to estrogen, they have been shown to have much less estrogenic activity than the body's naturally occurring estrogen. For example, a 1998 study (Routledge *et al*, 1998) found that the most potent paraben tested butylparaben was 10,000- to 100,000-fold less active than naturally occurring estradiol. Furthermore, the FDA states that parabens are used at very low levels in cosmetics. In a review of the estrogenic activity of parabens, (Golden *et al,* 2005) the author concluded that based on maximum daily exposure estimates, it was implausible that parabens could increase the risk associated with exposure to estrogenic chemicals (FDA, 2007).

Methyl-, ethyl-, propyl- and butylparaben are on the EU list of potential endocrine disruptors which are to be studied further for endocrine-disrupting properties (EU, 2012). They are entered as category 1 substances, which are substances for which endocrine activity have been documented in at least one study of a living organism. These substances are given the highest priority for further studies. Furthermore, propyl- and butylparaben were both added to the SIN list (Substitute It Now) at the latest update of that database (SIN list 2.0). The SIN project is an NGO-driven European Union project to speed up the transition to a toxic-free world for the purpose of identifying substances of very high concern, according to REACH criteria. Propyl- and butylparaben are considered to belong to this category solely due to their potential endocrine disrupting properties.

7.2.1 Methyl- and ethylparaben

Methyl- and ethylparaben induced uterotrophic effects in immature rats and mice (Lemini *et al*, 2003). However, negative effects have also been seen for methyl- and ethylparaben (Hossaini *et al*, 2000). On the other hand, methyl- and ethylparaben were not shown to adversely affect the secretion of sex hormones or male reproduction function up to about 1000 mg/kg bw/day (Oishi *et al*, 2004). Generally, methyl- and ethylparaben are considered to have a much lower potential for causing endocrine disrupting effects compared to propyl- and butylparaben (SCCS, 2005).

7.2.2 Propylparaben

Several studies have shown that propylparaben has estrogenic and/or antiandrogenic effects *in vivo* and *in vitro* (described in SCCS' Opinion 2010).Propylparaben is generally considered to be less potent than butylparaben, both *in vitro* and *in vivo* (SCCS 2010). In screening studies for estrogenic effects of propylparaben, 10-20 mg/kg bw/day (LOAEL) increased uterine weight (Lemini *et al*, 2003; Lemini *et al*,, 2004), and 10 mg/kg bw/day reduced epididymis weight and sperm production in young rats (Oishi 2002). In a recent French study, juvenile rats were exposed by the oral route (gavage) for 8 weeks post-weaning to propylparaben. These data are not published but are currently being assessed by the SCCS. According to the SCCS mandate, the study does not confirm previous conclusions about effects on reproduction (SCCS, 2012).

7.2.3 Butylparaben

The effects of butylparaben were investigated in a study by Fisher *et al. (*1999). Here, effects were followed on the male reproductive system in young rats. A NOEL of 2 mg/kg bw/day was determined in this study. Furthermore, reduced sperm count was observed in offspring of rats exposed during pregnancy and lactation (Kang *et al*, 2002). No antiandrogenic effects, seen as anogenital distance in males, were observed in studies with dosing during gestation (Kang *et al*, 2002, Boberg J, 2008; Taxvig C, 2008). In other studies, reduced sperm production has been observed in young rats at 10-20 mg/kg bw/day (LOAEL) (Oishi, 2001), but subsequent studies with the same study design have not shown the same type of effects (Hoberman AM, 2008). The estrogenic effect is supported by findings of increased uterine weight in several screening studies for estrogenic effect (Hossaini *et al*, 2000; Lemini *et al*, 2003; Lemini *et al*, 2004; Vo *et al*, 2009). A few studies of estrogenic effects in immature animals show effects at the same low doses (Lemini *et al*, 2003), while other studies only show effects at higher doses (Vo *et al*, 2009, Vo *et al*, 2010) or do not examine the low doses (Hossaini *et al*, 2000).

7.2.4 Isopropyl- and isobutylparaben

Uterotrophic effects in immature rats have been observed for both isopropyl- and isobutylparaben (Koda *et al*, 2005, Vo *et al*, 2009). A NOAEL of 62.5 mg isobutylparaben/kg bw/day was determined for increased uterine weight in immature female mice and immature female rats, respectively in screening studies for estrogenic effect (Darbre *et al*, 2002; Vo *et al*, 2009). Several studies show estrogenic effect in corresponding *in vivo* studies and in cell-based studies, and therefore it can be considered to be robust knowledge that isobutylparaben is an endocrine disrupter (Koda *et al*, 2005). Fewer studies, compared to other parabens, have studied the estrogenic potential of isopropylparaben. However, it is considered that isopropylparaben is an endocrine disrupter (Vo *et al*, 2009).

7.2.5 Risk assessment considering the endocrine disrupting effects

The literature points out that the method for evaluating the endocrine disrupting potential of parabens and the kinetics of the substances is still not agreed upon (e.g. CIR, 2008; Boberg *et al*, 2010; Witorsch and Thomas, 2010; SCCP, 2011; Scialli, 2011). Considering the endocrine disrupting effects of parabens, a final risk assessment still awaits which NOEL/NOAEL to use and which dermal absorption fraction to use.

7.2.6 Combination effects

The Danish EPA has lead two projects investigating the risks from combined exposure (exposure from several sources) and risks from exposure to "cocktails" (exposures from several substances with the same effect at the same time); one considering the exposure to infants, and one considering the exposure to pregnant women (Tønning *et al*, 2009, Andersen *et al*, 2012). In these projects, combined exposures to different parabens were investigated. However, the different assumptions these projects were built upon are not the same, as one would assume if the projects were done today. Thus, the results are not summarised in this report.

7.3 Conclusions

Concerns have been raised about the endocrine disrupting potential of parabens at high exposure levels. Some studies in young male rats have shown adverse effects on sperm production and testosterone levels following oral exposure to parabens, i.e. propyl- and butylparaben. However other studies with the same study design and of a more recent date did not confirm these finding even at very high doses. Both the studies with positive and negative findings on reproductive toxicity have shortcomings, which makes it difficult to assess and weigh the results. Parabens are known to be estrogenic *in vitro* and in uterotrophic assays *in vivo*, and estrogenicity appears to increase with side chain length. Therefore, methyl-, ethyl-, propyl- and butylparaben are on the EU list of potential endocrine disruptors in category 1. Isopropyl- and isobutylparaben are not on this EU list. Category 1 substances are substances for which endocrine disrupting activity has been documented in at least one study of a living organism and are given the highest priority for further studies.

This project reveals that the method for evaluating parabens for their endocrine disruption potential and their kinetics are still not agreed upon. In addition, discussions on the most relevant NOEL/NOAEL and the dermal absorption values have not yet come to a conclusion. Thus, considering the endocrine disrupting effects, a final risk assessment still awaits which NOEL/NOAEL to use and which dermal absorption fraction to use, and to further identify the overall exposure for children. Currently a new study concerning reproductive toxicity is being assessed by the SCCS. Only few studies are available on the combined exposure to several parabens from several products.

8. Information on alternatives

From the industry no common alternatives are suggested. In cosmetic products other allowed preservatives according to directive 76/768/EEC may be used. However, several of the alternative preservatives are skin sensitizers.
Some vitamins and essential oils e.g. E-vitamin, tea tree oil and grape seed oil that may be used in cosmetics have a preserving action without being added to the cosmetics with that purpose. In a project regarding cosmetic products marketed as “non-preserved”, sponsored by the Danish EPA, it was found that some non-preserved products contained fragrances in a concentration that has antibacterial effect (Poulsen, 2011). The disadvantage in adding some natural substances with preserving properties is, compared to parabens, that they may need to be added in high concentration to give an effect as good as parabens, which again may result in more allergies.

The “paraben-history” has had a lot of focus in the press and in campaigns from e.g. the Danish EPA which has led to a broad marketing of “paraben-free” cosmetics. The Danish EPA has through several campaigns encouraged children below the age of three and pregnant women to use “paraben-free” products (Danish EPA, 2010; 2012).
Initiatives have also been made toward changing the containers for cosmetics thereby to be able to reduce/avoid the use of preservatives in cosmetics. Appropriate packaging like use of dispensing mechanisms that make the entry of microorganisms into the product very difficult could be successful. However, there were no applications to a recently launched funding programme from the Danish EPA for technology development in this area (Danish EPA, 2012),
Some companies participating in this survey have indicated that alternatives are not possible at the moment (in pharmaceuticals e.g.), but investigations in alternatives takes place in the companies. The project group was not told what kind of alternatives the investigations include.

8.1 Conclusion

Alternatives to the parabens could be preservatives that are approved for use in other areas. However, before changing preservatives on a large scale, the sensitising potential of many other preservatives must be borne in mind. Parabens themselves are rarely seen as sensitizers, although some of the parabens have been self-classified as skin- or respiratory sensitizers. Technologies totally reducing the need for preservation have not yet been marketed.

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Abbreviations

ADI	Acceptable Daily Intake
AF	Assessment Factor
B	Bioaccumulation
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / Bw, bw
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEN	European Standards Organisation / European Committee for Normalisation
CEF	Panel on food contact materials, enzymes, flavourings and processing aids
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
CoRAP	Community Rolling Action Plan
dw	dry weight / dw
DG	Directorate General
DNEL	Derived No-Effect Level
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EFSA	European Food Safety Authority
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
FAO	Food and Agriculture Organisation of the United Nations
FCM	Food Contact Material
HPLC	High Pressure Liquid Chromatography
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient

Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOEL	Lowest Observed Effect Level
LOQ	Limits Of Quantification
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
n	Number (and here the number of repeating units in the molecule)
NAEL	No Adverse Effect Level
NAEOL	No Adverse Effect Observed level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PEC	Predicted Environmental Concentration
pH	Logarithm (to the base 10) (of the hydrogen ion concentration {H+}
PNEC	Predicted No Effect Concentration
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RC	Risk Characterization
RCR	Risk Characterization Ratio
RfD	Reference Dose
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SETAC	Society of Environmental Toxicology And Chemistry
SML	Specific Migration Limit
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T	Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNO	The Netherlands Organisation for Applied Scientific Research
TRV	Toxicity Reference Values
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme

US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative v/v volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant

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